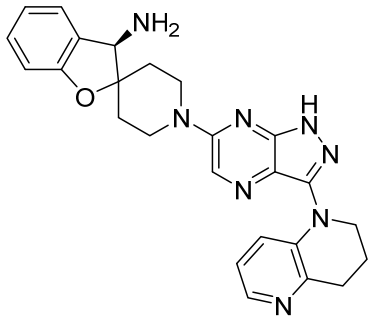
Thus, there is a need for SHP2 phosphatase inhibitor compounds and methods for treating cancer and other disorders with these compounds.

[0004] Polymorphism is the ability of a substance to crystallize in more than one crystal lattice arrangement. Crystallization, or polymorphism, can influence many aspects of solid state properties of a drug substance. A crystalline substance may differ considerably from an amorphous form, and different crystal modifications of a substance may differ considerably from one another in many respects including solubility, dissolution rate and/or bioavailability. Generally, it is difficult to predict whether or not a given compound will form various crystalline solid state forms. It is even more difficult to predict the physical properties of these crystalline solid state forms. Further, it can be advantageous to have a crystalline form of a therapeutic agent for certain formulations, e.g., formulations suitable for subcutaneous use.

SUMMARY

[0005] This disclosure is generally directed to, among other things, (*R*)-1'-(3-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine and salts thereof. Additionally, this disclosure is generally directed to, among other things, to the crystalline forms of (*R*)-1'-(3-(3,4-dihydro-1,5-naphthyridin-1(2H)-yl)-1H-pyrazolo[3,4-b]pyrazin-6-yl)-3H-spiro[benzofuran-2,4'-piperidin]-3-amine and salts thereof.

[0005a] In an aspect of the present disclosure, there is provided a solid form of Compound I-1:

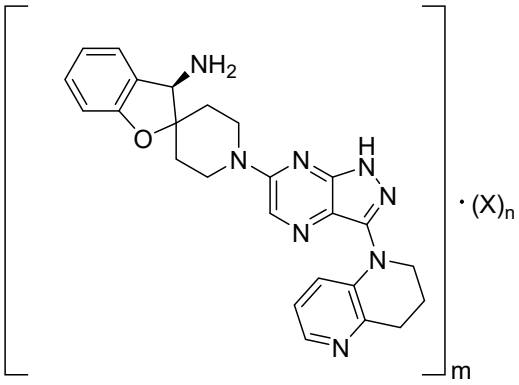


I-1,

or a ~~pharmaceutically acceptable salt~~ solvate thereof.~~,~~

~~characterized by a powder X-ray diffraction pattern having at least two characteristic peaks, in degrees 2θ, each selected from the group consisting of about 24.6, about 19.9, and about 16.0 2θ.~~

[0005b] In another aspect of the present disclosure, there is provided a compound of Formula (I)



(I),

or a ~~pharmaceutically acceptable salt~~ solvate thereof;

wherein,

m is 1-9;

n is 1-3; and

X is selected from ~~the~~ a group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfonic acid, phosphoric acid, *p*-toluene sulfonic acid, benzene sulfonic acid, oxalic acid, L-aspartic acid, maleic acid, malonic acid, L-tartaric acid, fumaric acid, citric acid, succinic acid, and glutaric acid.

[0005c] In a further aspect of the present disclosure, there is provided a pharmaceutical composition comprising a solid form disclosed herein and a pharmaceutically acceptable carrier.

~~**[0005d]** In another aspect of the present disclosure, there is provided a solid form disclosed herein, for use in therapy.~~

[0005~~e~~d] In a further aspect of the present disclosure, there is provided a use of a composition comprising the solid form of any of claims 1-7, a composition comprising the compound of any of claims 8-17, or the pharmaceutical composition of claim 18, ~~a solid form disclosed herein~~ in the manufacture of a medicament for inhibiting SHP2 phosphatase activity in a subject in need thereof.

