

CLAIMS

1. A stable amorphous solid dispersion comprising Compound 1 and a stabilizing polymer, wherein Compound 1 is molecularly dispersed within a polymer matrix formed by the stabilizing polymer in its solid state, wherein the stabilizing polymer is hydroxypropyl methylcellulose acetate succinate (HPMCAS), ~~preferably HPMCAS~~ with a high ratio of succinoyl substitution to acetyl substitution (S/A ratio), wherein the stabilizing polymer is any one of HPMCAS-LF, HPMCAS-MF, or HPMCAS-HF, or a mixture of two or more of the above substances, and the weight ratio of Compound 1 in the form of freebase and the polymer is between 1:9 and 9:1,

wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea, and

Wherein HPMCAS-LF has 5.0-9.0% of acetyl group and 14.0-18.0% of succinoyl group; HPMCAS-MF has 7.0-11.0% of acetyl group and 10.0-14.0% of succinoyl group; and HPMCAS-HF has 10.0-14.0% of acetyl group and 4.0-8.0% of succinoyl group.

~~2. The amorphous solid dispersion according to Claim 1, wherein the stabilizing polymer is any one of HPMCAS-LF, HPMCAS-MF, or HPMCAS-HF, or a mixture of two or more of the above substances.~~

~~23. The amorphous solid dispersion according to Claim 1, wherein the weight ratio of Compound 1 in the form of freebase and the polymer is between about 1:9 and about 9:1; preferably between about 1:4 to about 2:3; or preferably about 3:7 or about 1:4; more preferably about 1:4.~~

3. The amorphous solid dispersion according to Claim 1, wherein the weight ratio of Compound 1 in the form of freebase and the polymer is 1:4.

4. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion has a drug-loading content of ~~about~~ 10% to 40%.

5. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion comprises Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 2:3; Compound 1 in the form of freebase and HPMCAS-MF in a weight ratio of 1:4; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 1:9; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 1:4; Compound 1 in the form of freebase and HPMCAS-LF in weight ratio of 3:7; Compound 1 in the form of freebase and HPMCAS-LF in a weight ratio of 2:3; or Compound 1 in the form of freebase and HPMCAS-HF in a weight ratio of 1:4.

6. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion is prepared by microprecipitated bulk powder (MBP) technology.

7. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion has a glass transition temperature of about 110-115°C, preferably about 111°C.

8. The amorphous solid dispersion according to Claim 1, wherein the stable amorphous solid dispersion is formulated into an orally administrated formulation, e.g., tablet or capsule.

9. — A crystalline form of Compound 1, which is Form A, characterized by an XRPD pattern comprising at least three, four, five, or six diffraction peaks having 2θ angle values independently selected from the group consisting of: 4.7±0.2, 9.4±0.2, 13.6±0.2, 14.0±0.2, 14.9±0.2, and 15.6±0.2 degrees.

10. — A crystalline form according to Claim 9, wherein the crystalline form is Form A, characterized by an XRPD pattern comprising at least three, four, five, or six diffraction peaks having 2θ angle values independently selected from the group consisting of: 4.7±0.2, 9.4±0.2, 13.6±0.2, 14.0±0.2, 14.9±0.2, 15.6±0.2, 21.2±0.2, 24.3±0.2, 24.7±0.2, 25.1±0.2, and 29.1±0.2 degrees.

11. — A crystalline form according to Claim 9, wherein the crystalline form is Form A characterized by an XRPD pattern comprising diffraction peaks having 2θ angle values independently selected from the group consisting of: 4.7±0.2, 9.4±0.2, 10.2±0.2, 13.6±0.2, 14.0±0.2, 14.9±0.2, 15.6±0.2, 17.2±0.2, 17.4±0.2, 18.7±0.2, 20.0±0.2, 20.4±0.2, 21.2±0.2, 22.3±0.2, 24.3±0.2, 24.7±0.2, 25.1±0.2, 25.5±0.2, 26.8±0.2, 27.4±0.2, 27.8±0.2, 28.6±0.2, 29.1±0.2, 30.2±0.2, 31.8±0.2, 32.0±0.2, 33.1±0.2, 34.1±0.2, and 34.6±0.2 degrees.

