

SOLID FORMULATIONS AND POLYMORPHIC FORMS OF INDOLINE INHIBITORS OF KIF18A

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority benefit of United States Provisional Patent Application No. 63/486,611, filed February 23, 2023, United States Provisional Patent Application No. 63/486,613, filed February 23, 2023, and United States Provisional Patent Application No. 63/611,027, filed December 15, 2023, the disclosures of which are hereby incorporated herein by reference in their entirety.

FIELD

[0002] The present disclosure in some aspects relates to indoline inhibitors of KIF18A, solid-form formulations thereof, and polymorphic forms thereof. The present disclosure in some aspects relates to methods of preparing solid formulations and polymorphic forms of certain indoline KIF18A inhibitors and methods of their use for treating diseases mediated by KIF18A, such as cancer.

BACKGROUND

[0003] KIF18A is a kinesin involved in assisting kinetochore-microtubule (kt-MT) attachment and chromosomal alignment during cell mitosis. Its cargo domain binds directly to protein phosphatase 1 (PP1) and carries it to the plus end of MT where PP1 dephosphorylates Hec1, a kinetochore complex component, further enhancing kt-MT attachment throughout metaphase and anaphase. Its MT-binding motor domain has ATPase activity that powers KIF18A translocation along the MT lattice, enhanced by its C-terminal MT-binding site, and caps and depolymerizes the growing microtubule at the plus end, thus dampening MT dynamics. This modulation of MT dynamics by KIF18A often occurs at the following (or trailing) sister chromatid, thereby providing a counterbalancing tension to the leading sister chromatid movement catalyzed by another kinesin Kif2C/MCAK. Loss of KIF18A function causes defective kt-MT attachments and loss of tension within the spindle in cells of high chromosome instability (CIN), leading to hyper stable, longer and multipolar spindles, mitotic arrest, centrosome fragmentation and spindle assembly checkpoint activation or cell death. KIF18A is identified from DEPMAP RNAi data re-analysis as one of

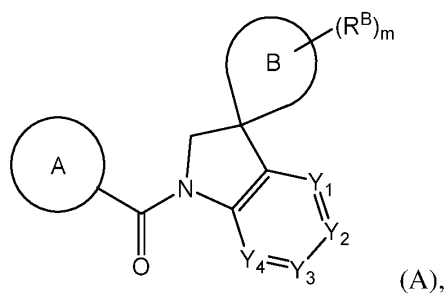
the top candidates essential for CIN-high cells. Reported synthetic lethality screens also singled out KIF18A as a potential anticancer target whose knockdown preferentially renders CIN-high (but not CIN-low) aneuploid and whole-genome doubled cells vulnerable to death. A cellular toxicity assay in isogenic cell lines confirmed the enhanced sensitivity of CIN-high cells to KIF18A inhibitors. Ongoing in vivo mouse models using KIF18A inhibitor or knockdown demonstrated effect of inhibited tumor growth. Thus, there is a need for new agents effective in treating diseases mediated by KIF18A.

[0004] In particular, there is a need for stable solid-form formulations of KIF18A inhibitors.

SUMMARY

[0005] In one aspect, provided herein is a solid pharmaceutical formulation, comprising:

- (1) a compound of Formula (A):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more

substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

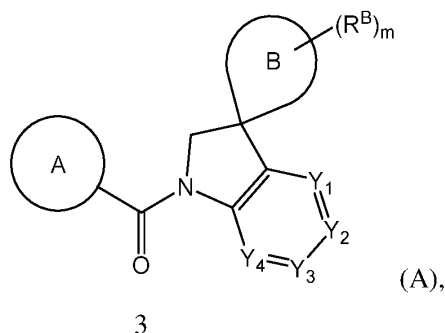
wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C₃₋₁₀ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and

(2) a pharmaceutically acceptable polymer.

[0006] In another aspect, provided herein is a solid formulation comprising a compound of Formula (A):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, - (CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

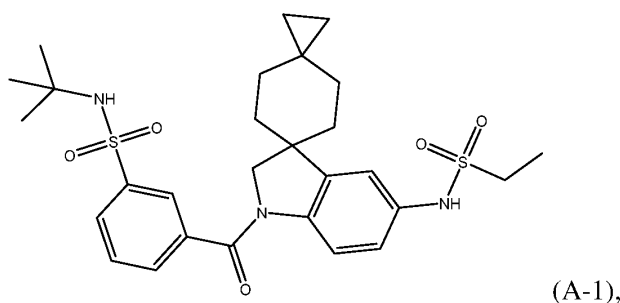
wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1} - R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and

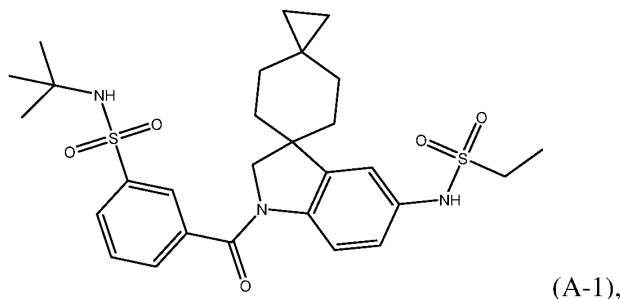
wherein the formulation is effective to provide a maximum plasma concentration (C_{max}) of the compound of Formula (A), or a pharmaceutically acceptable salt thereof, in a human subject of from about 1.5 $\mu\text{mol/mL}$ to about 5.0 $\mu\text{mol/mL}$.

[0007] In yet another aspect, provided herein is a crystalline form of a compound of Formula (A-1):



or a pharmaceutically acceptable salt thereof.

[0008] In yet another aspect, provided herein is a salt form of a compound of Formula (A-1):



or a pharmaceutically acceptable salt thereof.

[0009] In yet another aspect, provided herein is a method of inhibiting KIF18A comprising contacting a cell with an effective amount of (i) a formulation described herein, or (ii) a crystalline form of as described herein.

[0010] In yet another aspect, provided herein is a method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a

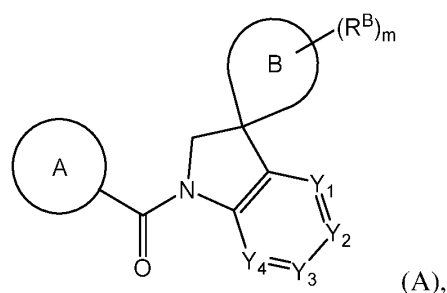
therapeutically effective amount of (i) a formulation described herein, or (ii) a crystalline form of described herein.

[0011] In yet another aspect, provided herein is a method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of (i) a formulation described herein, or (ii) a crystalline form described herein.

[0012] In yet another aspect, provided herein is a method of preparing the formulation described herein, wherein the process comprises spray-drying a solution of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and a polymer to obtain an amorphous solid dispersion of the compound of Formula (A), or a pharmaceutically acceptable salt thereof.

[0013] In yet another aspect, provided herein is a method of preparing the crystalline form described herein, comprising forming a mixture of the compound of Formula (A), or a pharmaceutically acceptable salt thereof, and a solvent selected from the group consisting of acetone, isobutyl acetate, water, acetone nitrile, 1-butanol, dimethylacetamide, N,N-dimethylformamide, nitromethane, toluene, dimethyl sulfoxide, dioxane, cyclopentyl methyl ether, tert-amyl methyl ether, 2-ethoxyethanol, ethyl acetate, ethanol, hexafluoroisopropanol, diisopropyl ether, methyl ethyl ketone, hexane, methanol, 2-methyltetrahydrofuran, N-methyl-2-pyrrolidone, 2,2,2-trifluoroethanol, 1-propanol, isopropanol alcohol, methylcyclohexane, tetrahydrofuran, anisole, methyl isopropyl ketone, dipropyl ether, chloroform, tert-amyl alcohol, and any mixture thereof.

[0014] In yet another aspect, provided herein is a method of preparing a substantially amorphous form of a compound of Formula (A):



comprising (1) forming a mixture of a compound of Formula (A) and a solvent selected from the group consisting of N,N-dimethylformamide (DMF), water, and mixtures thereof; (2)

isolating solid from the mixture of (1); (3) washing the solid of (2) with water; and (4) drying the solid of (3) at room temperature; wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, - (CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted

with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1} - R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

BRIEF DESCRIPTION OF THE DRAWINGS

[0015] The drawings illustrate certain embodiments of the features and advantages of this disclosure. These embodiments are not intended to limit the scope of the appended claims in any manner.

[0016] FIGS. 1A-1H show SEM micrographs of eight different SDDs captured at 5000× magnification. **FIGS. 1A to 1H** show the SEM micrograph of 25:75 compound of Formula (A-1):HPMCAS-M, 25:75 compound of Formula (A-1):HPMCP-HP55, 40:60 compound of Formula (A-1):HPMCP-HP55, 50:50 compound of Formula (A-1):HPMCP-HP55, 50:50 compound of Formula (A-1):HPMC E3LV, 25:75 compound of Formula (A-1):Eudragit L100-55, 40:60 compound of Formula (A-1):Eudragit L100-55, and 50:50 compound of Formula (A-1):Eudragit L100-55, respectively.

[0017] FIG. 2 shows the XRPD pattern of polymorphic Form A of compound of Formula (A-1).

[0018] FIG. 3 shows TGA and DSC thermograms of the polymorphic Form A of compound of Formula (A-1). Top: TGA; bottom: DSC.

[0019] FIG. 4 shows DVS isothermal plots of the polymorphic Form A of compound of Formula (A-1). The trace with diamonds is the sorption trace, and the trace with squares is the desorption trace.

[0020] FIG. 5 shows the XRPD pattern of the polymorphic Form C of compound of Formula (A-1), prepared by two methods. From top to bottom: polymorphic Form C prepared by slurring a gel from DMF in H_2O , polymorphic Form C prepared by adding H_2O to a DMF solution to obtain particulates, and polymorphic Form A for reference.

[0021] FIG. 6 shows TGA thermogram of the polymorphic Form C of compound of Formula (A-1).

[0022] FIG. 7 shows TMDSC thermogram of the polymorphic Form C of compound of Formula (A-1).

[0023] FIG. 8 shows DVS isothermal plots of the polymorphic Form C of compound of Formula (A-1). The trace with diamonds is the sorption trace, and the trace with squares is the desorption trace.

[0024] FIGS. 9A-9E show graphs of tumor volume of vehicle- and compound-treated mice plotted as a function of time after start of treatment.

[0025] FIG. 9A shows Compound of Formula (A-2) (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice. Trace with circle: vehicle. Trace with square: Compound of Formula (A-2) at 10mg/kg BID, PO. Trace with triangle: Compound of Formula (A-2) at 30mg/kg BID, PO. Trace with flipped triangle: Compound of Formula (A-2) at 60 mg/kg BID, PO.

[0026] FIG. 9B shows Compound of Formula (A-2) (10 mg/kg QD, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice. Trace with circle: vehicle. Trace with square: Compound of Formula (A-2) at 10mg/kg BID, PO. Trace with triangle: Compound of Formula (A-2) at 30mg/kg BID, PO. Trace with flipped triangle: Compound of Formula (A-2) at 60 mg/kg BID, PO.

[0027] FIG. 9C shows Compound of Formula (A-1) (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of HCC15 implanted SCID Beige mice. Trace with circle: vehicle. Trace with square: Compound of Formula (A-1) at 10mg/kg BID, PO. Trace with triangle: Compound of Formula (A-1) at 30mg/kg BID, PO. Trace with flipped triangle: Compound of Formula (A-1) at 60 mg/kg BID, PO.

[0028] FIG. 9D shows Compound of Formula (A-1) (10 mg/kg BID, 30 mg/kg BID, 60 mg/kg BID) treatment of OVCAR-3 implanted Balb/C nude mice. Trace with circle: vehicle. Trace with square: Compound of Formula (A-1) at 10mg/kg BID, PO. Trace with triangle: Compound of Formula (A-1) at 30mg/kg BID, PO. Trace with flipped triangle: Compound of Formula (A-1) at 60 mg/kg BID, PO.

[0029] FIG. 9E shows Compound of Formula (A-1) (30 mg/kg BID, 30 mg/kg QD, 60 mg/kg QD) treatment of OVCAR-3 implanted Balb/C nude mice. Trace with circle: vehicle. Trace with square: Compound of Formula (A-1) at 10mg/kg BID, PO. Trace with triangle: Compound of Formula (A-1) at 30mg/kg BID, PO. Trace with flipped triangle: Compound of Formula (A-1) at 60 mg/kg BID, PO.

[0030] FIG. 10 shows XRPD pattern of polymorphic Form B of compound of Formula (A-1).

[0031] FIG. 11 shows DSC thermogram of polymorphic Form B of compound of Formula (A-1).

[0032] FIG. 12 shows TGA thermogram of polymorphic Form B of compound of Formula (A-1).

[0033] FIG. 13 show DVS isothermal plots of polymorphic Form B of compound of Formula (A-1).

[0034] FIG. 14 shows XRPD pattern of polymorphic Form IV of mono-sodium salt of compound of Formula (A-1).

[0035] FIG. 15 shows DSC thermogram of polymorphic Form IV of mono-sodium salt of compound of Formula (A-1).

[0036] FIG. 16 shows TGA thermogram of polymorphic Form IV of mono-sodium salt of compound of Formula (A-1).

[0037] FIG. 17 shows XRPD pattern of polymorphic Form V of di-sodium salt of compound of Formula (A-1).

[0038] FIG. 18 shows DSC thermogram of polymorphic Form V of di-sodium salt of compound of Formula (A-1).

[0039] FIG. 19 shows TGA thermogram of polymorphic Form V of di-sodium salt of compound of Formula (A-1).

[0040] FIG. 20 shows XRPD pattern of polymorphic Form VI of mono-potassium salt of compound of Formula (A-1).

[0041] FIG. 21 shows DSC thermogram of polymorphic Form VI of mono-potassium salt of compound of Formula (A-1).

[0042] FIG. 22 shows TGA thermogram of polymorphic Form VI of mono-potassium salt of compound of Formula (A-1).

[0043] FIG. 23 shows XRPD pattern of polymorphic Form VII of di-potassium salt of compound of Formula (A-1).

[0044] FIG. 24 shows DSC thermogram of polymorphic Form VII of di-potassium salt of compound of Formula (A-1).

[0045] FIG. 25 shows TGA thermogram of polymorphic Form VII of di-potassium salt of compound of Formula (A-1).

[0046] FIG. 26 shows XRPD pattern of polymorphic Form VIII of di-sodium salt of compound of Formula (A-1).

- [0047] **FIG. 27** shows DSC thermogram of polymorphic Form VIII of di-sodium salt of compound of Formula (A-1).
- [0048] **FIG. 28** shows TGA thermogram of polymorphic Form VIII of di-sodium salt of compound of Formula (A-1).
- [0049] **FIG. 29** shows one exemplary XRPD pattern of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).
- [0050] **FIG. 30** shows one exemplary DSC thermogram of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).
- [0051] **FIG. 31** shows one exemplary TGA thermogram of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).
- [0052] **FIG. 32** shows one exemplary XRPD pattern of polymorphic Form X of di-sodium salt of compound of Formula (A-1).
- [0053] **FIG. 33** shows one exemplary DSC thermogram of polymorphic Form X of di-sodium salt of compound of Formula (A-1).
- [0054] **FIG. 34** shows one exemplary TGA thermogram of polymorphic Form X of di-sodium salt of compound of Formula (A-1).
- [0055] **FIG. 35** shows XRPD pattern of polymorphic Form XI of compound of di-sodium salt of Formula (A-1).
- [0056] **FIG. 36** shows DSC thermogram of polymorphic Form XI of compound of di-sodium salt of Formula (A-1).
- [0057] **FIG. 37** shows TGA thermogram of polymorphic Form XI of compound of di-sodium salt of Formula (A-1).
- [0058] **FIG. 38** shows XRPD pattern of polymorphic Form XII of compound of mono-sodium salt of Formula (A-1).
- [0059] **FIG. 39** shows DSC thermogram of polymorphic Form XII of compound of mono-sodium salt of Formula (A-1).
- [0060] **FIG. 40** shows TGA thermogram of polymorphic Form XII of compound of mono-sodium salt of Formula (A-1).
- [0061] **FIG. 41** shows another exemplary XRPD pattern of polymorphic Form X of di-sodium salt of compound of Formula (A-1).
- [0062] **FIG. 42** shows another exemplary DSC thermogram of polymorphic Form X of di-sodium salt of compound of Formula (A-1).

[0063] FIG. 43 shows another exemplary TGA thermogram of polymorphic Form X of di-sodium salt of compound of Formula (A-1).

[0064] FIG. 44 shows another exemplary DVS isothermal plot of polymorphic Form X of di-sodium salt of compound of Formula (A-1).

[0065] FIG. 45 shows another exemplary XRPD pattern of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).

[0066] FIG. 46 shows another exemplary DSC thermogram of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).

[0067] FIG. 47 shows another exemplary TGA thermogram of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).

[0068] FIG. 48 shows another exemplary DVS isothermal plot of polymorphic Form IX of di-potassium salt of compound of Formula (A-1).

[0069] FIG. 49 shows XRPD pattern of polymorphic Form XIII of mono-sodium salt of compound of Formula (A-1).

[0070] FIG. 50 shows DSC thermogram of polymorphic Form XIII of mono-sodium salt of compound of Formula (A-1).

[0071] FIG. 51 shows TGA thermogram of polymorphic Form XIII of mono-sodium salt of compound of Formula (A-1).

DETAILED DESCRIPTION

[0072] The following description is presented to enable a person of ordinary skill in the art to make and use the various embodiments. Descriptions of specific devices, techniques, and applications are provided only as examples. Various modifications to the examples described herein will be readily apparent to those of ordinary skill in the art, and the general principles defined herein may be applied to other examples and applications without departing from the spirit and scope of the various embodiments. Thus, the various embodiments are not intended to be limited to the examples described herein and shown but are to be accorded the scope consistent with the claims.

I. Definition

[0073] As used in the present specification, the following words and phrases are generally intended to have the meanings as set forth below, except to the extent that the context in which they are used indicates otherwise.

[0074] As used herein and in the appended claims, the singular forms “a”, “an” and “the” include plural forms, unless the context clearly dictates otherwise.

[0075] As used herein, and unless otherwise specified, the terms “about” and “approximately”, when used in connection with doses, amounts, or weight percent of ingredients of a composition or a dosage form, mean a dose, amount, or weight percent that is recognized by those of ordinary skill in the art to provide a pharmacological effect equivalent to that obtained from the specified dose, amount, or weight percent. Specifically, where applicable, the terms “about” and “approximately,” when used in this context, contemplate a dose, amount, or weight percent within 15% of the specified dose, amount, or weight percent.

[0076] Throughout this application, unless the context indicates otherwise, references to a compound of Formula (A), Formula (A-1), Formula (A-2), or Formula (A-3) include all subgroups defined herein, such as Formula (B), (C), (A-1), (A-2), or (A-3), including all substructures, subgenera, preferences, embodiments, examples and particular compounds defined and/or described herein. In some embodiments, unless indicated otherwise, references to a compound of Formula (A), (B), (C), (A-1), (A-2), or (A-3) and subgroups thereof, include ionic forms, solvates, co-crystals, chelates, isomers, tautomers, oxides (*e.g.*, N-oxides, S-oxides), esters, prodrugs, isotopes and/or protected forms thereof. In some embodiments, references to a compound of Formula (A), (B), (C), (A-1), (A-2), or (A-3) and subgroups thereof, include isomers, tautomers and/or oxides thereof. In some embodiments, references to a compound of Formula (A), (B), (C), (A-1), (A-2), or (A-3) and subgroups thereof, include solvates thereof.

[0077] “Alkyl” encompasses straight and branched carbon chains having the indicated number of carbon atoms, for example, from 1 to 20 carbon atoms, or 1 to 8 carbon atoms, or 1 to 6 carbon atoms, or 1 to 3 carbon atoms. For example, C₁₋₆ alkyl encompasses both straight and branched chain alkyl of from 1 to 6 carbon atoms. When an alkyl residue having a specific number of carbons is named, all branched and straight chain versions having that number of carbons are intended to be encompassed; thus, for example, “propyl” includes n-propyl and isopropyl; and “butyl” includes n-butyl, sec-butyl, isobutyl and t-butyl. Examples of alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, pentyl, 2-pentyl, 3-pentyl, isopentyl, neopentyl, hexyl, 2-hexyl, 3-hexyl, and 3-methylpentyl.

[0078] When a range of values is given (*e.g.*, C₁₋₆ alkyl), each value within the range as well as all intervening ranges are included. For example, “C₁₋₆ alkyl” includes C₁, C₂, C₃, C₄, C₅, C₆, C₁₋₆, C₂₋₆, C₃₋₆, C₄₋₆, C₅₋₆, C₁₋₅, C₂₋₅, C₃₋₅, C₄₋₅, C₁₋₄, C₂₋₄, C₃₋₄, C₁₋₃, C₂₋₃, and C₁₋₂ alkyl.

[0079] “Alkenyl” refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (*e.g.*, 2 to 8, or 2 to 6 carbon atoms) and at least one carbon-carbon double bond. The group may be in either the *cis* or *trans* configuration (*Z* or *E* configuration) about the double bond(s). Alkenyl groups include, but are not limited to, ethenyl, propenyl (*e.g.*, prop-1-en-1-yl, prop-1-en-2-yl, prop-2-en-1-yl (allyl), prop-2-en-2-yl), and butenyl (*e.g.*, but-1-en-1-yl, but-1-en-2-yl, 2-methyl-prop-1-en-1-yl, but-2-en-1-yl, but-2-en-1-yl, but-2-en-2-yl, buta-1,3-dien-1-yl, buta-1,3-dien-2-yl).

[0080] “Alkynyl” refers to an unsaturated branched or straight-chain alkyl group having the indicated number of carbon atoms (*e.g.*, 2 to 8 or 2 to 6 carbon atoms) and at least one carbon-carbon triple bond. Alkynyl groups include, but are not limited to, ethynyl, propynyl (*e.g.*, prop-1-yn-1-yl, prop-2-yn-1-yl) and butynyl (*e.g.*, but-1-yn-1-yl, but-1-yn-3-yl, but-3-yn-1-yl).

[0081] “Cycloalkyl” indicates a non-aromatic, fully saturated carbocyclic ring having the indicated number of carbon atoms, for example, 3 to 10, or 3 to 8, or 3 to 6 ring carbon atoms. Cycloalkyl groups may be monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic). Examples of cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, as well as bridged and caged ring groups (*e.g.*, norbornane, bicyclo[2.2.2]octane). In addition, one ring of a polycyclic cycloalkyl group may be aromatic, provided the polycyclic cycloalkyl group is bound to the parent structure via a non-aromatic carbon. For example, a 1,2,3,4-tetrahydronaphthalen-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is a cycloalkyl group, while 1,2,3,4-tetrahydronaphthalen-5-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkyl group. Examples of polycyclic cycloalkyl groups consisting of a cycloalkyl group fused to an aromatic ring are described below.

[0082] “Cycloalkenyl” indicates a non-aromatic carbocyclic ring, containing the indicated number of carbon atoms (*e.g.*, 3 to 10, or 3 to 8, or 3 to 6 ring carbon atoms) and at least one carbon-carbon double bond. Cycloalkenyl groups may be monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic). Examples of cycloalkenyl groups include cyclopropenyl, cyclobutenyl, cyclopentenyl, cyclopentadienyl, and cyclohexenyl, as well as bridged and caged ring groups (*e.g.*, bicyclo[2.2.2]octene). In addition, one ring of a polycyclic cycloalkenyl group may be

aromatic, provided the polycyclic alkenyl group is bound to the parent structure via a non-aromatic carbon atom. For example, inden-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is considered a cycloalkenyl group, while inden-4-yl (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a cycloalkenyl group. Examples of polycyclic cycloalkenyl groups consisting of a cycloalkenyl group fused to an aromatic ring are described below.

[0083] “Aryl” indicates an aromatic carbocyclic ring having the indicated number of carbon atoms, for example, 6 to 12 or 6 to 10 carbon atoms. Aryl groups may be monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic). In some instances, both rings of a polycyclic aryl group are aromatic (*e.g.*, naphthyl). In other instances, polycyclic aryl groups may include a non-aromatic ring fused to an aromatic ring, provided the polycyclic aryl group is bound to the parent structure via an atom in the aromatic ring. Thus, a 1,2,3,4-tetrahydronaphthalen-5-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydronaphthalen-1-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered an aryl group. Similarly, a 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered an aryl group, while 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is not considered an aryl group. However, the term “aryl” does not encompass or overlap with “heteroaryl”, as defined herein, regardless of the point of attachment (*e.g.*, both quinolin-5-yl and quinolin-2-yl are heteroaryl groups). In some instances, aryl is phenyl or naphthyl. In certain instances, aryl is phenyl. Additional examples of aryl groups comprising an aromatic carbon ring fused to a non-aromatic ring are described below.

[0084] “Heteroaryl” indicates an aromatic ring containing the indicated number of atoms (*e.g.*, 5 to 12, or 5 to 10 membered heteroaryl) made up of one or more heteroatoms (*e.g.*, 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon. Heteroaryl groups do not contain adjacent S and O atoms. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 2. In some embodiments, the total number of S and O atoms in the heteroaryl group is not more than 1. Unless otherwise indicated, heteroaryl groups may be bound to the parent structure by a carbon or nitrogen atom, as valency permits. For example, “pyridyl” includes 2-pyridyl, 3-

pyridyl and 4-pyridyl groups, and “pyrrolyl” includes 1-pyrrolyl, 2-pyrrolyl and 3-pyrrolyl groups.

[0085] In some instances, a heteroaryl group is monocyclic. Examples include pyrrole, pyrazole, imidazole, triazole (*e.g.*, 1,2,3-triazole, 1,2,4-triazole, 1,2,4-triazole), tetrazole, furan, isoxazole, oxazole, oxadiazole (*e.g.*, 1,2,3-oxadiazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole), thiophene, isothiazole, thiazole, thiadiazole (*e.g.*, 1,2,3-thiadiazole, 1,2,4-thiadiazole, 1,3,4-thiadiazole), pyridine, pyridazine, pyrimidine, pyrazine, triazine (*e.g.*, 1,2,4-triazine, 1,3,5-triazine) and tetrazine.

[0086] In some instances, both rings of a polycyclic heteroaryl group are aromatic. Examples include indole, isoindole, indazole, benzoimidazole, benzotriazole, benzofuran, benzoxazole, benzoisoxazole, benzoxadiazole, benzothiophene, benzothiazole, benzoisothiazole, benzothiadiazole, 1H-pyrrolo[2,3-b]pyridine, 1H-pyrazolo[3,4-b]pyridine, 3H-imidazo[4,5-b]pyridine, 3H-[1,2,3]triazolo[4,5-b]pyridine, 1H-pyrrolo[3,2-b]pyridine, 1H-pyrazolo[4,3-b]pyridine, 1H-imidazo[4,5-b]pyridine, 1H-[1,2,3]triazolo[4,5-b]pyridine, 1H-pyrrolo[2,3-c]pyridine, 1H-pyrazolo[3,4-c]pyridine, 3H-imidazo[4,5-c]pyridine, 3H-[1,2,3]triazolo[4,5-c]pyridine, 1H-pyrrolo[3,2-c]pyridine, 1H-pyrazolo[4,3-c]pyridine, 1H-imidazo[4,5-c]pyridine, 1H-[1,2,3]triazolo[4,5-c]pyridine, furo[2,3-b]pyridine, oxazolo[5,4-b]pyridine, isoxazolo[5,4-b]pyridine, [1,2,3]oxadiazolo[5,4-b]pyridine, furo[3,2-b]pyridine, oxazolo[4,5-b]pyridine, isoxazolo[4,5-b]pyridine, [1,2,3]oxadiazolo[4,5-b]pyridine, furo[2,3-c]pyridine, oxazolo[5,4-c]pyridine, isoxazolo[5,4-c]pyridine, [1,2,3]oxadiazolo[5,4-c]pyridine, furo[3,2-c]pyridine, oxazolo[4,5-c]pyridine, isoxazolo[4,5-c]pyridine, [1,2,3]oxadiazolo[4,5-c]pyridine, thieno[2,3-b]pyridine, thiazolo[5,4-b]pyridine, isothiazolo[5,4-b]pyridine, [1,2,3]thiadiazolo[5,4-b]pyridine, thieno[3,2-b]pyridine, thiazolo[4,5-b]pyridine, isothiazolo[4,5-b]pyridine, [1,2,3]thiadiazolo[4,5-b]pyridine, thieno[2,3-c]pyridine, thiazolo[5,4-c]pyridine, isothiazolo[5,4-c]pyridine, [1,2,3]thiadiazolo[5,4-c]pyridine, thieno[3,2-c]pyridine, thiazolo[4,5-c]pyridine, isothiazolo[4,5-c]pyridine, [1,2,3]thiadiazolo[4,5-c]pyridine, quinoline, isoquinoline, cinnoline, quinazoline, quinoxaline, phthalazine, naphthyridine (*e.g.*, 1,8-naphthyridine, 1,7-naphthyridine, 1,6-naphthyridine, 1,5-naphthyridine, 2,7-naphthyridine, 2,6-naphthyridine), imidazo[1,2-a]pyridine, 1H-pyrazolo[3,4-d]thiazole, 1H-pyrazolo[4,3-d]thiazole and imidazo[2,1-b]thiazole.

[0087] In other instances, polycyclic heteroaryl groups may include a non-aromatic ring (*e.g.*, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) fused to a heteroaryl ring,

provided the polycyclic heteroaryl group is bound to the parent structure via an atom in the aromatic ring. For example, a 4,5,6,7-tetrahydrobenzo[d]thiazol-2-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is considered a heteroaryl group, while 4,5,6,7-tetrahydrobenzo[d]thiazol-5-yl (wherein the moiety is bound to the parent structure via a non-aromatic carbon atom) is not considered a heteroaryl group. Examples of polycyclic heteroaryl groups consisting of a heteroaryl ring fused to a non-aromatic ring are described below.

[0088] “Heterocycloalkyl” indicates a non-aromatic, fully saturated ring having the indicated number of atoms (*e.g.*, 3- to 10-, or 3- to 7-, membered heterocycloalkyl) made up of one or more heteroatoms (*e.g.*, 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon. Heterocycloalkyl groups may be monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic). Examples of heterocycloalkyl groups include oxiranyl, aziridinyl, azetidiny, pyrrolidinyl, imidazolidinyl, pyrazolidinyl, piperidinyl, piperazinyl, morpholinyl and thiomorpholinyl. Examples include thiomorpholine S-oxide and thiomorpholine S,S-dioxide. In addition, one ring of a polycyclic heterocycloalkyl group may be aromatic (*e.g.*, aryl or heteroaryl), provided the polycyclic heterocycloalkyl group is bound to the parent structure via a non-aromatic carbon or nitrogen atom. For example, a 1,2,3,4-tetrahydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is considered a heterocycloalkyl group, while 1,2,3,4-tetrahydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a heterocycloalkyl group. Examples of polycyclic heterocycloalkyl groups consisting of a heterocycloalkyl group fused to an aromatic ring are described below.

[0089] “Heterocycloalkenyl” indicates a non-aromatic ring having the indicated number of atoms (*e.g.*, 3- to 10-, or 3- to 7-, membered heterocycloalkenyl) made up of one or more heteroatoms (*e.g.*, 1, 2, 3 or 4 heteroatoms) selected from N, O and S and with the remaining ring atoms being carbon, and at least one double bond derived by the removal of one molecule of hydrogen from adjacent carbon atoms, adjacent nitrogen atoms, or adjacent carbon and nitrogen atoms of the corresponding heterocycloalkyl. Heterocycloalkenyl groups may be monocyclic or polycyclic (*e.g.*, bicyclic, tricyclic). Examples of heterocycloalkenyl groups include dihydrofuranyl (*e.g.*, 2,3-dihydrofuranyl, 2,5-dihydrofuranyl), dihydrothiophenyl (*e.g.*, 2,3-dihydrothiophenyl, 2,5-dihydrothiophenyl), dihydropyrrolyl (*e.g.*, 2,3-dihydro-1H-pyrrolyl, 2,5-dihydro-1H-pyrrolyl), dihydroimidazolyl (*e.g.*, 2,3-

dihydro-1H-imidazolyl, 4,5-dihydro-1H-imidazolyl), pyranyl, dihydropyranyl (*e.g.*, 3,4-dihydro-2H-pyranyl, 3,6-dihydro-2H-pyranyl), tetrahydropyridinyl (*e.g.*, 1,2,3,4-tetrahydropyridinyl, 1,2,3,6-tetrahydropyridinyl) and dihydropyridine (*e.g.*, 1,2-dihydropyridine, 1,4-dihydropyridine). In addition, one ring of a polycyclic heterocycloalkenyl group may be aromatic (*e.g.*, aryl or heteroaryl), provided the polycyclic heterocycloalkenyl group is bound to the parent structure via a non-aromatic carbon or nitrogen atom. For example, a 1,2-dihydroquinolin-1-yl group (wherein the moiety is bound to the parent structure via a non-aromatic nitrogen atom) is considered a heterocycloalkenyl group, while 1,2-dihydroquinolin-8-yl group (wherein the moiety is bound to the parent structure via an aromatic carbon atom) is not considered a heterocycloalkenyl group. Examples of polycyclic heterocycloalkenyl groups consisting of a heterocycloalkenyl group fused to an aromatic ring are described below.

[0090] Examples of polycyclic rings consisting of an aromatic ring (*e.g.*, aryl or heteroaryl) fused to a non-aromatic ring (*e.g.*, cycloalkyl, cycloalkenyl, heterocycloalkyl, heterocycloalkenyl) include indenyl, 2,3-dihydro-1H-indenyl, 1,2,3,4-tetrahydronaphthalenyl, benzo[1,3]dioxolyl, tetrahydroquinolinyl, 2,3-dihydrobenzo[1,4]dioxinyl, indolinyl, isoindolinyl, 2,3-dihydro-1H-indazolyl, 2,3-dihydro-1H-benzo[d]imidazolyl, 2,3-dihydrobenzofuranyl, 1,3-dihydroisobenzofuranyl, 1,3-dihydrobenzo[c]isoxazolyl, 2,3-dihydrobenzo[d]isoxazolyl, 2,3-dihydrobenzo[d]oxazolyl, 2,3-dihydrobenzo[b]thiophenyl, 1,3-dihydrobenzo[c]thiophenyl, 1,3-dihydrobenzo[c]isothiazolyl, 2,3-dihydrobenzo[d]isothiazolyl, 2,3-dihydrobenzo[d]thiazolyl, 5,6-dihydro-4H-cyclopenta[d]thiazolyl, 4,5,6,7-tetrahydrobenzo[d]thiazolyl, 5,6-dihydro-4H-pyrrolo[3,4-d]thiazolyl, 4,5,6,7-tetrahydrothiazolo[5,4-c]pyridinyl, indolin-2-one, indolin-3-one, isoindolin-1-one, 1,2-dihydroindazol-3-one, 1H-benzo[d]imidazol-2(3H)-one, benzofuran-2(3H)-one, benzofuran-3(2H)-one, isobenzofuran-1(3H)-one, benzo[c]isoxazol-3(1H)-one, benzo[d]isoxazol-3(2H)-one, benzo[d]oxazol-2(3H)-one, benzo[b]thiophen-2(3H)-one, benzo[b]thiophen-3(2H)-one, benzo[c]thiophen-1(3H)-one, benzo[c]isothiazol-3(1H)-one, benzo[d]isothiazol-3(2H)-one, benzo[d]thiazol-2(3H)-one, 4,5-dihydropyrrolo[3,4-d]thiazol-6-one, 1,2-dihydropyrazolo[3,4-d]thiazol-3-one, quinolin-4(3H)-one, quinazolin-4(3H)-one, quinazoline-2,4(1H,3H)-dione, quinoxalin-2(1H)-one, quinoxaline-2,3(1H,4H)-dione, cinnolin-4(3H)-one, pyridin-2(1H)-one, pyrimidin-2(1H)-one, pyrimidin-4(3H)-one, pyridazin-3(2H)-one, 1H-pyrrolo[3,2-b]pyridin-2(3H)-one, 1H-pyrrolo[3,2-c]pyridin-2(3H)-one, 1H-pyrrolo[2,3-c]pyridin-2(3H)-

one, 1H-pyrrolo[2,3-b]pyridin-2(3H)-one, 1,2-dihydropyrazolo[3,4-d]thiazol-3-one and 4,5-dihydropyrrolo[3,4-d]thiazol-6-one. As discussed herein, whether each ring is considered an aryl, heteroaryl, cycloalkyl, cycloalkenyl, heterocycloalkyl or heterocycloalkenyl group is determined by the atom through which the moiety is bound to the parent structure.

[0091] “Halogen” or “halo” refers to fluoro, chloro, bromo or iodo.

[0092] “Haloalkyl” refers to alkyl substituted with one or more halogen. A haloalkyl group may have a halogen substituent at any valence-permitted location on the alkyl and may have any number of halogen substituents ranging from one to the maximum valence-permitted number. Particular haloalkyl groups have 1, 2, or 3 halogen substituents. Examples of haloalkyl groups include, but are not limited to, -CH₂F, -CHF₂, -CF₃, -CH₂CH₂F, -CH₂CHF₂, -CH₂CF₃, -CH₂Cl, -CHCl₂, -CCl₃, -CH₂CH₂Cl, -CH₂CHCl₂, -CH₂CCl₃.

[0093] Unless otherwise indicated, compounds disclosed and/or described herein include all possible enantiomers, diastereomers, meso isomers and other stereoisomeric forms, including racemic mixtures, optically pure forms and intermediate mixtures thereof. Enantiomers, diastereomers, meso isomers and other stereoisomeric forms can be prepared using chiral synthons or chiral reagents, or resolved using conventional techniques. Unless specified otherwise, when the compounds disclosed and/or described herein contain olefinic double bonds or other centers of geometric asymmetry, it is intended that the compounds include both E and Z isomers. When the compounds described herein contain moieties capable of tautomerization, and unless specified otherwise, it is intended that the compounds include all possible tautomers.

[0094] “Protecting group” has the meaning conventionally associated with it in organic synthesis, *i.e.*, a group that selectively blocks one or more reactive sites in a multifunctional compound such that a chemical reaction can be carried out selectively on another unprotected reactive site, and such that the group can readily be removed after the selective reaction is complete. A variety of protecting groups are disclosed, for example, in T.H. Greene and P. G. M. Wuts, *Protective Groups in Organic Synthesis*, Third Edition, John Wiley & Sons, New York (1999). For example, a “hydroxy protected form” contains at least one hydroxy group protected with a hydroxy protecting group. Likewise, amines and other reactive groups may similarly be protected.

[0095] The term “pharmaceutically acceptable salt” refers to a salt of any of the compounds herein which are known to be non-toxic and are commonly used in the pharmaceutical literature. In some embodiments, the pharmaceutically acceptable salt of a compound retains

the biological effectiveness of the compounds described herein and are not biologically or otherwise undesirable. Examples of pharmaceutically acceptable salts can be found in Berge *et al.*, *Pharmaceutical Salts*, *J. Pharmaceutical Sciences*, January 1977, 66(1), 1-19.

Pharmaceutically acceptable acid addition salts can be formed with inorganic acids and organic acids. Inorganic acids from which salts can be derived include, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, and phosphoric acid. Organic acids from which salts can be derived include, for example, acetic acid, propionic acid, glycolic acid, pyruvic acid, lactic acid, oxalic acid, malic acid, maleic acid, malonic acid, succinic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 2-hydroxyethylsulfonic acid, p-toluenesulfonic acid, stearic acid and salicylic acid. Pharmaceutically acceptable base addition salts can be formed with inorganic and organic bases. Inorganic bases from which salts can be derived include, for example, sodium, potassium, lithium, ammonium, calcium, magnesium, iron, zinc, copper, manganese, and aluminum. Organic bases from which salts can be derived include, for example, primary, secondary, and tertiary amines; substituted amines including naturally occurring substituted amines; cyclic amines; and basic ion exchange resins. Examples of organic bases include isopropylamine, trimethylamine, diethylamine, triethylamine, tripropylamine, and ethanolamine. In some embodiments, the pharmaceutically acceptable base addition salt is selected from ammonium, potassium, sodium, calcium, and magnesium salts.

[0096] If the compound described herein is obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the compound is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds (see, *e.g.*, Berge *et al.*, *Pharmaceutical Salts*, *J. Pharmaceutical Sciences*, January 1977, 66(1), 1-19). Those skilled in the art will recognize various synthetic methodologies that may be used to prepare pharmaceutically acceptable addition salts.

[0097] A “solvate” is formed by the interaction of a solvent and a compound. Suitable solvents include, for example, water and alcohols (*e.g.*, ethanol). Solvates include hydrates having any ratio of compound to water, such as monohydrates, dihydrates and hemi-hydrates.