[0005e] In a further aspect of the present disclosure, there is provided a composition comprising the solid form disclosed herein, a composition comprising the compound

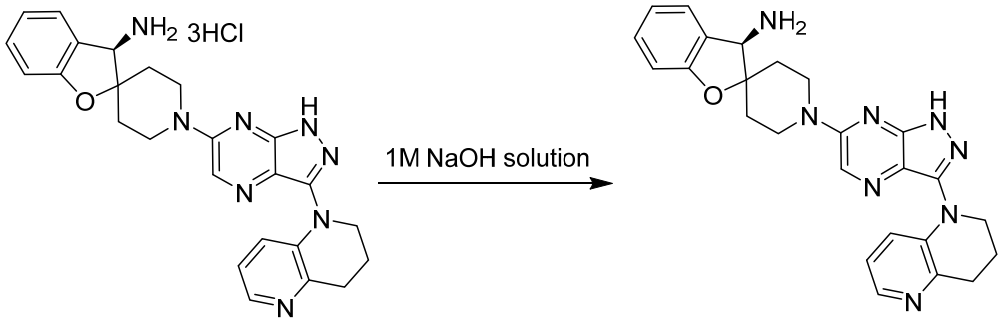
disclosed herein, or the pharmaceutical composition disclosed herein, for use in treating a disorder in a subject in need thereof.

[0005f] In another aspect of the present disclosure, there is provided a use of a composition comprising the solid form disclosed herein, a composition comprising the compound disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a disorder in a subject in need thereof.~~use of a solid disclosed herein in the manufacture of a medicament for treating a disorder mediated by SHP2 in a subject in need thereof.~~

[0005g] In a further aspect of the present disclosure, there is provided a kit comprising the solid form disclosed herein or a compound disclosed herein.~~a kit comprising the solid form disclosed herein and written instructions describing how to administer a pharmaceutical composition prepared using the solid form to a patient.~~

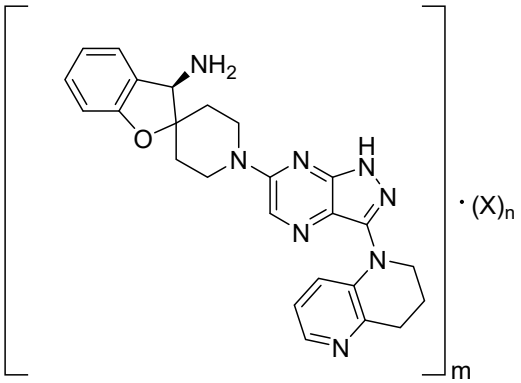
[0005h] In another aspect of the present disclosure, there is provided a process for preparing the crystalline form disclosed herein, comprising: a) preparing a solution of compound I-1 in a solvent comprising at least one of EtOH, ACN, MEK, EtOAc, IPAc, THF, MtBE, Toluene, 1,4 dioxane, and water; b) heating the solution to completely dissolve the compound I-1; c) adjusting the temperature so that solid precipitates out of the solution; and d) isolating the crystalline form of compound I-1.

[0005i] In a further aspect of the present disclosure, there is provided a process for preparing a compound of Formula I-1, the process comprising the step of neutralizing a compound of Formula I-3 with NaOH, thereby forming the compound of Formula I-1:



I-3 **I-1**

[0006] For example, provided herein is a compound of Formula (I)



(I),

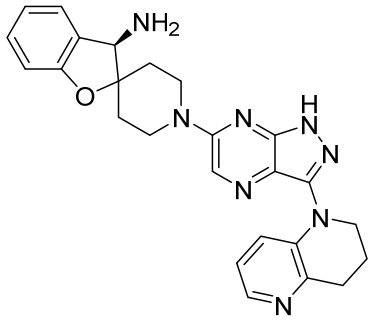
or a solvate thereof;

wherein,

CLAIMS

What is claimed:

1. A solid form of Compound I-1:



I-1,

or a ~~pharmaceutically acceptable salt~~solvate thereof~~,~~

~~characterized by a powder X-ray diffraction pattern having at least two characteristic peaks, in degrees 2θ, each selected from the group consisting of about 24.6, about 19.9, and about 16.0 2θ~~.