12. — A crystalline form according to Claim 9, wherein the crystalline form is Form A, substantially characterized by an XRPD pattern as shown in Figure 1.

13. — A crystalline form of Compound 1, which is Form A*, characterized by an XRPD pattern comprising at least three, four, five, or six diffraction peaks having 2θ angle values independently selected from the group consisting of: 9.2±0.2, 14.0±0.2, 15.4±0.2, 18.7±0.2, 20.5±0.2, 24.0±0.2, and 24.9±0.2 degrees.

14. — The crystalline form according to Claim 13, wherein the crystalline form is Form A* characterized by an XRPD pattern comprising diffraction peaks having 2θ angle values independently selected from the group consisting of: 9.2±0.2, 10.8±0.2, 12.3±0.2, 14.0±0.2, 15.4±0.2, 16.5±0.2, 18.1±0.2, 18.7±0.2, 19.3±0.2, 19.8±0.2, 20.5±0.2, 21.6±0.2, 22.3±0.2, 23.2±0.2, 24.0±0.2, 24.9±0.2, 26.7±0.2, 27.8±0.2, 28.7±0.2, 29.4±0.2, 30.9±0.2, 33.2±0.2, 37.9±0.2, and 38.2±0.2 degrees.

15. — The crystalline form according to Claim 13, wherein the crystalline form is Form A*, substantially characterized by an XRPD pattern as shown in Figure 2.

916. A method for preparing the stable amorphous solid dispersion, comprising the step of co-precipitating Compound 1 and HPMCAS,

wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea.

1017. The method according to Claim 916, wherein Compound 1 and HPMCAS simultaneously precipitate out to form a molecular dispersion of Compound 1 in the matrix formed by HPMCAS.

1118. The method according to Claim 916, said method comprises the step of a solvent controlled precipitation.

1219. The method according to Claim 916, said method comprises the step of microprecipitated bulk powder (MBP) technology.

1320. The method according to any one of Claims 916-1219, wherein HPMCAS has a high ratio of succinoyl substitution to acetyl substitution (S/A ratio).

1421. The method according to any one of Claims 916-1219, wherein HPMCAS is HPMCAS-LF, HPMCAS-MF, or HPMCAS-HF, or a mixture of two or more of the above substances.

1522. The method according to any one of Claims 916-1219, wherein Compound 1 is in a crystalline form or amorphous form; ~~preferably Form A as disclosed herein.~~

1623. The method according to any one of Claims 916-1219, wherein the weight ratio of Compound 1 in the form of freebase and HPMCAS is between ~~about 1:9 to about 9:1, or preferably between about 1:4 to about 2:3; or preferably about 3:7 or about 1:4; more preferably about 1:4.~~

1724. The method according to any one of Claims 916-1219, wherein HPMCAS is HPMCAS-LF, or HPMCAS-MF, or HPMCAS-HF; and Compound 1 in the form of freebase and HPMCAS-MF is in a weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-MF is in a weight ratio of 2:3; or Compound 1 in the form of freebase and HPMCAS-MF is in a weight ratio of 1:4; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 1:9; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 1:4; or Compound 1 in the form of freebase and HPMCAS-LF is in weight ratio of 3:7; or Compound 1 in the form of freebase and HPMCAS-LF is in a weight ratio of 2:3; or Compound 1 in the form of freebase and HPMCAS-HF in a weight ratio of 1:4.

1825. The method according to any one of Claims 916-1219, said method comprising dissolving Compound 1 and HPMCAS in an organic solvent.

1926. The method according to Claim 1825, wherein the organic solvent is N,N-dimethylformamide (DMF), N,N-dimethylacetamide (DMAc), dimethyl sulfoxide (DMSO) or N-methyl-2-pyrrolidone (NMP).

~~2027.~~ The method according to any one of Claims ~~916-1219~~, wherein the resulting solution of Compound 1 and HPMCAS is added into water or an acidic aqueous solution, whereby Compound 1 and HPMCAS simultaneously precipitate out to form a solid dispersion.