[0098] The term “substituted” means that the specified group or moiety bears one or more substituents including, but not limited to, substituents such as alkoxy, acyl, acyloxy,

alkoxycarbonyl, carbonylalkoxy, acylamino, amino, aminoacyl, aminocarbonylamino, aminocarbonyloxy, cycloalkyl, cycloalkenyl, aryl, heteroaryl, aryloxy, cyano, azido, halo, hydroxyl, nitro, carboxyl, thiol, thioalkyl, alkyl, alkenyl, alkynyl, heterocycloalkyl, heterocycloalkenyl, aralkyl, aminosulfonyl, sulfonylamino, sulfonyl, oxo and the like. The term “unsubstituted” means that the specified group bears no substituents. Where the term “substituted” is used to describe a structural system, the substitution is meant to occur at any valency-allowed position on the system. When a group or moiety bears more than one substituent, it is understood that the substituents may be the same or different from one another. In some embodiments, a substituted group or moiety bears from one to five substituents. In some embodiments, a substituted group or moiety bears one substituent. In some embodiments, a substituted group or moiety bears two substituents. In some embodiments, a substituted group or moiety bears three substituents. In some embodiments, a substituted group or moiety bears four substituents. In some embodiments, a substituted group or moiety bears five substituents.

[0099] By “optional” or “optionally” is meant that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, “optionally substituted alkyl” encompasses both “alkyl” and “substituted alkyl” as defined herein. It will be understood by those skilled in the art, with respect to any group containing one or more substituents, that such groups are not intended to introduce any substitution or substitution patterns that are sterically impractical, synthetically non-feasible, and/or inherently unstable. It will also be understood that where a group or moiety is optionally substituted, the disclosure includes both embodiments in which the group or moiety is substituted and embodiments in which the group or moiety is unsubstituted.

[0100] The compounds disclosed and/or described herein can be enriched isotopic forms, *e.g.*, enriched in the content of ^2H , ^3H , ^{11}C , ^{13}C and/or ^{14}C . In one embodiment, the compound contains at least one deuterium atom. Such deuterated forms can be made, for example, by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. Such deuterated compounds may improve the efficacy and increase the duration of action of compounds disclosed and/or described herein. Deuterium substituted compounds can be synthesized using various methods, such as those described in: Dean, D., Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development, *Curr. Pharm. Des.*, 2000; 6(10); Kabalka, G. *et al.*, The Synthesis of

Radiolabeled Compounds via Organometallic Intermediates, *Tetrahedron*, 1989, 45(21), 6601-21; and Evans, E., Synthesis of radiolabeled compounds, *J. Radioanal. Chem.*, 1981, 64(1-2), 9-32.

[0101] The term “pharmaceutically acceptable carrier” or “pharmaceutically acceptable excipient” includes any and all solvents, dispersion media, coatings, antibacterial and antifungal agents, isotonic and absorption delaying agents and the like. The use of such media and agents for pharmaceutically active substances is well known in the art. Except insofar as any conventional media or agent is incompatible with the active ingredient, its use in pharmaceutical compositions is contemplated. Supplementary active ingredients can also be incorporated into the pharmaceutical compositions.

[0102] As used herein, the terms “polymorph”, “polymorphic”, “polymorphic form”, or “crystalline form”, which are used interchangeably, refer to polymorphic form of a compound. The polymorphic form can be crystalline or amorphous. Different polymorphs may have different physical properties such as, for example, melting temperatures, heats of fusion, solubilities, dissolution rates, and/or vibrational spectra as a result of the arrangement or conformation of the molecules or ions in the crystal lattice. The differences in physical properties exhibited by polymorphs may affect pharmaceutical parameters, such as storage stability, compressibility, density (important in formulation and product manufacturing), and dissolution rate (an important factor in bioavailability). Differences in stability can result from changes in chemical reactivity (*e.g.*, differential oxidation, such that a dosage form discolors more rapidly when comprised of one polymorph than when comprised of another polymorph), mechanical changes (*e.g.*, tablets crumble on storage as a kinetically favored polymorph converts to thermodynamically more stable polymorph), or both (*e.g.*, tablets of one polymorph are more susceptible to breakdown at high humidity). As a result of solubility/dissolution differences, in the extreme case, some polymorphic transitions may result in lack of potency or, at the other extreme, toxicity. In addition, the physical properties of a crystalline form may be important in processing; for example, one polymorph might be more likely to form solvates or might be difficult to filter and wash free of impurities (*e.g.*, particle shape and size distribution might be different between polymorphs).

[0103] As used herein, the term “substantially as shown in” when referring, for example, to an XRPD pattern, a DSC graph, a TGA graph, or a GVS graph, includes a pattern or graph that is not necessarily identical to those depicted herein, but that falls within the limits of experimental error or deviations when considered by one of ordinary skill in the art.

[0104] As used herein, the term “substantially free of” means that the composition comprising the crystalline form contains less than 50%, less than 40%, less than 30%, less than 20%, less than 15%, less than 10%, less than 5%, less than 4%, less than 3%, less than 2%, or less than 1% by weight of the indicated substance or substances.

[0105] The terms “patient”, “individual”, and “subject” refer to an animal, such as a mammal, bird, or fish. In some embodiments, the patient or subject is a mammal. Mammals include, for example, mice, rats, dogs, cats, pigs, sheep, horses, cows and humans. In some embodiments, the patient, individual, or subject is a human, for example a human that has been or will be the object of treatment, observation or experiment. The compounds, compositions and methods described herein can be useful in both human therapy and veterinary applications.

[0106] The term “therapeutically effective amount” or “effective amount” refers to that amount of a compound disclosed and/or described herein that is sufficient to affect treatment, as defined herein, when administered to a patient in need of such treatment. A therapeutically effective amount of a compound may be an amount sufficient to treat a disease responsive to modulation (*e.g.*, inhibition) of KIF18a. The therapeutically effective amount will vary depending upon, for example, the subject and disease condition being treated, the weight and age of the subject, the severity of the disease condition, the particular compound, the dosing regimen to be followed, timing of administration, the manner of administration, all of which can readily be determined by one of ordinary skill in the art. The therapeutically effective amount may be ascertained experimentally, for example by assaying blood concentration of the chemical entity, or theoretically, by calculating bioavailability.

[0107] “Treatment” (and related terms, such as “treat”, “treated”, “treating”) includes one or more of: inhibiting a disease or disorder; slowing or arresting the development of clinical symptoms of a disease or disorder; and/or relieving a disease or disorder (*i.e.*, causing relief from or regression of clinical symptoms). The term covers both complete and partial reduction of the condition or disorder, and complete or partial reduction of clinical symptoms of a disease or disorder. Thus, compounds described and/or disclosed herein may prevent an existing disease or disorder from worsening, assist in the management of the disease or disorder, or reduce or eliminate the disease or disorder.

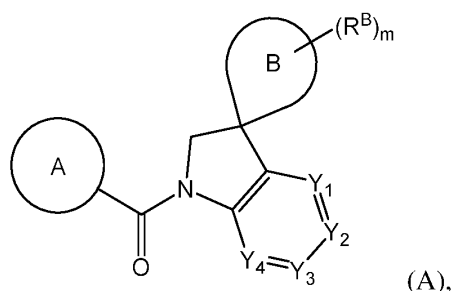
[0108] It is understood that embodiments described herein as “comprising” include “consisting of” and “consisting essentially of” embodiments.

II. Solid Formulations

II-a. Indoline inhibitors of KIF18A

[0109] In some aspects, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A), as described herein, or a pharmaceutically acceptable salt thereof. In some aspects, provided herein is a polymorphic form of a compound of Formula (A-1), as described herein, or a pharmaceutically acceptable salt thereof. In some aspects, provided herein is a salt form of a compound of Formula (A-1). All compounds of Formula (A) and any subgenus thereof described herein, including compounds of Formula (A-1), Formula (A-2), and Formula (A-3), intend to encompass any and all stereoisomers, including geometric isomers (cis/trans), E/Z isomers, enantiomers, diastereomers, and mixtures thereof in any ratio including racemic mixtures, salts, and solvates. Any compound described herein may also be referred to as a drug or active pharmaceutical ingredient (API).

[0110] In some aspects, provided herein is a solid formulation comprising a compound of Formula (A):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted

with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

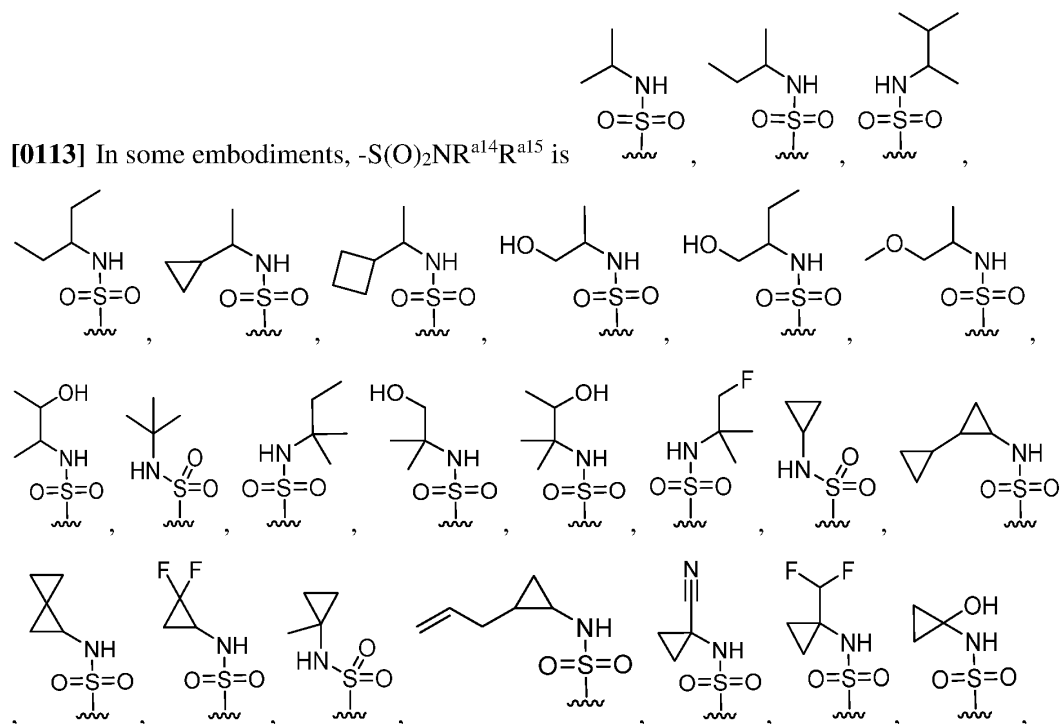
R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

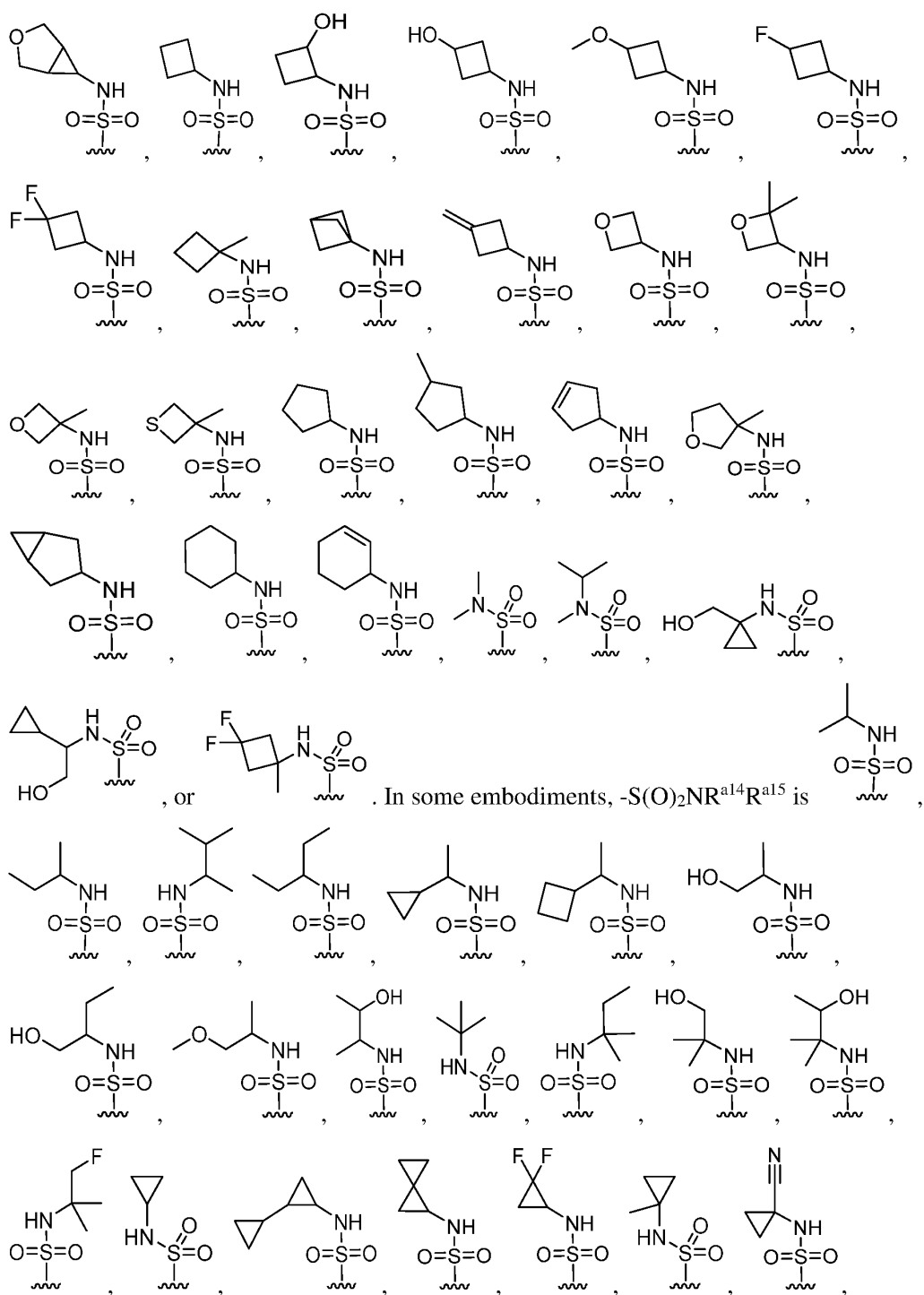
R^{c1}-R^{c18} are each independently hydrogen, C₃₋₁₀ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

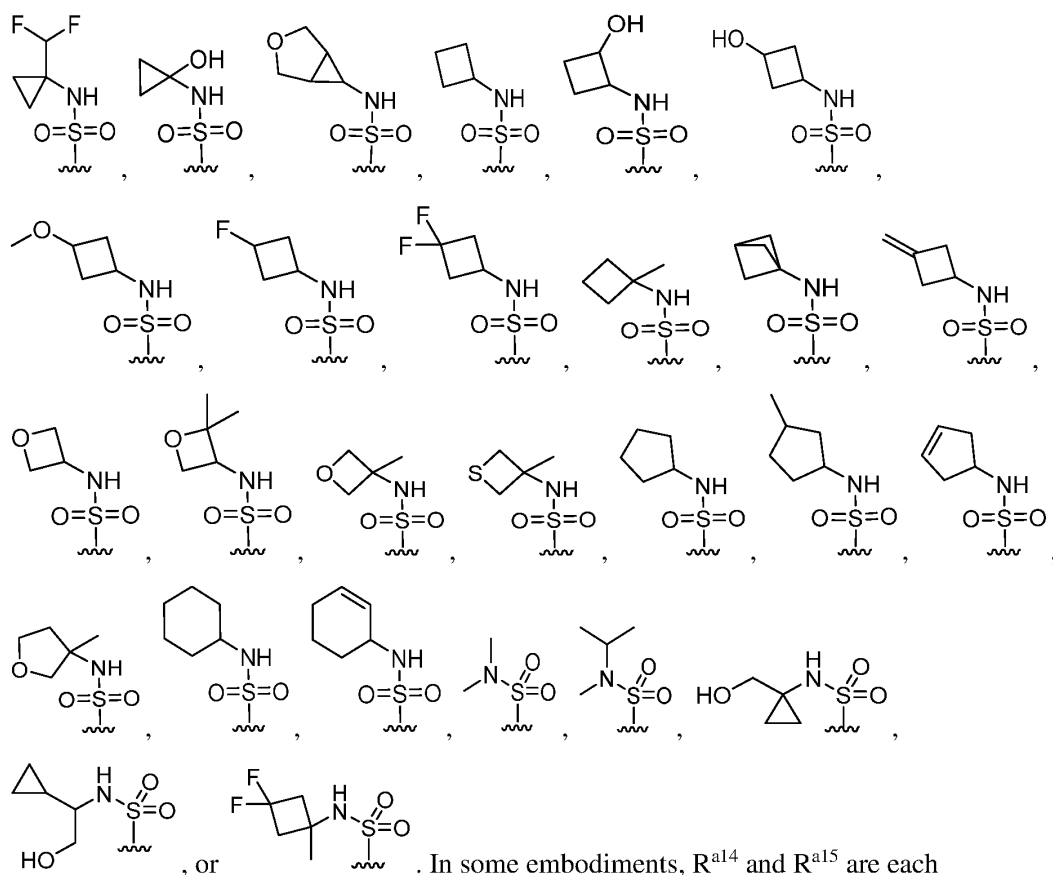
[0111] In some embodiments of Formula (A), or a pharmaceutically acceptable salt thereof, ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted as defined above or below. In some embodiments, ring A is optionally substituted C₆₋₁₄ aryl. In some embodiments, ring A is phenyl optionally substituted as defined above or below. In some embodiments, ring A is 5- to 12-membered heteroaryl optionally substituted as defined above or below. In some embodiments, ring A is 6-membered heteroaryl optionally substituted as defined above or below. In some embodiments, ring A is 5-membered heteroaryl optionally substituted as defined above or below. In some embodiments, ring A is indolyl, indazolyl, pyridinyl, thiophenyl, furanyl, pyrazolyl, pyrrolyl, oxazolyl, chromanyl, or quinolinyl, each

optionally substituted as defined above or below. In some embodiments, ring A is thiophenyl optionally substituted as defined above or below.

[0112] In some embodiments of Formula (A), ring A is optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo. In some embodiments, R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one, two, three, four, five, or more substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl.

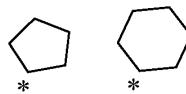






[0114] In some embodiments of Formula (A), or a pharmaceutically acceptable salt thereof, ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon.

In some embodiments, ring B is C₅₋₇ cycloalkyl. In some embodiments, ring B is cyclopentyl,



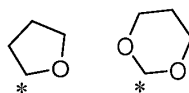
cyclohexyl, or cycloheptyl. In some embodiments, ring B is  or , wherein * denotes the point of attachment to the rest of Formula (A). In some embodiments, ring B is C₅₋₇ cycloalkenyl. In some embodiments, ring B is cyclopentenyl, cyclohexenyl, or



cycloheptenyl. In some embodiments, ring B is , wherein * denotes the point of

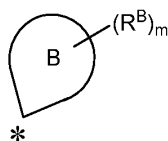


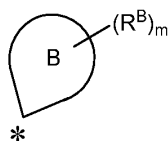
attachment to the rest of Formula (A). In some embodiments, ring B is , wherein * denotes the point of attachment to the rest of Formula (A). In some embodiments, ring B is 5- to 7-membered heterocycloalkyl. In some embodiments, ring B is 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon. In some embodiments, ring B is tetrahydrofuranyl or 1,3-



dioxanyl. In some embodiments, ring B is  or , wherein * denotes the point of attachment to the rest of Formula (A).

[0115] In some embodiments, ring B is substituted with two R^B groups, wherein the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl. In some embodiments, the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form a cyclopropyl.

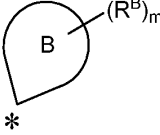
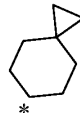


[0116] In some embodiments,  of Formula (A) is , wherein * denotes the point of attachment to the rest of Formula (A).

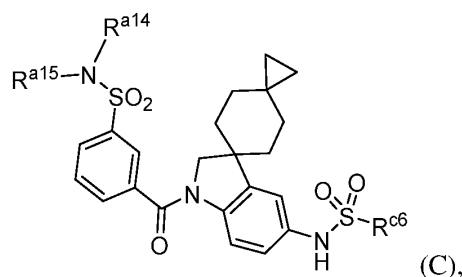
[0117] In some embodiments of Formula (A), or a pharmaceutically acceptable salt thereof, Y¹ is N or CR^{C1}; Y² is N or CR^{C2}; Y³ is N or CR^{C3}; and Y⁴ is N or CR^{C4}. In some embodiments, no more than three of Y¹, Y², Y³, and Y⁴ are N. In some embodiments, no more than two of Y¹, Y², Y³, and Y⁴ are N. In some embodiments, no more than one of Y¹,

R^{C2} is halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH. In some embodiments, R^{C2} is -NR^{c5}S(O)₂R^{c6}. In some embodiments, R^{c5} is hydrogen and R^{c6} is C₁₋₆ alkyl. In some embodiments, R^{c5} is hydrogen and R^{c6} is ethyl. In some embodiments, R^{c5} is hydrogen. In some embodiments, R^{c6} is ethyl. In some embodiments, R^{c6} is methyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is C₁₋₆ alkyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is *tert*-butyl. In some embodiments, R^{a14} is hydrogen. In some embodiments, R^{a15} is

tert-butyl. In some embodiments, ring B is , wherein * denotes the point of attachment

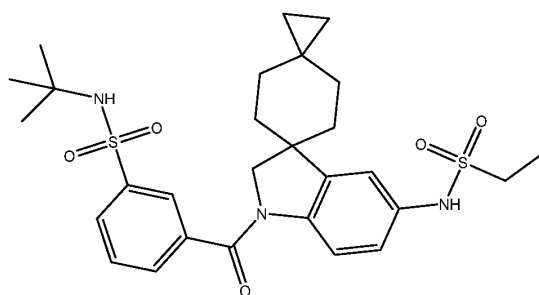
to the rest of Formula (B). In some embodiments, , of Formula (B) is .

[0121] In one aspect, the compound of Formula (A) is a compound of Formula (C):



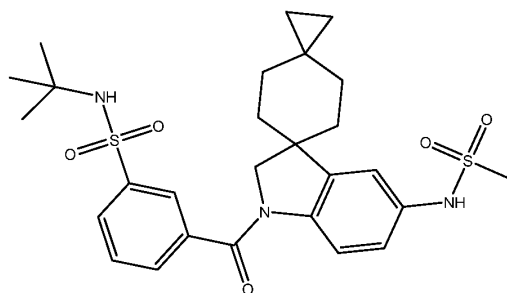
or a pharmaceutically acceptable salt thereof, wherein R^{a14} , R^{a15} , and R^{c6} are as defined for Formula (A) or any variation or embodiment thereof. In some embodiments, R^{a14} is hydrogen and R^{a15} is C₁₋₆ alkyl. In some embodiments, R^{a14} is hydrogen and R^{a15} is *tert*-butyl. In some embodiments, R^{a14} is hydrogen. In some embodiments, R^{a15} is *tert*-butyl. In some embodiments, R^{a14} and R^{a15} are each independently C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, or 3- to 10-membered heterocycloalkenyl. In some embodiments, R^{a14} and R^{a15} are taken together with the N atom to which they are attached to form a 3- to 10-membered heterocycloalkyl. In some embodiments, R^{c6} is C₁₋₆ alkyl optionally substituted with one or more halo. In some embodiments, R^{c6} is unsubstituted C₁₋₆ alkyl. In some embodiments, R^{c6} is ethyl. In some embodiments, R^{c6} is methyl.

[0122] In one aspect, the compound of Formula (A) is a compound of Formula (A-1):



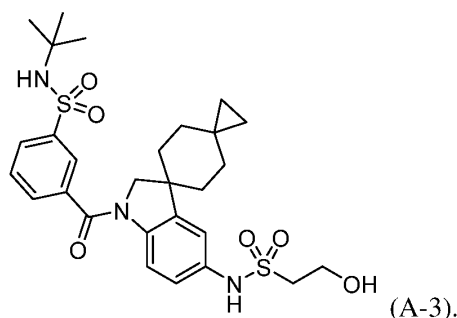
(A-1).

[0123] In one aspect, the compound of Formula (A) is a compound of Formula (A-2):



(A-2).

[0124] In one aspect, the compound of Formula (A) is a compound of Formula (A-3):



(A-3).

[0125] Compounds of Formula (A), particularly a compound of Formula (A-1), Formula (A-2), and Formula (A-3) as defined herein, are KIF18A inhibitors. However, these compounds are only sparingly soluble in aqueous media. Therefore, there exists a need to develop solid pharmaceutical formulations of the compounds of Formula (A), including Formula (B), Formula (C), Formula (A-1) Formula (A-2), and Formula (A-3) that can significantly improve the pharmaceutical performances of these compounds, such as stability and solubility. Such formulations may beneficially provide improved bioavailability and/or lower manufacturing cost. Challenges to develop such solid pharmaceutical formulations include: 1) increasing solubility; 2) stabilizing the compounds, including reducing moisture sensitivity

and potential ambient-temperature degradation, and 3) maintaining high physical stability and avoiding phase separation in a formulation.

[0126] Furthermore, it is also advantageous to develop various forms of the compounds, such as polymorphs, salts, hydrates, and solvates, of the compounds of Formula (A), including Formula (A-1), Formula (A-2), and Formula (A-3). Developing various solid forms, especially polymorphic forms or salt forms, can not only facilitate the understanding of the interactions between these compounds and various solvent, counterions, and conditions, but also afford potentially more stable and/or more soluble forms of these compounds, both of which will benefit the development of solid pharmaceutical formulations with high stability and bioavailability.

[0127] In some aspects, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A) and a polymer. In some aspects, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A), wherein the formulation results in at least 2-fold increase in solubility compared to neat compound of Formula (A). In some aspects, provided herein is a polymorphic form of a compound of Formula (A-1). In other aspects, provided herein is a method of preparing solid pharmaceutical formulations comprising a compound of Formula (A) and a polymer, particularly by a spray drying process. In yet other aspects, provided herein is a method of preparing both crystalline and amorphous forms of a compound of Formula (A), including Formula (A-1), Formula (A-2), and Formula (A-3).

II-b. Salt Forms

[0128] In some aspects, provided herein is a solid formulation comprising a pharmaceutically acceptable salt of the compound of Formula (A). In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A) retains the biological effectiveness of the compounds described herein. In some embodiment of the foregoing, the solid formulation is a spray dried formulation.

[0129] In some aspects, provided herein is a solid formulation comprising a pharmaceutically acceptable salt of the compound of Formula (A-1). In some aspects, provided herein is a spray dried formulation comprising a pharmaceutically acceptable salt of the compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the pharmaceutically acceptable salt of the compound of Formula (A-1) is formed with inorganic and/or organic bases. In some embodiments, the pharmaceutically acceptable salt

of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with a base comprising NaOH, KOH, Mg(OH)₂, Ca(OH)₂, L-arginine, L-lysine, choline, betaine, diethylamine, or any combination thereof.

[0130] In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with an inorganic base comprising NaOH, KOH, Mg(OH)₂, Ca(OH)₂, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) comprises a sodium salt, a potassium salt, a magnesium salt, a calcium salt, a zinc salt, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt, wherein the stoichiometry between compound of Formula (A-1) and sodium ion is about 1:0.8 to 1:3, such as about any of 1:0.9 to 1:2.7, 1:1 to 1:2.5, 1:1 to 1:2.3, 1:1 to 1:1.5, or 1:2 to 1:2.3. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a mono-sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a di-sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt, wherein the stoichiometry between compound of Formula (A-1) and potassium ion is about 1:0.8 to 1:3, such as about any of 1:0.9 to 1:2.7, 1:1 to 1:2.5, 1:1 to 1:2.3, 1:1 to 1:1.5, or 1:2 to 1:2.3. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a mono-potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a di-potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a magnesium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a calcium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a zinc salt.

[0131] In some embodiments, in conjunction with the embodiments above or below, the pharmaceutically acceptable salt of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with an organic base comprising L-arginine, L-lysine, choline, betaine, diethylamine, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) comprises a L-arginine salt, a L-lysine salt, a choline salt, a betaine salt, a diethylamine salt, or any combination

thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a L-arginine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a L-lysine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a choline salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a betaine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a diethylamine salt.

[0132] In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt, wherein the sodium salt is in a polymorphic form selected from the group consisting of polymorphic Form IV, polymorphic Form V, polymorphic Form VIII, polymorphic Form X, polymorphic Form XI, polymorphic Form XII, and any mixture thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt, wherein the potassium salt is in a polymorphic form selected from the group consisting of polymorphic Form VI, polymorphic Form VII, polymorphic Form IX, and any mixture thereof.

II-c. Compositions

[0133] In some embodiments, provided herein is a solid pharmaceutical formulation of a compound of Formula (A) comprising: (i) a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof and (ii) a pharmaceutically acceptable polymer. In some embodiments, a significant portion of the compound of Formula (A) is in amorphous form. For example, in some embodiments, at least 50 wt.% (*e.g.*, at least 50 wt.%, at least 60 wt.%, at least 70 wt.%, at least 80 wt.%, or at least 90 wt.%) of the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof in the solid pharmaceutical formulation is amorphous. In some embodiments, at least 75 wt.% (*e.g.*, 75-100 wt.%, 80-100 wt.%, 85-100 wt.%, 90-100 wt.%, or 95-100 wt.%) of the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof in the solid pharmaceutical formulation is amorphous. In some embodiments, at least 90 wt.% (*e.g.*, 91-100 wt.%, 92-100 wt.%, 93-100 wt.%, 94-100 wt.%, 95-100 wt.%, 96-100 wt.%, 97-100 wt.%, 98-100 wt.%, 99-100 wt.%, or 99.9-100 wt.%) of the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof in the solid pharmaceutical formulation is amorphous. In some embodiments, no recognizable characteristic peaks of a crystalline form of a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof are present in the powder X-ray

diffraction (PXRD) pattern of the solid pharmaceutical formulation. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0134] In some embodiments, the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof can exist within the solid pharmaceutical formulation as a homogeneous phase, as a solid solution of a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof homogeneously distributed throughout the polymer. In some embodiments, the solid pharmaceutical formulation is substantially homogeneous so that the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof is dispersed substantially homogeneously throughout the solid formulation. In some embodiments, a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof that is present in the solid dispersion as relatively high concentration domains and relatively low concentration domains. In some embodiments, the solid formulation has a single glass transition temperature, which demonstrates that the formulation is substantially homogeneous. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0135] In some embodiments, a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof is present in the formulation in an amount from about 10 % to about 70 % by weight, for example, from about 20 % to about 70 %, from about 20 % to about 60 %, from about 25 % to about 50 %, of about 25 %, of about 40 %, or of about 50 % by weight. In some embodiments, the a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof is present in the formulation in an amount of about 25 % by weight. In some embodiments, the a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof is present in the formulation in an amount of about 40 % by weight. In some embodiments, the a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof is present in the formulation in an amount of about 50 % by weight. In some embodiments, in conjunction with the embodiments above or below, the compound of

Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0136] In some embodiments, the solid pharmaceutical formulation provided herein comprises a polymer. In some embodiments, the polymer can comprise any pharmaceutically acceptable polymer that once co-processed with a compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof, functions to maintain the compound of Formula (A) or a pharmaceutically acceptable salt or solvate thereof in amorphous form or to improve its dissolution performance, stability, or bioavailability. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0137] While specific polymers are discussed in the formulations described herein, blends of such polymers may also be suitable. Thus, the term "polymer" is intended to include blends of polymers in addition to a single species of polymer.

[0138] In some embodiments, the polymer comprises an enteric polymer. In some embodiments, the polymer is at least partially ionizable at physiologically relevant pHs. In some other embodiments, the polymer is an ionizable polymer, wherein the ionizable polymer is an enteric polymer. Exemplary enteric polymers include, but are not limited to, hydroxypropyl methylcellulose acetate succinate (HPMCAS), which includes HPMCAS L-grade (HPMCAS-L), HPMCAS M-grade (HPMCAS-M), and HPMCAS H-grade (HPMCAS-H), hydroxypropyl methyl cellulose phthalate (HPMCP), which includes HPMCP-HP55, hydroxypropyl methyl cellulose acetate phthalate (HPMCAP), hydroxypropyl methylcellulose (HPMC), which includes HPMC E5, HPMC E3LV, and HPMC 5CPS, methacrylic acid-ethyl acrylate copolymer, which includes methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L100-55), cellulose acetate trimellitate (CAT), hydroxypropyl cellulose acetate phthalate succinate, cellulose propionate phthalate, hydroxypropyl cellulose butyrate phthalate, cellulose acetate trimellitate, methyl cellulose acetate trimellitate, ethyl cellulose acetate trimellitate, hydroxypropyl cellulose acetate trimellitate, hydroxypropyl methyl cellulose acetate trimellitate, hydroxypropyl cellulose

acetate trimellitate succinate, cellulose propionate trimellitate, cellulose butyrate trimellitate, cellulose acetate terephthalate, cellulose acetate isophthalate, cellulose acetate pyridinedicarboxylate, salicylic acid cellulose acetate, and hydroxypropyl salicylic acid cellulose acetate.

[0139] In some embodiments, the polymer comprises hydroxypropyl methylcellulose acetate succinate (HPMCAS). In some embodiments, the polymer is HPMCAS-L. In some embodiments, the polymer is HPMCAS-H. In some embodiments, the polymer is HPMCAS-M. In some embodiments, the polymer comprises hydroxypropyl methyl cellulose phthalate (HPMCP). In some embodiments, the polymer is HPMCP-HP55. In some embodiments, the polymer comprises hydroxypropyl methylcellulose (HPMC). In some embodiments, the polymer is HPMC E3LV. In some embodiments, the polymer comprises methacrylic acid-ethyl acrylate copolymer. In some embodiments, the polymer is methacrylic acid-ethyl acrylate copolymer (1:1), which is available as Eudragit® L 100-55.

[0140] In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 15:85 to about 90:10 (*e.g.*, from about 20:80 to about 70:30, from about 25:75 to about 50:50, from about 25:75 to about 40:60, or from 40:60 to about 50:50). In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 15:85 to about 90:10. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 15:85 to about 80:20. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 15:85 to about 70:30. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 20:80 to about 60:40. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 20:80 to about 30:70. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of about 25:75. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 35:65 to about 45:55. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of about 40:60. In some

embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of from about 45:55 to about 55:45. In some embodiments, the solid pharmaceutical formulation described herein has a weight ratio between the compound of Formula (A) and the polymer of about 50:50. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0141] In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 20:80 to about 90:10. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 20:80 to about 80:20. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 20:80 to about 60:40. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 20:80 to about 30:70. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 30:70 to about 50:50. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of from about 40:60 to about 60:40. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of about 25:75. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of about 40:60. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCP-HP55 in a weight ratio of about 50:50. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0142] In some embodiments, the formulation comprises a compound of Formula (A) and HPMCAS-M in a weight ratio of from about 10:90 to about 90:10. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCAS-M in a weight ratio of from about 10:90 to about 70:30. In some embodiments, the formulation comprises a

compound of Formula (A) and HPMCAS-M in a weight ratio of from about 10:90 to about 50:50. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCAS-M in a weight ratio of from about 10:90 to about 40:60. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCAS-M in a weight ratio of from about 20:80 to about 30:70. In some embodiments, the formulation comprises a compound of Formula (A) and HPMCAS-M in a weight ratio of about 25:75. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0143] In some embodiments, the formulation comprises a compound of Formula (A) and HPMC E3LV in a weight ratio of from about 20:80 to about 90:10. In some embodiments, the formulation comprises a compound of Formula (A) and HPMC E3LV in a weight ratio of from about 40:60 to about 60:40. In some embodiments, the formulation comprises a compound of Formula (A) and HPMC E3LV in a weight ratio of about 50:50. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0144] In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1), (available as Eudragit® L 100-55) in a weight ratio of from about 10:90 to about 90:10. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1), (available as Eudragit® L 100-55) in a weight ratio of from about 20:80 to about 60:40. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of from about 20:80 to about 30:70. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of from about 30:70 to about 50:50. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of from

about 40:60 to about 60:40. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of about 25:75. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of about 40:60. In some embodiments, the formulation comprises a compound of Formula (A) and methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55) in a weight ratio of about 50:50. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

II-d. Pharmacokinetics

[0145] The formulation provided herein may improve the dissolution and pharmacokinetic profile of the compound of Formula (A), including the compound of Formula (A-1), Formula (A-2), and Formula (A-3). The dissolution profile of a compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), and Formula (A-3)) can be described and evaluated with parameters such as area under a concentration-time curve over a time period t in a media ($AUC_{(t)}$), maximum plasma concentration (C_{max}), and total drug dissolved over a period of t (C_t).

[0146] In some embodiments, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)), or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation increases the dissolved concentration of a compound of Formula (A) (*e.g.*, a compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in simulated intestinal media compared to pure crystalline compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)). In some embodiments, the simulated intestinal media comprises a fasted state simulated intestinal fluid (FaSSIF). In some embodiments, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A) (*e.g.*, a compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation increases the dissolved concentration of the compound of Formula (A) (*e.g.*, compound of

Formula (A-1), Formula (A-2), or Formula (A-3)) in simulated intestinal media compared to pure crystalline compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) by at least about 2-fold (*e.g.*, at least about 3-fold, at least about 5-fold, at least about 7-fold, at least about 10-fold, at least about 12-fold, at least about 15-fold, or at least about 20-fold). In some embodiments, which can be combined with any embodiment described above or below, the solid formulation is a spray dried dispersion.

[0147] In some embodiments, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 30 $\mu\text{g/mL}$ to about 300 $\mu\text{g/mL}$ (*e.g.*, about 40 $\mu\text{g/mL}$ to about 300 $\mu\text{g/mL}$, about 50 $\mu\text{g/mL}$ to about 270 $\mu\text{g/mL}$, or about 100 $\mu\text{g/mL}$ to about 200 $\mu\text{g/mL}$). In some embodiments, the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 40 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 100 $\mu\text{g/mL}$ to about 150 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 150 $\mu\text{g/mL}$ to about 300 $\mu\text{g/mL}$. In some embodiments, which can be combined with any embodiment described above or below, the solid formulation is a spray dried dispersion.

[0148] In some embodiments, provided herein is a solid pharmaceutical formulation comprising a compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in Gastric Buffer (GB) of about 8 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$ (*e.g.*, about 8 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$, about 8 $\mu\text{g/mL}$ to about 20 $\mu\text{g/mL}$, or about 60 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$). In some embodiments, the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in GB of about 8 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical

formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in GB of about 50 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in GB of about 60 $\mu\text{g/mL}$ to about 90 $\mu\text{g/mL}$. In some embodiments, which can be combined with any embodiment described above or below, the solid formulation is a spray dried dispersion. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0149] In some embodiments, the solid pharmaceutical formulation is effective to provide a AUC_{35-210} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 1000 $\text{min} \cdot \mu\text{g/mL}$ to about 30000 $\text{min} \cdot \mu\text{g/mL}$ (*e.g.*, about 4000 $\text{min} \cdot \mu\text{g/mL}$ to about 25000 $\text{min} \cdot \mu\text{g/mL}$, about 4000 $\text{min} \cdot \mu\text{g/mL}$ to about 10000 $\text{min} \cdot \mu\text{g/mL}$, about 10000 $\text{min} \cdot \mu\text{g/mL}$ to about 15000 $\text{min} \cdot \mu\text{g/mL}$, or about 20000 $\text{min} \cdot \mu\text{g/mL}$ to about 30000 $\text{min} \cdot \mu\text{g/mL}$). In some embodiments, the solid pharmaceutical formulation is effective to provide a AUC_{35-210} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 4000 $\text{min} \cdot \mu\text{g/mL}$ to about 10000 $\text{min} \cdot \mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a AUC_{35-210} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1) or Formula (A-2)) in FaSSIF of about 10000 $\text{min} \cdot \mu\text{g/mL}$ to about 20000 $\text{min} \cdot \mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a AUC_{35-210} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in FaSSIF of about 20000 $\text{min} \cdot \mu\text{g/mL}$ to about 30000 $\text{min} \cdot \mu\text{g/mL}$. In some embodiments, which can be combined with any embodiment described above or below, the solid formulation is a spray dried dispersion. In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-1). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-2). In some embodiments, in conjunction with the embodiments above or below, the compound of Formula (A) is a compound of Formula (A-3).

[0150] In some embodiments, the solid pharmaceutical formulation is effective to provide a total drug dissolved in FaSSIF over 210 minutes of about 3 $\mu\text{g/mL}$ to about 120 $\mu\text{g/mL}$ (*e.g.*, about 3 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$, about 10 $\mu\text{g/mL}$ to about 120 $\mu\text{g/mL}$, about 10 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$, or about 50 $\mu\text{g/mL}$ to about 120 $\mu\text{g/mL}$). In some embodiments, the solid pharmaceutical formulation is effective to provide a total drug dissolved over 210 minutes of about 3 $\mu\text{g/mL}$ to about 10 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a total drug dissolved in FaSSIF over 210 minutes of about 10 $\mu\text{g/mL}$ to about 50 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a total drug dissolved in FaSSIF over 210 minutes of about 50 $\mu\text{g/mL}$ to about 100 $\mu\text{g/mL}$. In some embodiments, the solid pharmaceutical formulation is effective to provide a total drug dissolved in FaSSIF over 210 minutes of about 100 $\mu\text{g/mL}$ to about 120 $\mu\text{g/mL}$. In some embodiments, which can be combined with any embodiment described above or below, the solid formulation is a spray dried dispersion.