2. The solid form of claim 1, wherein the solid form is amorphous.

3. The solid form of claim 1, wherein the solid form is crystalline.

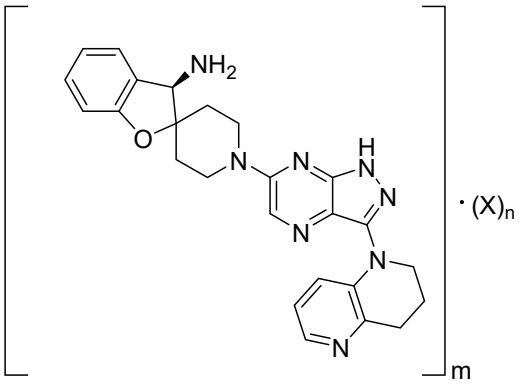
4. The solid form of claim 3, characterized by a powder X-ray diffraction pattern having at least two characteristic peaks, in degrees 2θ, each selected from the group consisting of about 24.6, about 19.9, and about 16.0 2θ.

~~4~~5. The solid form of claim 3, characterized by a powder X-ray diffraction pattern with at least two characteristic peaks, in degrees 2θ, each selected from the group consisting of about 24.6 2θ, about 19.9 2θ, about 16.0 2θ, about 6.7 2θ, about 12.8 2θ, about 13.4 2θ, and about 20.7 2θ.

~~5~~6. The solid form of claim 3, wherein the solid form is characterized by an XRPD pattern substantially similar to that depicted in FIG. 1A, or characterized by a X-ray powder diffraction pattern having peaks, in degrees 2θ, at about 24.6, about 19.9, about 16.0, about 6.7, about 12.8, about 13.4 and about 20.7.

~~6~~7. The solid form of any one of claims 3-6~~ claim 3~~, characterized by a differential scanning calorimetry (DSC) profile showing an endotherm with an onset of about 196 °C, and a peak of about 197 °C.

~~7~~8. A compound of Formula (I)



(I),

or a ~~pharmaceutically acceptable salt~~solvate thereof;

wherein,

m is 1-9;

n is 1-3; and

X is selected from ~~the~~ a group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, methane sulfonic acid, phosphoric acid, *p*-toluene sulfonic acid, benzene sulfonic acid, oxalic acid, L-aspartic acid, maleic acid, malonic acid, L-tartaric acid, fumaric acid, citric acid, succinic acid, and glutaric acid.

~~8~~9. The compound of claim ~~7~~8, wherein the compound is selected from the group consisting of Compound I-2, Compound I-3, Compound I-4, Compound I-5, Compound I-6, Compound I-7, Compound I-8, Compound I-9, Compound I-10, Compound I-11, Compound I-12, Compound I-13, Compound I-14, Compound I-15, Compound I-16, and Compound I-17.

~~9~~10. The compound of claim 8 or ~~9~~7, wherein the compound is in solid form.

~~10~~11. The compound of claim 8 or ~~9~~7, wherein the compound is amorphous.

~~11~~12. The compound of claim 8 or ~~9~~7, wherein the compound is crystalline.

~~12~~13. The compound of claim ~~11~~12, wherein the compound is compound I-2 and is characterized by an XRPD pattern substantially similar to that depicted in FIG. 2A or FIG. 2B.

~~13~~14. The compound of claim ~~11~~12, wherein the compound is compound I-4 and is characterized by an XRPD pattern substantially similar to that depicted in FIG. 4B.

~~14~~15. The compound of claim ~~11~~12, wherein the compound is compound I-8 and is characterized by an XRPD pattern substantially similar to that depicted in FIG. 8A.

~~15~~16. The compound of claim ~~11~~12, wherein the compound is compound I-12 and is characterized by an XRPD pattern substantially similar to that depicted in FIG. 12B.