~~2128.~~ The method according to Claim ~~2027~~, wherein the acidic aqueous solution is aqueous hydrochloric acid (HCl).

~~2229.~~ The method according to Claim ~~2128~~, wherein water or the acidic aqueous solution is optionally cooled.

~~2330.~~ The method according to Claim ~~2922~~, wherein water or the acidic aqueous solution is optionally cooled to 2-8 °C.

~~2431.~~ The method according to Claim ~~2027~~, wherein the resulting solid is dried to give the amorphous solid dispersion as MBP.

~~2532.~~ The method according to Claim ~~2431~~, wherein the resulting solid is further optionally micronized by, e.g., jet-milling to give a powder with a particle size suitable for drug formulation, e.g., of D₉₀ less than 150µm or 200µm.

~~2633.~~ The method according to Claim ~~2532~~, wherein the solid dispersion is in an amorphous form.

~~2734.~~ The method according to Claim ~~2532~~, wherein the solid dispersion has a glass transition temperature of ~~about 110-115°C, preferably about 111°C.~~

~~2835.~~ The method according to Claim ~~916~~, said comprising:

- a) dissolving Compound 1 and HPMCAS in an organic solvent;
- b) co-precipitating Compound 1 and HPMCAS by adding the solution of a) into water or an acidic aqueous solution; and
- c) washing the resulting solid with water and/or aqueous hydrochloric acid to remove the organic solvent.

~~2936.~~ A use of Compound 1 in the amorphous solid dispersion according to any one of Claims ~~1-8 or the crystalline form according to any one of Claims 9-15~~ in the manufacture of a medicament for treating or preventing a disease or disorder responsive to inhibition of Raf kinases in a subject.

~~37.~~ ~~The use according to Claim 36~~, wherein the disease or disorder is a cancer selected from the group consisting of brain cancer, lung cancer, kidney cancer, bone cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, lymphoma, or thyroid tumors and their complications, wherein Compound 1 is 1-((1S, 1aS, 6bS)-5-((7-oxo-5, 6, 7, 8-tetrahydro-1, 8-naphthyridin-4-yl)oxy)-1a, 6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2, 4, 5-trifluorophenyl)urea.

~~3038.~~ The use according to Claim ~~2936~~, wherein the disease is BRAF (V600E or non-V600E) or NRAS or KRAS mutant cancer selected from brain cancer, lung cancer, kidney cancer, bone

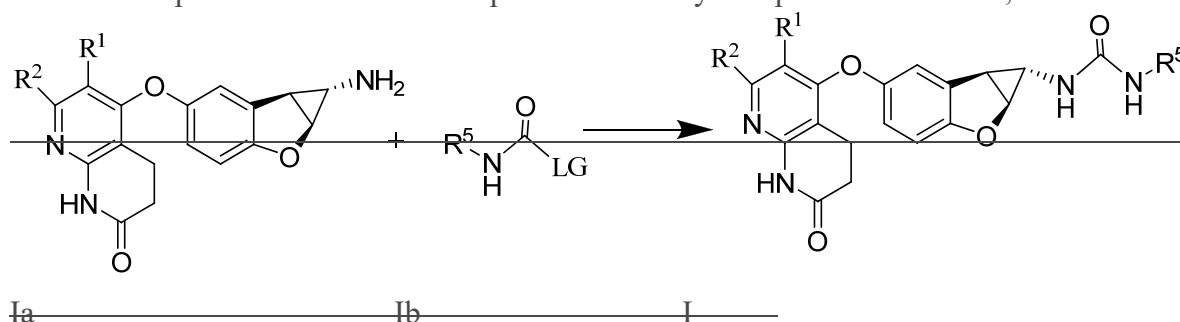
cancer, liver cancer, bladder cancer, breast, head and neck cancer, ovarian cancer, melanoma, skin cancer, adrenal cancer, cervical cancer, lymphoma, or thyroid tumors and their complications.

3139. The use according to Claim 2936, wherein the dosage of Compound 1 to be administered is 1-200 mg/day, and the administration frequency is one to three times a day.

3240. The use according to Claim 2936, wherein the dosage of Compound 1 to be administered is 2.5-100 mg/day, and the administration frequency is one to three times a day.