[0151] The pharmacokinetic profile of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) may be described with parameters such as area under a plasma concentration-time curve over a time period t ($\text{AUC}_{(t)}$), area under a plasma concentration-time curve to infinite time ($\text{AUC}_{(\text{inf})}$), maximum plasma concentration (C_{max}), and/or drug half-life ($t_{1/2}$). In some embodiments, in conjunction with the embodiments above or below, the pharmacokinetic profile of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) is determined in a mammal. In some embodiments, in conjunction with the embodiments above or below, the pharmacokinetic profile of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) is determined in a murine subject. In some embodiments, in conjunction with the embodiments above or below, the pharmacokinetic profile of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) is determined in a human subject.

[0152] In some aspects, provided herein is a solid pharmaceutical formulation comprising the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation, when administered to a murine subject, is effective to provide a maximum plasma concentration (C_{max}) of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in the subject of about 5000 ng/mL to about 20000 ng/mL (*e.g.*, about 5000 ng/mL to about 15000 ng/mL, about 7000 ng/mL to about 13000 ng/mL,

about 9000 ng/mL to about 11000 ng/mL, or about 10000 ng/mL). In some embodiments, the solid pharmaceutical formulation, when administered to a murine subject, is effective to provide a $C_{\max}$ of about 8000 ng/mL to about 12000 ng/mL. In some embodiments, the solid pharmaceutical formulation, when administered to a murine subject, is effective to provide a $C_{\max}$ of about 10000 ng/mL.

[0153] In some aspects, provided herein is a solid pharmaceutical formulation comprising the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation, when administered to a human subject, is effective to provide a maximum plasma concentration ($C_{\max}$) of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in the subject of about 1.5 $\mu\text{mol/mL}$ to about 5.0 $\mu\text{mol/mL}$ (*e.g.*, about 1.5 $\mu\text{mol/mL}$ to about 4.5 $\mu\text{mol/mL}$, about 1.5 $\mu\text{mol/mL}$ to about 4.0 $\mu\text{mol/mL}$, about 2.0 $\mu\text{mol/mL}$ to about 3.5 $\mu\text{mol/mL}$, or about 2.7 $\mu\text{mol/mL}$). In some embodiments, the solid pharmaceutical formulation, when administered to a human subject, is effective to provide a $C_{\max}$ of about 2.0 $\mu\text{mol/mL}$ to about 3.5 $\mu\text{mol/mL}$. In some embodiments, the solid pharmaceutical formulation, when administered to a human subject, is effective to provide a $C_{\max}$ of about 2.7 $\mu\text{mol/mL}$.

[0154] In some embodiments, the solid pharmaceutical formulation, when administered to a murine subject, is effective to achieve the $C_{\max}$ at about 0.5 to about 2 hours (*e.g.*, about 0.5 hour to 1.5 hours, about 0.7 hour to 1.3 hours, or about 0.9 to about 1.1 hours after administration of the formulation. In some embodiments, the solid pharmaceutical formulation, when administered to a murine subject, is effective to achieve the $C_{\max}$ at about 0.8 hours to about 1.2 hours. In some embodiments, the solid pharmaceutical formulation, when administered to a murine subject, is effective to achieve the $C_{\max}$ at about 1.0 hours.

[0155] In some embodiments, the solid pharmaceutical formulation, when administered to a human subject, is effective to achieve the $C_{\max}$ at about 2 to about 10 hours (*e.g.*, about 2 hour to 8 hours, about 3 hour to 7 hours, or about 4 to about 6 hours after administration of the formulation. In some embodiments, the solid pharmaceutical formulation, when administered to a human subject, is effective to achieve the $C_{\max}$ at about 4 hours to about 6 hours. In some embodiments, the solid pharmaceutical formulation, when administered to a human subject, is effective to achieve the $C_{\max}$ at about 5.4 hours.

[0156] In some embodiments, the solid pharmaceutical formulation described herein, when administered to a murine subject, is effective to provide a $C_{\max}$ of the compound of Formula

(A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in the subject at about 0.5 to about 2 hours after administration of the formulation, wherein the $C_{\max}$ is from about 5000 ng/mL to about 15000 ng/mL. In some embodiments, the solid pharmaceutical formulation described herein, when administered to a murine subject, is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in the subject from about 0.8 to about 1.2 hours after administration of the formulation, wherein the $C_{\max}$ is from about 7000 ng/mL to about 12000 ng/mL. In some embodiments, the solid pharmaceutical formulation described herein, when administered to a murine subject, is effective to provide a $C_{\max}$ of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in the subject from about 1 hours after administration of the formulation, wherein the $C_{\max}$ is about 10000 ng/mL.

[0157] In some other aspects, provided herein is a solid pharmaceutical formulation comprising the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation is effective to achieve an area under a plasma concentration-time curve between 0 to 24 hours (AUC_{0-24}) of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in a murine subject of about 20000 ng·h/mL to about 70000 ng·h/mL (*e.g.*, about 30000 ng·h/mL to about 60000 ng·h/mL, about 40000 ng·h/mL to about 60000 ng·h/mL, or about 50000 ng·h/mL). In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in a murine subject of about 30000 ng·h/mL to about 70000 ng·h/mL. In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} of at least 30000 ng·h/mL (*e.g.*, at least 35000 ng·h/mL, at least 40000 ng·h/mL, at least 45000 ng·h/mL, at least 50000 ng·h/mL, or at least 55000 ng·h/mL). In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} in a murine subject of no more than 70000 ng·h/mL (*e.g.*, no more than 70000 ng·h/mL, no more than 65000 ng·h/mL, no more than 60000 ng·h/mL, or no more than 55000 ng·h/mL).

[0158] In some other aspects, provided herein is a solid pharmaceutical formulation comprising the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or pharmaceutically acceptable salt thereof, wherein the solid pharmaceutical formulation is effective to achieve an area under a plasma concentration-time curve between 0 to 24 hour (AUC_{0-24}) of the compound of Formula (A) (*e.g.*, compound of

Formula (A-1), Formula (A-2), or Formula (A-3)) in a human subject of about 10 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ to about 100 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ (*e.g.*, about 10 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ to about 80 $\mu\text{mol}\cdot\text{hr}/\text{mL}$, about 20 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ to about 70 $\mu\text{mol}\cdot\text{hr}/\text{mL}$, or about 50 $\mu\text{mol}\cdot\text{hr}/\text{mL}$). In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} of the compound of Formula (A) (*e.g.*, compound of Formula (A-1), Formula (A-2), or Formula (A-3)) in a human subject of about 10 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ to about 100 $\mu\text{mol}\cdot\text{hr}/\text{mL}$. In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} in a human subject of at least 20 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ (*e.g.*, at least 30 $\mu\text{mol}\cdot\text{hr}/\text{mL}$, or at least 40 $\mu\text{mol}\cdot\text{hr}/\text{mL}$). In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} in a human subject of no more than 70 $\mu\text{mol}\cdot\text{hr}/\text{mL}$ (*e.g.*, no more than 60 $\mu\text{mol}\cdot\text{hr}/\text{mL}$, or no more than 50 $\mu\text{mol}\cdot\text{hr}/\text{mL}$). In some embodiments, the solid pharmaceutical formulation is effective to achieve an AUC_{0-24} in a human subject of about 40 $\mu\text{mol}\cdot\text{hr}/\text{mL}$.

II-e. Method of Preparation

[0159] Also provided herein is a process of preparing the solid pharmaceutical formulations described herein. In some embodiments, the process comprises spray-drying a solution of a compound of Formula (A) (*e.g.*, a compound of Formula (A-1), Formula (A-2), or Formula (A-3)) to obtain an amorphous solid dispersion of a compound of Formula (A) (*e.g.*, a compound of Formula (A-1), Formula (A-2), or Formula (A-3)).

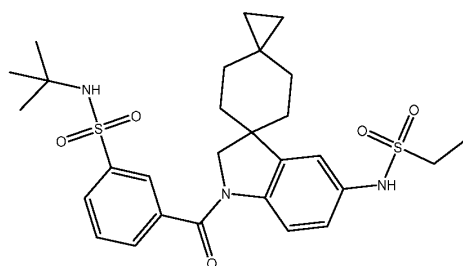
[0160] Spray-dried solid dispersion or spray-dried dispersion (SDD) is a solid dispersion produced using spray-drying technology. Spray drying processes generally involve breaking up liquid mixtures from a solution into small droplets, a step also known as atomization, and rapidly removing solvent from the mixture in a container (*e.g.*, a spray-drying apparatus), where a strong driving force is provided to evaporate solvent from the droplets. A portion of the driving force for evaporation of solvent from the droplets may be provided by heating the solution. Spray-drying processes and spray-drying equipment or apparatus are described generally in, for example, Perry's Chemical Engineers' Handbook (Eighth Edition 2007). The strong driving force for solvent evaporation is generally provided by maintaining the partial pressure of solvent in the spray-drying apparatus well below the vapor pressure of the solvent at the temperature of the drying droplets. The strong driving force for solvent evaporation may be accomplished by (1) maintaining the pressure in the spray-drying apparatus at a

partial vacuum (*e.g.*, 0.01 to 0.50 atm); (2) mixing the liquid droplets with a warm drying gas; or the combination of both (1) and (2).

[0161] In some embodiments, the process comprises spray-drying a solution comprising: (i) a compound of Formula (A) (*e.g.*, a compound of Formula (A-1), Formula (A-2), or Formula (A-3)) or a pharmaceutically acceptable salt thereof; (ii) a polymer; and (iii) a solvent. In some embodiments, the process comprises (1) preparing a solution comprising (i) a compound of Formula (A) (*e.g.*, a Formula (A-1), Formula (A-2), or Formula (A-3)) or a pharmaceutically acceptable salt thereof; (ii) a polymer; and (iii) a solvent; (2) spray-drying the solution to obtain a powder; and optionally (3) further drying the powder of step (2) under heat. In some embodiments, the solvent comprises dichloromethane (DCM). In some embodiments, the solvent comprises alcohol. In some embodiments, the solvent comprises methanol. In some embodiments, the solvent comprises DCM and methanol. In some embodiments, the solvent comprises water. In some embodiments, the solvent comprises acetone. In some embodiments, the solvent comprises acetone and water. In some embodiments, the solvent is a mixture of acetone and water, optionally in a volume ratio of about 50:1 to about 1:50, such as about any of 30:1 to 1:30, 30:1 to 1:10, 30:1 to 1:1, 20:1 to 1:1, 15:1 to 1:1, 10:1 to 1:10, 10:1 to 1:1, 10:1 to 5:1, 12:1, 11:1, 10:1, 9:1, 8:1, 7:1, 6:1, or 5:1. In some embodiments, the solvent is a mixture of DCM and methanol in a weight ratio of about 70:30 to about 90:10. In some embodiments, the solvent is a mixture of DCM and methanol in a weight ratio of about 87:13. In some embodiments, the polymer comprises HPMCAS-M. In some embodiments, the polymer comprises methacrylic acid-ethyl acrylate copolymer (1:1) (available as Eudragit® L 100-55). In some embodiments, the polymer comprises HPMC E3LV. In some embodiments, the polymer comprises HPMCP-HP55.

III. Polymorphic Forms

[0162] In one aspect, provided herein are polymorphic forms of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, also referred herein as a compound of Formula (A-1), having the structure shown below,



(A-1).

[0163] In some embodiments, compound of Formula (A-1) is also referred to as N-(tert-butyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide.

[0164] The polymorphs may have properties such as bioavailability and stability under certain conditions that are suitable for medical or pharmaceutical uses.

[0165] A polymorph of the compound of Formula (A-1) may provide the advantages of bioavailability and stability and may be suitable for use as an active agent in a pharmaceutical composition. Variations in the crystal structure of a pharmaceutical drug substance may affect the dissolution rate (which may affect bioavailability, *etc.*), manufacturability (*e.g.*, ease of handling, ease of purification, ability to consistently prepare doses of known strength, *etc.*) and stability (*e.g.*, thermal stability, shelf life (including resistance to degradation), *etc.*) of a pharmaceutical drug product. Such variations may affect the methods of preparation or formulation of pharmaceutical compositions in different dosage or delivery forms, such as solid oral dosage forms including tablets and capsules. Compared to other forms such as non-crystalline or amorphous forms, polymorphs may provide desired or suitable hygroscopicity or lack thereof, particle size control, dissolution rate, solubility, purity, physical and chemical stability, manufacturability, yield, reproducibility, and/or process control. Thus, polymorphs of the compound of Formula (A-1) may provide advantages of improving the manufacturing process of the active agent or the stability or storability of a drug product form of the active agent, or having suitable bioavailability and/or stability as an active agent.

[0166] The use of certain conditions, such as the use of different solvents and/or temperatures, may produce different polymorphs of the compound of Formula (A-1) or a solvate thereof, including the polymorphic Form A and polymorphic form C described herein, which may exhibit one or more favorable characteristics described herein. The processes for the preparation of the polymorphs described herein and characterization of these polymorphs are described in greater detail below.

III-a. Polymorphic Form A (Free-Form Pattern A)

[0167] In some embodiments, provided herein is polymorphic Form A of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form A hereinafter. In some embodiments, polymorphic Form A may also be referred to as polymorphic Form I.

[0168] In some embodiments, polymorphic Form A has an XRPD pattern substantially as shown in **FIG. 2**.

[0169] Angles 2-theta and relative peak intensities observed for polymorphic Form A using XRPD are shown in Table III-1.

Table III-1

2θ (°)	d space (Å)	Relative Intensity (%)
6.13±0.20	14.406±0.470	22
7.50±0.20	11.778±0.314	5
8.61±0.20	10.262±0.238	35
10.37±0.20	8.524±0.164	29
10.59±0.20	8.347±0.157	16
12.30±0.20	7.190±0.116	19
12.80±0.20	6.910±0.108	9
13.54±0.20	6.534±0.096	95
14.34±0.20	6.172±0.086	12
15.04±0.20	5.886±0.078	30
15.46±0.20	5.727±0.074	36
16.05±0.20	5.518±0.068	22
17.29±0.20	5.125±0.059	39
17.89±0.20	4.954±0.055	100
18.39±0.20	4.821±0.052	93
19.01±0.20	4.665±0.049	26
19.39±0.20	4.574±0.047	64
19.73±0.20	4.496±0.045	61
19.86±0.20	4.467±0.045	29
20.44±0.20	4.341±0.042	3
20.84±0.20	4.259±0.040	17
21.61±0.20	4.109±0.038	19
22.13±0.20	4.014±0.036	12
22.65±0.20	3.923±0.034	15
22.98±0.20	3.867±0.033	26
23.41±0.20	3.797±0.032	15
23.68±0.20	3.754±0.031	11
24.78±0.20	3.590±0.029	6
25.04±0.20	3.553±0.028	11
25.46±0.20	3.496±0.027	7
25.78±0.20	3.453±0.026	6
26.16±0.20	3.404±0.026	8

26.91±0.20	3.311±0.024	13
27.39±0.20	3.254±0.023	8
27.51±0.20	3.240±0.023	12
27.78±0.20	3.209±0.023	5
27.99±0.20	3.185±0.022	6
28.22±0.20	3.160±0.022	6
28.54±0.20	3.125±0.021	13
28.92±0.20	3.085±0.021	16
29.74±0.20	3.002±0.020	5
29.92±0.20	2.984±0.019	3
30.19±0.20	2.958±0.019	2
30.66±0.20	2.914±0.019	3
30.95±0.20	2.887±0.018	3
31.20±0.20	2.864±0.018	4
31.44±0.20	2.843±0.018	7
32.18±0.20	2.779±0.017	5
32.38±0.20	2.763±0.017	7
33.60±0.20	2.665±0.015	6
34.01±0.20	2.634±0.015	6
35.00±0.20	2.561±0.014	3
35.58±0.20	2.521±0.014	4
36.25±0.20	2.476±0.013	7
36.56±0.20	2.456±0.013	3
36.76±0.20	2.443±0.013	4
37.09±0.20	2.422±0.013	8
37.99±0.20	2.367±0.012	7
38.36±0.20	2.344±0.012	3
39.12±0.20	2.301±0.011	4

[0170] In some embodiments, polymorphic Form A has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 2** or as provided in Table III-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form A, can vary by about ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0171] In some embodiments, polymorphic Form A has an XRPD pattern comprising peaks at angles 2-theta of 13.54 ± 0.20 , 17.89 ± 0.20 , 18.39 ± 0.20 , 19.39 ± 0.20 , and 19.73 ± 0.20 degrees. In some embodiments, the polymorphic Form A has an XRPD pattern comprising

additional peaks at angles 2-theta of 15.46 ± 0.20 and 17.29 ± 0.20 degrees. In some embodiments, polymorphic Form A has an XRPD pattern further comprising additional peaks at angles 2-theta of 8.61 ± 0.20 and 15.04 ± 0.20 degrees. In some embodiments, polymorphic Form A has an XRPD pattern comprising peaks at angles 2-theta of 6.13 ± 0.20 , 8.61 ± 0.20 , 10.37 ± 0.20 , 12.30 ± 0.20 , 13.54 ± 0.20 , 15.04 ± 0.20 , 15.46 ± 0.20 , 16.05 ± 0.20 , 17.29 ± 0.20 , 17.89 ± 0.20 , 18.39 ± 0.20 , 19.01 ± 0.20 , 19.39 ± 0.20 , 19.73 ± 0.20 , 19.86 ± 0.20 , 22.98 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 2** or as provided in Table III-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0172] In some embodiments, polymorphic Form A has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 3**. In some embodiments, polymorphic Form A is characterized as having an endotherm onset at about $188\text{ }^{\circ}\text{C}$ as determined by DSC. In some embodiments, polymorphic Form A is characterized as having an endotherm onset at $188\pm2\text{ }^{\circ}\text{C}$ (*e.g.*, $188\pm1.9\text{ }^{\circ}\text{C}$, $188\pm1.8\text{ }^{\circ}\text{C}$, $188\pm1.7\text{ }^{\circ}\text{C}$, $188\pm1.6\text{ }^{\circ}\text{C}$, $188\pm1.5\text{ }^{\circ}\text{C}$, $188\pm1.4\text{ }^{\circ}\text{C}$, $188\pm1.3\text{ }^{\circ}\text{C}$, $188\pm1.2\text{ }^{\circ}\text{C}$, $188\pm1.1\text{ }^{\circ}\text{C}$, $188\pm1.0\text{ }^{\circ}\text{C}$, $188\pm0.9\text{ }^{\circ}\text{C}$, $188\pm0.8\text{ }^{\circ}\text{C}$, $188\pm0.7\text{ }^{\circ}\text{C}$, $188\pm0.6\text{ }^{\circ}\text{C}$, $188\pm0.5\text{ }^{\circ}\text{C}$, $188\pm0.4\text{ }^{\circ}\text{C}$, $188\pm0.3\text{ }^{\circ}\text{C}$, $188\pm0.2\text{ }^{\circ}\text{C}$, or $188\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC. In some embodiments, Form A is characterized as having an endotherm peak at about $194\text{ }^{\circ}\text{C}$ as determined by DSC. In some embodiments, Form A is characterized as having an endotherm peak at $194\pm2\text{ }^{\circ}\text{C}$ (*e.g.*, $194\pm1.9\text{ }^{\circ}\text{C}$, $194\pm1.8\text{ }^{\circ}\text{C}$, $194\pm1.7\text{ }^{\circ}\text{C}$, $194\pm1.6\text{ }^{\circ}\text{C}$, $194\pm1.5\text{ }^{\circ}\text{C}$, $194\pm1.4\text{ }^{\circ}\text{C}$, $194\pm1.3\text{ }^{\circ}\text{C}$, $194\pm1.2\text{ }^{\circ}\text{C}$, $194\pm1.1\text{ }^{\circ}\text{C}$, $194\pm1.0\text{ }^{\circ}\text{C}$, $194\pm0.9\text{ }^{\circ}\text{C}$, $194\pm0.8\text{ }^{\circ}\text{C}$, $194\pm0.7\text{ }^{\circ}\text{C}$, $194\pm0.6\text{ }^{\circ}\text{C}$, $194\pm0.5\text{ }^{\circ}\text{C}$, $194\pm0.4\text{ }^{\circ}\text{C}$, $194\pm0.3\text{ }^{\circ}\text{C}$, $194\pm0.2\text{ }^{\circ}\text{C}$, or $194\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC.

[0173] In some embodiments, polymorphic Form A has a thermographic analysis (TGA) graph substantially as shown in **FIG. 3**. In some embodiments, polymorphic Form A exhibits a weight loss of about 0.01% or $0.01\%\pm0.005\%$ (*e.g.*, $0.01\%\pm0.004\%$, $0.01\%\pm0.003\%$, $0.01\%\pm0.002\%$, or $0.01\%\pm0.001\%$) between $52\text{ }^{\circ}\text{C}$ and $150\text{ }^{\circ}\text{C}$ as determined by TGA. In some embodiments, polymorphic Form A exhibits an apparent decomposition at $316\pm5\text{ }^{\circ}\text{C}$ (*e.g.*, $316\pm4.5\text{ }^{\circ}\text{C}$, $316\pm4.0\text{ }^{\circ}\text{C}$, $316\pm3.5\text{ }^{\circ}\text{C}$, $316\pm3.0\text{ }^{\circ}\text{C}$, $316\pm2.5\text{ }^{\circ}\text{C}$, $316\pm2.0\text{ }^{\circ}\text{C}$, $316\pm1.9\text{ }^{\circ}\text{C}$, $316\pm1.8\text{ }^{\circ}\text{C}$, $316\pm1.7\text{ }^{\circ}\text{C}$, $316\pm1.6\text{ }^{\circ}\text{C}$, $316\pm1.5\text{ }^{\circ}\text{C}$, $316\pm1.4\text{ }^{\circ}\text{C}$, $316\pm1.3\text{ }^{\circ}\text{C}$, $316\pm1.2\text{ }^{\circ}\text{C}$, $316\pm1.1\text{ }^{\circ}\text{C}$, $316\pm1.0\text{ }^{\circ}\text{C}$, $316\pm0.9\text{ }^{\circ}\text{C}$, $316\pm0.8\text{ }^{\circ}\text{C}$, $316\pm0.7\text{ }^{\circ}\text{C}$, $316\pm0.6\text{ }^{\circ}\text{C}$, $316\pm0.5\text{ }^{\circ}\text{C}$, $316\pm0.4\text{ }^{\circ}\text{C}$, $316\pm0.3\text{ }^{\circ}\text{C}$, $316\pm0.2\text{ }^{\circ}\text{C}$, or $316\pm0.1\text{ }^{\circ}\text{C}$).

[0174] In some embodiments, polymorphic Form A has a Dynamic Vapor Sorption (DVS) graph substantially as shown in **FIG. 4**. In some embodiments, polymorphic Form A exhibits a weight gain of about 0.095% or 0.095%±0.005% (*e.g.*, 0.095%±0.004%, 0.095%±0.003%, 0.095%±0.002%, or 0.095%±0.001%) from 5% relative humidity (RH) to 95% RH, as determined by DVS. In some embodiments, polymorphic Form A exhibits a weight loss of about 0.097% or 0.097%±0.005% (*e.g.*, 0.097%±0.004%, 0.097%±0.003%, 0.097%±0.002%, or 0.097%±0.001%) from 95% RH to 5% RH, as determined by DVS.

[0175] In some embodiments, polymorphic Form A shows substantially no changes or no changes before and after the DVS measurement as determined by XRPD.

[0176] In some embodiments of polymorphic Form A, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or all of the following (a)-(k) apply:

(a) polymorphic Form A has an XRPD pattern comprising peaks at angles 2-theta of 13.54±0.20, 17.89±0.20, 18.39±0.20, 19.39±0.20, and 19.73±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 15.46±0.20 and 17.29±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 8.61±0.20 and 15.04±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.13±0.20, 8.61±0.20, 10.37±0.20, 12.30±0.20, 13.54±0.20, 15.04±0.20, 15.46±0.20, 16.05±0.20, 17.29±0.20, 17.89±0.20, 18.39±0.20, 19.01±0.20, 19.39±0.20, 19.73±0.20, 19.86±0.20, 22.98±0.20 degrees;

(b) polymorphic Form A has an XRPD pattern substantially as shown in **FIG. 2**;

(c) polymorphic Form A has a DSC graph substantially as shown in **FIG. 3**;

(d) polymorphic Form A is characterized as having an endotherm onset at 188±2 °C as determined by DSC;

(e) polymorphic Form A is characterized as having an endotherm peak at 194±2 °C as determined by DSC;

(f) polymorphic Form A has a TGA graph substantially as shown in **FIG. 3**;

(g) polymorphic Form A has a weight loss of about 0.01% or 0.01%±0.005% between 52 °C and 150 °C as determined by TGA;

(h) polymorphic Form A has an apparent decomposition at 316±5 °C;

(i) polymorphic Form A has a DVS graph substantially as shown in **FIG. 4**.

(j) polymorphic Form A has a weight gain of about 0.095% or 0.095%±0.005% from 5% RH to 95% RH, as determined by DVS;

(k) polymorphic Form A has a weight loss of about 0.097% or 0.097%±0.005% from 95% RH to 5% RH, as determined by DVS.

III-b. Polymorphic Form B (Free-Form Pattern B)

[0177] In some embodiments, provided herein is polymorphic Form B of N-(1"-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide, which is referred to as polymorphic Form B hereinafter. In some embodiments, polymorphic Form B comprises less than 10% w/w (e.g., less than any of 8% w/w, 5% w/w, 3% w/w, 2% w/w, 1% w/w, 0.5% w/w, 0.1% w/w, 0.05% w/w, or 0.01% w/w) water. In some embodiments, polymorphic Form B is substantially free of water. In some embodiments, polymorphic Form B comprises about 0.01% to 1% w/w (e.g., about any of 0.01% to 0.5% w/w, 0.02% to 0.2% w/w, 0.02% to 0.1% w/w, 0.05% to 0.1% w/w, or 0.07% w/w) acetonitrile.

[0178] In some embodiments, polymorphic Form B has an XRPD pattern substantially as shown in **FIG. 10**.

[0179] Angles 2-theta and relative peak intensities observed for polymorphic Form B using XRPD are shown in Table III-1.

Table III-1

2θ (°)	d space (Å)	Intensity (%)
8.23	10.740	29.7
9.05	9.759	1.9
9.94	8.893	3.8
10.80	8.189	0.6
11.17	7.918	2.1
11.72	7.543	23.5
12.89	6.862	18.6
13.15	6.729	6.6
13.41	6.595	4.4
14.83	5.968	2.9
15.62	5.671	100.0
16.60	5.336	34.4
16.83	5.264	17.6
17.28	5.129	2.4
17.50	5.064	30.3
17.65	5.020	10.5
18.18	4.876	2.1

18.60	4.766	13.5
18.77	4.724	13.0
19.12	4.639	20.9
19.87	4.465	54.7
20.11	4.412	59.6
20.81	4.266	2.7
21.13	4.201	31.6
21.61	4.108	2.8
22.07	4.024	7.7
22.55	3.941	5.8
22.83	3.892	3.5
22.96	3.870	6.5
23.29	3.817	7.8
23.51	3.781	1.7
24.88	3.575	15.9
25.17	3.536	3.6
25.76	3.456	40.8
26.49	3.362	16.4
27.29	3.266	8.6
27.53	3.237	2.1
27.70	3.218	2.4
28.31	3.149	13.2
28.69	3.109	1.1
29.21	3.055	2.5
29.39	3.037	3.3
29.55	3.021	4.6
29.92	2.984	5.4
30.64	2.915	1.6
31.13	2.871	23.0
31.46	2.841	7.5
32.02	2.793	1.1
32.99	2.713	2.8
33.18	2.698	3.2
33.97	2.637	2.8
34.30	2.612	3.8
34.72	2.582	1.1
35.63	2.518	0.8
35.95	2.496	4.0
36.79	2.441	1.2

37.11	2.421	0.2
37.65	2.387	0.8
38.22	2.353	0.8
38.71	2.324	1.4

[0180] In some embodiments, polymorphic Form B has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 10** or as provided in Table III-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form B, can vary by about ± 1 degrees, ± 0.8 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0181] In some embodiments, polymorphic Form B has an XRPD pattern comprising peaks at angles 2-theta of 15.62 ± 0.20 , 16.60 ± 0.20 , 19.87 ± 0.20 , 20.11 ± 0.20 , and 25.76 ± 0.20 degrees. In some embodiments, the polymorphic Form B has an XRPD pattern comprising additional peaks at angles 2-theta of 17.50 ± 0.20 and 21.13 ± 0.20 degrees. In some embodiments, polymorphic Form B has an XRPD pattern further comprising additional peaks at angles 2-theta of 8.23 ± 0.20 and 11.72 ± 0.20 degrees. In some embodiments, polymorphic Form B has an XRPD pattern comprising peaks at angles 2-theta of 8.23 ± 0.20 , 11.72 ± 0.20 , 12.89 ± 0.20 , 15.62 ± 0.20 , 16.60 ± 0.20 , 16.83 ± 0.20 , 17.50 ± 0.20 , 18.60 ± 0.20 , 19.12 ± 0.20 , 19.87 ± 0.20 , 20.11 ± 0.20 , 21.13 ± 0.20 , 24.88 ± 0.20 , 25.76 ± 0.20 , 26.49 ± 0.20 , and 31.13 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 10** or as provided in Table III-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0182] In some embodiments, polymorphic Form B has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 11**. In some embodiments, polymorphic Form B is characterized as having an endotherm onset at about 196°C as determined by DSC. In some embodiments, polymorphic Form B is characterized as having an endotherm onset at $196 \pm 2^\circ\text{C}$ (e.g., $196 \pm 1.9^\circ\text{C}$, $196 \pm 1.8^\circ\text{C}$, $196 \pm 1.7^\circ\text{C}$, $196 \pm 1.6^\circ\text{C}$, $196 \pm 1.5^\circ\text{C}$, $196 \pm 1.4^\circ\text{C}$, $196 \pm 1.3^\circ\text{C}$, $196 \pm 1.2^\circ\text{C}$, $196 \pm 1.1^\circ\text{C}$, $196 \pm 1.0^\circ\text{C}$, $196 \pm 0.9^\circ\text{C}$, $196 \pm 0.8^\circ\text{C}$, $196 \pm 0.7^\circ\text{C}$,

196±0.6 °C, 196±0.5 °C, 196±0.4 °C, 196±0.3 °C, 196±0.2 °C, or 196±0.1 °C) as determined by DSC. In some embodiments, Form B is characterized as having an endotherm peak at about 197 °C as determined by DSC. In some embodiments, Form B is characterized as having an endotherm peak at 197±2 °C (*e.g.*, 197±1.9 °C, 197±1.8 °C, 197±1.7 °C, 197±1.6 °C, 197±1.5 °C, 197±1.4 °C, 197±1.3 °C, 197±1.2 °C, 197±1.1 °C, 197±1.0 °C, 197±0.9 °C, 197±0.8 °C, 197±0.7 °C, 197±0.6 °C, 197±0.5 °C, 197±0.4 °C, 197±0.3 °C, 197±0.2 °C, or 197±0.1 °C) as determined by DSC.

[0183] In some embodiments, polymorphic Form B has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 12**. In some embodiments, polymorphic Form B exhibits a weight loss of about 0.05% or 0.05%±0.01% (*e.g.*, 0.05%±0.005%, 0.05%±0.004%, 0.05%±0.003%, 0.05%±0.002%, or 0.05%±0.001%) from about 25 °C to about 100 °C (*e.g.*, 100±5 °C, 100±4.5 °C, 100±4.0 °C, 100±3.5 °C, 100±3.0 °C, 100±2.5 °C, 100±2.0 °C, 100±1.9 °C, 100±1.8 °C, 100±1.7 °C, 100±1.6 °C, 100±1.5 °C, 100±1.4 °C, 100±1.3 °C, 100±1.2 °C, 100±1.1 °C, 100±1.0 °C, 100±0.9 °C, 100±0.8 °C, 100±0.7 °C, 100±0.6 °C, 100±0.5 °C, 100±0.4 °C, 100±0.3 °C, 100±0.2 °C, or 100±0.1 °C) as determined by TGA. In some embodiments, polymorphic Form B exhibits a weight loss of about 0.1% or 0.1%±0.05% (*e.g.*, 0.1%±0.04%, 0.1%±0.03%, 0.1%±0.03%, 0.1%±0.01%, or 0.1%±0.001%) about 100 °C to about 180 °C.

[0184] In some embodiments, polymorphic Form B has a Dynamic Vapor Sorption (DVS) graph substantially as shown in **FIG. 13**. In some embodiments, polymorphic Form B exhibits a weight gain of about 0.03% or 0.03 %±0.005% (*e.g.*, 0.03%±0.004%, 0.03%±0.003%, 0.03%±0.002%, or 0.03%±0.001%) from 0.1 % relative humidity (RH) to 95% RH, as determined by DVS. In some embodiments, polymorphic Form B exhibits a weight loss of about 0.05% or 0.05%±0.005% (*e.g.*, 0.05%±0.004%, 0.05%±0.003%, 0.05%±0.002%, or 0.05%±0.001%) from 95 % relative humidity (RH) to 0.1% RH, as determined by DVS.

[0185] In some embodiments, polymorphic Form B shows substantially no changes or no changes before and after the DVS measurement as determined by XRPD.

[0186] In some embodiments of polymorphic Form B, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, or all of the following (a)-(k) apply:

(a) polymorphic Form B has an XRPD pattern comprising peaks at angles 2-theta of 15.62±0.20, 16.60±0.20, 19.87±0.20, 20.11±0.20, and 25.76±0.20 degrees; an XRPD pattern

comprising additional peaks at angles 2-theta of 17.50 ± 0.20 and 21.13 ± 0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 8.23 ± 0.20 and 11.72 ± 0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 8.23 ± 0.20 , 11.72 ± 0.20 , 12.89 ± 0.20 , 15.62 ± 0.20 , 16.60 ± 0.20 , 16.83 ± 0.20 , 17.50 ± 0.20 , 18.60 ± 0.20 , 19.12 ± 0.20 , 19.87 ± 0.20 , 20.11 ± 0.20 , 21.13 ± 0.20 , 24.88 ± 0.20 , 25.76 ± 0.20 , 26.49 ± 0.20 , and 31.13 ± 0.20 degrees;

(b) polymorphic Form B has an XRPD pattern substantially as shown in **FIG. 10**;

(c) polymorphic Form B has a DSC graph substantially as shown in **FIG. 11**;

(d) polymorphic Form B is characterized as having an endotherm onset at 196 ± 2 °C as determined by DSC;

(e) polymorphic Form B is characterized as having an endotherm peak at 197 ± 2 °C as determined by DSC;

(f) polymorphic Form B has a TGA graph substantially as shown in **FIG. 12**;

(g) polymorphic Form B has a weight loss of about 0.05% or $0.05\% \pm 0.01\%$ between 25 and 100°C as determined by TGA;

(h) polymorphic Form B has a weight loss of about 0.1% or $0.1\% \pm 0.01\%$ between 100 and 180°C as determined by TGA;

(i) polymorphic Form B has a DVS graph substantially as shown in **FIG. 13**;

(j) polymorphic Form B has a weight gain of about 0.030% or $0.030\% \pm 0.005\%$ from 0.1 % RH to 95 % RH, as determined by DVS; and

(k) polymorphic Form B has a weight loss of about 0.050% or $0.050\% \pm 0.005\%$ from 95% RH to 0.1% RH, as determined by DVS.

III-c. Polymorphic Form C (Amorphous Free-Form)

[0187] In some embodiments, provided herein is a polymorphic Form C of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide (*i.e.*, compound of Formula (A-1)), which is referred to as polymorphic Form C hereinafter. In some embodiments, the polymorphic Form C can also be referred to as polymorphic Form II.

[0188] In some embodiments, polymorphic Form C is substantially amorphous. In some embodiments, polymorphic Form C is a solvate of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-

5"-yl)ethanesulfonamide (*i.e.*, compound of Formula (A-1)) with DMF and/or water. In some embodiments, polymorphic Form C comprises DMF and a compound of Formula (A-1), wherein the molar ratio between DMF and the compound of Formula (A-1) is about 0.12:1. In some embodiments, polymorphic Form C comprises DMF and a compound of Formula (A-1), wherein the weight ratio of DMF is about 1.5 wt.%. In some embodiments, polymorphic Form C comprises water and a compound of Formula (A-1), wherein the weight ratio of water is about 0.5 wt.%.

[0189] In some embodiments, polymorphic Form C has an XRPD pattern substantially as shown in **FIG. 5**. In some embodiments, polymorphic Form C has an XRPD pattern without recognizable characteristic peaks of a crystalline phase.

[0190] In some embodiments, polymorphic Form C has a TGA graph substantially as shown in **FIG. 6**. In some embodiments, polymorphic Form C exhibits a weight loss of about 0.9% or $0.9\% \pm 0.1\%$ (*e.g.*, $0.9\% \pm 0.09\%$, $0.9\% \pm 0.08\%$, $0.9\% \pm 0.07\%$, $0.9\% \pm 0.06\%$, $0.9\% \pm 0.05\%$, $0.9\% \pm 0.04\%$, $0.9\% \pm 0.03\%$, $0.9\% \pm 0.02\%$, or $0.9\% \pm 0.01\%$) between 53 °C and 120 °C, as determined by TGA. In some embodiments, polymorphic Form C exhibits a weight loss of about 1.1% or $1.1\% \pm 0.1\%$ (*e.g.*, $1.1\% \pm 0.09\%$, $1.1\% \pm 0.08\%$, $1.1\% \pm 0.07\%$, $1.1\% \pm 0.06\%$, $1.1\% \pm 0.05\%$, $1.1\% \pm 0.04\%$, $1.1\% \pm 0.03\%$, $1.1\% \pm 0.02\%$, or $1.1\% \pm 0.01\%$) between 120 °C and 200 °C, as determined by TGA. In some embodiments, polymorphic Form C has a weight loss of about 0.9% or $0.9\% \pm 0.1\%$ (*e.g.*, $0.9\% \pm 0.09\%$, $0.9\% \pm 0.08\%$, $0.9\% \pm 0.07\%$, $0.9\% \pm 0.06\%$, $0.9\% \pm 0.05\%$, $0.9\% \pm 0.04\%$, $0.9\% \pm 0.03\%$, $0.9\% \pm 0.02\%$, or $0.9\% \pm 0.01\%$) between 53 °C and 120 °C, and a weight loss of about 1.1% or $1.1\% \pm 0.1\%$ (*e.g.*, $1.1\% \pm 0.09\%$, $1.1\% \pm 0.08\%$, $1.1\% \pm 0.07\%$, $1.1\% \pm 0.06\%$, $1.1\% \pm 0.05\%$, $1.1\% \pm 0.04\%$, $1.1\% \pm 0.03\%$, $1.1\% \pm 0.02\%$, or $1.1\% \pm 0.01\%$) between 120 °C and 200 °C, as determined by TGA. In some embodiments, polymorphic Form C exhibits an apparent decomposition at 319 ± 5 °C (*e.g.*, 319 ± 4.5 °C, 319 ± 4.0 °C, 319 ± 3.5 °C, 319 ± 3.0 °C, 319 ± 2.5 °C, 319 ± 2.0 °C, 319 ± 1.9 °C, 319 ± 1.8 °C, 319 ± 1.7 °C, 319 ± 1.6 °C, 319 ± 1.5 °C, 319 ± 1.4 °C, 319 ± 1.3 °C, 319 ± 1.2 °C, 319 ± 1.1 °C, 319 ± 1.0 °C, 319 ± 0.9 °C, 319 ± 0.8 °C, 319 ± 0.7 °C, 319 ± 0.6 °C, 319 ± 0.5 °C, 319 ± 0.4 °C, 319 ± 0.3 °C, 319 ± 0.2 °C, or 319 ± 0.1 °C).

[0191] In some embodiments, polymorphic Form C has a DSC graph substantially as shown in **FIG. 7**. In some embodiments, polymorphic Form C is characterized as having a glass transition onset at 80 ± 5 °C (*e.g.*, 80 ± 4.5 °C, 80 ± 4.0 °C, 80 ± 3.5 °C, 80 ± 3.0 °C, 80 ± 2.5 °C, 80 ± 2.0 °C, 80 ± 1.9 °C, 80 ± 1.8 °C, 80 ± 1.7 °C, 80 ± 1.6 °C, 80 ± 1.5 °C, 80 ± 1.4 °C, 80 ± 1.3 °C, 80 ± 1.2 °C, 80 ± 1.1 °C, 80 ± 1.0 °C, 80 ± 0.9 °C, 80 ± 0.8 °C, 80 ± 0.7 °C, 80 ± 0.6 °C, 80 ± 0.5 °C,

80±0.4 °C, 80±0.3 °C, 80±0.2 °C, or 80±0.1 °C), as determined by TMDSC. In some embodiments, polymorphic Form C is characterized as having a glass transition midpoint at 85±5 °C (*e.g.*, 85±4.5 °C, 85±4.0 °C, 85±3.5 °C, 85±3.0 °C, 85±2.5 °C, 85±2.0 °C, 85±1.9 °C, 85±1.8 °C, 85±1.7 °C, 85±1.6 °C, 85±1.5 °C, 85±1.4 °C, 85±1.3 °C, 85±1.2 °C, 85±1.1 °C, 85±1.0 °C, 85±0.9 °C, 85±0.8 °C, 85±0.7 °C, 85±0.6 °C, 85±0.5 °C, 85±0.4 °C, 85±0.3 °C, 85±0.2 °C, or 85±0.1 °C), as determined by TMDSC. In some embodiments, the glass transition temperature of polymorphic Form C can vary because of the type and/or amount of solvents therein. In some embodiments, polymorphic Form C is characterized as having an endotherm peak at about 191 °C as determined by DSC. In some embodiments, the polymorphic Form C is characterized as having an endotherm peak at 191±2 °C (*e.g.*, 191±1.9 °C, 191±1.8 °C, 191±1.7 °C, 191±1.6 °C, 191±1.5 °C, 191±1.4 °C, 191±1.3 °C, 191±1.2 °C, 191±1.1 °C, 191±1.0 °C, 191±0.9 °C, 191±0.8 °C, 191±0.7 °C, 191±0.6 °C, 191±0.5 °C, 191±0.4 °C, 191±0.3 °C, 191±0.2 °C, or 191±0.1 °C) as determined by TMDSC. In some embodiments, part of polymorphic Form C may crystallize above glass transition temperature and converts into polymorphic Form A.