~~16~~17. The compound of claim ~~11~~12, wherein the compound is compound I-17 and is characterized by an XRPD pattern substantially similar to that depicted in FIG. 17A, FIG. 17C, or FIG. 17D.

~~17~~18. A pharmaceutical composition comprising a solid form of any of claims 1-7 or a compound of any of claims 8-17~~claim 1~~ and a pharmaceutically acceptable carrier.

~~18. A solid form of claim 1, for use in therapy.~~

19. Use of a composition comprising the solid form of any of claims 1-7, a composition comprising the compound of any of claims 8-17, or the pharmaceutical composition of claim 18, ~~solid form of claim 1~~ in the manufacture of a medicament for inhibiting SHP2 phosphatase activity in a subject in need thereof.

20. The use of claim 19, wherein the composition is to be administered in combination with an antibody, an antibody-drug conjugate, an immunomodulator, or a histone deacetylase inhibitor.

~~20~~21. The use of claim 19 or 20, wherein the subject is a human.

22. A composition comprising the solid form of any of claims 1-7, a composition comprising the compound of any of claims 8-17, or the pharmaceutical composition of claim 18, for use in treating a disorder in a subject in need thereof.

~~21~~23. Use of a composition comprising the solid form of any of claims 1-7, a composition comprising the compound of any of claims 8-17, or the pharmaceutical composition of claim 18~~solid form of claim 1,~~ in the manufacture of a medicament for treating a disorder ~~mediated by SHP2~~ in a subject in need thereof.

~~22~~24. The composition for use of claim 22 or use of claim 23~~use of claim 21~~, wherein the composition is to be administered in combination with ~~a therapeutically effective amount of the solid form is to be administered to the subject in need thereof, and wherein a therapeutically effective amount of~~ an antibody, an antibody-drug conjugate, an immunomodulator, or a histone deacetylase inhibitor ~~is to be further administered~~.

~~23~~25. The composition for use or use of ~~claim 21~~any one of claims 22 to 24, wherein the disorder is Noonan syndrome, neutropenia, diabetes, ~~or~~ neuroblastoma~~.~~,

~~24. The use of claim 21, wherein the disorder is~~ melanoma, acute myeloid leukemia, juvenile leukemia, ~~or~~ juvenile myelomonocytic leukemia~~.~~,

~~25. The use of claim 21, wherein the disorder is~~ breast cancer, lung cancer, or colorectal cancer.

26. A kit comprising the solid form of claim 1 or a compound of any of claims 1-7.

27. The kit of claim 26, further comprising written instructions describing preparation of a pharmaceutical composition suitable for administration to a patient from the solid form or compound.

~~26~~28. The~~A~~ kit of claim 27, further comprising ~~the solid form of claim 1 and~~ written instructions describing how to administer the resulting ~~a pharmaceutical~~ composition ~~prepared using the solid form~~ to ~~a~~ the patient.

29. The kit of claim 26, further comprising a pharmaceutically acceptable excipient.

~~27~~30. A process for preparing the crystalline form of claim 3, comprising: a) preparing a solution of compound I-1 in a solvent comprising at least one of EtOH, ACN, MEK, EtOAc, IPAc, THF, MtBE, Toluene, 1,4 dioxane~~,~~ and water; b) heating the solution to completely dissolve the compound I-1; c) adjusting the temperature so that solid precipitates out of the solution; and d) isolating the crystalline form of compound I-1.

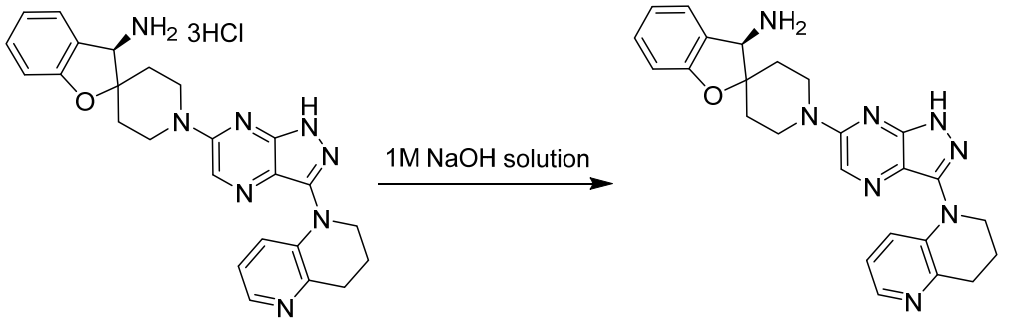
31. The process of claim 30, wherein the solvent is EtOH, ACN, EtOAc, IPAc, THF, MtBE, toluene, or 1,4 dioxane.