3341. The use according to Claim 2936, wherein the dosage of Compound 1 to be administered is 5-50 mg/day, and the administration frequency is one time a day.

42. A method for preparing a compound of Formula I, comprising: an amine of Formula Ia and a protected carbamoyl compound of Formula Ib are subjected to a condensation reaction to obtain a compound of Formula I or a pharmaceutically acceptable salt thereof,



wherein,

R^1 and R^2 , which may be the same or different, are each independently selected from hydrogen, halogen, alkyl, alkenyl, cycloalkyl, aryl, heterocyclyl, heteroaryl, alkynyl, CN, NR^6R^7 , OR^6 , COR^6 , CO_2R^6 , $CONR^6R^7$, $C(=NR^6)NR^7R^8$, NR^6COR^7 , $NR^6CONR^7R^8$, $NR^6CO_2R^7$, SO_2R^6 , $NR^6SO_2NR^7R^8$, $NR^6SO_2R^7$ and NR^6SO_2aryl , wherein said alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, heteroaryl, aryl and heterocyclyl are each independently optionally substituted with one or two or three substituents R^9 ;

R^5 is selected from alkyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, each of which is independently optionally substituted with one or two or three substituents R^9 ;

LG is a leaving group;

R^6 , R^7 and R^8 , which may be the same or different, are each independently selected from H, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl; or (R^6 and R^7) and/or (R^7 and R^8) together with the atom(s) to which they are attached, each form a ring selected from heterocyclyl and heteroaryl rings optionally substituted with one or two or three substituents R^9 ; R^9 is selected from halogen, haloalkyl, alkyl, alkenyl, cycloalkyl, aryl, heteroaryl, heterocyclyl, alkynyl, oxo, alkyl NR^aR^b , CN, OR^a , NR^aR^b , COR^a , CO_2R^a , $CONR^aR^b$, $C(=NR^a)NR^bR^c$, nitro, NR^aCOR^b , $NR^aCONR^aR^b$, $NR^aCO_2R^b$, SO_2R^a , SO_2aryl , $NR^aSO_2NR^bR^c$, $NR^aSO_2R^b$ and NR^aSO_2aryl , wherein said cycloalkyl, aryl, heteroaryl or heterocyclyl are each

independently substituted with one or two or three substituents selected from halogen, alkyl and haloalkyl, wherein R^a , R^b and R^c are each independently selected from H, haloalkyl, alkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl and heteroaryl, or (R^a and R^b) and/or (R^b and R^c) together with the atom(s) to which they are attached, each form a ring selected from

heterocyclyl and heteroaryl rings optionally substituted with halogen and alkyl.

43. The method according to Claim 42, wherein the condensation reaction of an amine of Formula Ia and a protected carbamoyl compound of Formula Ib is conducted in an organic solvent.

44. The method according to Claim 42, wherein the organic solvent is selected from the group consisting of a non-polar solvent, a polar protic solvent and a polar aprotic solvent, or a mixture thereof.

45. The method according to Claim 44, wherein the polar aprotic solvent is selected from N-methylpyrrolidone, N-methylmorpholine, methyl isobutyl ketone, methyl ethyl ketone, tetrahydrofuran, dichloromethane, ethyl acetate, acetone, N, N-dimethylformamide, acetonitrile and dimethyl sulfoxide; the polar protic solvents is selected from methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, tert-butanol, and acetic acid.; the non-polar solvent is selected from dioxane, toluene, hexane, cyclohexane and diethyl ether.

46. The method according to any one of Claims 42-45, wherein the condensation reaction is conducted in vacuum.

47. The method according to any one of Claims 42-45, wherein the condensation reaction is conducted at a temperature of about 10 to 50°C or at a temperature of about 15 to 25°C.

48. The method according to any one of Claims 42-47, wherein the condensation reaction is carried out for at least about 0.5 hours, at least about 1 hour, at least about 2 hours, at least about 3 hours, at least about 4 hours.