[0192] In some embodiments, polymorphic Form C has a Dynamic Vapor Sorption (DVS) graph substantially as shown in **FIG. 8**. In some embodiments, polymorphic Form C exhibits a weight gain of about 1.13% or 1.13%±0.1% (*e.g.*, 1.13%±0.09%, 1.13%±0.08%, 1.13%±0.07%, 1.13%±0.06%, 1.13%±0.05%, 1.13%±0.04%, 1.13%±0.03%, 1.13%±0.02%, or 1.13%±0.01%) from 5% relative humidity (RH) to 95% RH, as determined by DVS. In some embodiments, polymorphic Form C exhibits a weight loss of about 1.57% or 1.57%±0.1% (*e.g.*, 1.57%±0.09%, 1.57%±0.08%, 1.57%±0.07%, 1.57%±0.06%, 1.57%±0.05%, 1.57%±0.04%, 1.57%±0.03%, 1.57%±0.02%, or 1.57%±0.01%) from 95% RH to 5% RH, as determined by DVS.

[0193] In some embodiments of polymorphic Form C, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, at least ten, at least eleven, at least twelve, or all of the following (a)-(m) apply:

- (a) polymorphic Form C has an XRPD pattern without recognizable characteristic peaks of crystalline materials;
- (b) polymorphic Form C has an XRPD pattern substantially as shown in **FIG. 5**;
- (c) polymorphic Form C has a DSC graph substantially as shown in **FIG. 7**;
- (d) polymorphic Form C is characterized as having glass transition onset temperature at 80±2 °C as determined by DSC;

- (e) polymorphic Form C is characterized as having glass transition midpoint temperature at 85 ± 2 °C as determined by DSC;
- (f) polymorphic Form C is characterized as having an endotherm peak at 191 ± 2 °C as determined by DSC;
- (g) polymorphic Form C has a TGA graph substantially as shown in **FIG. 6**;
- (h) polymorphic Form C has a weight loss of about 0.9% or $0.9\% \pm 0.1\%$ between 53 °C and 120 °C as determined by TGA;
- (i) polymorphic Form C has a weight loss of about 1.1% or $1.1\% \pm 0.1\%$ between 120 °C and 200 °C as determined by TGA;
- (j) polymorphic Form C has an apparent decomposition at 319 ± 5 °C;
- (k) polymorphic Form C has a DVS graph substantially as shown in **FIG. 8**.
- (l) polymorphic Form C has a weight gain of about 1.13% or $1.13\% \pm 0.1\%$ from 5% RH to 95% RH, as determined by DVS;
- (m) polymorphic Form C has a weight loss of about 1.57% or $1.57\% \pm 0.1\%$ from 95% RH to 5% RH, as determined by DVS.

[0194] Also provided herein are compositions containing polymorphs described herein, such as polymorphic Form A, polymorphic Form C, or a mixture thereof. In some embodiments, the composition contains polymorphic Form A. In some embodiments, the composition contains polymorphic Form C. In some embodiments, the composition contains a mixture of polymorphic Form A and polymorphic Form C.

[0195] In some embodiments, provided is a composition containing polymorphic Form A of the compound of Formula (A-1). In some embodiments, the composition is substantially free of polymorphic Form C of the compound of Formula (A-1). In some embodiments, the composition is substantially free of salts of the compound of Formula (A-1).

[0196] In some embodiments of the composition containing Form A of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the total composition is polymorphic Form A. In some embodiments of the composition containing polymorphic Form A of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about

5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the compound of Formula (A-1) exists in Form A.

[0197] In some embodiments, provided is a composition containing polymorphic Form C of the compound of Formula (A-1). In some embodiments, the composition is substantially free of polymorphic Form A of the compound of Formula (A-1). In some embodiments, the composition is substantially free of salts of the compound of Formula (A-1).

[0198] In some embodiments of the composition containing Form C of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the total composition is polymorphic Form C. In some embodiments of the composition containing polymorphic Form C of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the compound of Formula (A-1) exists in Form C.

III-d. Polymorphic Form IV (Mono-Sodium Salt Pattern A)

[0199] In some embodiments, provided herein is polymorphic Form IV of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form IV hereinafter. In some embodiments, in polymorphic Form IV, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the

compound of Formula (A-1) and metal ion (e.g., Na⁺) is about 1:0.8 to about 1:1.5, or about 1:1. In some embodiments, the salt is mono-sodium salt. In some embodiments, polymorphic Form IV comprises less than 10 wt.%, such as less than about any of 8%, 6%, 4%, 2%, 1%, or 0.1% water. In some embodiments, polymorphic Form IV is an anhydrate salt of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide.

[0200] In some embodiments, polymorphic Form IV has an XRPD pattern substantially as shown in **FIG. 14**.

[0201] Angles 2-theta and relative peak intensities observed for polymorphic Form IV using XRPD are shown in Table IV-1.

Table IV-1

2θ (°)	d space (Å)	Intensity (%)
6.17	14.322	9.3
7.66	11.539	100.0
8.45	10.459	29.9
8.94	9.887	1.4
10.63	8.320	8.4
11.13	7.943	9.8
11.64	7.597	62.4
12.35	7.164	17.0
13.30	6.653	3.6
13.60	6.508	19.1
14.74	6.004	5.1
15.13	5.850	3.7
15.37	5.759	6.2
15.79	5.606	3.2
16.09	5.504	2.8
16.91	5.238	25.3
17.13	5.173	20.8
17.92	4.947	64.2
18.34	4.833	19.7
18.62	4.761	13.1
19.05	4.655	18.5
19.44	4.561	5.1
19.90	4.458	9.6
20.44	4.342	17.4
20.83	4.262	6.7

21.22	4.184	3.2
22.82	3.895	26.1
23.43	3.794	12.3
24.22	3.671	1.2
24.83	3.584	5.7
25.08	3.548	11.4
25.43	3.500	5.9
26.73	3.333	8.3
26.94	3.307	11.2
28.26	3.155	2.0
29.19	3.057	4.3
29.79	2.997	4.9
30.62	2.917	2.7
31.72	2.818	2.5
32.83	2.726	2.0
35.40	2.533	2.7
35.99	2.493	2.2
36.73	2.445	1.1
38.11	2.360	2.6

[0202] In some embodiments, polymorphic Form IV has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 14** or as provided in Table IV-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form IV, can vary by about ± 1 degrees, ± 0.8 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0203] In some embodiments, polymorphic Form IV has an XRPD pattern comprising peaks at angles 2-theta of 7.66 ± 0.20 , 8.45 ± 0.20 , 11.64 ± 0.20 , 17.92 ± 0.20 , and 22.82 ± 0.20 degrees. In some embodiments, the polymorphic Form IV has an XRPD pattern comprising additional peaks at angles 2-theta of 16.91 ± 0.20 and 17.13 ± 0.20 degrees. In some embodiments, polymorphic Form IV has an XRPD pattern further comprising additional peaks at angles 2-theta of 13.60 ± 0.20 and 18.34 ± 0.20 degrees. In some embodiments, polymorphic Form IV

has an XRPD pattern comprising peaks at angles 2-theta of 7.66 ± 0.20 , 8.45 ± 0.20 , 11.64 ± 0.20 , 12.35 ± 0.20 , 13.60 ± 0.20 , 16.91 ± 0.20 , 17.13 ± 0.20 , 17.92 ± 0.20 , 18.34 ± 0.20 , 18.62 ± 0.20 , 19.05 ± 0.20 , 20.44 ± 0.20 , 22.82 ± 0.20 , 23.43 ± 0.20 , 25.08 ± 0.20 , and 26.94 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 14** or as provided in Table IV-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0204] In some embodiments, polymorphic Form IV has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 15**. In some embodiments, polymorphic Form IV is characterized as having an endotherm onset at about $186\text{ }^{\circ}\text{C}$ as determined by DSC. In some embodiments, polymorphic Form IV is characterized as having an endotherm onset at $186\pm2\text{ }^{\circ}\text{C}$ (*e.g.*, $186\pm1.9\text{ }^{\circ}\text{C}$, $186\pm1.8\text{ }^{\circ}\text{C}$, $186\pm1.7\text{ }^{\circ}\text{C}$, $186\pm1.6\text{ }^{\circ}\text{C}$, $186\pm1.5\text{ }^{\circ}\text{C}$, $186\pm1.4\text{ }^{\circ}\text{C}$, $186\pm1.3\text{ }^{\circ}\text{C}$, $186\pm1.2\text{ }^{\circ}\text{C}$, $186\pm1.1\text{ }^{\circ}\text{C}$, $186\pm1.0\text{ }^{\circ}\text{C}$, $186\pm0.9\text{ }^{\circ}\text{C}$, $186\pm0.8\text{ }^{\circ}\text{C}$, $186\pm0.7\text{ }^{\circ}\text{C}$, $186\pm0.6\text{ }^{\circ}\text{C}$, $186\pm0.5\text{ }^{\circ}\text{C}$, $186\pm0.4\text{ }^{\circ}\text{C}$, $186\pm0.3\text{ }^{\circ}\text{C}$, $186\pm0.2\text{ }^{\circ}\text{C}$, or $186\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC. In some embodiments, Form IV is characterized as having an endotherm peak at about $190\text{ }^{\circ}\text{C}$ as determined by DSC. In some embodiments, Form IV is characterized as having an endotherm peak at $190\pm2\text{ }^{\circ}\text{C}$ (*e.g.*, $190\pm1.9\text{ }^{\circ}\text{C}$, $190\pm1.8\text{ }^{\circ}\text{C}$, $190\pm1.7\text{ }^{\circ}\text{C}$, $190\pm1.6\text{ }^{\circ}\text{C}$, $190\pm1.5\text{ }^{\circ}\text{C}$, $190\pm1.4\text{ }^{\circ}\text{C}$, $190\pm1.3\text{ }^{\circ}\text{C}$, $190\pm1.2\text{ }^{\circ}\text{C}$, $190\pm1.1\text{ }^{\circ}\text{C}$, $190\pm1.0\text{ }^{\circ}\text{C}$, $190\pm0.9\text{ }^{\circ}\text{C}$, $190\pm0.8\text{ }^{\circ}\text{C}$, $190\pm0.7\text{ }^{\circ}\text{C}$, $190\pm0.6\text{ }^{\circ}\text{C}$, $190\pm0.5\text{ }^{\circ}\text{C}$, $190\pm0.4\text{ }^{\circ}\text{C}$, $190\pm0.3\text{ }^{\circ}\text{C}$, $190\pm0.2\text{ }^{\circ}\text{C}$, or $190\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC. In some embodiments, polymorphic Form IV is characterized as having an endotherm onset at $18\pm5\text{ }^{\circ}\text{C}$ (*e.g.*, $18\pm4\text{ }^{\circ}\text{C}$, $18\pm3\text{ }^{\circ}\text{C}$, $18\pm3\text{ }^{\circ}\text{C}$, $18\pm1.9\text{ }^{\circ}\text{C}$, $18\pm1.8\text{ }^{\circ}\text{C}$, $18\pm1.7\text{ }^{\circ}\text{C}$, $18\pm1.6\text{ }^{\circ}\text{C}$, $18\pm1.5\text{ }^{\circ}\text{C}$, $18\pm1.4\text{ }^{\circ}\text{C}$, $18\pm1.3\text{ }^{\circ}\text{C}$, $18\pm1.2\text{ }^{\circ}\text{C}$, $18\pm1.1\text{ }^{\circ}\text{C}$, $18\pm1.0\text{ }^{\circ}\text{C}$, $18\pm0.9\text{ }^{\circ}\text{C}$, $18\pm0.8\text{ }^{\circ}\text{C}$, $18\pm0.7\text{ }^{\circ}\text{C}$, $18\pm0.6\text{ }^{\circ}\text{C}$, $18\pm0.5\text{ }^{\circ}\text{C}$, $18\pm0.4\text{ }^{\circ}\text{C}$, $18\pm0.3\text{ }^{\circ}\text{C}$, $18\pm0.2\text{ }^{\circ}\text{C}$, or $18\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC. In some embodiments, Form IV is characterized as having an endotherm peak at about $43\text{ }^{\circ}\text{C}$ as determined by DSC. In some embodiments, Form IV is characterized as having an endotherm peak at $43\pm5\text{ }^{\circ}\text{C}$ (*e.g.*, $43\pm4\text{ }^{\circ}\text{C}$, $43\pm3\text{ }^{\circ}\text{C}$, $43\pm2\text{ }^{\circ}\text{C}$, $43\pm1.9\text{ }^{\circ}\text{C}$, $43\pm1.8\text{ }^{\circ}\text{C}$, $43\pm1.7\text{ }^{\circ}\text{C}$, $43\pm1.6\text{ }^{\circ}\text{C}$, $43\pm1.5\text{ }^{\circ}\text{C}$, $43\pm1.4\text{ }^{\circ}\text{C}$, $43\pm1.3\text{ }^{\circ}\text{C}$, $43\pm1.2\text{ }^{\circ}\text{C}$, $43\pm1.1\text{ }^{\circ}\text{C}$, $43\pm1.0\text{ }^{\circ}\text{C}$, $43\pm0.9\text{ }^{\circ}\text{C}$, $43\pm0.8\text{ }^{\circ}\text{C}$, $43\pm0.7\text{ }^{\circ}\text{C}$, $43\pm0.6\text{ }^{\circ}\text{C}$, $43\pm0.5\text{ }^{\circ}\text{C}$, $43\pm0.4\text{ }^{\circ}\text{C}$, $43\pm0.3\text{ }^{\circ}\text{C}$, $43\pm0.2\text{ }^{\circ}\text{C}$, or $43\pm0.1\text{ }^{\circ}\text{C}$) as determined by DSC.

[0205] In some embodiments, polymorphic Form IV has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 16**. In some embodiments, polymorphic Form IV exhibits a weight loss of about 0.7% or $0.7\%\pm0.1\%$ (*e.g.*, $0.7\%\pm0.09\%$, $0.7\%\pm0.07\%$,

0.7%±0.06%, 0.7%±0.05%, 0.7%±0.04%, 0.7%±0.03%, 0.7%±0.02%, or 0.7%±0.01%) between 25 °C and 170 °C as determined by TGA.

[0206] In some embodiments of polymorphic Form IV, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following (a)-(g) apply:

(a) polymorphic Form IV has an XRPD pattern comprising peaks at angles 2-theta of 7.66±0.20, 8.45±0.20, 11.64±0.20, 17.92±0.20, and 22.82±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 16.91±0.20 and 17.13±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 13.60±0.20 and 18.34±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 7.66±0.20, 8.45±0.20, 11.64±0.20, 12.35±0.20, 13.60±0.20, 16.91±0.20, 17.13±0.20, 17.92±0.20, 18.34±0.20, 18.62±0.20, 19.05±0.20, 20.44±0.20, 22.82±0.20, 23.43±0.20, 25.08±0.20, and 26.94±0.20 degrees;

(b) polymorphic Form IV has an XRPD pattern substantially as shown in **FIG. 14**;

(c) polymorphic Form IV has a DSC graph substantially as shown in **FIG. 15**;

(d) polymorphic Form IV is characterized as having an endotherm onset at 186±2 °C as determined by DSC;

(e) polymorphic Form IV is characterized as having an endotherm peak at 190±2 °C as determined by DSC;

(f) polymorphic Form IV has a TGA graph substantially as shown in **FIG. 16**; and

(g) polymorphic Form IV has a weight loss of about 0.7% or 0.7%±0.1% between 25 °C and 170 °C as determined by TGA.

III-e. Polymorphic Form V (Di-Sodium Salt Pattern A)

[0207] In some embodiments, provided herein is polymorphic Form V of N-(1"-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide, which is referred to as polymorphic Form V hereinafter. In some embodiments, in polymorphic Form V, N-(1"-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indolin]-5"-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., Na⁺) is about 1:1.5 to about 1:2.5, about

1:1.5 to about 1:2, or about 1:2. In some embodiments, the salt is di-sodium salt. In some embodiments, polymorphic Form V comprises less than 10 wt.%, such as less than about any of 8%, 6%, 4%, 2%, 1%, or 0.1% water. In some embodiments, polymorphic Form V is an anhydrate salt of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide.

[0208] In some embodiments, polymorphic Form V has an XRPD pattern substantially as shown in **FIG. 17**.

[0209] Angles 2-theta and relative peak intensities observed for polymorphic Form V using XRPD are shown in Table V-1.

Table V-1

2 θ (°)	<i>d</i> space (Å)	Intensity (%)
4.98	17.734	7.0
5.50	16.062	8.8
6.39	13.816	71.0
6.89	12.823	100.0
8.23	10.741	23.8
8.59	10.284	24.0
9.48	9.326	14.6
11.04	8.010	27.8
11.46	7.718	29.7
11.83	7.474	9.0
12.50	7.077	55.6
12.88	6.868	17.6
13.48	6.562	38.9
14.34	6.173	44.3
15.17	5.836	23.9
16.32	5.428	67.0
16.52	5.361	64.3
17.01	5.208	91.1
17.98	4.929	28.5
19.03	4.661	30.3
19.30	4.596	30.2
19.73	4.497	31.1
19.91	4.456	36.8
20.68	4.291	18.1

[0210] In some embodiments, polymorphic Form V has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 17** or as provided in Table V-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form V, can vary by about ± 1 degrees, ± 0.8 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0211] In some embodiments, polymorphic Form V has an XRPD pattern comprising peaks at angles 2-theta of 6.39 ± 0.20 , 6.89 ± 0.20 , 16.32 ± 0.20 , 17.01 ± 0.20 , and 22.82 ± 0.20 degrees. In some embodiments, the polymorphic Form V has an XRPD pattern comprising additional peaks at angles 2-theta of 12.50 ± 0.20 and 16.52 ± 0.20 degrees. In some embodiments, polymorphic Form V has an XRPD pattern further comprising additional peaks at angles 2-theta of 13.48 ± 0.20 and 14.34 ± 0.20 degrees. In some embodiments, polymorphic Form V has an XRPD pattern comprising peaks at angles 2-theta of 6.39 ± 0.20 , 6.89 ± 0.20 , 11.46 ± 0.20 , 12.50 ± 0.20 , 13.48 ± 0.20 , 14.34 ± 0.20 , 16.32 ± 0.20 , 16.52 ± 0.20 , 17.01 ± 0.20 , 19.03 ± 0.20 , 19.30 ± 0.20 , 19.73 ± 0.20 , and 19.91 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 17** or as provided in Table V-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0212] In some embodiments, polymorphic Form V has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 18**. In some embodiments, polymorphic Form V is characterized as having an endotherm onset at about 203°C as determined by DSC. In some embodiments, polymorphic Form V is characterized as having an endotherm onset at $203 \pm 2^\circ\text{C}$ (e.g., $203 \pm 1.9^\circ\text{C}$, $203 \pm 1.8^\circ\text{C}$, $203 \pm 1.7^\circ\text{C}$, $203 \pm 1.6^\circ\text{C}$, $203 \pm 1.5^\circ\text{C}$, $203 \pm 1.4^\circ\text{C}$, $203 \pm 1.3^\circ\text{C}$, $203 \pm 1.2^\circ\text{C}$, $203 \pm 1.1^\circ\text{C}$, $203 \pm 1.0^\circ\text{C}$, $203 \pm 0.9^\circ\text{C}$, $203 \pm 0.8^\circ\text{C}$, $203 \pm 0.7^\circ\text{C}$, $203 \pm 0.6^\circ\text{C}$, $203 \pm 0.5^\circ\text{C}$, $203 \pm 0.4^\circ\text{C}$, $203 \pm 0.3^\circ\text{C}$, $203 \pm 0.2^\circ\text{C}$, or $203 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at about 212°C as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at $212 \pm 2^\circ\text{C}$ (e.g., $212 \pm 1.9^\circ\text{C}$, $212 \pm 1.8^\circ\text{C}$, $212 \pm 1.7^\circ\text{C}$, $212 \pm 1.6^\circ\text{C}$, $212 \pm 1.5^\circ\text{C}$, $212 \pm 1.4^\circ\text{C}$, $212 \pm 1.3^\circ\text{C}$, $212 \pm 1.2^\circ\text{C}$, $212 \pm 1.1^\circ\text{C}$, $212 \pm 1.0^\circ\text{C}$, $212 \pm 0.9^\circ\text{C}$,

212±0.8 °C, 212±0.7 °C, 212±0.6 °C, 212±0.5 °C, 212±0.4 °C, 212±0.3 °C, 212±0.2 °C, or 212±0.1 °C) as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at about 60 °C as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at 60±2 °C (*e.g.*, 60±1.9 °C, 60±1.8 °C, 60±1.7 °C, 60±1.6 °C, 60±1.5 °C, 60±1.4 °C, 60±1.3 °C, 60±1.2 °C, 60±1.1 °C, 60±1.0 °C, 60±0.9 °C, 60±0.8 °C, 60±0.7 °C, 60±0.6 °C, 60±0.5 °C, 60±0.4 °C, 60±0.3 °C, 60±0.2 °C, or 60±0.1 °C) as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at about 89 °C as determined by DSC. In some embodiments, Form V is characterized as having an endotherm peak at 89±2 °C (*e.g.*, 89±1.9 °C, 89±1.8 °C, 89±1.7 °C, 89±1.6 °C, 89±1.5 °C, 89±1.4 °C, 89±1.3 °C, 89±1.2 °C, 89±1.1 °C, 89±1.0 °C, 89±0.9 °C, 89±0.8 °C, 89±0.7 °C, 89±0.6 °C, 89±0.5 °C, 89±0.4 °C, 89±0.3 °C, 89±0.2 °C, or 89±0.1 °C) as determined by DSC.

[0213] In some embodiments, polymorphic Form V has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 19**. In some embodiments, polymorphic Form V exhibits a weight loss of about 3.3% or 3.3%±0.5% (*e.g.*, 3.3%±0.4%, 3.3%±0.3%, 3.3%±0.2%, 3.3%±0.1%, 3.3%±0.09%, 3.3%±0.07%, 3.3%±0.06%, 3.3%±0.05%, 3.3%±0.04%, 3.3%±0.03%, 3.3%±0.02%, or 3.3%±0.01%) between 25 °C and 48 °C as determined by TGA. In some embodiments, polymorphic Form V exhibits a weight loss of about 2.1% or 2.1%±0.5% (*e.g.*, 2.1%±0.4%, 2.1%±0.3%, 2.1%±0.2%, 2.1%±0.1%, 2.1%±0.09%, 2.1%±0.07%, 2.1%±0.06%, 2.1%±0.05%, 2.1%±0.04%, 2.1%±0.03%, 2.1%±0.02%, or 2.1%±0.01%) between 48 °C and 100 °C as determined by TGA.

[0214] In some embodiments of polymorphic Form V, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(i) apply:

(a) polymorphic Form V has an XRPD pattern comprising peaks at angles 2-theta of 6.39±0.20, 6.89±0.20, 16.32±0.20, 17.01±0.20, and 22.82±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 12.50±0.20 and 16.52±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 13.48±0.20 and 14.34±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.39±0.20, 6.89±0.20, 11.46±0.20, 12.50±0.20, 13.48±0.20, 14.34±0.20, 16.32±0.20, 16.52±0.20, 17.01±0.20, 19.03±0.20, 19.30±0.20, 19.73±0.20, and 19.91±0.20 degrees;

(b) polymorphic Form V has an XRPD pattern substantially as shown in **FIG. 17**;

(c) polymorphic Form V has a DSC graph substantially as shown in **FIG. 18**;

(d) polymorphic Form V is characterized as having an endotherm onset at 203 ± 2 °C as determined by DSC;

(e) polymorphic Form V is characterized as having an endotherm peak at 212 ± 2 °C as determined by DSC;

(f) polymorphic Form V is characterized as having an endotherm peak at 60 ± 2 °C as determined by DSC;

(g) polymorphic Form V has a TGA graph substantially as shown in **FIG. 19**;

(h) polymorphic Form V has a weight loss of about 3.3% or $3.3\pm 0.5\%$ between 25 °C and 48 °C as determined by TGA; and

(i) polymorphic Form V has a weight loss of about 2.1 % or $2.1\pm 0.5\%$ between 48 °C and 100 °C as determined by TGA.

III-f. Polymorphic Form VI (Mono-Potassium Salt Pattern A)

[0215] In some embodiments, provided herein is polymorphic Form VI of N''1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-',1'-cyclohexan'-4''3''-indolin''5''-yl)ethanesulfonamide, which is referred to as polymorphic Form VI hereinafter.

In some embodiments, in polymorphic Form VI, N''1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-',1'-cyclohexan'-4''3''-indolin''5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., K⁺) is about 1:0.8 to about 1:1.5, or about 1:1.2, or about 1:1. In some embodiments, the salt is mono-potassium salt. In some embodiments, polymorphic Form VI comprises less than 10 wt.%, such as less than about any of 8%, 6%, 4%, 2%, 1%, or 0.1% solvent. In some embodiments, polymorphic Form VI is an anhydrate salt of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide.

[0216] In some embodiments, polymorphic Form VI has an XRPD pattern substantially as shown in **FIG. 20**.

[0217] Angles 2-theta and relative peak intensities observed for polymorphic Form VI using XRPD are shown in Table VI-1.

Table VI-1

2 θ (°)	<i>d</i> space (Å)	Intensity (%)
5.62	15.709	5.4
6.28	14.066	6.4
11.21	7.886	6.9
12.25	7.218	17.1
13.48	6.564	41.5
16.62	5.329	100.0
17.14	5.169	24.6
19.69	4.505	13.6
24.83	3.582	9.5
27.76	3.211	6.6

[0218] In some embodiments, polymorphic Form VI has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 20** or as provided in Table VI-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form VI, can vary by about ± 1 degrees, about ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0219] In some embodiments, polymorphic Form VI has an XRPD pattern comprising peaks at angles 2-theta of 13.48 ± 0.20 , 16.62 ± 0.20 , and 16.62 ± 0.20 degrees. In some embodiments, the polymorphic Form VI has an XRPD pattern comprising additional peaks at angles 2-theta of 12.25 ± 0.20 and 19.69 ± 0.20 degrees. In some embodiments, polymorphic Form VI has an XRPD pattern further comprising additional peaks at angles 2-theta of 11.21 ± 0.20 and 24.83 ± 0.20 degrees. In some embodiments, polymorphic Form VI has an XRPD pattern comprising peaks at angles 2-theta of 5.62 ± 0.20 , 6.28 ± 0.20 , 11.21 ± 0.20 , 12.25 ± 0.20 , 13.48 ± 0.20 , 16.62 ± 0.20 , 17.14 ± 0.20 , 19.69 ± 0.20 , 24.83 ± 0.20 , and 27.76 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 20** or as provided in Table VI-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0220] In some embodiments, polymorphic Form VI has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 21**. In some embodiments, Form VI is

characterized as having an endotherm peak at about 39 °C as determined by DSC. In some embodiments, Form VI is characterized as having an endotherm peak at 39±5 °C (*e.g.*, 39±4 °C, 39±3 °C, 39±2 °C, 39±1.9 °C, 39±1.8 °C, 39±1.7 °C, 39±1.6 °C, 39±1.5 °C, 39±1.4 °C, 39±1.3 °C, 39±1.2 °C, 39±1.1 °C, 39±1.0 °C, 39±0.9 °C, 39±0.8 °C, 39±0.7 °C, 39±0.6 °C, 39±0.5 °C, 39±0.4 °C, 39±0.3 °C, 39±0.2 °C, or 39±0.1 °C) as determined by DSC. In some embodiments, Form VI is characterized as having an endotherm peak at about 194 °C as determined by DSC. In some embodiments, Form VI is characterized as having an endotherm peak at 156±5 °C (*e.g.*, 156±4 °C, 156±3 °C, 156±2 °C, 156±1.9 °C, 156±1.8 °C, 156±1.7 °C, 156±1.6 °C, 156±1.5 °C, 156±1.4 °C, 156±1.3 °C, 156±1.2 °C, 156±1.1 °C, 156±1.0 °C, 156±0.9 °C, 156±0.8 °C, 156±0.7 °C, 156±0.6 °C, 156±0.5 °C, 156±0.4 °C, 156±0.3 °C, 156±0.2 °C, or 156±0.1 °C) as determined by DSC.

[0221] In some embodiments, polymorphic Form VI has a thermographic analysis (TGA) graph substantially as shown in **FIG. 22**. In some embodiments, polymorphic Form VI exhibits a weight loss of about 3.2% or 3.2%±0.1% (*e.g.*, 3.2%±0.09%, 3.2%±0.07%, 3.2%±0.06%, 3.2%±0.05%, 3.2%±0.04%, 3.2%±0.03%, 3.2%±0.02%, or 3.2%±0.01%) between 25 °C and 100 °C as determined by TGA. In some embodiments, polymorphic Form VI exhibits substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0222] In some embodiments of polymorphic Form VI, at least one, at least two, at least three, at least four, at least five, at least six, or all of the following (a)-(g) apply:

(a) polymorphic Form VI has an XRPD pattern comprising peaks at angles 2-theta of 13.48±0.20, 16.62±0.20, and 16.62±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 12.25±0.20 and 19.69±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 11.21±0.20 and 24.83±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 5.62±0.20, 6.28±0.20, 11.21±0.20, 12.25±0.20, 13.48±0.20, 16.62±0.20, 17.14±0.20, 19.69±0.20, 24.83±0.20, and 27.76±0.20degrees;

(b) polymorphic Form VI has an XRPD pattern substantially as shown in **FIG. 20**;

(c) polymorphic Form VI has a DSC graph substantially as shown in **FIG. 21**;

(d) polymorphic Form VI is characterized as having an endotherm peak at 39±5 °C as determined by DSC;

(e) polymorphic Form VI is characterized as having an endotherm peak at 156±5 °C as determined by DSC;

- (f) polymorphic Form VI has a TGA graph substantially as shown in **FIG. 22**; and
- (g) polymorphic Form VI has a weight loss of about 3.2% or $3.2\% \pm 0.1\%$ between 25 °C and 100 °C as determined by TGA.

III-g. Polymorphic Form VII (Di-Potassium Salt Pattern A)

[0223] In some embodiments, provided herein is polymorphic Form VII of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form VII hereinafter. In some embodiments, in polymorphic Form VII, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ratio between the compound of Formula (A-1) and metal ion (e.g., K^+) is about 1:2 to about 1:2.5, or about 1:2.25. In some embodiments, the salt is di-potassium salt. In some embodiments, polymorphic Form VII comprises about 0.5 equiv. to about 1.5 equiv. such as about 1 equiv. of ethanol by molar ratio.

[0224] In some embodiments, polymorphic Form VII has an XRPD pattern substantially as shown in **FIG. 23**.

[0225] Angles 2-theta and relative peak intensities observed for polymorphic Form VII using XRPD are shown in Table VII-1.

Table VII-1

2θ (°)	d space (Å)	Intensity (%)
5.84	15.120	70.9
5.91	14.935	100.0
9.21	9.597	39.2
11.83	7.478	9.6
13.58	6.517	16.6
14.29	6.195	10.4
15.56	5.692	19.8
16.00	5.535	8.6
16.72	5.298	9.1
16.74	5.293	11.7
17.79	4.983	13.0
18.13	4.889	7.5

18.56	4.776	40.3
19.02	4.662	22.0
21.30	4.168	13.8
22.27	3.988	5.3
23.16	3.838	9.6
23.84	3.730	9.5
25.27	3.521	18.8
30.13	2.964	12.7
31.43	2.844	14.2
32.86	2.724	9.4

[0226] In some embodiments, polymorphic Form VII has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 23** or as provided in Table VII-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form VII, can vary by about ± 1.0 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0227] In some embodiments, polymorphic Form VII has an XRPD pattern comprising peaks at angles 2-theta of 5.84 ± 0.50 , 5.91 ± 0.50 , 9.21 ± 0.50 , and 18.56 ± 0.50 degrees. In some embodiments, the polymorphic Form VII has an XRPD pattern comprising additional peaks at angles 2-theta of 15.56 ± 0.50 and 19.02 ± 0.50 degrees. In some embodiments, polymorphic Form VII has an XRPD pattern further comprising additional peaks at angles 2-theta of 13.58 ± 0.50 and 25.27 ± 0.50 degrees. In some embodiments, polymorphic Form VII has an XRPD pattern comprising peaks at angles 2-theta of 5.84 ± 0.50 , 5.91 ± 0.50 , 9.21 ± 0.50 , 13.58 ± 0.50 , 14.29 ± 0.50 , 15.56 ± 0.50 , 16.74 ± 0.50 , 17.79 ± 0.50 , 18.56 ± 0.50 , 19.02 ± 0.50 , 21.30 ± 0.50 , 25.27 ± 0.50 , and 30.13 ± 0.50 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 23** or as provided in Table VII-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0228] In some embodiments, polymorphic Form VII has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 24**. In some embodiments, Form VII is

characterized as having an endotherm peak at about 70 °C as determined by DSC. In some embodiments, Form VII is characterized as having an endotherm peak at 70 ± 10 °C (*e.g.*, 70 ± 8 °C, 70 ± 6 °C, 70 ± 5 °C, 70 ± 4 °C, 70 ± 2 °C, 70 ± 2 °C, 70 ± 1.7 °C, 70 ± 1.6 °C, 70 ± 1.5 °C, 70 ± 1.4 °C, 70 ± 1.3 °C, 70 ± 1.2 °C, 70 ± 1.1 °C, 70 ± 1.0 °C, 70 ± 0.9 °C, 70 ± 0.8 °C, 70 ± 0.7 °C, 70 ± 0.6 °C, 70 ± 0.5 °C, 70 ± 0.4 °C, 70 ± 0.3 °C, 70 ± 0.2 °C, or 70 ± 0.1 °C) as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm onset at about 122 °C as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm onset at 122 ± 2 °C (*e.g.*, 122 ± 1.9 °C, 122 ± 1.8 °C, 122 ± 1.7 °C, 122 ± 1.6 °C, 122 ± 1.5 °C, 122 ± 1.4 °C, 122 ± 1.3 °C, 122 ± 1.2 °C, 122 ± 1.1 °C, 122 ± 1.0 °C, 122 ± 0.9 °C, 122 ± 0.8 °C, 122 ± 0.7 °C, 122 ± 0.6 °C, 122 ± 0.5 °C, 122 ± 0.4 °C, 122 ± 0.3 °C, 122 ± 0.2 °C, or 122 ± 0.1 °C) as determined by DSC. In some embodiments, Form VII is characterized as having an endotherm peak at about 132 °C as determined by DSC. In some embodiments, Form VII is characterized as having an endotherm peak at 132 ± 2 °C (*e.g.*, 132 ± 1.9 °C, 132 ± 1.8 °C, 132 ± 1.7 °C, 132 ± 1.6 °C, 132 ± 1.5 °C, 132 ± 1.4 °C, 132 ± 1.3 °C, 132 ± 1.2 °C, 132 ± 1.1 °C, 132 ± 1.0 °C, 132 ± 0.9 °C, 132 ± 0.8 °C, 132 ± 0.7 °C, 132 ± 0.6 °C, 132 ± 0.5 °C, 132 ± 0.4 °C, 132 ± 0.3 °C, 132 ± 0.2 °C, or 132 ± 0.1 °C) as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm onset at about 151 °C as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm onset at 151 ± 2 °C (*e.g.*, 151 ± 1.9 °C, 151 ± 1.8 °C, 151 ± 1.7 °C, 151 ± 1.6 °C, 151 ± 1.5 °C, 151 ± 1.4 °C, 151 ± 1.3 °C, 151 ± 1.2 °C, 151 ± 1.1 °C, 151 ± 1.0 °C, 151 ± 0.9 °C, 151 ± 0.8 °C, 151 ± 0.7 °C, 151 ± 0.6 °C, 151 ± 0.5 °C, 151 ± 0.4 °C, 151 ± 0.3 °C, 151 ± 0.2 °C, or 151 ± 0.1 °C) as determined by DSC.

[0229] In some embodiments, polymorphic Form VII has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 25**. In some embodiments, polymorphic Form VII exhibits substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0230] In some embodiments of polymorphic Form VII, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(h) apply:

(a) polymorphic Form VII has an XRPD pattern comprising peaks at angles 2-theta of 5.84 ± 0.50 , 5.91 ± 0.50 , 9.21 ± 0.50 , and 18.56 ± 0.50 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 15.56 ± 0.50 and 19.02 ± 0.50 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 13.58 ± 0.50 and 25.27 ± 0.50 degrees;

or an XRPD pattern comprising peaks at angles 2-theta of 5.84 ± 0.50 , 5.91 ± 0.50 , 9.21 ± 0.50 , 13.58 ± 0.50 , 14.29 ± 0.50 , 15.56 ± 0.50 , 16.74 ± 0.50 , 17.79 ± 0.50 , 18.56 ± 0.50 , 19.02 ± 0.50 , 21.30 ± 0.50 , 25.27 ± 0.50 , and 30.13 ± 0.50 degrees;

(b) polymorphic Form VII has an XRPD pattern substantially as shown in **FIG. 23**;

(c) polymorphic Form VII has a DSC graph substantially as shown in **FIG. 24**;

(d) polymorphic Form VII is characterized as having an endotherm peak at 70 ± 10 °C as determined by DSC;

(e) polymorphic Form VII is characterized as having an endotherm onset at 122 ± 2 °C as determined by DSC;

(f) polymorphic Form VII is characterized as having an endotherm onset at 132 ± 2 °C as determined by DSC;

(g) polymorphic Form VII has a TGA graph substantially as shown in **FIG. 25**; and

(h) polymorphic Form VII has a substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

III-h. Polymorphic Form VIII (Di-Sodium Salt Pattern B)

[0231] In some embodiments, provided herein is polymorphic Form VIII of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form VIII hereinafter. In some embodiments, in polymorphic Form VIII, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., Na⁺) is about 1:2 to about 1:2.5, or about 1:2.3. In some embodiments, the salt is di-sodium salt. In some embodiments, polymorphic Form VIII comprises about 0.5 equiv. to about 1.5 equiv. such as about 1 equiv. of ethanol by molar ratio.

[0232] In some embodiments, polymorphic Form VIII has an XRPD pattern substantially as shown in **FIG. 26**.

[0233] Angles 2-theta and relative peak intensities observed for polymorphic Form VIII using XRPD are shown in Table VIII-1.

Table VIII-1

2 θ (°)	<i>d</i> space (Å)	Intensity (%)
5.26	16.801	100.0
6.41	13.783	8.6
6.82	12.954	11.3
7.10	12.438	5.5
8.37	10.557	20.6
8.80	10.041	24.7
9.28	9.520	22.4
10.03	8.812	4.4
10.47	8.442	22.9
11.37	7.780	5.4
14.06	6.292	10.2
14.36	6.165	6.2
15.52	5.705	9.6
16.75	5.289	39.0
17.72	5.002	33.6
20.65	4.297	17.6
21.32	4.165	18.7
21.47	4.135	13.2
22.72	3.910	5.1
23.24	3.825	10.9

[0234] In some embodiments, polymorphic Form VIII has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 26** or as provided in Table VIII-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form VIII, can vary by about ± 1 degrees, ± 0.8 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0235] In some embodiments, polymorphic Form VIII has an XRPD pattern comprising peaks at angles 2-theta of 5.26 ± 0.50 , 8.78 ± 0.50 , 16.75 ± 0.50 , and 17.72 ± 0.50 degrees. In some embodiments, the polymorphic Form VIII has an XRPD pattern comprising additional peaks at angles 2-theta of 9.28 ± 0.50 and 10.47 ± 0.50 degrees. In some embodiments, polymorphic Form VIII has an XRPD pattern further comprising additional peaks at angles 2-

theta of 8.37 ± 0.50 and 21.32 ± 0.50 degrees. In some embodiments, polymorphic Form VIII has an XRPD pattern comprising peaks at angles 2-theta of 5.26 ± 0.50 , 6.82 ± 0.50 , 8.37 ± 0.50 , 8.80 ± 0.50 , 9.28 ± 0.50 , 10.47 ± 0.50 , 14.06 ± 0.50 , 16.75 ± 0.50 , 17.72 ± 0.50 , 20.65 ± 0.50 , 21.32 ± 0.50 , 21.47 ± 0.50 , and 23.24 ± 0.50 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 26** or as provided in Table VIII-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0236] In some embodiments, polymorphic Form VIII has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 27**.