32. The process of claim 30, wherein the solvent comprises EtOH and water (9v/1v).

~~28~~33. The process of claim ~~27~~30, wherein heating the solution comprises heating the solution to about 50 ºC.

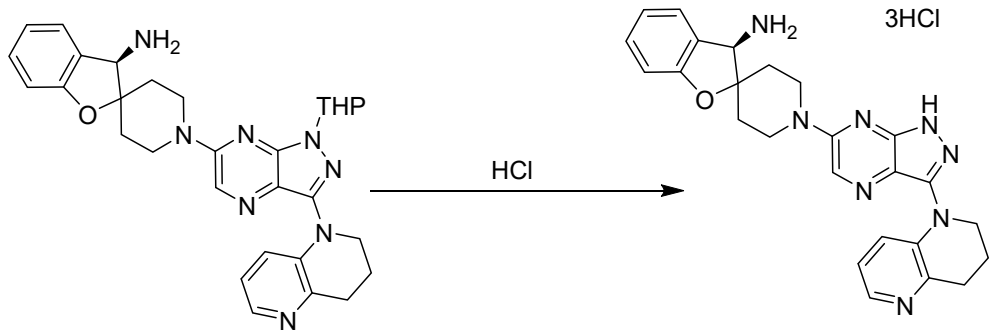
~~29~~34. The process of claim ~~27~~30, wherein adjusting the temperature comprises cooling the solution to about 5 ºC.

~~30~~35. A process for preparing a compound of Formula I-1, the process comprising the step of neutralizing a compound of Formula I-3 with NaOH, thereby forming the compound of Formula I-1:



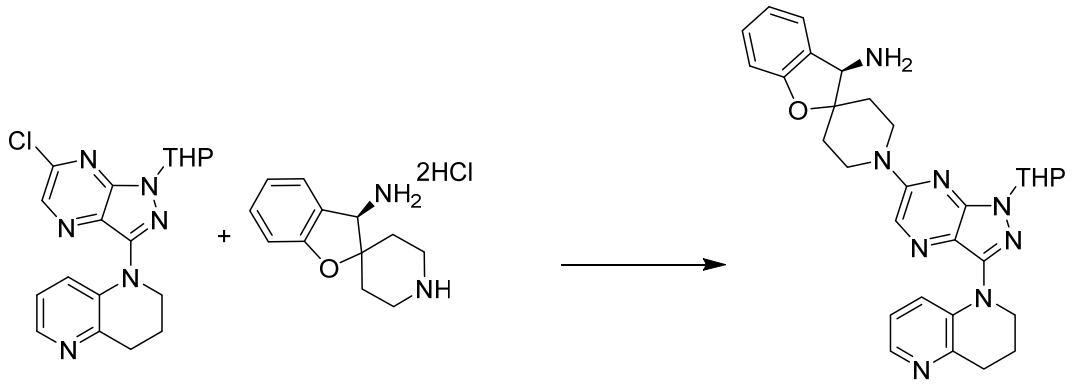
I-3 **I-1**

~~31~~36. The process of claim ~~30~~35, further comprising the step of reacting a compound of Formula 18 with HCl, thereby forming the compound of Formula I-3:



18 **I-3**

~~32~~37. The process of claim ~~30~~35 or 36, further comprising the step of coupling a compound of Formula 17 with compound of Formula 9, thereby forming the compound of Formula 18:



17 **9** **18**