49. The method according to any one of Claims 42-48, wherein R^1 and R^2 are both hydrogen.

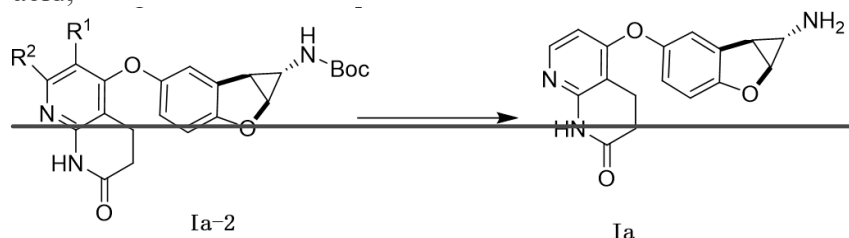
50. The method according to any one of Claims 42-49, wherein R^5 is aryl, optionally substituted with one or two or three substituents R^9 ; preferably R^5 is phenyl, optionally substituted with one or two or three halogen; more preferably R^5 is 2, 4, 5-trifluorophenyl.

51. The method according to any one of Claims 42-50, wherein LG is alkyl, cycloalkyl, aryl, heteroaryl, heterocyclyl or OR^a ; wherein the alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl is optionally substituted with one or more substituents selected from halogen, nitro, hydroxy or alkoxy, and wherein R^a is alkyl, cycloalkyl, aryl, heteroaryl or heterocyclyl, optionally substituted with one or more substituents selected from halogen, nitro, CN, hydroxy or alkoxy.

52. The method according to Claim 51, wherein LG is OR^a , wherein R^a is phenyl, optionally substituted with one or more substituents selected from halogen, nitro, CN , hydroxy or alkoxy.

53. The method according to Claim 52, wherein LG is unsubstituted phenoxy.

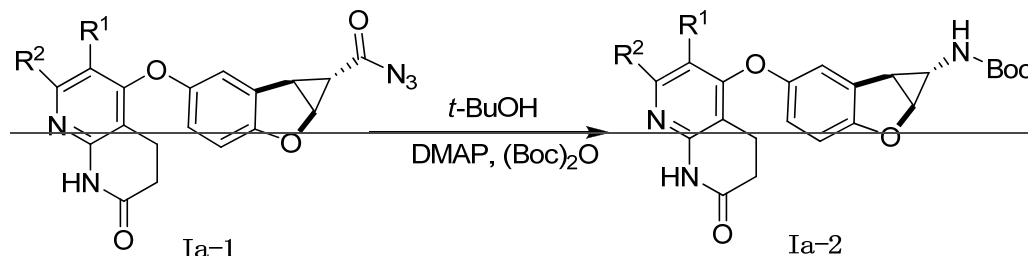
5 54. The method according to any one of Claims 42-53, wherein the compound of Formula Ia is prepared by reacting a compound of Formula Ia-2 in an organic solvent in the presence of an acid,



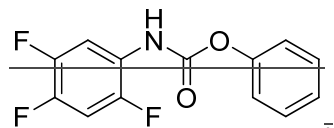
10 55. The method according to Claim 54, wherein the organic solvent is selected from the group consisting of a non polar solvent, a polar protic solvent, and a polar aprotic solvent, or a mixture thereof.

56. The method according to Claim 55, wherein the acid is a mineral acid or an organic acid.

15 57. The method according to any one of Claims 54-55, wherein the compound of Formula Ia-2 is prepared by reacting a compound of Formula Ia-1 in $(\text{Boc})_2\text{O}/t\text{-BuOH}$ in the presence of a catalyst,



58. The method according to Claim 50, wherein the compound of Formula Ib is



20 59. The method according to any one of Claims 42-58, wherein the compound of Formula I is 1-((1S, 1aS, 6bS)-5-((7-oxo-5,6,7,8-tetrahydro-1,8-naphthyridin-4-yl)oxy)-1a,6b-dihydro-1H-cyclopropa[b]benzofuran-1-yl)-3-(2,4,5-trifluorophenyl)urea or a pharmaceutically acceptable salt thereof.

60. The method according to Claim 59, wherein the content of impurity-1 in the product of the condensation reaction is less than about 0.5% (detected by HPLC), or less than about 0.2% (detected by HPLC) or less than about 0.05% (detected by HPLC).