[0237] In some embodiments, polymorphic Form VIII has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 28**. In some embodiments, polymorphic Form VIII exhibits a weight loss of about 5.4% or $5.4\%\pm0.1\%$ (e.g., $5.4\%\pm0.09\%$, $5.4\%\pm0.07\%$, $5.4\%\pm0.06\%$, $5.4\%\pm0.05\%$, $5.4\%\pm0.04\%$, $5.4\%\pm0.03\%$, $5.4\%\pm0.02\%$, or $5.4\%\pm0.01\%$) between 25 °C and 140 °C as determined by TGA. In some embodiments, polymorphic Form VIII exhibits substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0238] In some embodiments of polymorphic Form VIII, at least one, at least two, at least three, at least four, or all of the following (a)-(e) apply:

(a) polymorphic Form VIII has an XRPD pattern comprising peaks at angles 2-theta of 5.26 ± 0.50 , 8.80 ± 0.50 , 16.75 ± 0.50 , and 17.72 ± 0.50 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 9.28 ± 0.50 and 10.47 ± 0.50 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 8.37 ± 0.50 and 21.32 ± 0.50 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 5.26 ± 0.50 , 6.82 ± 0.50 , 8.37 ± 0.50 , 8.80 ± 0.50 , 9.28 ± 0.50 , 10.47 ± 0.50 , 14.06 ± 0.50 , 16.75 ± 0.50 , 17.72 ± 0.50 , 20.65 ± 0.50 , 21.32 ± 0.50 , 21.47 ± 0.50 , and 23.24 ± 0.50 degrees;

(b) polymorphic Form VIII has an XRPD pattern substantially as shown in **FIG. 26**;

(c) polymorphic Form VIII has a DSC graph substantially as shown in **FIG. 27**;

(d) polymorphic Form VIII has a TGA graph substantially as shown in **FIG.**

28; and

(e) polymorphic Form VIII has a weight loss of $5.4\%\pm0.1\%$ between 25 °C and 140 °C as determined by TGA.

III-i. Polymorphic Form IX (Di-Potassium Salt Pattern B)

[0239] In some embodiments, provided herein is polymorphic Form IX of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form IX hereinafter. In some embodiments, in polymorphic Form IX, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., K⁺) is about 1:2 to about 1:3, or about 1:2.5. In some embodiments, the salt is di-potassium salt. In some embodiments, polymorphic Form IX comprises about 0.01 equiv. to about 0.1 equiv. such as about 0.06 equiv. of ACN by molar ratio. In some embodiments, polymorphic Form IX comprises about 1.5 equiv. to about 3 equiv. such as about 2.2 equiv. of water by molar ratio.

[0240] In some embodiments, polymorphic Form IX has an XRPD pattern substantially as shown in **FIG. 29**.

[0241] Exemplary angles 2-theta and relative peak intensities observed for polymorphic Form IX using XRPD are shown in Table IX-1.

Table IX-1

2θ (°)	d space (Å)	Intensity (%)
6.66	13.265	100.0
7.29	12.110	13.6
9.16	9.643	8.2
9.86	8.962	3.5
10.52	8.404	6.9
13.12	6.741	35.3
13.30	6.653	15.4
14.27	6.202	5.4
14.38	6.155	11.3
14.74	6.006	9.2
15.06	5.877	5.4
15.25	5.806	4.0
15.38	5.756	4.9
16.13	5.491	13.6
16.33	5.423	3.5
16.74	5.292	19.6
17.14	5.169	19.5
17.43	5.083	57.5
17.58	5.042	7.8
18.08	4.901	1.6

18.34	4.833	28.9
18.82	4.712	29.7
19.31	4.594	89.6
19.75	4.492	11.5
19.99	4.437	41.8
20.40	4.350	14.5
21.16	4.195	3.6
21.70	4.092	13.5
21.93	4.050	3.7
22.28	3.987	4.3
22.76	3.904	34.6
23.72	3.748	48.8
24.04	3.699	7.6
24.33	3.656	18.3
25.08	3.548	1.1
25.22	3.528	5.0
25.65	3.470	7.9
25.82	3.448	6.7
26.02	3.421	16.0
26.61	3.347	6.9
26.73	3.333	9.0
26.98	3.302	12.4
27.39	3.254	12.8
27.68	3.220	2.7
27.99	3.185	8.8
28.34	3.147	19.9
28.70	3.108	7.2
28.95	3.081	7.7
29.39	3.036	11.4
29.64	3.012	11.2
29.99	2.977	13.7
30.25	2.952	6.4
30.41	2.937	10.4
30.68	2.911	6.5
30.87	2.895	4.4
31.48	2.840	5.3
32.03	2.792	8.5
32.51	2.752	2.4
32.72	2.735	5.5
32.96	2.715	5.6
33.61	2.664	6.2
33.84	2.647	8.5
34.56	2.593	10.0
34.91	2.568	5.1
35.29	2.541	1.9
35.57	2.522	3.3
36.03	2.491	4.1
36.36	2.469	3.3

36.89	2.435	7.0
37.31	2.408	2.0
37.52	2.395	4.7
37.80	2.378	6.2
37.92	2.371	6.1
38.40	2.343	4.1
38.98	2.309	5.4
39.37	2.287	5.0
39.65	2.271	3.7

[0242] In some embodiments, polymorphic Form IX has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 29** or as provided in Table IX -1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form VIII, can vary by about ± 1 degrees, ± 0.8 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0243] In some embodiments, polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.66 ± 0.20 , 17.43 ± 0.20 , 19.31 ± 0.20 , and 23.72 ± 0.20 degrees. In some embodiments, the polymorphic Form IX has an XRPD pattern comprising additional peaks at angles 2-theta of 13.12 ± 0.20 and 19.99 ± 0.20 degrees. In some embodiments, polymorphic Form IX has an XRPD pattern further comprising additional peaks at angles 2-theta of 18.82 ± 0.20 and 22.76 ± 0.20 degrees. In some embodiments, polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.66 ± 0.20 , 13.12 ± 0.20 , 16.74 ± 0.20 , 17.14 ± 0.20 , 17.43 ± 0.20 , 18.34 ± 0.20 , 18.82 ± 0.20 , 19.31 ± 0.20 , 19.99 ± 0.20 , 22.76 ± 0.20 , 23.72 ± 0.20 , and 28.34 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 29** or as provided in Table IX -1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0244] In some embodiments, polymorphic Form IX has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 30**. In some embodiments, Form VII is characterized as having an endotherm onset at about 31 °C as determined by DSC. In some

embodiments, Form IX is characterized as having an endotherm onset at 31 ± 10 °C (*e.g.*, 31 ± 8 °C, 31 ± 6 °C, 31 ± 5 °C, 31 ± 4 °C, 31 ± 2 °C, 31 ± 2 °C, 31 ± 1.7 °C, 31 ± 1.6 °C, 31 ± 1.5 °C, 31 ± 1.4 °C, 31 ± 1.3 °C, 31 ± 1.2 °C, 31 ± 1.1 °C, 31 ± 1.0 °C, 31 ± 0.9 °C, 31 ± 0.8 °C, 31 ± 0.7 °C, 31 ± 0.6 °C, 31 ± 0.5 °C, 31 ± 0.4 °C, 31 ± 0.3 °C, 31 ± 0.2 °C, or 31 ± 0.1 °C) as determined by DSC. In some embodiments, polymorphic Form IX is characterized as having an endotherm peak at about 83 °C as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm peak at 83 ± 2 °C (*e.g.*, 83 ± 1.9 °C, 83 ± 1.8 °C, 83 ± 1.7 °C, 83 ± 1.6 °C, 83 ± 1.5 °C, 83 ± 1.4 °C, 83 ± 1.3 °C, 83 ± 1.2 °C, 83 ± 1.1 °C, 83 ± 1.0 °C, 83 ± 0.9 °C, 83 ± 0.8 °C, 83 ± 0.7 °C, 83 ± 0.6 °C, 83 ± 0.5 °C, 83 ± 0.4 °C, 83 ± 0.3 °C, 83 ± 0.2 °C, or 83 ± 0.1 °C) as determined by DSC. In some embodiments, Form IX is characterized as having an endotherm peak at about 134 °C as determined by DSC. In some embodiments, Form IX is characterized as having an endotherm peak at 134 ± 2 °C (*e.g.*, 134 ± 1.9 °C, 134 ± 1.8 °C, 134 ± 1.7 °C, 134 ± 1.6 °C, 134 ± 1.5 °C, 134 ± 1.4 °C, 134 ± 1.3 °C, 134 ± 1.2 °C, 134 ± 1.1 °C, 134 ± 1.0 °C, 134 ± 0.9 °C, 134 ± 0.8 °C, 134 ± 0.7 °C, 134 ± 0.6 °C, 134 ± 0.5 °C, 134 ± 0.4 °C, 134 ± 0.3 °C, 134 ± 0.2 °C, or 134 ± 0.1 °C) as determined by DSC.

[0245] In some embodiments, polymorphic Form IX has a thermographic analysis (TGA) graph substantially as shown in **FIG. 31**. In some embodiments, polymorphic Form IX exhibits a weight loss of about 0.3% or $0.3\% \pm 0.1\%$ (*e.g.*, $0.3\% \pm 0.09\%$, $0.3\% \pm 0.07\%$, $0.3\% \pm 0.06\%$, $0.3\% \pm 0.05\%$, $0.3\% \pm 0.04\%$, $0.3\% \pm 0.03\%$, $0.3\% \pm 0.02\%$, or $0.3\% \pm 0.01\%$) between 25 °C and 40 °C as determined by TGA. In some embodiments, polymorphic Form IX exhibits a weight loss of about 2.7% or $2.7\% \pm 0.1\%$ (*e.g.*, $2.7\% \pm 0.09\%$, $2.7\% \pm 0.07\%$, $2.7\% \pm 0.06\%$, $2.7\% \pm 0.05\%$, $2.7\% \pm 0.04\%$, $2.7\% \pm 0.03\%$, $2.7\% \pm 0.02\%$, or $2.7\% \pm 0.01\%$) between 40 °C and 75 °C as determined by TGA. In some embodiments, polymorphic Form IX exhibits a weight loss of about 3.1% or $3.1\% \pm 0.1\%$ (*e.g.*, $3.1\% \pm 0.09\%$, $3.1\% \pm 0.07\%$, $3.1\% \pm 0.06\%$, $3.1\% \pm 0.05\%$, $3.1\% \pm 0.04\%$, $3.1\% \pm 0.03\%$, $3.1\% \pm 0.02\%$, or $3.1\% \pm 0.01\%$) between 75 °C and 170 °C as determined by TGA. In some embodiments, polymorphic Form IX exhibits substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0246] In some embodiments of polymorphic Form IX, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(k) apply:

(a) polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.66 ± 0.20 , 17.43 ± 0.20 , 19.31 ± 0.20 , and 23.72 ± 0.20 degrees; an XRPD pattern comprising

additional peaks at angles 2-theta of 13.12 ± 0.20 and 19.99 ± 0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 18.82 ± 0.20 and 22.76 ± 0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.66 ± 0.20 , 13.12 ± 0.20 , 16.74 ± 0.20 , 17.14 ± 0.20 , 17.43 ± 0.20 , 18.34 ± 0.20 , 18.82 ± 0.20 , 19.31 ± 0.20 , 19.99 ± 0.20 , 22.76 ± 0.20 , 23.72 ± 0.20 , and 28.34 ± 0.20 degrees;

(b) polymorphic Form IX has an XRPD pattern substantially as shown in **FIG. 29**;

(c) polymorphic Form IX has a DSC graph substantially as shown in **FIG. 30**;

(d) polymorphic Form IX is characterized as having an endotherm onset at 31 ± 10 °C as determined by DSC;

(e) polymorphic Form IX is characterized as having an endotherm peak at 83 ± 2 °C as determined by DSC;

(f) polymorphic Form IX is characterized as having an endotherm peak 134 ± 2 °C as determined by DSC;

(g) polymorphic Form IX has a TGA graph substantially as shown in **FIG. 31**; and

(h) polymorphic Form IX has a weight loss of about 0.3% or $0.3\% \pm 0.1\%$ between 25 °C and 40 °C as determined by TGA;

(i) polymorphic Form IX exhibits a weight loss of about 2.7% or $2.7\% \pm 0.1\%$ between 40 °C and 75 °C as determined by TGA;

(j) polymorphic Form IX exhibits a weight loss of about 3.1% or $3.1\% \pm 0.1\%$ between 75 °C and 170 °C as determined by TGA;

(k) polymorphic Form IX exhibits a substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0247] In some embodiments, polymorphic Form IX has an XRPD pattern substantially as shown in **FIG. 45**.

[0248] Exemplary angles 2-theta and relative peak intensities observed for polymorphic Form IX using XRPD are shown in Table IX-2.

Table IX-2

2 θ (°)	<i>d</i> space (Å)	Intensity (%)
6.65	13.280	100.0
7.05	12.531	5.0
7.28	12.129	13.2
8.53	10.358	0.8
9.16	9.646	6.4
9.84	8.985	3.2

10.50	8.421	6.8
13.13	6.738	37.5
13.31	6.649	12.3
14.11	6.273	3.9
14.40	6.147	17.4
14.73	6.009	10.3
15.08	5.871	7.3
15.39	5.754	6.1
16.15	5.485	17.4
16.37	5.409	4.7
16.75	5.290	25.8
17.15	5.166	27.7
17.42	5.086	65.2
18.07	4.904	2.2
18.35	4.831	28.5
18.82	4.711	37.2
19.30	4.596	92.4
19.75	4.492	15.8
20.00	4.436	48.5
20.42	4.347	18.5
21.18	4.191	5.9
21.72	4.089	17.2
21.92	4.051	4.5
22.29	3.985	6.0
22.78	3.901	40.8
23.35	3.806	1.2
23.75	3.744	61.1
24.05	3.697	8.7
24.35	3.652	22.8
25.24	3.526	6.8
25.66	3.468	13.4
25.85	3.444	9.7
26.04	3.419	20.5
26.60	3.349	8.5
26.73	3.332	11.5
27.01	3.299	16.1
27.41	3.252	16.2
27.70	3.218	2.7
28.00	3.184	10.4

28.37	3.143	25.9
28.72	3.106	9.0
28.99	3.078	12.2
29.41	3.035	12.7
29.65	3.010	16.3
30.02	2.974	16.1
30.43	2.936	22.5
30.69	2.911	7.4
30.90	2.892	7.1
30.97	2.885	3.0
31.49	2.839	5.7
32.04	2.792	10.7
32.56	2.748	2.5
32.74	2.734	7.1
33.01	2.712	12.1
33.40	2.681	2.7
33.66	2.660	7.0
33.89	2.643	10.2
34.48	2.599	10.0
34.62	2.589	11.5
34.90	2.569	6.6
35.30	2.541	3.0
35.60	2.520	5.6
36.07	2.488	4.6
36.37	2.468	4.7
36.90	2.434	8.1
37.51	2.396	7.8
37.92	2.371	5.4
37.99	2.367	5.3
38.37	2.344	5.3
38.99	2.308	7.4
39.37	2.287	5.4

[0249] In some embodiments, polymorphic Form IX has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 45** or as provided in Table IX-2. It should be understood that relative intensities can vary depending on a number of factors, including

sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form IX, can vary by about ± 1.0 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0250] In some embodiments, polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.65 ± 0.20 , 17.42 ± 0.20 , 19.30 ± 0.20 , and 23.75 ± 0.20 degrees. In some embodiments, the polymorphic Form IX has an XRPD pattern comprising additional peaks at angles 2-theta of 20.00 ± 0.20 and 22.78 ± 0.20 degrees. In some embodiments, polymorphic Form IX has an XRPD pattern further comprising additional peaks at angles 2-theta of 13.13 ± 0.20 and 18.82 ± 0.20 degrees. In some embodiments, polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.65 ± 0.20 , 13.13 ± 0.20 , 16.75 ± 0.20 , 17.15 ± 0.20 , 17.42 ± 0.20 , 18.35 ± 0.20 , 18.82 ± 0.20 , 19.30 ± 0.20 , 20.00 ± 0.20 , 22.78 ± 0.20 , 23.75 ± 0.20 , 24.35 ± 0.20 , and 28.37 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 45** or as provided in Table IX-2 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0251] In some embodiments, polymorphic Form IX has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 46**. In some embodiments, Form VII is characterized as having an endotherm peak at about 86°C as determined by DSC. In some embodiments, Form IX is characterized as having an endotherm peak at $86 \pm 10^\circ\text{C}$ (*e.g.*, $86 \pm 8^\circ\text{C}$, $86 \pm 6^\circ\text{C}$, $86 \pm 5^\circ\text{C}$, $86 \pm 4^\circ\text{C}$, $86 \pm 2^\circ\text{C}$, $86 \pm 2^\circ\text{C}$, $86 \pm 1.7^\circ\text{C}$, $86 \pm 1.6^\circ\text{C}$, $86 \pm 1.5^\circ\text{C}$, $86 \pm 1.4^\circ\text{C}$, $86 \pm 1.3^\circ\text{C}$, $86 \pm 1.2^\circ\text{C}$, $86 \pm 1.1^\circ\text{C}$, $86 \pm 1.0^\circ\text{C}$, $86 \pm 0.9^\circ\text{C}$, $86 \pm 0.8^\circ\text{C}$, $86 \pm 0.7^\circ\text{C}$, $86 \pm 0.6^\circ\text{C}$, $86 \pm 0.5^\circ\text{C}$, $86 \pm 0.4^\circ\text{C}$, $86 \pm 0.3^\circ\text{C}$, $86 \pm 0.2^\circ\text{C}$, or $86 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, polymorphic Form IX is characterized as having an endotherm peak at about 140°C as determined by DSC. In some embodiments, polymorphic Form VII is characterized as having an endotherm peak at $140 \pm 2^\circ\text{C}$ (*e.g.*, $140 \pm 1.9^\circ\text{C}$, $140 \pm 1.8^\circ\text{C}$, $140 \pm 1.7^\circ\text{C}$, $140 \pm 1.6^\circ\text{C}$, $140 \pm 1.5^\circ\text{C}$, $140 \pm 1.4^\circ\text{C}$, $140 \pm 1.3^\circ\text{C}$, $140 \pm 1.2^\circ\text{C}$, $140 \pm 1.1^\circ\text{C}$, $140 \pm 1.0^\circ\text{C}$, $140 \pm 0.9^\circ\text{C}$, $140 \pm 0.8^\circ\text{C}$, $140 \pm 0.7^\circ\text{C}$, $140 \pm 0.6^\circ\text{C}$, $140 \pm 0.5^\circ\text{C}$, $140 \pm 0.4^\circ\text{C}$, $140 \pm 0.3^\circ\text{C}$, $140 \pm 0.2^\circ\text{C}$, or $140 \pm 0.1^\circ\text{C}$) as determined by DSC.

[0252] In some embodiments, polymorphic Form IX has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 47**. In some embodiments, polymorphic Form IX exhibits a weight loss of about 0.7% or $0.7\% \pm 0.1\%$ (*e.g.*, $0.7\% \pm 0.09\%$, $0.7\% \pm 0.07\%$,

0.7%±0.06%, 0.7%±0.05%, 0.7%±0.04%, 0.7%±0.03%, 0.7%±0.02%, or 0.7%±0.01%) between 25 °C and 42 °C as determined by TGA. In some embodiments, polymorphic Form IX exhibits a weight loss of about 6.0% or 6.0%±0.1% (e.g., 6.0%±0.09%, 6.0%±0.07%, 6.0%±0.06%, 6.0%±0.05%, 6.0%±0.04%, 6.0%±0.03%, 6.0%±0.02%, or 6.0%±0.01%) between 42 °C and 94 °C as determined by TGA.

[0253] In some embodiments, polymorphic Form IX has a Dynamic Vapor Sorption (DVS) graph substantially as shown in **FIG. 48**. In some embodiments, polymorphic Form IX exhibits a weight gain of about 62% or 62%±5% (e.g., 62%±4%, 62%±3%, 62%±2%, 62%±1%, 62%±0.5%, 62%±0.04%, 62%±0.03%, 62%±0.02%, or 62%±0.01%) from 1% relative humidity (RH) to 95% RH, as determined by DVS. In some embodiments, polymorphic Form IX exhibits a weight loss of about 70% or 70%±5% (e.g., 70%±4%, 70%±3%, 70%±2%, 70%±1%, 70%±0.5%, 70%±0.04%, 70%±0.03%, 70%±0.02%, or 70%±0.01%) from 95% RH to 1% RH, as determined by DVS.

[0254] In some embodiments of polymorphic Form IX, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(h) apply:

(a) polymorphic Form IX has an XRPD pattern comprising peaks at angles 2-theta of 6.65±0.20, 17.42±0.20, 19.30±0.20, and 23.75±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 20.00±0.20 and 22.78±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 13.13±0.20 and 18.82±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.65±0.20, 13.13±0.20, 16.75±0.20, 17.15±0.20, 17.42±0.20, 18.35±0.20, 18.82±0.20, 19.30±0.20, 20.00±0.20, 22.76±0.20, 23.75±0.20, 24.35±0.20, and 28.37±0.20 degrees;

(b) polymorphic Form IX has an XRPD pattern substantially as shown in **FIG. 45**;

(c) polymorphic Form IX has a DSC graph substantially as shown in **FIG. 46**;

(d) polymorphic Form IX is characterized as having an endotherm peak at 86±10 °C as determined by DSC;

(e) polymorphic Form IX is characterized as having an endotherm peak at 140±2 °C as determined by DSC;

(f) polymorphic Form IX has a TGA graph substantially as shown in **FIG. 47**; and

(g) polymorphic Form IX has a weight loss of about 0.7% or 0.7%±0.1% between 25 °C and 42 °C as determined by TGA;

- (h) polymorphic Form IX has a weight loss of about 6.0% or 6.0%±0.1% between 42 °C and 94 °C as determined by TGA;
- (i) polymorphic Form IX has a DVS graph substantially as shown in **FIG. 48**.
- (j) polymorphic Form IX has a weight gain of about 62% or 62%±5% from 1% RH to 95% RH, as determined by DVS;
- (h) polymorphic Form IX has a weight loss of about 70% or 70%±5% from 95% RH to 1% RH, as determined by DVS.

III-j. Polymorphic Form X (Di-Sodium Salt Pattern C)

[0255] In some embodiments, provided herein is polymorphic Form X of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form X hereinafter. In some embodiments, in polymorphic Form X, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., K⁺) is about 1:2 to about 1:3, or about 1:2.4. In some embodiments, the salt is di-sodium salt. In some embodiments, polymorphic Form IX comprises about 1 equiv. to about 3 equiv. such as about 1.9 equiv. of water by molar ratio. In some embodiments, polymorphic Form X comprises less than 10% w/w (e.g., less than any of 8% w/w, 5% w/w, 3% w/w, 2% w/w, 1% w/w, 0.5% w/w, 0.1% w/w, 0.05% w/w, or 0.01% w/w) water.

[0256] In some embodiments, polymorphic Form X has an XRPD pattern substantially as shown in **FIG. 32**.

[0257] It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 32** or as provided in Table X-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

Table X-1

2θ (°)	d space (Å)	Intensity (%)
4.75	18.575	7.3
6.03	14.647	75.1

6.81	12.973	11.2
7.66	11.539	58.1
9.23	9.572	2.1
9.47	9.332	3.7
11.26	7.851	2.3
12.04	7.347	100.0
12.93	6.843	34.9
13.62	6.495	3.1
13.80	6.410	5.9
14.22	6.222	5.6
14.72	6.012	1.9
15.45	5.731	25.3
16.26	5.445	14.4
16.52	5.363	6.5
16.91	5.238	10.6
17.59	5.037	9.4
18.08	4.902	23.0
18.73	4.735	58.9
18.97	4.675	37.6
19.91	4.456	32.9
20.43	4.344	12.0
20.79	4.269	5.0
22.63	3.926	8.4
23.09	3.848	11.5
24.62	3.614	31.9
25.13	3.541	3.8
25.60	3.478	7.3
26.29	3.387	6.2
27.86	3.200	3.2
28.18	3.165	9.1
28.97	3.080	1.9
29.41	3.034	14.4
30.00	2.976	7.8
30.35	2.943	14.6
30.71	2.909	10.6
31.88	2.805	6.5
33.33	2.686	8.2
33.67	2.660	17.3
34.11	2.627	6.8
36.51	2.459	13.1
36.90	2.434	11.4
37.78	2.379	4.2
38.41	2.342	5.0
39.45	2.282	2.1

[0258] In some embodiments, polymorphic Form X has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 33**. In some embodiments, polymorphic Form X is characterized as having an endotherm peak at about 52 °C as determined by DSC. In some embodiments, polymorphic Form X is characterized as having an endotherm onset at 52±2 °C (*e.g.*, 52±1.9 °C, 52±1.8 °C, 52±1.7 °C, 52±1.6 °C, 52±1.5 °C, 52±1.4 °C, 52±1.3 °C, 52±1.2 °C, 52±1.1 °C, 52±1.0 °C, 52±0.9 °C, 52±0.8 °C, 52±0.7 °C, 52±0.6 °C, 52±0.5 °C, 52±0.4 °C, 52±0.3 °C, 52±0.2 °C, or 52±0.1 °C) as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at about 84 °C as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at 84±2 °C (*e.g.*, 84±1.9 °C, 84±1.8 °C, 84±1.7 °C, 84±1.6 °C, 84±1.5 °C, 84±1.4 °C, 84±1.3 °C, 84±1.2 °C, 84±1.1 °C, 84±1.0 °C, 84±0.9 °C, 84±0.8 °C, 84±0.7 °C, 84±0.6 °C, 84±0.5 °C, 84±0.4 °C, 84±0.3 °C, 84±0.2 °C, or 84±0.1 °C) as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at about 104 °C as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at 104±2 °C (*e.g.*, 104±1.9 °C, 104±1.8 °C, 104±1.7 °C, 104±1.6 °C, 104±1.5 °C, 104±1.4 °C, 104±1.3 °C, 104±1.2 °C, 104±1.1 °C, 104±1.0 °C, 104±0.9 °C, 104±0.8 °C, 104±0.7 °C, 104±0.6 °C, 104±0.5 °C, 104±0.4 °C, 104±0.3 °C, 104±0.2 °C, or 104±0.1 °C) as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at about 128 °C as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at 128±2 °C (*e.g.*, 128±1.9 °C, 128±1.8 °C, 128±1.7 °C, 128±1.6 °C, 128±1.5 °C, 128±1.4 °C, 128±1.3 °C, 128±1.2 °C, 128±1.1 °C, 128±1.0 °C, 128±0.9 °C, 128±0.8 °C, 128±0.7 °C, 128±0.6 °C, 128±0.5 °C, 128±0.4 °C, 128±0.3 °C, 128±0.2 °C, or 128±0.1 °C) as determined by DSC.

[0259] In some embodiments, polymorphic Form X has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 34**. In some embodiments, polymorphic Form X exhibits a weight loss of about 11.9% or 11.9%±3.0% (*e.g.*, 11.9%±2.0%, 11.9%±1.5%, 11.9%±1.0%, 11.9%±0.05%, 11.9%±0.004%, 11.9%±0.003%, 11.9%±0.002%, or 11.9%±0.001%) between 30 °C and 110 °C. as determined by TGA.

[0260] In some embodiments of polymorphic Form X, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(i) apply:

(a) polymorphic Form X has an XRPD pattern comprising peaks at angles 2-theta of 6.03±0.20, 7.66±0.20, 12.04±0.20, and 18.73±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 12.93±0.20 and 18.97±0.20 degrees; an XRPD pattern

further comprising additional peaks at angles 2-theta of 19.91 ± 0.20 and 24.62 ± 0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.03 ± 0.20 , 7.66 ± 0.20 , 12.04 ± 0.20 , 12.93 ± 0.20 , 15.45 ± 0.20 , 18.08 ± 0.20 , 18.73 ± 0.20 , 18.97 ± 0.20 , 19.91 ± 0.20 , 24.62 ± 0.20 , 30.35 ± 0.20 , and 33.67 ± 0.20 degrees;

(b) polymorphic Form X has an XRPD pattern substantially as shown in **FIG. 32**;

(c) polymorphic Form X has a DSC graph substantially as shown in **FIG. 33**;

(d) polymorphic Form X is characterized as having an endotherm peak at 52 ± 2 °C as determined by DSC;

(e) polymorphic Form X is characterized as having an endotherm peak at 84 ± 2 °C as determined by DSC;

(f) polymorphic Form X is characterized as having an endotherm peak at 104 ± 2 °C as determined by DSC;

(g) polymorphic Form X is characterized as having an endotherm peak at 128 ± 2 °C as determined by DSC;

(h) polymorphic Form X has a TGA graph substantially as shown in **FIG. 34**;

(i) polymorphic Form X has a weight loss of about 11.9%; and $11.9\% \pm 3.0\%$ between 30 °C and 110 °C as determined by TGA.

[0261] In some embodiments, polymorphic Form X has an XRPD pattern substantially as shown in **FIG. 41**.

[0262] Angles 2-theta and relative peak intensities observed for polymorphic Form XIII using XRPD are shown in Table X-2.

Table X-2

2θ (°)	d space (Å)	Intensity (%)
4.80	18.416	7.1
5.03	17.569	6.0
6.07	14.558	64.2
6.84	12.904	100.0
7.70	11.478	55.6
9.25	9.552	35.4
9.51	9.295	2.1
10.89	8.115	2.7
11.27	7.842	2.9
11.59	7.629	1.0
12.07	7.324	91.9
12.97	6.822	29.0

13.21	6.699	8.8
13.63	6.491	48.5
13.85	6.391	10.1
14.05	6.300	9.9
14.23	6.220	17.1
14.68	6.028	18.4
15.16	5.840	10.6
15.48	5.719	34.9
16.27	5.442	27.4
16.61	5.332	40.3
17.02	5.205	24.7
17.25	5.137	23.4
17.60	5.036	28.4
18.10	4.898	60.0
18.49	4.794	28.2
18.75	4.728	87.7
19.96	4.445	81.1
20.47	4.336	58.1
20.83	4.262	8.2
21.29	4.170	1.2
21.69	4.095	1.9
22.05	4.027	8.5
22.25	3.992	8.4
22.65	3.922	10.1
23.10	3.847	18.8
23.36	3.805	4.1
23.58	3.770	4.4
24.00	3.705	27.5
24.63	3.611	36.0
25.16	3.537	4.7
25.62	3.475	14.2
26.03	3.421	4.7
26.34	3.381	19.1
26.81	3.323	12.5
27.35	3.258	25.4
27.71	3.216	5.2
27.91	3.194	7.1
28.22	3.160	10.4
28.86	3.091	6.3

29.38	3.037	13.4
29.65	3.010	8.3
30.00	2.976	8.1
30.37	2.941	14.2
30.75	2.905	7.7
31.00	2.883	6.6
31.36	2.850	6.4
31.92	2.802	12.5
32.36	2.764	1.5
33.34	2.686	11.8
33.68	2.659	16.0
34.13	2.625	8.0
34.35	2.609	2.9
34.70	2.583	1.0
35.29	2.542	2.4
35.80	2.506	5.9
36.39	2.467	11.0
37.06	2.424	9.8
37.70	2.384	3.3
37.85	2.375	3.9
38.32	2.347	6.4
38.45	2.339	5.6
39.07	2.304	1.7
39.51	2.279	3.1

[0263] In some embodiments, polymorphic Form X has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 41** or as provided in Table X-2. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form X, can vary by about ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0264] In some embodiments, polymorphic Form X has an XRPD pattern comprising peaks at angles 2-theta of 6.07 ± 0.20 , 6.84 ± 0.20 , 12.07 ± 0.20 , 18.75 ± 0.20 , and 19.96 ± 0.20 degrees.

In some embodiments, the polymorphic Form X has an XRPD pattern comprising additional peaks at angles 2-theta of 18.10 ± 0.20 and 20.47 ± 0.20 degrees. In some embodiments, polymorphic Form X has an XRPD pattern further comprising additional peaks at angles 2-theta of 7.70 ± 0.20 and 13.63 ± 0.20 degrees. In some embodiments, polymorphic Form X has an XRPD pattern comprising peaks at angles 2-theta of 6.07 ± 0.20 , 6.84 ± 0.20 , 7.70 ± 0.20 , 9.25 ± 0.20 , 12.07 ± 0.20 , 12.97 ± 0.20 , 13.63 ± 0.20 , 18.10 ± 0.20 , 18.75 ± 0.20 , 19.96 ± 0.20 , and 20.47 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 41** or as provided in Table X-2 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0265] In some embodiments, polymorphic Form X has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 42**. In some embodiments, polymorphic Form XIII is characterized as having an endotherm peak at about 73°C as determined by DSC. In some embodiments, polymorphic Form XIII is characterized as having an endotherm onset at $73 \pm 2^\circ\text{C}$ (e.g., $73 \pm 1.9^\circ\text{C}$, $73 \pm 1.8^\circ\text{C}$, $73 \pm 1.7^\circ\text{C}$, $73 \pm 1.6^\circ\text{C}$, $73 \pm 1.5^\circ\text{C}$, $73 \pm 1.4^\circ\text{C}$, $73 \pm 1.3^\circ\text{C}$, $73 \pm 1.2^\circ\text{C}$, $73 \pm 1.1^\circ\text{C}$, $73 \pm 1.0^\circ\text{C}$, $73 \pm 0.9^\circ\text{C}$, $73 \pm 0.8^\circ\text{C}$, $73 \pm 0.7^\circ\text{C}$, $73 \pm 0.6^\circ\text{C}$, $73 \pm 0.5^\circ\text{C}$, $73 \pm 0.4^\circ\text{C}$, $73 \pm 0.3^\circ\text{C}$, $73 \pm 0.2^\circ\text{C}$, or $73 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at about 99°C as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at $99 \pm 2^\circ\text{C}$ (e.g., $99 \pm 1.9^\circ\text{C}$, $99 \pm 1.8^\circ\text{C}$, $99 \pm 1.7^\circ\text{C}$, $99 \pm 1.6^\circ\text{C}$, $99 \pm 1.5^\circ\text{C}$, $99 \pm 1.4^\circ\text{C}$, $99 \pm 1.3^\circ\text{C}$, $99 \pm 1.2^\circ\text{C}$, $99 \pm 1.1^\circ\text{C}$, $99 \pm 1.0^\circ\text{C}$, $99 \pm 0.9^\circ\text{C}$, $99 \pm 0.8^\circ\text{C}$, $99 \pm 0.7^\circ\text{C}$, $99 \pm 0.6^\circ\text{C}$, $99 \pm 0.5^\circ\text{C}$, $99 \pm 0.4^\circ\text{C}$, $99 \pm 0.3^\circ\text{C}$, $99 \pm 0.2^\circ\text{C}$, or $99 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at about 120°C as determined by DSC. In some embodiments, Form X is characterized as having an endotherm peak at $120 \pm 2^\circ\text{C}$ (e.g., $120 \pm 1.9^\circ\text{C}$, $120 \pm 1.8^\circ\text{C}$, $120 \pm 1.7^\circ\text{C}$, $120 \pm 1.6^\circ\text{C}$, $120 \pm 1.5^\circ\text{C}$, $120 \pm 1.4^\circ\text{C}$, $120 \pm 1.3^\circ\text{C}$, $120 \pm 1.2^\circ\text{C}$, $120 \pm 1.1^\circ\text{C}$, $120 \pm 1.0^\circ\text{C}$, $120 \pm 0.9^\circ\text{C}$, $120 \pm 0.8^\circ\text{C}$, $120 \pm 0.7^\circ\text{C}$, $120 \pm 0.6^\circ\text{C}$, $120 \pm 0.5^\circ\text{C}$, $120 \pm 0.4^\circ\text{C}$, $120 \pm 0.3^\circ\text{C}$, $120 \pm 0.2^\circ\text{C}$, or $120 \pm 0.1^\circ\text{C}$) as determined by DSC.

[0266] In some embodiments, polymorphic Form X has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 43**. In some embodiments, polymorphic Form X exhibits a weight loss of about 0.6% or $0.6\% \pm 0.5\%$ (e.g., $0.6\% \pm 0.4\%$, $0.6\% \pm 0.3\%$, $0.6\% \pm 0.2\%$, $0.6\% \pm 0.1\%$, $0.6\% \pm 0.05\%$, $0.6\% \pm 0.004\%$, $0.6\% \pm 0.003\%$, $0.6\% \pm 0.002\%$, or $0.6\% \pm 0.001\%$) between 30°C and 48°C , as determined by TGA. In some embodiments,

polymorphic Form XIII exhibits a weight loss of about 4.2% or 4.2%±0.5% (*e.g.*, 4.2%±0.4%, 4.2%±0.3%, 4.2%±0.2%, 4.2%±0.1%, 4.2%±0.05%, 4.2%±0.004%, 4.2%±0.003%, 4.2%±0.002%, or 4.2%±0.001%) between 48 °C and 81 °C. as determined by TGA. In some embodiments, polymorphic Form X exhibits a weight loss of about 2.7% or 2.7%±0.5% (*e.g.*, 2.7%±0.4%, 2.7%±0.3%, 2.7%±0.2%, 2.7%±0.1%, 2.7%±0.05%, 2.7%±0.004%, 2.7%±0.003%, 2.7%±0.002%, or 2.7%±0.001%) between 81 °C and 140 °C. as determined by TGA.

[0267] In some embodiments, polymorphic Form X has a Dynamic Vapor Sorption (DVS) graph substantially as shown in **FIG. 44**. In some embodiments, polymorphic Form X exhibits a weight gain of about 60% or 60%±5% (*e.g.*, 60%±4%, 60%±3%, 60%±2%, 60%±1%, 60%±0.5%, 60%±0.04%, 60%±0.03%, 60%±0.02%, or 60%±0.01%) from 1% relative humidity (RH) to 95% RH, as determined by DVS. In some embodiments, polymorphic Form XIII exhibits a weight loss of about 58% or 58%±5% (*e.g.*, 58%±4%, 58%±3%, 58%±2%, 58%±1%, 58%±0.5%, 58%±0.04%, 58%±0.03%, 58%±0.02%, or 58%±0.01%) from 95% RH to 1% RH, as determined by DVS.

[0268] In some embodiments of polymorphic Form X, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, or all of the following (a)-(h) apply:

(a) polymorphic Form X has an XRPD pattern comprising peaks at angles 2-theta of 6.07±0.20, 6.84±0.20, 12.07±0.20, 18.75±0.20, and 19.96±0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 18.10±0.20 and 20.47±0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 7.70±0.20 and 13.63±0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.07±0.20, 6.84±0.20, 7.70±0.20, 9.25±0.20, 12.07±0.20, 12.97±0.20, 13.63±0.20, 18.10±0.20, 18.75±0.20, 19.96±0.20, and 20.47±0.20 degrees;

(b) polymorphic Form X has an XRPD pattern substantially as shown in **FIG. 41**;

(c) polymorphic Form X has a DSC graph substantially as shown in **FIG. 42**;

(d) polymorphic Form X is characterized as having an endotherm peak at 73±2 °C as determined by DSC;

(e) polymorphic Form X is characterized as having an endotherm peak at 99±2 °C as determined by DSC;

(f) polymorphic Form X is characterized as having an endotherm peak at 120±2 °C as determined by DSC;

(g) polymorphic Form X has a TGA graph substantially as shown in **FIG. 43**;

(h) polymorphic Form X has a weight loss of about 0.6%; or $0.6\% \pm 0.5\%$ between 30 °C and 48 °C as determined by TGA;

(i) polymorphic Form X has a weight loss of about 4.1%; or $4.1\% \pm 0.5\%$ between 48 °C and 81 °C as determined by TGA;

(j) polymorphic Form X has a weight loss of about 2.7%; or $2.7\% \pm 0.5\%$ between 81 °C and 140 °C as determined by TGA;

(k) polymorphic Form X has a DVS graph substantially as shown in **FIG. 44**.

(l) polymorphic Form X has a weight gain of about 60% or $60\% \pm 5\%$ from 1% RH to 95% RH, as determined by DVS;

(m) polymorphic Form X has a weight loss of about 58% or $58\% \pm 5\%$ from 95% RH to 1% RH, as determined by DVS.

III-k. Polymorphic Form XI (Di-Sodium Salt Pattern D)

[0269] In some embodiments, provided herein is polymorphic Form XI of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form XI hereinafter. In some embodiments, in polymorphic Form XI, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., Na^+) is about 1:2 to about 1:2.7, or about 1:2.4. In some embodiments, the salt is di-sodium salt.

[0270] In some embodiments, polymorphic Form XI has an XRPD pattern substantially as shown in **FIG. 35**.

[0271] Angles 2-theta and relative peak intensities observed for polymorphic Form XI using XRPD are shown in Table XI-1.

Table XI-1

2 θ (°)	<i>d</i> space (Å)	Intensity (%)
6.93	12.754	81.1
8.53	10.354	14.3
12.17	7.264	8.2
13.53	6.542	29.1

13.86	6.386	68.5
14.49	6.107	17.3
15.05	5.883	29.9
15.46	5.727	35.5
16.58	5.342	24.9
16.96	5.223	52.3
17.26	5.134	62.8
17.33	5.113	56.2
18.13	4.889	42.9
19.42	4.568	19.3
19.46	4.558	13.6
20.10	4.415	94.9
20.80	4.267	58.7
21.55	4.120	27.0
22.56	3.938	12.5
23.19	3.832	12.4
25.17	3.536	23.8
32.35	2.765	100.0
32.53	2.751	56.9
33.39	2.681	20.9
33.62	2.664	39.3
34.18	2.621	11.3
36.30	2.473	27.1
36.68	2.448	11.0
37.94	2.370	76.8

[0272] In some embodiments, polymorphic Form XI has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 35** or as provided in Table XI-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form XI, can vary by about ± 1.0 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0273] In some embodiments, polymorphic Form XI has an XRPD pattern comprising peaks at angles 2-theta of 6.93 ± 0.50 , 20.10 ± 0.50 , 32.35 ± 0.50 , and 37.94 ± 0.50 degrees. In some embodiments, the polymorphic Form XI has an XRPD pattern comprising additional peaks at angles 2-theta of 13.86 ± 0.50 and 17.26 ± 0.50 degrees. In some embodiments, polymorphic Form XI has an XRPD pattern further comprising additional peaks at angles 2-theta of 20.80 ± 0.50 and 32.53 ± 0.50 degrees. In some embodiments, polymorphic Form XI has an XRPD pattern comprising peaks at angles 2-theta of 6.93 ± 0.50 , 13.86 ± 0.50 , 15.46 ± 0.50 , 16.96 ± 0.50 , 17.26 ± 0.50 , 17.33 ± 0.50 , 18.13 ± 0.50 , 20.10 ± 0.50 , 20.80 ± 0.50 , 32.35 ± 0.50 , 32.53 ± 0.50 , 33.62 ± 0.50 , and 37.94 ± 0.50 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 35** or as provided in Table XI-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0274] In some embodiments, polymorphic Form XI has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 36**. In some embodiments, polymorphic Form XI is characterized as having an endotherm peak at about 35 °C as determined by DSC. In some embodiments, polymorphic Form XI is characterized as having an endotherm peak at 35 ± 2 °C (*e.g.*, 35 ± 1.9 °C, 35 ± 1.8 °C, 35 ± 1.7 °C, 35 ± 1.6 °C, 35 ± 1.5 °C, 35 ± 1.4 °C, 35 ± 1.3 °C, 35 ± 1.2 °C, 35 ± 1.1 °C, 35 ± 1.0 °C, 35 ± 0.9 °C, 35 ± 0.8 °C, 35 ± 0.7 °C, 35 ± 0.6 °C, 35 ± 0.5 °C, 35 ± 0.4 °C, 35 ± 0.3 °C, 35 ± 0.2 °C, or 35 ± 0.1 °C) as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at about 77 °C as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at 77 ± 2 °C (*e.g.*, 77 ± 1.9 °C, 77 ± 1.8 °C, 77 ± 1.7 °C, 77 ± 1.6 °C, 77 ± 1.5 °C, 77 ± 1.4 °C, 77 ± 1.3 °C, 77 ± 1.2 °C, 77 ± 1.1 °C, 77 ± 1.0 °C, 77 ± 0.9 °C, 77 ± 0.8 °C, 77 ± 0.7 °C, 77 ± 0.6 °C, 77 ± 0.5 °C, 77 ± 0.4 °C, 77 ± 0.3 °C, 77 ± 0.2 °C, or 77 ± 0.1 °C) as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at about 128 °C as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at 128 ± 2 °C (*e.g.*, 128 ± 1.9 °C, 128 ± 1.8 °C, 128 ± 1.7 °C, 128 ± 1.6 °C, 128 ± 1.5 °C, 128 ± 1.4 °C, 128 ± 1.3 °C, 128 ± 1.2 °C, 128 ± 1.1 °C, 128 ± 1.0 °C, 128 ± 0.9 °C, 128 ± 0.8 °C, 128 ± 0.7 °C, 128 ± 0.6 °C, 128 ± 0.5 °C, 128 ± 0.4 °C, 128 ± 0.3 °C, 128 ± 0.2 °C, or 128 ± 0.1 °C) as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at about 151 °C as determined by DSC. In some embodiments, Form XI is characterized as having an endotherm peak at 151 ± 2 °C (*e.g.*, 151 ± 1.9 °C, 151 ± 1.8 °C, 151 ± 1.7 °C, 151 ± 1.6 °C, 151 ± 1.5 °C, 151 ± 1.4 °C, 151 ± 1.3 °C, 151 ± 1.2 °C, 151 ± 1.1 °C,

151±1.0 °C, 151±0.9 °C, 151±0.8 °C, 151±0.7 °C, 151±0.6 °C, 151±0.5 °C, 151±0.4 °C, 151±0.3 °C, 151±0.2 °C, or 151±0.1 °C) as determined by DSC.

[0275] In some embodiments, polymorphic Form XI has a thermographic analysis (TGA) graph substantially as shown in **FIG. 37**. In some embodiments, polymorphic Form XI exhibits a weight loss of about 2.7% or 2.7%±0.1% (e.g., 2.7%±0.09%, 2.7%±0.07%, 2.7%±0.06%, 2.7%±0.05%, 2.7%±0.04%, 2.7%±0.03%, 2.7%±0.02%, or 2.7%±0.01%) between 25 °C and 64 °C as determined by TGA. In some embodiments, polymorphic Form XI exhibits a weight loss of about 2.4% or 2.4%±0.1% (e.g., 2.4%±0.09%, 2.4%±0.07%, 2.4%±0.06%, 2.4%±0.05%, 2.4%±0.04%, 2.4%±0.03%, 2.4%±0.02%, or 2.4%±0.01%) between 65 °C and 100 °C as determined by TGA. In some embodiments, polymorphic Form XI exhibits a weight loss of about 0.9% or 0.9%±0.1% (e.g., 0.9%±0.09%, 0.9%±0.07%, 0.9%±0.06%, 0.9%±0.05%, 0.9%±0.04%, 0.9%±0.03%, 0.9%±0.02%, or 0.9%±0.01%) between 100 °C and 140 °C as determined by TGA. In some embodiments, polymorphic Form XI exhibits substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

[0276] In some embodiments of polymorphic Form XI, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, or all of the following (a)-(i) apply:

(a) polymorphic Form XI has an XRPD pattern comprising peaks at angles 2-theta of 6.93±0.50, 20.10±0.50, 32.35±0.50, and 37.94±0.50 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 13.86±0.50 and 17.26±0.50 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 20.80±0.50 and 32.53±0.50 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.93±0.50, 13.86±0.50, 15.46±0.50, 16.96±0.50, 17.26±0.50, 17.33±0.50, 18.13±0.50, 20.10±0.50, 20.80±0.50, 32.35±0.50, 32.53±0.50, 33.62±0.50, and 37.94±0.50 degrees;

(b) polymorphic Form XI has an XRPD pattern substantially as shown in **FIG. 35**;

(c) polymorphic Form XI has a DSC graph substantially as shown in **FIG. 36**;

(d) polymorphic Form XI is characterized as having an endotherm peak at 35±2 °C as determined by DSC;

(e) polymorphic Form XI is characterized as having an endotherm peak at 77±2 °C as determined by DSC;

(f) polymorphic Form XI is characterized as having an endotherm peak at 128±2 °C as determined by DSC;

(g) polymorphic Form XI is characterized as having an endotherm peak at 151 ± 2 °C as determined by DSC;

(h) polymorphic Form XI has a TGA graph substantially as shown in **FIG. 37**; and

(i) polymorphic Form XI has a substantially continuous weight loss between 25 °C and 300 °C as determined by TGA.

III-I. Polymorphic Form XII (Mono-Sodium Salt Pattern B)

[0277] In some embodiments, provided herein is polymorphic Form XII of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form XII hereinafter. In some embodiments, in polymorphic Form XII, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., Na⁺) is about 1:0.8 to about 1:1.5, or about 1:1. In some embodiments, the salt is mono-sodium salt. In some embodiments, polymorphic Form XII comprises about 0.5 equiv. to about 1.5 equiv. such as about 1 equiv. of ethanol by molar ratio.

[0278] In some embodiments, polymorphic Form XII has an XRPD pattern substantially as shown in **FIG. 38**.

[0279] Angles 2-theta and relative peak intensities observed for polymorphic Form XII using XRPD are shown in Table XII-1.

Table XII-1

2θ (°)	d space (Å)	Intensity (%)
4.34	20.327	9.3
8.63	10.233	6.8
9.31	9.496	6.9
11.17	7.916	3.4
12.10	7.311	18.2
12.57	7.035	6.8
13.41	6.598	2.0
14.19	6.236	100.0
14.61	6.058	9.5

15.63	5.664	7.4
15.87	5.579	13.1
16.87	5.252	22.9
17.44	5.082	34.7
17.70	5.008	53.8
18.14	4.886	85.6
18.61	4.764	27.5
19.25	4.608	1.7
20.06	4.422	3.7
20.66	4.297	4.1
21.02	4.223	11.2
21.64	4.103	25.1
22.28	3.987	3.8
22.61	3.929	6.2
23.09	3.850	8.1
23.71	3.750	6.2
24.08	3.693	4.1
24.46	3.637	14.9
25.13	3.541	10.9
25.74	3.458	7.8
26.25	3.393	3.9
26.69	3.338	1.6
27.18	3.278	14.5
27.38	3.254	30.5
27.98	3.187	4.7
28.40	3.140	1.8
28.89	3.088	8.9
29.41	3.035	3.3
30.24	2.953	0.6
30.94	2.888	1.7
32.06	2.790	6.5
32.65	2.740	2.4
33.88	2.644	2.4
34.24	2.616	1.8
34.70	2.583	3.0
35.36	2.537	1.4
35.89	2.500	4.0
36.16	2.482	2.7
36.73	2.445	2.9

37.76	2.381	1.9
38.50	2.336	1.6
38.62	2.330	1.9
38.89	2.314	2.3

[0280] In some embodiments, polymorphic Form XII has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 38** or as provided in Table XII-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form XII, can vary by about ± 1.0 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0281] In some embodiments, polymorphic Form XII has an XRPD pattern comprising peaks at angles 2-theta of 14.19 ± 0.20 , 17.44 ± 0.20 , 17.70 ± 0.20 , and 18.14 ± 0.20 degrees. In some embodiments, the polymorphic Form XII has an XRPD pattern comprising additional peaks at angles 2-theta of 18.61 ± 0.20 and 27.38 ± 0.20 degrees. In some embodiments, polymorphic Form XII has an XRPD pattern further comprising additional peaks at angles 2-theta of 16.87 ± 0.20 and 21.64 ± 0.20 degrees. In some embodiments, polymorphic Form XII has an XRPD pattern comprising peaks at angles 2-theta of 12.10 ± 0.20 , 14.19 ± 0.20 , 15.87 ± 0.20 , 16.87 ± 0.20 , 17.44 ± 0.20 , 17.70 ± 0.20 , 18.14 ± 0.20 , 18.61 ± 0.20 , 21.02 ± 0.20 , 21.64 ± 0.20 , 24.46 ± 0.20 , 27.18 ± 0.20 , and 27.38 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 38** or as provided in Table XII-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0282] In some embodiments, polymorphic Form XII has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 39**. In some embodiments, polymorphic Form XII is characterized as having an endotherm onset at about 135°C as determined by DSC. In some embodiments, polymorphic Form XII is characterized as having an endotherm onset at $135 \pm 2^\circ\text{C}$ (e.g., $135 \pm 1.9^\circ\text{C}$, $135 \pm 1.8^\circ\text{C}$, $135 \pm 1.7^\circ\text{C}$, $135 \pm 1.6^\circ\text{C}$, $135 \pm 1.5^\circ\text{C}$, $135 \pm 1.4^\circ\text{C}$, $135 \pm 1.3^\circ\text{C}$, $135 \pm 1.2^\circ\text{C}$, $135 \pm 1.1^\circ\text{C}$, $135 \pm 1.0^\circ\text{C}$, $135 \pm 0.9^\circ\text{C}$, $135 \pm 0.8^\circ\text{C}$, $135 \pm 0.7^\circ\text{C}$, $135 \pm 0.6^\circ\text{C}$, $135 \pm 0.5^\circ\text{C}$, $135 \pm 0.4^\circ\text{C}$, $135 \pm 0.3^\circ\text{C}$, $135 \pm 0.2^\circ\text{C}$, or $135 \pm 0.1^\circ\text{C}$) as determined

by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at about 166 °C as determined by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at 166 ± 2 °C (*e.g.*, 166 ± 1.9 °C, 166 ± 1.8 °C, 166 ± 1.7 °C, 166 ± 1.6 °C, 166 ± 1.5 °C, 166 ± 1.4 °C, 166 ± 1.3 °C, 166 ± 1.2 °C, 166 ± 1.1 °C, 166 ± 1.0 °C, 166 ± 0.9 °C, 166 ± 0.8 °C, 166 ± 0.7 °C, 166 ± 0.6 °C, 166 ± 0.5 °C, 166 ± 0.4 °C, 166 ± 0.3 °C, 166 ± 0.2 °C, or 166 ± 0.1 °C) as determined by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at about 192 °C as determined by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at 192 ± 2 °C (*e.g.*, 192 ± 1.9 °C, 192 ± 1.8 °C, 192 ± 1.7 °C, 192 ± 1.6 °C, 192 ± 1.5 °C, 192 ± 1.4 °C, 192 ± 1.3 °C, 192 ± 1.2 °C, 192 ± 1.1 °C, 192 ± 1.0 °C, 192 ± 0.9 °C, 192 ± 0.8 °C, 192 ± 0.7 °C, 192 ± 0.6 °C, 192 ± 0.5 °C, 192 ± 0.4 °C, 192 ± 0.3 °C, 192 ± 0.2 °C, or 192 ± 0.1 °C) as determined by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at about 208 °C as determined by DSC. In some embodiments, Form XII is characterized as having an endotherm peak at 208 ± 2 °C (*e.g.*, 208 ± 1.9 °C, 208 ± 1.8 °C, 208 ± 1.7 °C, 208 ± 1.6 °C, 208 ± 1.5 °C, 208 ± 1.4 °C, 208 ± 1.3 °C, 208 ± 1.2 °C, 208 ± 1.1 °C, 208 ± 1.0 °C, 208 ± 0.9 °C, 208 ± 0.8 °C, 208 ± 0.7 °C, 208 ± 0.6 °C, 208 ± 0.5 °C, 208 ± 0.4 °C, 208 ± 0.3 °C, 208 ± 0.2 °C, or 208 ± 0.1 °C) as determined by DSC.

[0283] In some embodiments, polymorphic Form XII has a thermographic analysis (TGA) graph substantially as shown in **FIG. 40**. In some embodiments, polymorphic Form XII exhibits a weight loss of about 0.3% or $0.3\% \pm 0.1\%$ (*e.g.*, $0.3\% \pm 0.09\%$, $0.3\% \pm 0.07\%$, $0.3\% \pm 0.06\%$, $0.3\% \pm 0.05\%$, $0.3\% \pm 0.04\%$, $0.3\% \pm 0.03\%$, $0.3\% \pm 0.02\%$, or $0.3\% \pm 0.01\%$) between 25 °C and 80 °C as determined by TGA. In some embodiments, polymorphic Form XII exhibits a weight loss of about 7.3% or $7.3\% \pm 0.1\%$ (*e.g.*, $7.3\% \pm 0.09\%$, $7.3\% \pm 0.07\%$, $7.3\% \pm 0.06\%$, $7.3\% \pm 0.05\%$, $7.3\% \pm 0.04\%$, $7.3\% \pm 0.03\%$, $7.3\% \pm 0.02\%$, or $7.3\% \pm 0.01\%$) between 80 °C and 190 °C as determined by TGA.

[0284] In some embodiments of polymorphic Form XII, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of the following (a)-(j) apply:

(a) polymorphic Form XII has an XRPD pattern comprising peaks at angles 2-theta of 14.19 ± 0.20 , 17.44 ± 0.20 , 17.70 ± 0.20 , and 18.14 ± 0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 18.61 ± 0.20 and 27.38 ± 0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 16.87 ± 0.20 and 21.64 ± 0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 12.10 ± 0.20 ,

14.19±0.20, 15.87±0.20, 16.87±0.20, 17.44±0.20, 17.70±0.20, 18.14±0.20, 18.61±0.20, 21.02±0.20, 21.64±0.20, 24.46±0.20, 27.18±0.20, and 27.38±0.20 degrees;

(b) polymorphic Form XII has an XRPD pattern substantially as shown in **FIG. 38**;

(c) polymorphic Form XII has a DSC graph substantially as shown in **FIG. 39**;

(d) polymorphic Form XII is characterized as having an endotherm onset at 135±2 °C as determined by DSC;

(e) polymorphic Form XII is characterized as having an endotherm peak at 166±2 °C as determined by DSC;

(f) polymorphic Form XII is characterized as having an endotherm peak at 192±2 °C as determined by DSC;

(g) polymorphic Form XII is characterized as having an endotherm peak at 208±2 °C as determined by DSC;

(h) polymorphic Form XII has a TGA graph substantially as shown in **FIG. 40**; and

(i) polymorphic Form XII has a weight loss of 0.3% or 0.3%±0.1% between 25 °C and 80 °C as determined by TGA; and

(j) polymorphic Form XII has a weight loss of 7.3% or 7.3%±0.1% between 80 °C and 190 °C as determined by TGA.

III-m. Polymorphic Form XIII (Mono-Sodium Salt Pattern C)

[0285] In some embodiments, provided herein is polymorphic Form XIII of N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide, which is referred to as polymorphic Form XIII hereinafter. In some embodiments, in polymorphic Form XIII, N-(1''-(3-(((tert-butylamino)methyl)sulfonyl)benzoyl)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indolin]-5''-yl)ethanesulfonamide is in the form of a salt. In some embodiments, the salt is an alkali metal salt (e.g., Na salt or K salt). In some embodiments, the molar ration between the compound of Formula (A-1) and metal ion (e.g., Na⁺) is about 1:0.8 to about 1:1.5, or about 1:1.

[0286] In some embodiments, polymorphic Form XIII has an XRPD pattern substantially as shown in **FIG. 49**.

[0287] Angles 2-theta and relative peak intensities observed for polymorphic Form XIII using XRPD are shown in Table XIII-1.

Table XIII-1

2θ (°)	d space (Å)	Intensity (%)
4.37	20.214	4.0
6.85	12.904	100.0
7.54	11.719	41.5
9.12	9.688	36.9
10.01	8.826	10.1
10.48	8.439	4.8
10.82	8.171	5.1
11.74	7.53	72.4
12.3	7.189	29.1
12.61	7.013	9.2
13.21	6.698	12.8
13.35	6.625	14.1
13.66	6.477	7.8
14.27	6.203	4.1
14.53	6.093	4.7
14.85	5.962	28.9
15.19	5.829	40.1
16.24	5.454	12.0
16.64	5.324	49.5
17.14	5.17	85.8
17.65	5.021	12.3
18.13	4.888	21.4
18.51	4.789	59.9
18.92	4.687	94.2
19.34	4.585	22.6
19.7	4.502	15.3
19.89	4.461	14.9
20.38	4.353	20.0
20.95	4.237	53.1
21.82	4.07	8.1
22.17	4.007	25.8
22.42	3.962	27.1
22.61	3.93	33.9
22.96	3.871	18.3
23.23	3.826	15.6
23.55	3.775	20.6
24.02	3.701	9.7

24.16	3.681	8.4
24.73	3.598	48.4
25.33	3.513	12.6
25.77	3.454	5.9
26.24	3.393	3.4
26.97	3.303	3.5
27.63	3.226	20.0
28.38	3.143	8.0
28.79	3.098	6.8
29.15	3.061	12.5
29.89	2.987	7.6
30.29	2.949	11.5
30.56	2.923	4.8
31.21	2.863	2.8
31.63	2.827	4.7
32.72	2.735	2.8
33.2	2.696	2.9
33.59	2.666	5.3
34.5	2.598	5.1
35.78	2.508	5.4
36.38	2.468	9.0
37.23	2.413	7.3
37.91	2.372	2.4
38.58	2.332	2.4

[0288] In some embodiments, polymorphic Form XIII has an XRPD pattern displaying at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or at least ten of the peaks at angles 2-theta with the greatest intensity in the XRPD pattern substantially as shown in **FIG. 49** or as provided in Table XIII-1. It should be understood that relative intensities can vary depending on a number of factors, including sample preparation, mounting, and the instrument and analytical procedure and settings used to obtain the spectrum. Relative peak intensities and peak assignments can vary within experimental error. In some embodiments, peak assignments listed herein, including for polymorphic Form XIII, can vary by about ± 1.0 degrees, ± 0.6 degrees, ± 0.4 degrees, ± 0.2 degrees, or ± 0.1 degrees 2-theta.

[0289] In some embodiments, polymorphic Form XIII has an XRPD pattern comprising peaks at angles 2-theta of 6.85 ± 0.20 , 11.74 ± 0.20 , 17.14 ± 0.20 , and 18.92 ± 0.20 degrees. In

some embodiments, the polymorphic Form XIII has an XRPD pattern comprising additional peaks at angles 2-theta of 18.51 ± 0.20 and 20.95 ± 0.20 degrees. In some embodiments, polymorphic Form XIII has an XRPD pattern further comprising additional peaks at angles 2-theta of 16.64 ± 0.20 and 24.73 ± 0.20 degrees. In some embodiments, polymorphic Form XIII has an XRPD pattern comprising peaks at angles 2-theta of 6.85 ± 0.20 , 7.54 ± 0.20 , 9.12 ± 0.20 , 11.74 ± 0.20 , 15.19 ± 0.20 , 16.64 ± 0.20 , 17.14 ± 0.20 , 18.51 ± 0.20 , 18.92 ± 0.20 , 20.95 ± 0.20 , 22.61 ± 0.20 , and 24.73 ± 0.20 degrees. It is to be understood that additional peaks in the XRPD pattern other than those shown in **FIG. 49** or as provided in Table XIII-1 may be observed, for instance, due to the presence of impurities, solvent, or other polymorphs or amorphous forms present in the test sample.

[0290] In some embodiments, polymorphic Form XIII has a differential scanning calorimetry (DSC) graph substantially as shown in **FIG. 50**. In some embodiments, polymorphic Form XIII is characterized as having an endotherm peak at about 53°C as determined by DSC. In some embodiments, polymorphic Form XIII is characterized as having an endotherm peak at $53 \pm 2^\circ\text{C}$ (*e.g.*, $53 \pm 1.9^\circ\text{C}$, $53 \pm 1.8^\circ\text{C}$, $53 \pm 1.7^\circ\text{C}$, $53 \pm 1.6^\circ\text{C}$, $53 \pm 1.5^\circ\text{C}$, $53 \pm 1.4^\circ\text{C}$, $53 \pm 1.3^\circ\text{C}$, $53 \pm 1.2^\circ\text{C}$, $53 \pm 1.1^\circ\text{C}$, $53 \pm 1.0^\circ\text{C}$, $53 \pm 0.9^\circ\text{C}$, $53 \pm 0.8^\circ\text{C}$, $53 \pm 0.7^\circ\text{C}$, $53 \pm 0.6^\circ\text{C}$, $53 \pm 0.5^\circ\text{C}$, $53 \pm 0.4^\circ\text{C}$, $53 \pm 0.3^\circ\text{C}$, $53 \pm 0.2^\circ\text{C}$, or $53 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, Form XIII is characterized as having an endotherm peak at about 98°C as determined by DSC. In some embodiments, Form XIII is characterized as having an endotherm peak at $98 \pm 2^\circ\text{C}$ (*e.g.*, $98 \pm 1.9^\circ\text{C}$, $98 \pm 1.8^\circ\text{C}$, $98 \pm 1.7^\circ\text{C}$, $98 \pm 1.6^\circ\text{C}$, $98 \pm 1.5^\circ\text{C}$, $98 \pm 1.4^\circ\text{C}$, $98 \pm 1.3^\circ\text{C}$, $98 \pm 1.2^\circ\text{C}$, $98 \pm 1.1^\circ\text{C}$, $98 \pm 1.0^\circ\text{C}$, $98 \pm 0.9^\circ\text{C}$, $98 \pm 0.8^\circ\text{C}$, $98 \pm 0.7^\circ\text{C}$, $98 \pm 0.6^\circ\text{C}$, $98 \pm 0.5^\circ\text{C}$, $98 \pm 0.4^\circ\text{C}$, $98 \pm 0.3^\circ\text{C}$, $98 \pm 0.2^\circ\text{C}$, or $98 \pm 0.1^\circ\text{C}$) as determined by DSC. In some embodiments, Form XIII is characterized as having an endotherm peak at about 183°C as determined by DSC. In some embodiments, Form XIII is characterized as having an endotherm peak at $183 \pm 2^\circ\text{C}$ (*e.g.*, $183 \pm 1.9^\circ\text{C}$, $183 \pm 1.8^\circ\text{C}$, $183 \pm 1.7^\circ\text{C}$, $183 \pm 1.6^\circ\text{C}$, $183 \pm 1.5^\circ\text{C}$, $183 \pm 1.4^\circ\text{C}$, $183 \pm 1.3^\circ\text{C}$, $183 \pm 1.2^\circ\text{C}$, $183 \pm 1.1^\circ\text{C}$, $183 \pm 1.0^\circ\text{C}$, $183 \pm 0.9^\circ\text{C}$, $183 \pm 0.8^\circ\text{C}$, $183 \pm 0.7^\circ\text{C}$, $183 \pm 0.6^\circ\text{C}$, $183 \pm 0.5^\circ\text{C}$, $183 \pm 0.4^\circ\text{C}$, $183 \pm 0.3^\circ\text{C}$, $183 \pm 0.2^\circ\text{C}$, or $183 \pm 0.1^\circ\text{C}$) as determined by DSC.

[0291] In some embodiments, polymorphic Form XIII has a thermogravimetric analysis (TGA) graph substantially as shown in **FIG. 51**. In some embodiments, polymorphic Form XIII exhibits a weight loss of about 0.7% or $0.7\% \pm 0.1\%$ (*e.g.*, $0.7\% \pm 0.09\%$, $0.7\% \pm 0.07\%$, $0.7\% \pm 0.06\%$, $0.7\% \pm 0.05\%$, $0.7\% \pm 0.04\%$, $0.7\% \pm 0.03\%$, $0.7\% \pm 0.02\%$, or $0.7\% \pm 0.01\%$) between 30°C and 120°C as determined by TGA. In some embodiments, polymorphic Form

XIII exhibits a weight loss of about 8.0% or $8.0\% \pm 0.1\%$ (e.g., $8.0\% \pm 0.09\%$, $8.0\% \pm 0.07\%$, $8.0\% \pm 0.06\%$, $8.0\% \pm 0.05\%$, $8.0\% \pm 0.04\%$, $8.0\% \pm 0.03\%$, $8.0\% \pm 0.02\%$, or $8.0\% \pm 0.01\%$) between 120 °C and 180 °C as determined by TGA. In some embodiments, polymorphic Form XIII exhibits a weight loss of about 4.2% or $4.2\% \pm 0.1\%$ (e.g., $4.2\% \pm 0.09\%$, $4.2\% \pm 0.07\%$, $4.2\% \pm 0.06\%$, $4.2\% \pm 0.05\%$, $4.2\% \pm 0.04\%$, $4.2\% \pm 0.03\%$, $4.2\% \pm 0.02\%$, or $4.2\% \pm 0.01\%$) between 120 °C and 230 °C as determined by TGA.

[0292] In some embodiments of polymorphic Form XIII, at least one, at least two, at least three, at least four, at least five, at least six, at least seven, at least eight, at least nine, or all of the following (a)-(j) apply:

(a) polymorphic Form XIII has an XRPD pattern comprising peaks at angles 2-theta of 6.85 ± 0.20 , 11.74 ± 0.20 , 17.14 ± 0.20 , and 18.92 ± 0.20 degrees; an XRPD pattern comprising additional peaks at angles 2-theta of 18.51 ± 0.20 and 20.95 ± 0.20 degrees; an XRPD pattern further comprising additional peaks at angles 2-theta of 16.64 ± 0.20 and 24.73 ± 0.20 degrees; or an XRPD pattern comprising peaks at angles 2-theta of 6.85 ± 0.20 , 7.54 ± 0.20 , 9.12 ± 0.20 , 11.74 ± 0.20 , 15.19 ± 0.20 , 16.64 ± 0.20 , 17.14 ± 0.20 , 18.51 ± 0.20 , 18.92 ± 0.20 , 20.95 ± 0.20 , 22.61 ± 0.20 , and 24.73 ± 0.20 degrees;

(b) polymorphic Form XIII has an XRPD pattern substantially as shown in **FIG. 49**;

(c) polymorphic Form XIII has a DSC graph substantially as shown in **FIG. 50**;

(d) polymorphic Form XIII is characterized as having an endotherm peak at 53 ± 2 °C as determined by DSC;

(e) polymorphic Form XIII is characterized as having an endotherm peak at 98 ± 2 °C as determined by DSC;

(f) polymorphic Form XIII is characterized as having an endotherm peak at 183 ± 2 °C as determined by DSC;

(g) polymorphic Form XIII has a TGA graph substantially as shown in **FIG. 51**; and

(h) polymorphic Form XIII has a weight loss of 0.7% or $0.7\% \pm 0.1\%$ between 30 °C and 120 °C as determined by TGA;

(i) polymorphic Form XIII has a weight loss of 8.0 % or $8.0\% \pm 0.1\%$ between 120 °C and 180 °C as determined by TGA; and

(j) polymorphic Form XIII has a weight loss of 4.2 % or $4.2\% \pm 0.1\%$ between 120 °C and 230 °C as determined by TGA.

[0293] Also provided herein are compositions containing polymorphs described herein, such as polymorphic Form A, C, B, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII, or any mixture

thereof. In some embodiments, the composition contains polymorphic Form A. In some embodiments, the composition contains polymorphic Form C. In some embodiments, the composition contains polymorphic Form B.

[0294] In some embodiments, provided is a composition containing polymorphic Form A of the compound of Formula (A-1). In some embodiments, the composition is substantially free of polymorphic Form C, B, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII of the compound of Formula (A-1). In some embodiments, the composition is substantially free of salts of the compound of Formula (A-1).

[0295] In some embodiments of the composition containing Form A of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the total composition is polymorphic Form A. In some embodiments of the composition containing polymorphic Form A of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the compound of Formula (A-1) exists in Form A.

[0296] In some embodiments, provided is a composition containing polymorphic Form C of the compound of Formula (A-1). In some embodiments, the composition is substantially free of polymorphic Form A, B, IV, V, VI, VII, VIII, IX, X, XI, XII, XIII of the compound of Formula (A-1). In some embodiments, the composition is substantially free of salts of the compound of Formula (A-1).

[0297] In some embodiments of the composition containing Form C of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight

of the total composition is polymorphic Form C. In some embodiments of the composition containing polymorphic Form C of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the compound of Formula (A-1) exists in Form C.

[0298] In some embodiments, provided is a composition containing polymorphic Form B of the compound of Formula (A-1). In some embodiments, the composition is substantially free of polymorphic Form A, II, IV, V, VI, VII, VIII, IX, X, XI, XII of the compound of Formula (A-1). In some embodiments, the composition is substantially free of salts of the compound of Formula (A-1).

[0299] In some embodiments of the composition containing Form B of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the total composition is polymorphic Form B. In some embodiments of the composition containing polymorphic Form B of the compound of Formula (A-1), at least about 0.1%, at least about 0.3%, at least about 0.5%, at least about 0.8%, at least about 1.0%, at least about 5.0%, at least about 10%, at least about 20%, at least about 30%, at least about 40%, at least about 50%, at least about 60%, at least about 70%, at least about 80%, at least about 85%, at least about 90%, at least about 95%, at least about 96%, at least about 97%, at least about 98%, at least about 99%, or at least 99.9% by weight of the compound of Formula (A-1) exists in Form B.

III-n. Method of Preparation – Polymorphic Form A

[0300] In some embodiments, provided is a method of preparing polymorphic Form A of the compound of Formula (A-1), the method comprising: (1) mixing the compound of Formula (A-1) with a solvent; and (2) evaporating the mixture of (1). In some embodiments, the

solvent comprises acetone, 2-MeTHF, TFE, THF, methylcyclohexane, and water. In some embodiments, the solvent comprises acetone. In some embodiments, the solvent comprises 2-MeTHF. In some embodiments, the solvent comprises TFE. In some embodiments, the solvent comprises THF. In some embodiments, the solvent comprises THF and methylcyclohexane. In some embodiments, the solvent comprises acetone and water. In some embodiments, the solvent comprises ethyl acetate. In some embodiments, the solvent is ethyl acetate. In some embodiments, step (2) is evaporating the mixture of (1) fast. In some embodiments, step (2) is evaporating the mixture of step (1) when the mixture is directly exposed to air. In some embodiments, step (2) is achieved by drying the mixture under vacuum. In some embodiments, step (2) is evaporating the mixture of (1) slowly. In some embodiments, step (2) is evaporating the mixture of (1) at a controlled rate. In some embodiments, step (2) is evaporating the mixture of (1) at a controlled rate, wherein the rate is controlled by the extent to which the mixture that is exposed to air. In some embodiments, step (2) is evaporating the mixture of (1) at a temperature that is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the method further comprises: (1') filtering the mixture of step (1), wherein the step (2) is evaporating the filtered mixture of (1').

[0301] In some embodiments, provided is a method of preparing polymorphic Form A of the compound of Formula (A-1), the method comprising: (1) mixing the compound of Formula (A-1) with a solvent at a first temperature; (2) cooling the mixture of (1) to a second temperature; and (3) keeping the mixture of (2) at a third temperature. In some embodiments, the solvent comprises alcohol. In some embodiments, the solvent is ethanol. In some embodiments, the first temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the solvent is methanol. In some embodiments, the second temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the third temperature is higher than -50 °C, -40 °C, -35 °C, -30 °C, -25 °C, -20 °C, -15 °C, or -10 °C. In some embodiments, the third temperature is lower than 10 °C, 5 °C, 0 °C, -5 °C, or -10 °C. In some embodiments, the third temperature is from about -40 °C to about 10 °C, from about -30 °C to about 0 °C, from about -25 °C to about -5 °C, or from about -25 °C to about -10 °C.

[0302] In some embodiments, provided is a method of preparing polymorphic Form A of the compound of Formula (A-1), the method comprising: (1) mixing the compound of Formula (A-1) with a first solvent and a second solvent at a first temperature; and (2) keeping the mixture of (1) at a second temperature. In some embodiments, the first solvent and the second solvent are selected from the group consisting of acetone, isobutyl acetate, water, acetone nitrile, 1-butanol, dimethylacetamide, N,N-dimethylformamide, nitromethane, toluene, dimethyl sulfoxide, dioxane, cyclopentyl methyl ether, tert-amyl methyl ether, 2-ethoxyethanol, ethyl acetate, ethanol, hexafluoroisopropanol, diisopropyl ether, methyl ethyl ketone, hexane, methanol, 2-methyltetrahydrofuran (2-MeTHF), N-methyl-2-pyrrolidone, 2,2,2-trifluoroethanol (TFE), 1-propanol, isopropanol alcohol, methylcyclohexane, tetrahydrofuran (THF), anisole, methyl isopropyl ketone, dipropyl ether, chloroform, and tert-amyl alcohol, provided that the first solvent is different from the second solvent. In some embodiments, the first solvent is DMSO and the second solvent is nitromethane, or vice versa. In some embodiments, the first solvent is dioxane and the second solvent is TAME, or vice versa. In some embodiments, the first solvent is MEK and the second solvent is hexane, or vice versa. In some embodiments, the first solvent is TFE and the second solvent is 1-PrOH, or vice versa. In some embodiments, the first solvent is HFIPA and the second solvent is IPE, or vice versa. In some embodiments, the first solvent is acetone nitrile and the second solvent is 1-butanol, or vice versa. In some embodiments, the first solvent is DMF and the second solvent is water, or vice versa. In some embodiments, the first solvent is dioxane and the second solvent is CPME, or vice versa. In some embodiments, the first solvent is NMP and the second solvent is toluene, or vice versa. In some embodiments, the first solvent is THF and the second solvent is IPA, or vice versa. In some embodiments, the first temperature is higher than -50 °C, -40 °C, -35 °C, -30 °C, -25 °C, -20 °C, -15 °C, or -10 °C. In some embodiments, the first temperature is lower than 10 °C, 5 °C, 0 °C, -5 °C, or -10 °C. In some embodiments, the first temperature is from about -40 °C to about 10 °C, from about -30 °C to about 0 °C, from about -25 °C to about -5 °C, or from about -25 °C to about -10 °C. In some embodiments, the first temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the second temperature is higher than -50 °C, -40 °C, -35 °C, -30 °C, -25 °C, -20 °C, -15 °C, or -10 °C. In some embodiments, the second temperature is lower than 10 °C, 5 °C, 0 °C, -5 °C, or -10 °C. In some embodiments, the second temperature is from about -40 °C to about 10 °C, from about -30 °C to about 0 °C, from about -25 °C to about -5 °C, or from about -25 °C to about -10 °C. In some

embodiments, the second temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the mixture of (1) is kept at the second temperature for 1 days to 5 days, 2 days to 4 days, or about 3 days. In some embodiments, the method further comprises: (3) evaporating the mixture of (2). In some embodiments, the mixture of (2) is evaporated in a fast way. In some embodiments, step (3) is evaporating the mixture of (2) wherein the mixture of (2) is fully exposed to air. In some embodiments, step (3) is evaporating the mixture of (2) wherein the mixture of (2) is fully exposed to air and under purged N₂. In some embodiments, the method further comprises: (4) adding a third solvent to the mixture of (2) or the mixture of (3) under a third temperature. In some embodiments, the third solvent is the same as the first solvent. In some embodiments, the third solvent is the same as the second solvent. In some embodiments, the third solvent is different from both the first and the second solvent. In some embodiments, the third solvent is toluene. In some embodiments, the third temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the mixture of (4) is stirred at about room temperature for about 3h to about 30h, from about 5h to about 24h, or about 5h, or about 24h.

[0303] In some embodiments, provided is a method of preparing polymorphic Form A of the compound of Formula (A-1), the method comprising: (1) mixing the compound of Formula (A-1) with a first solvent at a first temperature; and (2) adding the mixture of (1) to a second solvent at a second temperature. In some embodiments, the first solvent and the second solvent are selected from the group consisting of acetone, isobutyl acetate, water, dimethylacetamide, 2-ethoxyethanol (EGEE), ethyl acetate, and cyclohexane, provided that the first solvent is different from the second solvent. In some embodiments, the first solvent is iBuOAc and the second solvent is acetone, or vice versa. In some embodiments, the first solvent is DMA and the second solvent is water, or vice versa. In some embodiments, the first solvent is EGEE and the second solvent is water, or vice versa. In some embodiments, the first solvent is EtOAc and the second solvent is cyclohexane, or vice versa. In some embodiments, the first temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the second temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the first temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room

temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the second temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the second temperature is from 30 °C to 70 °C, from 40 °C to 60 °C, about 50 °C, or about 55 °C. In some embodiments, the second temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the method further comprises: (3) cooling the mixture of (2) to a third temperature. In some embodiments, the third temperature is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments, the third temperature is higher than -5 °C, -3 °C, -1 °C, 0 °C, 1 °C, or 2 °C. In some embodiments, the third temperature is lower than 15 °C, 13 °C, 10 °C, 9 °C, or 8 °C. In some embodiments, the third temperature is from about -5 °C to about 15 °C, from about -3 °C to about 13 °C, from about 0 °C to about 10 °C, or from about 2 °C to about 8 °C. In some embodiments of step (3), the cooling is a fast cooling, wherein the mixture of (2) is directly removed from heating source and kept under the third temperature. In some embodiments, the method further comprises evaporating the mixture of step (2). In some embodiments, the method further comprises evaporating the mixture of step (3). In some embodiments, the method further comprises evaporating the mixture of step (4).

III-o. Method of Preparation – Polymorphic Form B

[0304] In some embodiments, provided is a method of preparing polymorphic Form B of the compound of Formula (A-1), the method comprising suspending the polymorphic Form A described herein in a solvent for a period of time, and re-isolating the solid in the mixture. In some embodiments, the polymorphic Form A is suspended in the solvent for at least 3 days, such as at least any of 4 days, 5 days, 6 days, or 7 days. In some embodiments, the polymorphic Form A is suspended in the solvent at about 0 °C to about 60 °C, such as about any of 5 °C to 50 °C, 5 °C to 25 °C, 15 °C, 25 °C, or 50 °C. In some embodiments, the solvent is selected from the group consisting of MeOH, MEK, EA, 2-MeTHF, ACN, water, and any combination thereof. In some embodiments, the solvent is a mixture of ACN and water. In some embodiments, polymorphic Form B seeds can be added to the suspension of polymorphic Form A in the solvent. In some embodiments, the suspension of polymorphic Form A in the solvent is cooled slowly (e.g., by natural cooling) to isolate the solid in the

mixture is isolated. In some embodiments, polymorphic Form B can be prepared by crystallization (e.g., direct crystallization) from a solution. In some embodiments, the solution comprises a single solvent. In some embodiments, the solution comprises a mixture of more than one solvents.

[0305] In some embodiments, provided herein is a method of preparing polymorphic Form B of the compound of Formula (A-1), the method comprising: (i) suspending compound of Formula (A-1) in a solvent to form a mixture; (ii) heating the mixture of step (i) at an elevated temperature and stirring the mixture for a period of time; and (iii) cooling the mixture of (ii). In some embodiments, the compound of Formula (A-1) in step (i) is a polymorphic form provided herein. In some embodiments, the compound of Formula (A-1) in step (i) is polymorphic Form A. In some embodiments, the compound of Formula (A-1) in step (i) (e.g., polymorphic Form A) is suspended in the solvent together with a base. In some embodiments, the base comprises L-Lysine, Betaine, or a combination thereof. In some embodiments, the base is L-Lysine. In some embodiments, the base is betaine. In some embodiments, the solvent comprises acetonitrile, water, or a mixture thereof. In some embodiments, the solvent is a mixture of acetonitrile and water. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is at least about 1:1, such as at least about any of 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is no more than about 20:1, such as no more than about any of 18:1, 17:1, 16:1, 15:1, 14:1, 13:1, 12:1, 11:1, or 10:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is about 1:1 to about 10:1 or about 5:1 to 15:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is about any of 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, or 15:1. In some embodiments, the molar ratio between the base and the compound of Formula (A-1) in the mixture of step (i) is at least about 0.1:1, such as at least about any of 0.2:1, 0.4:1, 0.6:1, 0.8:1, 1:1, or 1.2:1. In some embodiments, the molar ratio between the base and the compound of Formula (A-1) in the mixture of (i) is no more than about 2:1, such as no more than about any of 1.8:1, 1.6:1, 1.4:1, 1.2:1, 1.1:1, or 1:1. In some embodiments, the molar ratio between the base and the compound of Formula (A-1) in the mixture of (i) is about 0.1:1 to about 1.5:1, such as about any of 0.5:1 to 1.2:1, 0.5:1 to 1.05:1, or about any of 0.5:1, 0.8:1, or 1.05:1. In some embodiments, the mixture of (i) is heated to an elevated temperature at or above about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, or 70 °C. In some embodiments, the mixture of (i) is heated to an

elevated temperature no more than about any of 90 °C, 85 °C, 80 °C, 75 °C, 70 °C, 65 °C, 50 °C, 45 °C, or 40 °C. In some embodiments, the mixture of (i) is heated to an elevated temperature of about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, 70 °C, 75 °C, 80 °C, 90 °C, or 95 °C. In some embodiments, the mixture of (i) is heated to an elevated temperature of about 50 °C. In some embodiments, the mixture of (i), after reaching an elevated temperature, is stirred for about or more than about any of 1 min, 10 min, 20 min, 30 min, 40 min, 50 min, 1 hour, 1.5 hour, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours. In some embodiments, the mixture of (i), after reaching an elevated temperature, is stirred for no more than about any of 10 hours, 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, 4.5 hours, 4 hours, 3.5 hours, 3 hours, 2.5 hours, 2 hours, or 1.5 hours. In some embodiments, the mixture of (i), after reaching an elevated temperature, is stirred for about or more than about 2 hours. In some embodiments, the mixture of (i), after reaching an elevated temperature, is stirred for about any of 1 min, 10 min, 20 min, 30 min, 40 min, 50 min, 1 hour, 1.5 hour, 2 hours, 2.5 hours, 3 hours, 3.5 hours, 4 hours, 4.5 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, or 10 hours. In some embodiments, the mixture of (i), after reaching an elevated temperature, is stirred for about 2 hours. In some embodiments, the mixture of (ii) is cooled to a temperature of no more than 30 °C, such as about any of 25 °C, 20 °C, 15 °C, or 10 °C. In some embodiments, the mixture of (ii) is cooled to a temperature of at least 0 °C, such as at least about any of 5 °C, 10 °C, 15 °C, 20 °C, or 25 °C. In some embodiments, the mixture of (ii) is cooled over a period of at least a day, such as at least about any of 2 days, 3 days, 4 days, 5 days, 6 days, or 7 days. In some embodiments, the mixture of (ii) is cooled over a period of no more than 20 days, such as no more than about any of 18 days, 16 days, 14 days, 12 days, 10 days, or 7 days. In some embodiments, the mixture of (ii) is cooled over a period of about any of a day 2 days, 3 days, 4 days, 5 days, 6 days, 7 days, 8 days, 9 days, 10 days, 11 days, 12 days, 13 days, 14 days, or 15 days. In some embodiments, the method further comprises (iv) filtering the solid from the mixture of (iii). In some embodiments, the method further comprises (v) drying the solid from step (vi) to obtain polymorphic Form B.

[0306] In some embodiments, provided herein is a method of preparing polymorphic Form B, comprising (i) suspending compound of Formula (A-1) in a solvent to form a mixture; (ii) heating the mixture of step (i) at an elevated temperature and for a period of time; (iii) cooling the mixture of (ii); (iv) adding polymorphic Form B as seed; (v) heating the mixture of (iv); and (vi) cooling the mixture of (v). In some embodiments, the compound of Formula

(A-1) in step (i) can be a polymorphic form provided herein. In some embodiments, the compound of Formula (A-1) in step (i) is polymorphic Form A. In some embodiments, the solvent comprises acetonitrile, water, or a mixture thereof. In some embodiments, the solvent is a mixture of acetonitrile and water. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is at least about 1:1, such as at least about any of 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or 10:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is no more than about 20:1, such as no more than about any of 18:1, 17:1, 16:1, 15:1, 14:1, 13:1, 12:1, 11:1, or 10:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is about 1:1 to about 10:1 or about 5:1 to 15:1. In some embodiments, the volumetric ratio between acetonitrile and water in the solvent is about any of 5:1, 6:1, 7:1, 8:1, 9:1, 10:1, 11:1, 12:1, 13:1, 14:1, or 15:1. In some embodiments, the mixture of (i) is heated to an elevated temperature of at or above about 30°C, such as about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, or 70 °C. In some embodiments, the mixture of (i) is heated to an elevated temperature no more than about any of 90°C, 85 °C, 80 °C, 75 °C, 70 °C, 65 °C, 50 °C, 45 °C, or 40 °C. In some embodiments, the mixture of (i) is heated to an elevated temperature of about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, 70 °C, 75 °C, 80 °C, 90 °C, or 95 °C. In some embodiments, the mixture of (i) is heated and stirred for at least about 1 minute, such as about any of 1 minute, 2 minutes, 3 minutes, 5 minutes, 7 minutes, or 10 minutes. In some embodiments, the mixture of (i) is heated and stirred for no more than about 120 minutes, such as no more than about any of 90 minute, 60 minutes, 45 minutes, 40 minutes, 30 minutes, 20 minutes, or 10 minutes. In some embodiments, the mixture of (i) is heated and stirred for about 10 minute, such as about any of 10 minute, 15 minutes, 20 minutes, 25 minutes, or 30 minutes. In some embodiments, the mixture of (ii) is cooled to a temperature of no more than 30 °C, such as about any of 30 °C, 25 °C, 20 °C, 15 °C, 10 °C, or 5 °C. In some embodiments, the mixture of (ii) is cooled to a temperature of at least about 0 °C, such as at least about any of 5 °C, 10 °C, 15 °C, 20 °C, or 25 °C. In some embodiments, the mixture of (ii) is cooled to a temperature of about any of 5 °C, 10 °C, 15 °C, 20 °C, or 25 °C. In some embodiments, after adding polymorphic Form B as seed, the mixture of (iv) is heated up to an elevated temperature of at least about 30°C, such as at least about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, or 70 °C. In some embodiments, the mixture of (iv) is heated to an elevated temperature no more than about any of 90°C, 85 °C, 80 °C, 75 °C, 70 °C, 65 °C, 50 °C, 45 °C, or 40 °C. In some embodiments, the mixture of (iv) is heated

to an elevated temperature of about any of 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, or 65 °C. In some embodiments, after adding polymorphic Form B as seed, the mixture of (iv) is heated up to an elevated temperature within an hour (e.g., within about any of 40 minutes, 30 minutes, 20 minutes, 10 minutes, or 5 minutes). In some embodiments, after adding polymorphic Form B as seed, the mixture of (iv) is heated up to an elevated temperature over a period of at least 1 minute, such as at least about any of 1 min, 10 min, 20 min, 30 min, 40 min, 50 min, or 1 hour. In some embodiments, the mixture of (v) is cooled to a temperature of no more than 30 °C, such as about any of 25 °C, 20 °C, 15 °C, or 10 °C. In some embodiments, the mixture of (v) is cooled to a temperature of at least about 0 °C, such as at least about any of 5 °C, 10 °C, 15 °C, 20 °C, or 25 °C. In some embodiments, the mixture of (v) is cooled to a temperature of about any of 5 °C, 10 °C, 15 °C, 20 °C, or 25 °C. In some embodiments, the mixture of (v) is cooled to a temperature of no more than 30 °C at a cooling rate of about 1 °C/h to 20 °C/h, such as about any of 1 °C/h to 15 °C/h, 1 °C/h to 10 °C/h, or about 6 °C/h. In some embodiments, the method further comprises filtering the suspension obtained from step (vi). In some embodiments, the method further comprises drying the obtained polymorphic Form B.

[0307] In some embodiments, provided herein is a method of preparing polymorphic Form B, comprising (i) suspending compound of Formula (A-1) (that is not the polymorphic Form B) in a solvent to form a mixture; and (ii) stirring the mixture of step (i) for a period of time. In some embodiments, the compound of Formula (A-1) in step (i) can be a polymorphic form provided herein (other than polymorphic Form B). In some embodiments, the compound of Formula (A-1) in step (i) is polymorphic Form A. In some embodiments, the method further comprises (i-a) adding polymorph Form B seed in the mixture of (i). In some embodiments, the mass ratio between polymorphic Form A and polymorphic Form B is about 1:1 to about 200:1, such as about any of 1:1 to 150:1, 50:1 to 150:1, or 100:1. In some embodiments, the purity of polymorphic Form A is higher than about any of 95%, 95.5%, 96%, 96.5%, 97%, 97.5%, 98%, 98.5%, 99%, or 99.5%. In some embodiments, the purity of polymorphic Form A is higher than about 96%. In some embodiments, the purity of polymorphic Form A is higher than or equal to 97%. In some embodiments, the solvent comprises methanol (MeOH), methyl ethyl ketone (MEK), ethyl acetate (EA), 2-methyltetrahydrofuran (2-Me-THF), acetonitrile (ACN), or any mixture thereof. In some embodiments, the solvent is MeOH, MEK, EA, 2-Me-THF, or ACN. In some embodiments, the solvent is MEK. In some embodiments, the solvent comprises about 0% to about any of 1%, 0.5%, 0.4%, 0.3%, 0.2%,

0.1%, 0.05%, 0.01%, 0.005%, or 0.001% EA. In some embodiments, the solvent comprises about 0% to about 0.3% EA. In some embodiments, the solvent does not comprise EA. In some embodiments, the solvent is ACN. In some embodiments, the mixture of (i) is stirred at or above about any of 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, 70 °C, 75 °C, or 80 °C. In some embodiments, the mixture of (i) is stirred at no more than about any of 120 °C, 115 °C, 110 °C, 105 °C, 100 °C, 95 °C, 80 °C, 75 °C, 70 °C, 65 °C, 60 °C, 55 °C, or 50 °C. In some embodiments, the mixture of (i) is stirred at or above about 50 °C. In some embodiments, the mixture of (i) is stirred at a temperature at about any of 20 °C, 25 °C, 30 °C, 35 °C, 40 °C, 45 °C, 50 °C, 55 °C, 60 °C, 65 °C, 70 °C, 75 °C, or 80 °C. In some embodiments, the mixture of (i) is stirred at about 50 °C. In some embodiments, the mixture of (i) is stirred at a temperature at or above about 50 °C. In some embodiments, the mixture of (i) is stirred at a given temperature for less than about any of 5 days, 4 days, 3 days, 2 days, 25 hours, 24 hours, 23 hours, 22 hours, 21 hours, 20 hours, 19 hours, 18 hours, 17 hours, 16 hours, 15 hours, 14 hours, 13 hours, 12 hours, 11 hours, 10 hours, 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, or 1 hour. In some embodiments, the mixture of (i) is stirred at a given temperature for at least about any of 1 hour, 2 hours, 3 hours, 4 hours, 5 hours, 6 hours, 7 hours, 8 hours, 9 hours, 10 hours, 11 hours, 12 hours, 13 hours, 14 hours, 15 hours, 16 hours, 17 hours, 18 hours, 19 hours, 20 hours, 21 hours, 22 hours, 23 hours, or 24 hours. In some embodiments, the mixture of (i) is stirred at a given temperature for less than about 25 hours. In some embodiments, the mixture of (i) is stirred at a given temperature for about any of 5 days, 4 days, 3 days, 2 days, 25 hours, 24 hours, 23 hours, 22 hours, 21 hours, 20 hours, 19 hours, 18 hours, 17 hours, 16 hours, 15 hours, 14 hours, 13 hours, 12 hours, 11 hours, 10 hours, 9 hours, 8 hours, 7 hours, 6 hours, 5 hours, 4 hours, 3 hours, 2 hours, or 1 hour. In some embodiments, the mixture of (i) is stirred at a given temperature for about 24 hours. In some embodiments, the mixture of (i) is stirred at about 40 °C to about 60 °C for less than about 25 hours. In some embodiments, the mixture of (i) is stirred at about 50 °C for about 24 hours. In some embodiments, the method further comprises (iii) cooling the mixture of (ii). In some embodiments, the mixture of (ii) is cooled to a temperature of about 20 °C to about 30 °C, such as about 25 °C. In some embodiments, the mixture of (ii) is cooled quickly, such as within a period of less than 10 hours, such as less than about any of 7 hours, 5 hours, or 3 hours. In some embodiments, the method further comprises (iv) adding an antisolvent to the cooled mixture of (iii). In some embodiments, the

antisolvent comprises n-heptane (HEP). In some embodiments, the solvent is MEK and the antisolvent is HEP.

III-p. Method of Preparation – Polymorphic Form C

[0308] In some embodiments, provided is a method of preparing polymorphic Form C of the compound of Formula (A-1), the method comprising: (1) mixing the compound of Formula (A-1) with a first solvent; (2) adding a second solvent to the mixture of (1) and obtaining a solid; (3) washing the solid of (2) by the second solvent; and (4) drying the solid of (3). In some embodiments, the first solvent is DMF. In some embodiments, the second solvent is water. In some embodiments, the first solvent is DMF and the second solvent is water. In some embodiments of (2), the second solvent is added at a temperature that is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments of (4), the solid of (3) is dried at a temperature that is 10 °C higher or lower than the room temperature, 5 °C higher or lower than the room temperature, 3 °C higher or lower than the room temperature, or about the room temperature. In some embodiments of (4), the solid of (3) is dried under vacuum.

IV. Salt Forms

[0309] In some aspects, provided herein is a pharmaceutically acceptable salt of the compound of Formula (A-1). In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is formed with inorganic and/or organic bases. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with a base comprising NaOH, KOH, Mg(OH)₂, Ca(OH)₂, L-arginine, L-lysine, choline, betaine, diethylamine, or any combination thereof.

[0310] In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with an inorganic base comprising NaOH, KOH, Mg(OH)₂, Ca(OH)₂, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) comprises a sodium salt, a potassium salt, a magnesium salt, a calcium salt, a zinc salt, or any

combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt, wherein the stoichiometry between compound of Formula (A-1) and sodium ion is about 1:0.8 to 1:3, such as about any of 1:0.9 to 1:2.7, 1:1 to 1:2.5, 1:1 to 1:2.3, 1:1 to 1:1.5, or 1:2 to 1:2.3. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a mono-sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a di-sodium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt, wherein the stoichiometry between compound of Formula (A-1) and potassium ion is about 1:0.8 to 1:3, such as about any of 1:0.9 to 1:2.7, 1:1 to 1:2.5, 1:1 to 1:2.3, 1:1 to 1:1.5, or 1:2 to 1:2.3. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a mono-potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a di-potassium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a magnesium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a calcium salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a zinc salt.

[0311] In some embodiments, in conjunction with the embodiments above or below, the pharmaceutically acceptable salt of the compound of Formula (A-1) is derived from reacting the compound of Formula (A-1) with an organic base comprising L-arginine, L-lysine, choline, betaine, diethylamine, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) comprises a L-arginine salt, a L-lysine salt, a choline salt, a betaine salt, a diethylamine salt, or any combination thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a L-arginine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a L-lysine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a choline salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a betaine salt. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a diethylamine salt.

[0312] In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a sodium salt, wherein the sodium salt is in a polymorphic form selected from the group consisting of polymorphic Form IV, polymorphic Form V, polymorphic Form VIII, polymorphic Form X, polymorphic Form XI, polymorphic Form XII, and any mixture thereof. In some embodiments, the pharmaceutically acceptable salt of the compound of Formula (A-1) is a potassium salt, wherein the potassium salt is in a polymorphic form selected from the group consisting of polymorphic Form VI, polymorphic Form VII, polymorphic Form IX, and any mixture thereof.

V. Methods of Use

V-a. Method of Treatment

[0313] In one aspect, the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein, may be used to inhibit KIF18A. In another aspect, the solid formulation comprising a compound of Formula (A) or the polymorphic form of a compound of Formula (A-1), as described herein, may be used to treat or prevent a disease or condition in an individual.

[0314] The inhibitory activity of the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein, against KIF18A may be determined and measured by methods known in the art including, but not limited to, inhibition of ATP hydrolysis in the presence of microtubules (Hackney D.D., Jiang W. (2001) Assays for Kinesin Microtubule-Stimulated ATPase Activity. In: Vernos I. (eds) Kinesin Protocols. Methods in Molecular Biology™, vol 164. Humana Press. <https://doi.org/10.1385/1-59259-069-1:65>).

[0315] In one aspect, provided herein is a method of inhibiting KIF18A comprising contacting a cell with an effective amount of the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. In some embodiments, provided herein are methods of inhibiting KIF18A comprising contacting a cell with an effective amount of a solid formulation

comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), and Formula (A-3) or pharmaceutically acceptable salt thereof, as described herein. In some embodiments, provided herein are methods of inhibiting KIF18A comprising contacting a cell with an effective amount of a polymorphic form of a compound of Formula (A-1), as described herein. In some embodiments, provided herein are methods of inhibiting KIF18A comprising contacting a cell with an effective amount of a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. In one variation of the aforementioned embodiments, the cell is contacted *in vitro*. In other variations of the aforementioned embodiments, the cell is contacted *in vivo*.

[0316] In another aspect, the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein, may be used to treat or prevent a disease or condition in an individual, comprising administering an effective amount of a compound or a pharmaceutical composition as described herein. When used in a prophylactic manner, the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, the polymorphic form of a compound of Formula (A-1), or the pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein, may prevent a disease or disorder from developing in an individual at risk of developing the disease or disorder, or lessen the extent of a disease or disorder that may develop.

[0317] In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a solid formulation comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3), or a pharmaceutically acceptable salt thereof, as described herein. In some embodiments, provided herein are methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a polymorphic form of a compound of Formula (A-1), as described herein. In some embodiments, provided herein are

methods of treating or preventing a disease or condition in an individual, comprising administering to the subject a therapeutically effective amount of a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein.

[0318] In some embodiments, the disease or condition is mediated by KIF18A. In some embodiments, the disease or condition is cancer. In some embodiments, the disease or condition is a cellular proliferation disorder, including uncontrolled cell growth, aberrant cell cycle regulation, centrosome abnormalities (structural and or numeric, fragmentation), a solid tumor, hematopoietic cancer and hyperproliferative disorder, such as thyroid hyperplasia (especially Grave's disease), and cyst (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome). Solid and hematologically derived tumors, such as carcinomas, may include but are not limited to cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung (including squamous cell and small cell lung cancer), pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, and skin (including squamous cell carcinoma), hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma), hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia), hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, *e.g.*, soft tissue and bone), tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas), tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors (including retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, Ewing's sarcoma, Kaposi's sarcoma), and other cancer-related disorders that are a consequence of cancer presence or progression such as tumor-induced pleural or pericardial effusions, and malignant ascites. In some embodiments, the disease or condition is cancer, and the cancer is selected from the group consisting of advanced solid tumor, high grade serous adenocarcinoma of ovary, squamous non-small-cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, colorectal adenocarcinoma, esophageal squamous cell

carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, transitional cell carcinoma of bladder, head and neck squamous cell carcinoma, ovarian carcinosarcoma, uterine carcinosarcoma, uterine serous carcinoma, and endometrium cancer. In some embodiments, the disease or condition (e.g., cancer) is associated with chromosomal instability.

[0319] In some embodiments, provided are methods of treating or preventing cancer in an individual, comprising administering to the individual in need thereof a solid formulation comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3) or a pharmaceutically acceptable salt thereof, as described herein. In some embodiments, provided are methods of treating or preventing cancer in an individual, comprising administering to the individual in need thereof, comprising administering to the subject a therapeutically effective amount of a polymorphic form of a compound of Formula (A-1), as described herein. In some embodiments, provided are methods of treating or preventing cancer in an individual, comprising administering to the individual in need thereof, comprising administering to the subject a therapeutically effective amount of a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. In some embodiments, provided are methods of treating or preventing cancer in a subject in need thereof comprising administering to the subject a therapeutically effective amount of at least one chemical entity as described herein. Also provided herein is the use of a solid formulation comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3), or a pharmaceutically acceptable salt thereof, as described herein, in the manufacture of a medicament for treatment of a disease in a subject. Also provided herein is the use of a polymorphic form of a compound of Formula (A-1), as described herein, in the manufacture of a medicament for treatment of a disease in a subject. Also provided herein is the use of a pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein, in the manufacture of a medicament for treatment of a disease in a subject. In some embodiments of the foregoing, the cancer is selected from the group consisting of advanced solid tumor, high grade serous adenocarcinoma of ovary, squamous non-small-cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, colorectal adenocarcinoma, esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, transitional cell carcinoma of bladder, head and neck squamous cell carcinoma, ovarian carcinosarcoma, uterine carcinosarcoma, uterine serous carcinoma, endometrium cancer and endometrium cancer. In

some embodiments, the disease or condition (e.g., cancer) is associated with chromosomal instability.

[0320] In some embodiments, provided herein are methods of treating cancer, comprising administering to an individual in need thereof a solid formulation comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3), or a pharmaceutically acceptable salt thereof, as described herein. In some embodiments, provided herein are methods of treating cancer, comprising administering to an individual in need thereof a polymorphic form of a compound of Formula (A-1), or a pharmaceutically acceptable salt thereof, as described herein. Also provided herein is the use of a solid formulation comprising a compound of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3), or a pharmaceutically acceptable salt thereof, as described herein, in the manufacture of a medicament for treatment of a cancer. Also provided herein is the use of a polymorphic form of a compound of Formula (A-1), as described herein, in the manufacture of a medicament for treatment of a cancer. Also provided herein is the use of a pharmaceutically acceptable salt form of a compound of Formula (A-1), or a pharmaceutically acceptable salt thereof, as described herein, in the manufacture of a medicament for treatment of a cancer.

[0321] In some embodiments, provided herein are methods of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a formulation or polymorphic form as described herein.

[0322] In some embodiments, provided herein are methods of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, the polymorphic form of a compound of Formula (A-1), or the pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. In some embodiments, the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin,

small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression. In some embodiments, the cancer is selected from the group consisting of advanced solid tumor, high grade serous adenocarcinoma of ovary, squamous non-small-cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, colorectal adenocarcinoma, esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, transitional cell carcinoma of bladder, head and neck squamous cell carcinoma, ovarian carcinosarcoma, uterine carcinosarcoma, uterine serous carcinoma, and endometrium cancer. In some embodiments, the disease or condition (e.g., cancer) is associated with chromosomal instability.

[0323] Administration of the compounds and formulations described herein can be via any accepted mode of administration for therapeutic agents including, but not limited to, oral, sublingual, subcutaneous, parenteral, intravenous, intranasal, topical, transdermal, intraperitoneal, intramuscular, intrapulmonary, vaginal, rectal, or intraocular administration. In some embodiments, the compound or formulation is administered orally or intravenously. In some embodiments, the compound or formulation described herein is administered orally.

[0324] In some embodiments, the compounds and formulations described herein is administered periodically. In some embodiments, the compound or formulation is administered daily. In some embodiments, the compound or formulation is administered every 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 days. In some embodiments, the compound or formulation is administered every 28 days. In some embodiments, administrations of the compound or formulation are at least 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, or 36 days apart. In some embodiments, administrations of the compound or formulation are at least 28 days apart. In some embodiments, the compound or formulation is administered in 2-, 3-, 4-, 5-, 6-, 7-, 8-, 9-, 10-, 11-, 12-, 13-, 14-, 15-, 16-, 17-, 18-, 19-, 20-, 21-, 22-, 23-, 24-, 25-, 26-, 27-, 28-, 29-, 30-, 31-, 32-, 33-, 34-, 35-, or 36-day cycles. In some embodiments, the compound or formulation is administered in 28-day cycles. In some embodiments, the compound or formulation is administered orally in 28-day cycles.

V-b. Kits

[0325] Also provided are articles of manufacture and kits containing any of the solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, the polymorphic form of a compound of Formula (A-1), or the pharmaceutically acceptable salt form of a compound of Formula (A-1), as described herein. The article of manufacture may comprise a container with a label. Suitable containers include, for example, bottles, vials, and test tubes. The containers may be formed from a variety of materials such as glass or plastic. The container may hold a pharmaceutical composition provided herein. The label on the container may indicate that the pharmaceutical composition is used for preventing, treating or suppressing a condition described herein, and may also indicate directions for either *in vivo* or *in vitro* use.

[0326] In one aspect, provided herein are kits containing a solid formulation comprising a compound of Formula (A) or a polymorphic form of a compound of Formula (A-1), as described herein, and instructions for use. The kits may contain instructions for use in the treatment of any disease or condition described herein in an individual in need thereof. A kit may additionally contain any materials or equipment that may be used in the administration of the compound or composition, such as vials, syringes, or IV bags. A kit may also contain sterile packaging.

V-c. Combinations

[0327] The solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, the polymorphic form of a compound of Formula (A-1), or the pharmaceutically acceptable salt form of a compound of Formula (A-1) described herein may be administered alone or in combination with other therapies and/or therapeutic agents useful in the treatment of the aforementioned disorders.

[0328] The solid formulation comprising a compound of Formula (A) or pharmaceutically acceptable salt thereof, the polymorphic form of a compound of Formula (A-1), or the pharmaceutically acceptable salt form of a compound of Formula (A-1) described herein may be combined with one or more other therapies to treat the diseases or conditions described herein. In some embodiments, the disease or condition is cancer. In some embodiments, the disease or condition is a cellular proliferation disorder, including uncontrolled cell growth, aberrant cell cycle regulation, centrosome abnormalities (structural and or numeric, fragmentation), a solid tumor, hematopoietic cancer and hyperproliferative disorder, such as

thyroid hyperplasia (especially Grave's disease), and cyst (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein-Leventhal syndrome). Solid and hematologically derived tumors, such as carcinomas, may include but are not limited to cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung (including squamous cell and small cell lung cancer), pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, and skin (including squamous cell carcinoma), hematopoietic tumors of lymphoid lineage (including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma), hematopoietic tumors of myeloid lineage (including acute and chronic myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia), hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, *e.g.*, soft tissue and bone), tumors of the central and peripheral nervous system (including astrocytoma, neuroblastoma, glioma and schwannomas), tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors (including retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, Ewing's sarcoma, Kaposi's sarcoma), and other cancer-related disorders that are a consequence of cancer presence or progression such as tumor-induced pleural or pericardial effusions, and malignant ascites. In some embodiments, the cancer is selected from the group consisting of advanced solid tumor, high grade serous adenocarcinoma of ovary, squamous non-small-cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, colorectal adenocarcinoma, esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, transitional cell carcinoma of bladder, head and neck squamous cell carcinoma, ovarian carcinosarcoma, uterine carcinosarcoma, uterine serous carcinoma, and endometrium cancer. In some embodiments, the disease or condition (*e.g.*, cancer) is associated with chromosomal instability.

EXAMPLES

Example 1. Materials, Methods, and Abbreviations

Differential Scanning Calorimetry (DSC)

[0329] DSC was performed using a TA Instruments Discovery DSC2500 differential scanning calorimeter equipped with a TA instruments Refrigerated Cooling System 90 operating in either modulated or ramp mode. DSC was used to measure thermodynamic properties SDIs prepared herein, including the following: glass transition temperature (T_g) defined as the temperature at which amorphous materials transition from a low mobility glassy state to a high mobility rubbery state, cold crystallization temperature (T_c), defined as a crystallization event at a temperature lower than the melt temperature, and melting temperature (T_m). The system was purged by nitrogen flow at 50 mL/min to ensure inert atmosphere through the course of measurement.

[0330] Spray dried samples were placed in non-hermetic aluminum pans and heated at a constant rate of 2.0 °C/min. DSC parameters are summarized in Table 1-1.

Table 1-1

Instrument	TA Discovery DSC2500, RCS 90
Sample Pans	Tzero AI, non-hermetic
Temperature Range	20 - 250 °C
Heating Rate	2 °C/min
Scanning Mode	Modulated
Modulation Frequency	60 s
Modulation Amplitude	1 °C

X-Ray Powder Diffraction (XRPD)

[0331] For characterization of solid formulations, XRPD was performed using a Rigaku Miniflex 6G X-ray diffractometer to evaluate the crystallinity of bulk compounds and SDDs. Amorphous materials give an “amorphous halo” diffraction pattern, absent of discrete peaks that are found in crystalline material. Samples were irradiated with monochromatized Cu $K\alpha$ radiation and analyzed from 5° and 40° with a continuous scanning mode. Samples were rotated during analysis to minimize preferred orientation effects. XRPD parameters are shown in Table 1-2.

Table 1-2

Instrument	Rigaku Miniflex 6G
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Radiation Source	Cu-K α (1.5406 Å), Line Focus 0.4mm x 12mm
Scan Type	Coupled 2 θ / θ
Scan Range	5°-40°
Step Increment	0.005°
Ramp Rate	2.0°/min (SDI); 20.0°/min (API)
Voltage	40kV
Current	15mA
Rotation	30rpm
Holder	Zero-Background Cup
Receiving Slit Width	13.0mm (open)
Divergent Slit Width	0.625mm
Knife Edge Width	1.0mm

[0332] For characterization of polymorphic forms, both transmission geometry and reflection geometry were used.

[0333] In transmission geometry, XRPD patterns were collected with PANalytical X'Pert PRO MPD or Empyrean diffractometers using an incident beam of Cu radiation produced using an Optix long, fine-focus source. An elliptically graded multilayer mirror was used to focus Cu K α X-rays through the specimen and onto the detector. Prior to the analysis, a silicon specimen (NIST SRM 640f) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was sandwiched between 3- μ m-thick films and analyzed in transmission geometry. A beam-stop, short anti-scatter extension, and an anti-scatter knife edge were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a scanning position-sensitive detector (X'Celerator) located 240 mm from the specimen and Data Collector software v. 5.5.

[0334] In reflection geometry, XRPD patterns were collected with a PANalytical X'Pert PRO MPD diffractometer using an incident beam of Cu K α radiation produced using a long, fine-focus source and a nickel filter. The diffractometer was configured using the symmetric Bragg-Brentano geometry. Prior to the analysis, a silicon specimen (NIST SRM 640f) was analyzed to verify the observed position of the Si 111 peak is consistent with the NIST-certified position. A specimen of the sample was prepared as a thin, circular layer centered on a silicon zero-background substrate. Anti-scatter slits (SS) were used to minimize the background generated by air. Soller slits for the incident and diffracted beams were used to minimize broadening from axial divergence. Diffraction patterns were collected using a

scanning position-sensitive detector (X'Celerator) located 240 mm from the sample and Data Collector software v. 5.5.

¹H NMR

[0335] The proton solution NMR spectra were acquired with a Bruker AVANCE 600 MHz Spectrometer using DMSO-*d*₆.

Polarized Light Microscopy (PLM)

[0336] Light microscopy was performed using a Leica MZ12.5 stereomicroscope. Samples were observed using 0.8-10× objectives with crossed polarizers and a first order red compensator. Samples were either viewed in situ or in a drop of mineral oil. The PLM images of polymorphic forms were taken using a Leica DM LP microscope equipped with an Infinity2 color camera. Crossed polarizers with a first order red compensator and Koehler illumination was used. Samples were placed on a glass microscope slide and a 1½ cover glass is placed over the sample. Then mineral oil was added to the edge of the cover glass to cover the sample by capillarity. Images were acquired at ambient temperature using Teledyne Lumenera INFINITY ANALYZE software version 7.1.0.1215. The camera was white balanced in accordance with the Initial Camera Configuration in the software.

Particle Morphology by Scanning Electron Microscopy (SEM)

[0337] SEM samples were prepared by dispersing powder onto an adhesive carbon-coated sample stub and coating with a thin conductive layer of gold-palladium using a Cressington 108 Auto. Samples were analyzed using a Phenom XL fitted with an Everhart-Thornley (secondary electron) detector or backscatter detector operating in high vacuum mode. Micrographs at various magnifications were captured for qualitative particle morphology analysis. Experimental parameters were varied from sample to sample to obtain the best imaging conditions and are documented in the caption of each micrograph.

Particle Size Distribution (PSD) by Light Diffraction

[0338] The particle size distribution of SDI samples was determined by laser diffraction using a Mastersizer 3000 with an Aero S unit (Malvern Instruments). The parameters are listed in Table 1-3. Dv₁₀, Dv₅₀ and Dv₉₀ diameters were used to describe the particle size

distribution. For instance, the Dv_{50} diameter is the diameter at which 50% of a sample's volume is comprised of smaller particles.

Table 1-3

Instrument	Malvern Mastersizer 3000
Dispersion Unit	Aero S (Dry)
Dispersion Gas	Nitrogen
Gas Pressure	2.0 bar
Feed Rate	20-60%
Obscuration Limits	0.1%-10%
Refractive Index Name	Drug and Polymer Dispersion
Refractive Index	1.52
Density	1 g/mL
Measurement Duration	3 s
Measurement Replicates	n=3
Method	DM-0166

Assay and Impurities by High Performance Liquid Chromatography (HPLC)

[0339] Assay and impurities of SDI samples were evaluated using an HPLC method provided by the client. Parameters are listed in Table 1-4. The method demonstrated passing system suitability criteria for early development work, including but not limited to reproducibility, standard agreement, injector precision, tailing, and signal to noise.

Table 1-4

Column	Waters SunFire® C18, 4.6x150mm, 3.5 μ m, PN:186002554, SN: 01743135613891		
Mobile Phase A	0.05% TFA in Water (v/v)		
Mobile Phase B	0.05% TFA in ACN (v/v)		
Diluent	1:1 MeOH:ACN (v/v)		
Program Type	Gradient		
Gradient Program	Time (min)	% MPA	% MPB
	0.0	95	5
	5.0	30	70
	10.0	30	70
	10.1	95	5
	15.0	95	5
Flow Rate	1.0 mL/min		
Column Temperature	30°C		
Sample Temperature	Room Temperature		
Injection Volume	15 μ L		
Needle Wash	Diluent		
Detection Method	UV		
Detection Wavelength	220 nm		
Detection Bandwidth	4 nm		

Slit Width	4 nm
Reference Wavelength	OFF
Collect Spectra	YES
Run Time	15 min

Residual Solvent by Gas Chromatography – Headspace Sampling

[0340] The residual solvent content of SDIs was measured by GC-HS after secondary drying. Measurements were made using an HP 6890 series GC equipped with an Agilent 7697A headspace sampler. A 30 m × 0.32 mm × 1.8 μ capillary column with 6% cyanopropylphenyl 94% dimethylpolysiloxane Agilent GC column PN: 123-1334 was used for the testing. GC samples were prepared by dissolving approximately 100 mg sample in 4 mL dimethyl sulfoxide (DMSO). The GC method parameters are summarized in Table 1-5, Table 1-6, and Table 1-7.

Table 1-5. HP 7697A Headspace Autosampler Parameters

Sample Temperature	105 °C
Sample Loop Temperature	110 °C
Transfer Line Temperature	115 °C
GC Cycle Time	30 min
Vial Equilibration Time	30 min
Injection Time	1.00 min
Injection Loop Size	1 mL
Post Injection Purge	100 mL/min; 1 min
Carrier Gas	N2, ≥99.999%
Carrier Gas Flow	25 mL/min
Vial Pressure	15.0 psi
LOQ	200 ppm

Table 1-6. Gas Chromatograph Operating Parameters

Injector Temperature	180 °C
Detector Temperature	300 °C
Detector Type	FID
Carrier Gas	N2
Flow Rate (Flow Control Mode)	1.6 mL/min (Constant Flow)
Split Ratio	30:1
Split Flow	40
Inlet Type	S/SL EPC
Inlet Mode	Split
Injection Port Liner	Appropriate headspace injection port liner

Table 1-7. Oven Temperature Gradient.

Oven	Rate (°C/min)	Temperature (°C)	Hold Time (min)	Total Time (min)
Initial	NA	40	5	5
Ramp 1	2	50	0	10
Ramp 2	10	60	0	11
Ramp 3	50	225	1	15.3
Ramp 4	50	120	0.5	17.9
Ramp 5	10	60	0.5	24.4
Ramp 6	5	40	1	29.4

TGA/DSC Combination Analyses

[0341] TGA/DSC combination analyses were performed using a Mettler Toledo TGA/DSC3+ analyzer. Temperature and enthalpy adjustments were performed using phenyl salicylate, indium, tin, and zinc, and then verified with indium. Balance was verified with calcium oxalate. The sample was placed in an aluminum pan. The pan was hermetically sealed, the lid pierced, then inserted into the TG furnace. A weighed aluminum pan configured as the sample pan was placed on the reference platform. The furnace was heated under nitrogen.

Dynamic vapor sorption (DVS)

[0342] Moisture sorption/desorption data were collected on a Surface Measurement System DVS Intrinsic instrument. Samples were not dried prior to analysis. Sorption and desorption data were collected over a range from 5% to 95% RH at 10% RH increments. The equilibrium criterion used for analysis was less than 0.0100% weight change in 5 minutes with a maximum equilibration time of 3 hours.

Temperature modulated differential scanning calorimetry (TMDSC)

[0343] Temperature-modulated DSC (TMDSC) was performed using a Mettler Toledo DSC3+ differential scanning calorimeter. Temperature calibration was performed using octane, phenyl salicylate, indium, tin, and zinc. The sample was placed into a hermetically sealed aluminum DSC pan, the weight was accurately recorded, and the sample was inserted into the DSC cell. A weighed aluminum pan configured as the sample pan was placed on the reference side of the cell. The pan lid was pierced prior to sample analysis. The sample was analyzed from −50 °C to 250 °C at 2 °C/min with a pulse height of 0.5 °C.

Abbreviations

1-BuOH	1-Butanol
1-PrOH	1-Propanol
2-BuOH	2-Butanol
2-Me-THF	2-Methyltetrahydrofuran
ACN	acetonitrile
agg.	aggregates/agglomerates
API	active pharmaceutical ingredient
aq	aqueous
B/E	birefringence/extinction
BCS	Biopharmaceutics Classification System
BSA	bovine serum albumin
BTN	Butyronitrile
BuOAc	Butyl acetate
CHCl ₃	Chloroform
CPME	Cyclopentyl methyl ether
DAST	diaminosulfur trifluoride
dba	bibenzylidene acetone
DCM	dichloromethane
DMA	Dimethylacetamide
DME	Dimethoxyethane
DMF	dimethylformamide
DMSO	dimethyl sulfoxide
DSC	differential scanning calorimetry
Dv	volume distribution
DVS	Dynamic vapor sorption
EA	Ethyl acetate
EDCI	1-ethyl-3-(3-dimethylaminopropyl)carbodiimide
EGEE	Ethylene glycol ethyl ether
ESI MS	electrospray mass spectrometry
EtOAc	Ethyl acetate
EtOH	Ethanol
FC	Fast cooling
FE	Fast evaporation
GC	gas chromatography
GC-HS	gas chromatography – headspace sampling
GLP	Good Laboratory Practices
HATU	1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxide hexafluorophosphate
HEP	n-heptane
HFIPA	Hexafluoroisopropanol
HOBT	1-hydroxybenzotriazole
HPLC	high-performance liquid chromatography
HPMCAS	hydroxypropyl methylcellulose acetate succinate
iBuOAc	Isobutyl acetate
i-BuOH	Isobutanol
IC ₅₀	50% inhibitory concentration
ICH	International Conference on Harmonization
IPA	Isopropyl alcohol

IPE	Diisopropyl ether
LDA	lithium diisopropylamide
LOQ	limit of quantitation
mCPBA	meta-chloroperoxybenzoic acid
MDSC	modulated differential scanning calorimetry
MEK	Methyl ethyl ketone
MeOH	Methanol
MIBK	Methyl isobutyl ketone
MIPK	Methyl isopropyl ketone
MPA	mobile phase A
MPB	mobile phase B
MsCl	methanesulfonyl chloride
MTBE	Methyl tert-butyl ether
N/A	not applicable
NCI	N-iodosuccinimide
NCS	N-chlorosuccinimide
ND	not detected
NMP	N-Methylpyrrolidone
NMR	Nuclear magnetic resonance spectroscopy
PBS	phosphate-buffered saline
PE	petroleum ether
pH	negative logarithm of hydronium ion concentration
PLM	Polarized laser microscopy
ppm	parts per million
PSD	particle size distribution
psi	pounds per square inch
RH	relative humidity
rpm	rotations per minute
RRT	relative retention time
RT	retention time
S/N	signal to noise ratio
s/n	serial number
SDD	spray dry dispersion
SDI	spray dry intermediate
SE	Slow evaporation
SEM	scanning electron microscopy
TAME	tert-Amyl methyl ether
t-AmOH	tert-Amyl alcohol
T _c	crystallization temperature
TFA	trifluoroacetic acid
TFE	2,2,2-Trifluoroethanol
T _g	glass-transition temperature
TGA	Thermogravimetric analysis
THF	Tetrahydrofuran
T _m	melting point
TMDSC	Temperature modulated differential scanning calorimetry
VD	Vapor diffusion
w/w	weight per weight

wt%	weight percent
Xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene
Xphos Pd G4	dicyclohexyl-[2-[2,4,6-tri(propan-2-yl)phenyl]phenyl]phosphonium; methanesulfonic acid; N-methyl-2-phenylaniline; palladium (CAS: 1599466-81-5)
XRPD	x-ray powder diffraction

Example S-1. Synthesis of compounds of Formula (A)

General synthetic methods

[0344] Compounds of Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), and Formula (A-3) will now be described by reference to illustrative synthetic schemes for their general preparation below and the specific examples that follow. Artisans will recognize that, to obtain the various compounds herein, starting materials may be suitably selected so that the ultimately desired substituents will be carried through the reaction scheme with or without protection as appropriate to yield the desired product. Alternatively, it may be necessary or desirable to employ, in the place of the ultimately desired substituent, a suitable group that may be carried through the reaction scheme and replaced as appropriate with the desired substituent. In addition, one of skill in the art will recognize that protecting groups may be used to protect certain functional groups (amino, carboxy, or side chain groups) from reaction conditions, and that such groups are removed under standard conditions when appropriate. Unless otherwise specified, the variables are as defined above in reference to Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3).

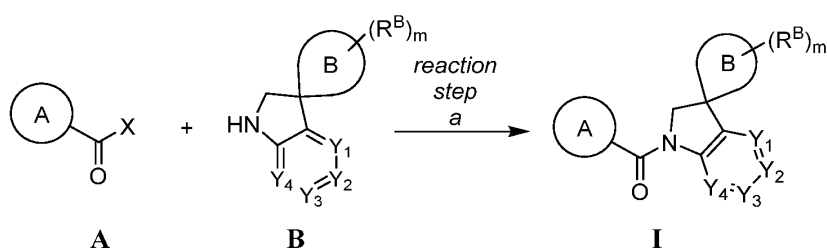
[0345] Where it is desired to obtain a particular enantiomer of a compound, this may be accomplished from a corresponding mixture of enantiomers using any suitable conventional procedure for separating or resolving enantiomers. Thus, for example, diastereomeric derivatives may be produced by reaction of a mixture of enantiomers, *e.g.*, a racemate, and an appropriate chiral compound. The diastereomers may then be separated by any convenient means, for example by crystallization and the desired enantiomer recovered. In another resolution process, a racemate may be separated using chiral High Performance Liquid Chromatography. Alternatively, if desired a particular enantiomer may be obtained by using an appropriate chiral intermediate in one of the processes described.

[0346] Chromatography, recrystallization and other conventional separation procedures may also be used with intermediates or final products where it is desired to obtain a particular isomer of a compound or to otherwise purify a product of a reaction.

[0347] General methods of preparing compounds described herein are depicted in exemplified methods below. Variable groups in the schemes provided herein are defined as for Formula (A), Formula (B), Formula (C), Formula (A-1), Formula (A-2), or Formula (A-3), or any variation thereof. Other compounds described herein may be prepared by similar methods.

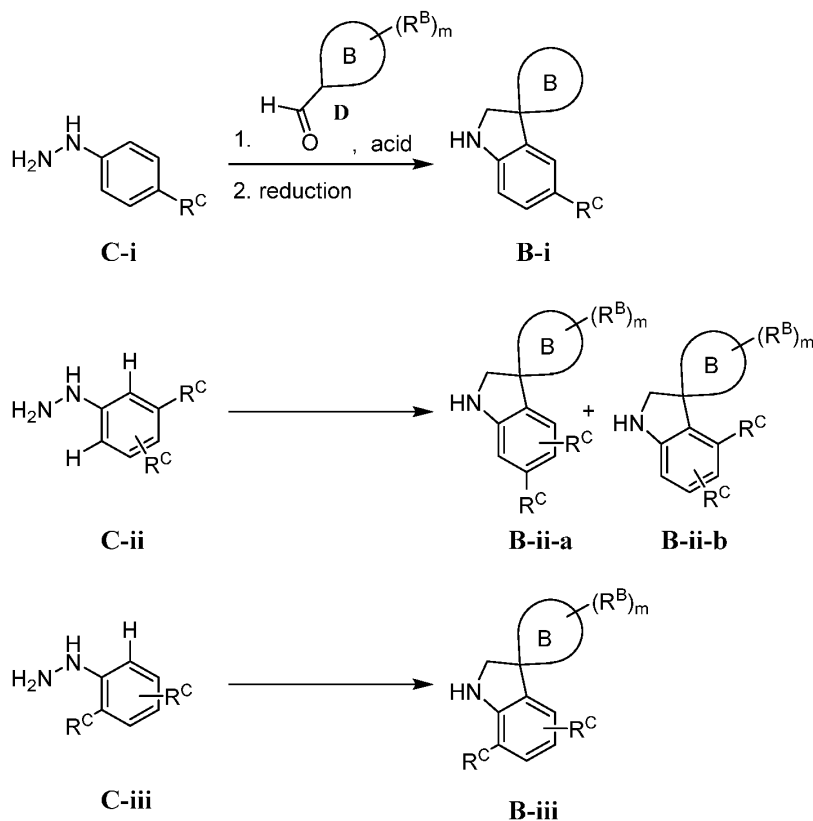
[0348] In some embodiments, compounds provided herein may be synthesized according to Scheme 1, Scheme 2, Scheme 3, and/or Scheme 4. Ring A, Ring B, Y¹, Y², Y³, Y⁴, m, R^B, and R^C, as shown in Schemes 1-4 below, are as defined for the compounds of Formula I.

Scheme 1.

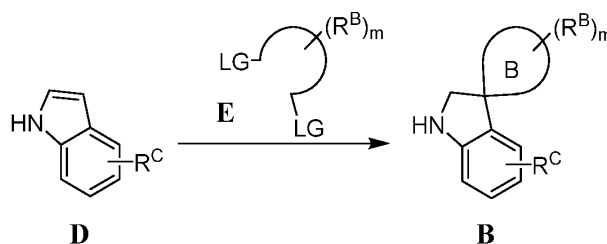


[0349] **Scheme 1** outlines an exemplary route to the synthesis of compound of general formula **I**. Compounds of formula **I** are prepared by the reaction of a carboxylic acid of formula **A** (*e.g.*, X = OH) and an indoline of formula **B** in the presence of coupling reagent, such as HATU with a base such as iPr₂NEt, or EDCI with a HOBt or DMAP. Alternatively, an acid halide of formula **A** (*e.g.*, X = Cl or F) is reacted directly with the compound of formula **B** with an acid scavenger, such as Et₃N.

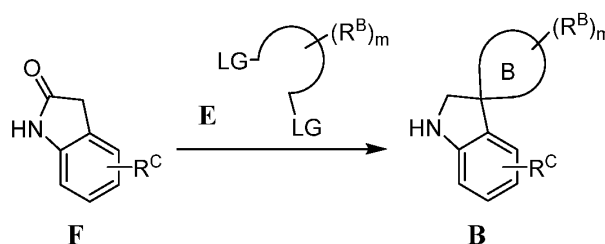
Scheme 2.



[0350] Indoline intermediates of formula **B** may be prepared *via* the Fisher Indole Synthesis as described in **Scheme 2**. Arylhydrazines of formula **C** (*e.g.*, formula **C-i**, formula **C-ii**, and formula **C-iii**) are reacted with a Ring **B**-substituted carbaldehyde of formula **D** in the presence of acid, followed by reaction with a reducing agent such as NaBH_4 , Pd/C and H_2 gas, or Et_3SiH . Arylhydrazines of formula **C-i**, which are para-mono-substituted, provide indolines of formula **B-i**, while hydrazines of formula **C-ii**, which contain at least one meta substituent and are not substituted in the ortho positions, provide a mixture of indolines of formulae **B-ii-a** and **B-ii-b**. Arylhydrazines of formula **C-iii**, that are substituted at one ortho position, provide indolines of formula **B-iii**.

Scheme 3.

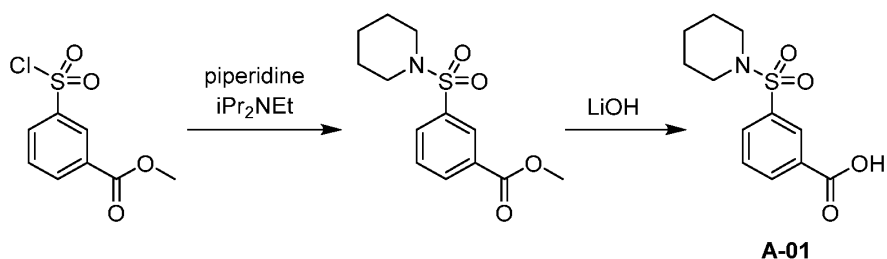
[0351] Indolines of formula **B** may also be prepared via an 3,3-dialkylation method described in **Scheme 3**. An indole of formula **D** is reacted with an optionally substituted 3-6 atom aliphatic and heteroaliphatic linear chain with two terminal leaving groups “LG” (formula **E**). LG may be Cl, Br, I, or sulfonate ester, or another suitable group displaceable by a nucleophile. The transformation may be mediated by a trialkylboron, such as Et_3B , and base, such as potassium t-butoxide. The spiroannulation reaction is followed by a reaction with a reducing agent such as NaBH_4 , Pd/C and H_2 gas, or Et_3SiH .

Scheme 4.

[0352] Indolines of formula **B** may also be prepared via the enolate alkylation of an indolin-2-one of formula **F**. The indolin-2-one of formula **F** is deprotonated with a strong base, such as butyllithium, sodium hexamethylsilazide, or potassium t-butoxide, and reacted with an optionally substituted 3-6 atom aliphatic and heteroaliphatic linear chain with two terminal leaving groups “LG” (formula **E**). LG may be Cl, Br, I, or sulfonate ester, or another suitable group displaceable by a nucleophile. This reaction may be mediated by an additive such as tetramethyldiaminoethane or hexamethylphosphorous triamide. The spiroannulation reaction is followed by a reaction with a reducing agent such as LiAlH_4 or borane.

Synthesis of Intermediates

Synthesis of 3-(piperidin-1-ylsulfonyl)benzoic acid (A-01)



[0353] Step 1. A mixture of piperidine (0.25 mL, 2.6 mmol), CH₂Cl₂ (5.0 mL), iPr₂NEt (1.3 mL, 7.7 mmol) and methyl 3-chlorosulfonylbenzoate (900 mg, 3.84 mmol, 1.5 eq) was stirred for 2 h, concentrated, poured into H₂O (20 mL), and extracted with EtOAc (2 x 10 mL). The extracts were combined, washed with brine (10.0 mL), dried over Na₂SO₄, filtered, and concentrated to provide methyl 3-(1-piperidylsulfonyl) benzoate (0.95 g).

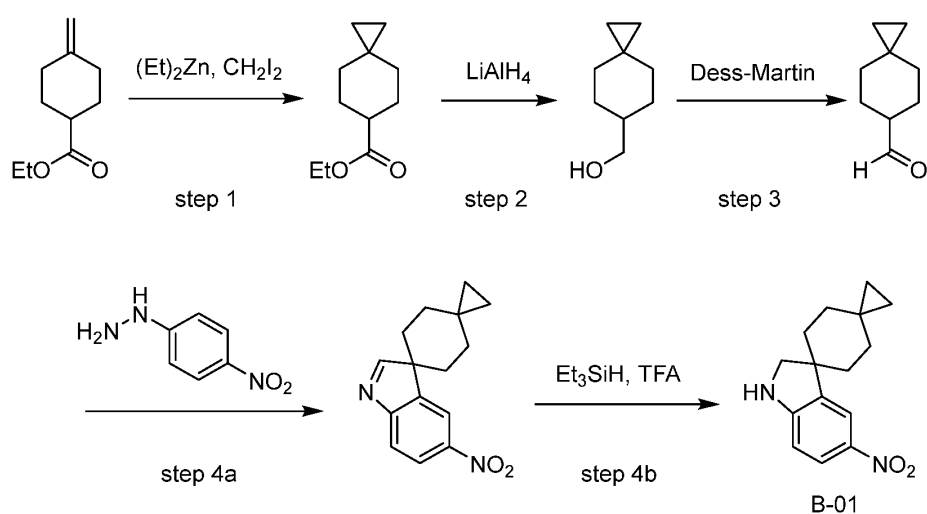
[0354] Step 2. A mixture of methyl 3-(1-piperidylsulfonyl) benzoate (0.90 g, 3.2 mmol), THF (6.0 mL), H₂O (2.0 mL), and LiOH•H₂O (0.67 g, 16 mmol) was stirred for 2 h, then was concentrated. The mixture was treated with HCl (4N) to bring the pH to 3, poured into H₂O (10 mL), and extracted with EtOAc (2 x 10 mL). The extracts were combined, washed with brine (10 mL), dried over Na₂SO₄, filtered, and concentrated to provide 3-(1-piperidylsulfonyl) benzoic acid (**A-01**, 0.72 g). ESI MS m/z: 270.0 (M+H)⁺.

[0355] Compounds **A-03** and **A-04** were prepared in the same manner as **A-01** from the sulfonyl chloride and amine indicated in Table S-1 below.

Table S-1

Compound	Structure	Sulfonyl Chloride	Amine
A-03			
A-04			

Synthesis of 5''-nitrodispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline] (B-01)



[0356] Step 1. To a mixture of ZnEt_2 (1 M in hexanes, 180 mL), CH_2Cl_2 (200 mL) at 0 °C under N_2 was added slowly CH_2I_2 (26 mL, 320 mmol), in CH_2Cl_2 (60 mL). The mixture was stirred at 0 °C for 30 min and ethyl 4-methylenecyclohexanecarboxylate (12 g, 71 mmol) in CH_2Cl_2 (50 mL) was slowly added. The mixture was stirred at 20 °C for 12 h, cooled to 0 °C, and saturated NH_4Cl (100 mL) was added. The organic phase separated, washed with water (50 mL x 2), brine (50 mL), dried over Na_2SO_4 , filtered, concentrated, and purified by silica chromatography (1-10% CH_2Cl_2 in petroleum ether) to afford the compound ethyl spiro[2.5]octane-6-carboxylate (10 g).

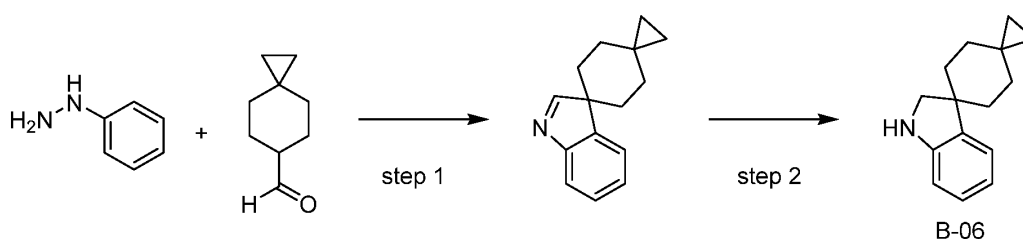
[0357] Step 2. To a mixture of ethyl spiro[2.5]octane-6-carboxylate (10 g, 55 mmol), THF (300 mL) at 0 °C under N_2 was added LiAlH_4 (3.1 g, 81 mmol) in portions. The mixture was stirred at 0 °C for 1 h, then at 22 °C for another 1 h. Aqueous 2M NaOH (3.0 mL) was slowly added to the stirring mixture, followed by Na_2SO_4 (30 g). The suspension was filtered, and the filtrate was concentrated to provide spiro[2.5]octan-6-ylmethanol (7.5 g). ^1H NMR (DMSO-d_6 , 400 MHz) δ 3.51 (d, J = 6.38 Hz, 2H), 1.82-1.68 (m, 4H), 1.53 (tdt, J = 14.71, 6.38, 3.24 Hz, 1H), 1.40-1.29 (m, 1H), 1.12-1.07 (m, 2H), 0.96-0.84 (m, 2H), 0.35-0.24 (m, 2H), 0.23-0.12 (m, 2H).

[0358] Step 3. To a mixture of spiro[2.5]octan-6-ylmethanol (7.5 g, 54 mmol) and CH_2Cl_2 (250 mL) was added Dess-Martin periodinane (28 g, 66 mmol) at 0 °C. The mixture was stirred for 5 h as the temperature was allowed to rise to 25 °C. The mixture was filtered through celite and the filter solid was washed with CH_2Cl_2 (50 mL x 3). The filtrate was concentrated and purified by silica chromatography (0-10% EtOAc in petroleum ether) to provide spiro[2.5]octane-6-carbaldehyde (7.30 g). ^1H NMR (DMSO-d_6 , 400 MHz) δ 9.68 (d,

$J = 1.25$ Hz, 1H), 2.35-2.23 (m, 1H), 1.97-1.85 (m, 2H), 1.70-1.51 (m, 4H), 1.12-1.03 (m, 2H), 0.35-0.27 (m, 2H), 0.26-0.18 (m, 2H).

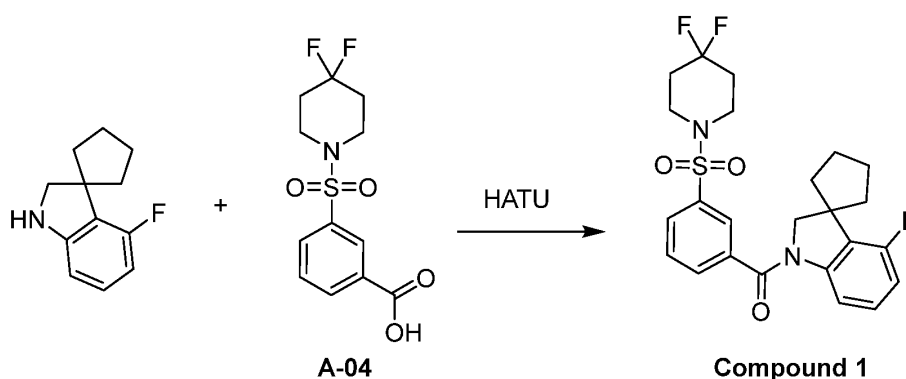
[0359] Step 4. a) A mixture of (4-nitrophenyl)hydrazine (1.8 g, 12 mmol), TFA (4.5 mL, 61 mmol), CH_2Cl_2 (40 mL), and spiro[2.5]octane-6-carbaldehyde (2.0 g, 15 mmol) was stirred at 40 °C for 15 h. b) Additional TFA (6.3 mL, 85 mmol), CH_2Cl_2 , and Et_3SiH (6.3 mL, 4.6 mmol) were added at 0 °C and the mixture stirred at 25 °C for 2 h, then was concentrated and purified by silica chromatography (0-15% [1:1 Me-THF in EtOAc] in petroleum ether) to provide 5"-nitrodispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline] (**B-01**, 0.88 g).

Synthesis of dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline] (B-06)



[0360] Step 1. Dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indole] was prepared from phenylhydrazine and spiro[2.5]octane-6-carbaldehyde in the manner described in Step 4a of the synthesis of **B-01**.

[0361] Step 2. To a mixture of dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indole] (1.0 g, 4.7 mmol) in MeOH (15 mL) and THF (15 mL) at 0 °C was added NaBH_3CN (0.90 g, 14 mmol) in portions. The mixture was stirred at 20 °C for 12 h and NaBH_3CN (0.50 g) and THF (15 mL) was added, and the mixture was stirred at 40 °C for 2 h. The reaction mixture was concentrated and purified by chromatography (silica, 0-15 % [1:1 THF/EtOAc] in petroleum ether) to afford dispiro[cyclopropane-1,1'-cyclohexane-4',3"-indoline] (**B-06**, 0.64 g).

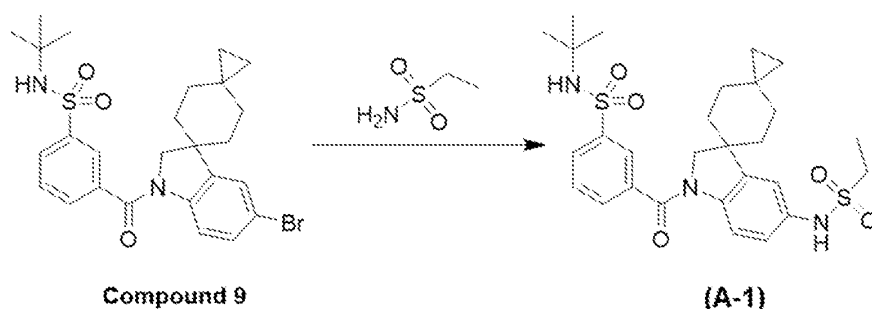
Example S-2. Synthesis of Compound 1, Compound 2 and Compound 9

[0362] A mixture of 3-[(4, 4-difluoro-1-piperidinyl)sulfonyl]benzoic acid (88 mg, 0.28 mmol), DMF (1.5 mL), Et₃N (0.11 mL, 0.78 mmol), and HATU (0.20 g, 0.52 mmol) was stirred at 20 °C for 30 min, and 4'-fluorospiro [cyclopentane-1,3'-indoline] (50 mg, 0.26 mmol) in DMF (1.0 mL) was added. The resulting mixture was stirred at 20°C for 3.5 h, concentrated, and purified by prep-HPLC (45-75% MeCN in H₂O [10 mM NH₄HCO₃]) to afford (3-((4,4-difluoropiperidin-1-yl)sulfonyl)phenyl)(4'-fluorospiro[cyclopentane-1,3'-indolin]-1'-yl)methanone (**Compound 1**) (35 mg). ESI MS m/z: 479.2 (M+H).

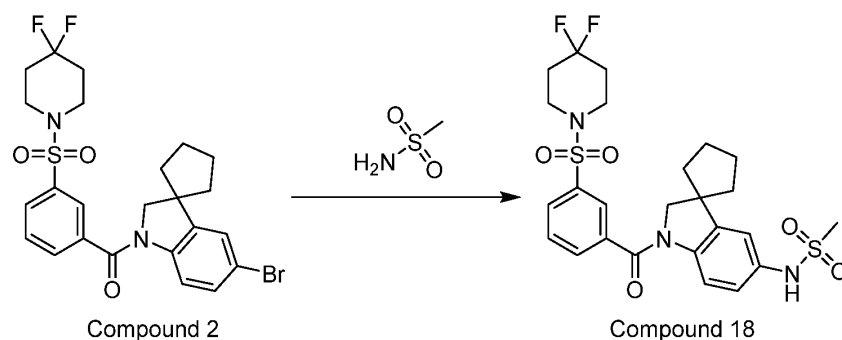
[0363] **Compound 2** and **Compound 9** were prepared from the carboxylic acid and indoline analog indicated by the method described above for the synthesis of **Compound 1**. The carboxylic acid and indoline intermediates used for the synthesis of **Compound 2** and **Compound 9** are shown in Table S-2.

Table S-2

Compound	Structure	Carboxylic Acid	Indoline
Compound 2		A-04	
Compound 9		A-03	B-07

Example S-3. Synthesis of compound of Formula (A-1)

[0364] A degassed mixture of **Compound 9** (1.0 g, 1.9 mmol), ethanesulfonamide (0.60 g, 5.5 mmol), CuI (0.37 g, 1.9 mmol), K₃PO₄ (1.3 g, 6.0 mmol), N¹,N²-dimethylcyclohexane-1,2-diamine (0.27 g, 1.9 mmol), and DMF (14 mL) was stirred at 150 °C for 3 h. The mixture was combined with H₂O (40 mL). The resulting precipitate was filtered, washed with H₂O (5 mL × 3), dissolved in EtOAc (50 mL), washed with water (20 mL × 2), dried over Na₂SO₄, concentrated, and purified by prep-HPLC (50-20% H₂O [0.1% formic acid] in MeCN) to provide N-(tert-butyl)-3-(5''-(ethylsulfonamido)dispiro[cyclopropane-1,1'-cyclohexane-4',3''-indoline]-1''-carbonyl)benzenesulfonamide (**Compound of Formula (A-1)**, 1.3 g).

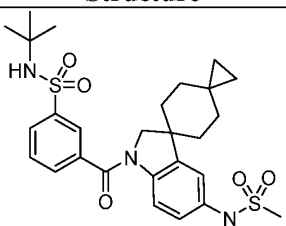
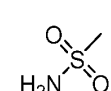
Example S-4. Synthesis of Compound 18 and compound of Formula (A-2)

[0365] A degassed mixture of **Compound 2** (50 mg, 93 μmol), methanesulfonamide (13 mg, 0.14 mmol), CuI (9.0 mg, 46 μmol), K₃PO₄ (59 mg, 0.28 mmol), N¹,N²-dimethylcyclohexane-1,2-diamine (7.0 mg, 46 μmol), and DMF (2.0 mL) was stirred at 150 °C for 2 h in a microwave reactor. The mixture was combined with H₂O (30 mL) and extracted with EtOAc (2 × 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na₂SO₄, concentrated, and purified by prep-HPLC (35-0% H₂O [10 mM NH₄CO₃] in MeCN) to provide N-(1'-(3-((4,4-difluoropiperidin-1-

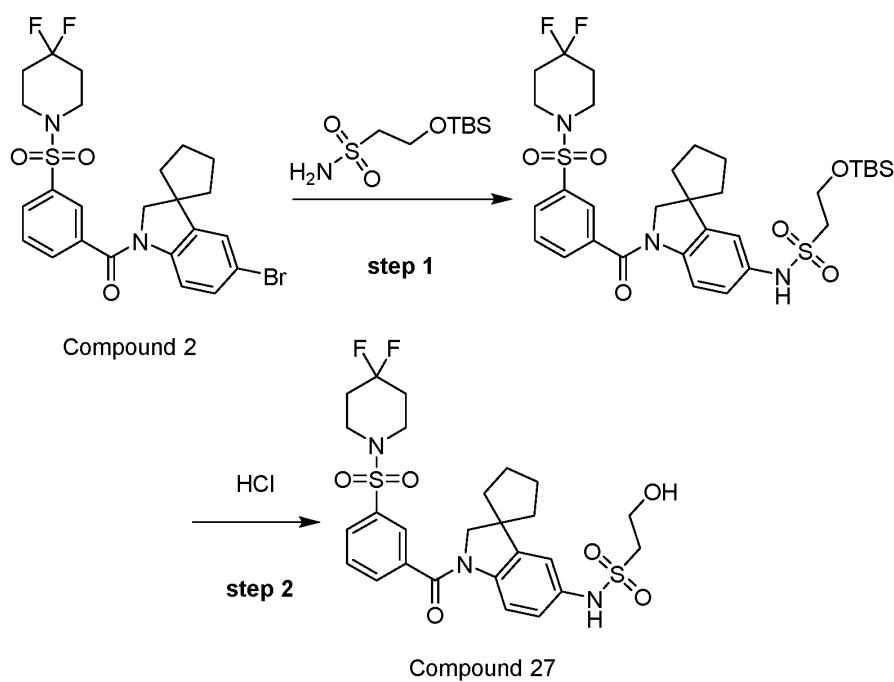
yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)methanesulfonamide (**Compound 18**, 8.6 mg).

[0366] Compound of Formula (A-2) was prepared from the indicated bromoindoline and primary sulfonamide in the same manner as **Compound 18**. Bromoindoline and sulfonamide used for the synthesis of compound of Formula (A-2) are summarized in Table S-3.

Table S-3

Compound	Structure	Bromide	Sulfonamide
Compound of Formula (A-2)		Compound 9	

Example S-5. Synthesis of Compound 27 and compound of Formula (A-3)



[0367] **Step 1.** A degassed mixture of **Compound 2** (50 mg, 93 μ mol), 2-((tert-butyltrimethylsilyl)oxy)ethanesulfonamide (33 mg, 0.14 mmol), CuI (9 mg, 46 μ mol), K₃PO₄ (59 mg, 0.28 mmol) and N¹,N²-dimethylcyclohexane-1,2-diamine (7 mg, 46 μ mol), and DMF (2.0 mL) was stirred at 150 °C for 2 h in a microwave reactor. The mixture was

poured into water H₂O (30 mL) and extracted with EtOAc (2 x 30 mL). The extracts were combined, washed with brine (10 mL), dried over Na₂SO₄, and concentrated to provide 2-(((tert-butyldimethylsilyl)oxy)-N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)ethane-1-sulfonamide (65 mg).

[0368] Step 2. A mixture of 2-(((tert-butyldimethylsilyl)oxy)-N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)ethane-1-sulfonamide (65 mg, 93 μ mol), MeOH (5.0 mL), and HCl (2M, 5.0 mL) was stirred at 20 °C for 1 h, concentrated, aqueous saturated NaHCO₃ was added to bring the pH to 9. The mixture was extracted with EtOAc (2 x 30 mL) and the extracts were combined, washed with brine (10 mL), dried over Na₂SO₄, concentrated, and purified by prep-HPLC (30-60% MeCN in H₂O [10 mM NH₄HCO₃]) to provide N-(1'-(3-((4,4-difluoropiperidin-1-yl)sulfonyl)benzoyl)spiro[cyclopentane-1,3'-indolin]-5'-yl)-2-hydroxyethane-1-sulfonamide (**Compound 27**, 8.5 mg).

[0369] Compound of Formula (A-3) was prepared from the indicated bromoindoline and 2-[(tert-butyldimethylsilyl)oxy]ethane-1-sulfonamide in the same manner as **Compound 27**. Bromoindoline used for the synthesis of compound of Formula (A-3) is summarized in Table S-4.

Table S-4

Compound	Structure	Bromide
Compound of Formula (A-3)		Compound 9

[0370] Characterization of the compounds described in above examples is summarized in Table S-5.

Table S-5

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 1	479.2 (M+H)	(DMSO-d ₆) δ 7.98 (dt, J = 15.13, 7.44 Hz, 4H), 7.86-7.77 (m, 1H), 7.29 (br s, 1H), 6.94 (br t, J = 8.94 Hz, 1H), 3.85 (br s, 2H), 3.33 (s, 1H), 3.15 (br d, J = 5.00 Hz, 4H), 2.14-1.96 (m, 6H), 1.86 (br s, 2H), 1.77 (br s, 2H), 1.56 (br s, 2H).

Compound	ESI MS (m/z)	NMR summary (400 MHz) ppm
Compound 2		(DMSO-d ₆) δ 8.11-7.89 (m, 3H), 7.85-7.77 (m, 1H), 7.51 (d, J = 2.00 Hz, 2H), 3.82 (br s, 2H), 3.21-3.09 (m, 4H), 2.16-1.98 (m, 4H), 1.91-1.70 (m, 6H), 1.66-1.43 (m, 2H)
Compound 9		(DMSO-d ₆) δ 8.04 (s, 1H), 7.99 (d, J = 7.2 Hz 2H), 7.85 (d, J = 7.2 Hz, 1H), 7.73- 7.69 (t, J = 7.2 Hz, 1H), 7.67 (s, 1H), 7.51 (s, 1H), 7.41 (br s, 1H), 3.90 (s, 2H), 1.77-1.74 (m, 2H), 1.65-1.62 (m, 4H), 1.11 (s, 9H), 0.84-0.81 (br d, J = 12.8 Hz, 2H), 0.26 (m, 4H)
Compound 18	554.0 (M+H) ⁺	(CD ₃ OD) δ 8.23-7.96 (m, 3H), 7.93 (br d, J = 5.63 Hz, 1H), 7.85-7.77 (m, 1H), 7.32-6.96 (m, 2H), 4.09-3.83 (m, 2H), 3.26 (br s, 4H), 2.96 (br s, 3H), 2.18-2.04 (m, 4H), 1.89 (br s, 6H), 1.80-1.57 (m, 2H).
Compound of Formula (A-1)	560.1 (M+H) ⁺	(DMSO-d ₆) δ 9.69 (br s, 1H), 8.03-7.96 (m, 3H), 7.84 (br s, 1H), 7.73-7.69 (m, 2H), 7.14-7.12 (m, 2H), 3.87 (s, 2H), 3.05-3.03 (m, 2H), 1.64-1.57 (m, 6H), 1.20-1.16 (t, J = 7.2 Hz, 3H), 1.10 (s, 9H), 0.88~0.85 (m, 2H), 0.27 (br s, 4H)
Compound of Formula (A-2)	546.1 (M+H) ⁺	(DMSO-d ₆) δ 9.58 (br s, 1H), 8.11-7.91 (m, 3H), 7.88-7.67 (m, 1H), 7.74-7.59 (m, 2H), 7.14 (d, J = 1.88 Hz, 2H) 3.88 (br d, J = 1.63 Hz, 2H), 2.94 (s, 3H), 1.74-1.49 (m, 6H), 1.11 (s, 9H), 0.94-0.80 (m, 2H), 0.34-0.18 (m, 4H).
Compound of Formula (A-3)	576.1 (M+H) ⁺	(DMSO-d ₆) δ 8.02-7.96 (m, 2H), 7.84-7.82 (m, 1H), 7.77-7.69 (m, 2H), 7.14-7.09 (m, 2H), 3.90 (s, 2H), 3.75-3.71 (t, J = 6.4 Hz, 2H), 3.19-3.16 (m, 2H), 1.65-1.54 (m, 6H), 1.11 (s, 9H), 1.10 (s, 1H), 0.97-0.86 (m, 2H), 0.38-0.18 (m, 4H)

Example F-1. Preparation of a spray-dried dispersion

[0371] Organic solubility of bulk compound of Formula (A-1) was determined visually in common spray drying solvents. This data is summarized in Table F-1. The compound of Formula (A-1) showed no less than 10 wt. % solubility in the evaluated DCM:MeOH solvent system. 87:13 (w/w) DCM:MeOH was selected as the spray drying solvent based on sufficient compound solubility and manufacturability.

Table F-1. Organic solubility of the compound of Formula (A-1)

Solvent System	Visual Solubility S (wt.%)	Visual Observations
87:13 DCM:MeOH	S ≥ 10%	Yellow and transparent solution. Appearance of the solution did not change after overnight hold.

[0372] Eight spray dried dispersion (SDD) formulations comprising the compound of Formula (A-1) and various SDD polymers in varied weight ratios were prepared. The eight SDD formulations prepared are shown in Table F-2. The total solid for all eight samples was 7.0 wt%. Drying gas mode was set as recycle, with a condenser temperature of about -21 °C to about -17°C. Solution flow rate was about 16g/min and atomization pressure was set to 28 psi. Inlet temperature for all eight samples was about 98 °C to about 115°C, and the outlet temperature was about 43 °C to about 59°C. Secondary drying was carried out to further remove residual solvents. The spray solvent used and net dry yield for each SDD are summarized in Table F-2.

Table F-2

SDD Formulation	Spray Solvent	Dry SDD Yield (wt%)
25:75 compound of Formula (A-1) : HPMCAS-M	87:13 DCM:MeOH	~86
25:75 compound of Formula (A-1):HPMCP-HP55	87:13 DCM:MeOH	~86
40:60 compound of Formula (A-1):HPMCP-HP55	87:13 DCM:MeOH	~82
50:50 compound of Formula (A-1):HPMCP-HP55	87:13 DCM:MeOH	~82
50:50 compound of Formula (A-1):HPMC E3LV	80:20 Acetone: Water	~81
25:75 compound of Formula (A-1):Eudragit L100-55	87:13 DCM:MeOH	~65
40:60 compound of Formula (A-1):Eudragit L100-55	87:13 DCM:MeOH	~66
50:50 compound of Formula (A-1):Eudragit L100-55	87:13 DCM:MeOH	~63

[0373] The physical appearance and coloration of the eight SDDs comprising a compound of Formula (A-1) prepared above were off-white powders. The residual solvents in all eight SDD formulations were below the limit set forth by the International Conference on Harmonization (ICH) as determined by GC-HS and below the limit of quantitation.

Example F-2. Characterization of spray-dried dispersions

[0374] Thermal analysis by MDSC of SDDs in Table F-2 is shown in in Table F-3. All the prepared SDDs had a single T_g , indicating a homogeneous amorphous solid dispersion. 25:75 compound of Formula (A-1):HPMCP-HP55 SDD had the highest T_g , which was determined

to be at around 118 °C. 50:50 compound of Formula (A-1):HPMC E3LV SDD had the lowest T_g , which was determined to be at around 90 °C.

Table F-3

Formulation	T_g Onset (°C)	T_g Half-Height (°C)
25:75 compound of Formula (A-1) : HPMCAS-M	91	99
25:75 compound of Formula (A-1):HPMCP-HP55	110	118
40:60 compound of Formula (A-1):HPMCP-HP55	104	111
50:50 compound of Formula (A-1):HPMCP-HP55	102	108
50:50 compound of Formula (A-1):HPMC E3LV	84	90
25:75 compound of Formula (A-1):Eudragit L100-55	100	112
40:60 compound of Formula (A-1):Eudragit L100-55	93	109
50:50 compound of Formula (A-1):Eudragit L100-55	94	104

[0375] XRPD indicated that all SDDs prepared in Example F-1 were amorphous dispersions with no crystalline peaks observed.

[0376] Surface morphology of particles of the SDDs prepared in Example F-1 was characterized using scanning electron microscopy (SEM). The SEM images in **FIGS. 1A-1H** show images of SDDs with different formulations captured at 5000× magnification. All SDDs have been observed with typical SDD morphology consisting of collapsed and un-collapsed spheres with smooth surfaces. No crystalline material was observed in any sample. For all SDDs, sizes of most observed individual particles were within 1-20 μm .

[0377] The particle size distribution of the 25:75 compound of Formula (A-1) : HPMCAS-M SDDs was determined by laser diffraction using a Malvern Mastersizer 3000 with an Aero S unit (Malvern Instruments). Particle size data showed that the SDD exhibited a narrow size distribution, with a D_{V10} of 2.5 μm , a D_{V50} of 9.2 μm , and a D_{V100} of 24.5 μm .

[0378] Change of T_g under different relative humidity (%RH) for four SDDs was analyzed and evaluated by DSC. The four SDDs being tested were 25:75 compound of Formula (A-1):HPMCP-HP55, 40:60 compound of Formula (A-1):HPMCP-HP55, 40:60 compound of Formula (A-1):Eudragit L100-55, and 50:50 compound of Formula (A-1):Eudragit L100-55, and the results are shown in Table F-4. As shown in Table F-4, for all SDDs being tested, a single T_g was observed at all relative humidity conditions, indicating all SDDs were still

homogeneous. No significant differences were observed between different drug loadings in different SDD formulations for T_g vs %RH. All SDDs tested showed significant T_g suppression at 75% RH. All SDDs had T_g values around 60°C at 75.3% RH. No SDDs had a T_g below 40°C.

Table F-4

Sample Description	Relative Humidity	Avg. T_g Half-Height (°C)
25:75 compound of Formula (A-1):HPMCP-HP55 SDD	0.0%*	118±0.5
	32.8%	93±0.8
	50.0%	77±1.7
	75.3%	63±0.9
40:60 compound of Formula (A-1):HPMCP-HP55 SDD	0.0%*	111±1.3
	32.8%	91±1.8
	50.0%	78±1.3
	75.3%	62±0.3
40:60 compound of Formula (A-1):Eudragit L100-55 SDD	0.0%*	109±1.3
	32.8%	90±3.4
	50.0%	75±0.2
	75.3%	59±0.5
50:50 compound of Formula (A-1):Eudragit L100-55 SDD	0.0%*	104±1.0
	32.8%	86±0.5
	50.0%	76±0.2
	75.3%	63±1.1

[0379] In summary, SDDs comprising the compound of Formula (A-1) with eight different formulations were successfully prepared. All prepared SDDs were analyzed by DSC, XRPD, SEM, PSD and potency and related substances for chemical and physical properties. Results indicated that the SDDs were fully amorphous by XRPD, homogeneous by DSC due to the single T_g , had typical SDD surface morphology by SEM and tight particle size distribution by PSD. No new impurities were detected nor were increases in existing impurities observed in the SDDs when compared to neat compound of Formula (A-1) via potency and related substances, indicating that the manufacturing processes did not introduce new impurities or impact existing impurities.

[0380] Biorelevant non-sink dissolution experiment was carried out on the SDDs prepared in Example F-1 and neat compound of Formula (A-1) to evaluate their total solubilized drug and sustainment over time (C_{max} and AUC of SDDs compared with neat compound of Formula (A-1)). Powder of different SDDs were loaded in vials wetted with gastric media. The vials were vortexed for 10s, after which the contents were emptied into vessel containing 0.1N HCl media. The vials were rinsed with additional media, vortexed 10s, and then the contents were

emptied into vessels. After 30 minutes, media was modulated from simulated gastric fluid (SGF) to FaSSIF by adding equivalent volume of 2×FaSSIF. At each timepoint for each sample, an aliquot was centrifuged to pellet undissolved material and supernatant was diluted and analyzed by HPLC. Details of the dissolution experiment are summarized in Table F-5. Results are summarized in Table F-6.

Table F-5

Parameter	Value
Apparatus	Distek 2100 C Dissolution Apparatus, USP Type II
Gastric Media (SGF)	0.1N HCl
Gastric Dose	1000 µg/mL
Intestinal Media (FaSSIF)	2.24mg/mL FaSSIF in 100mM PBS buffer, pH 6.8
Intestinal Dose	500 µg/mL
Paddle RPM	100
Bath Temp	37.0 ± 0.5°C
Vessel Volume	100 mL
Centrifuged	3 min @ 13k RPM
Replicates	One vessel double sampled

Table F-6

Sample	Total Drug C _{maxGB} (µg/mL)	Total Drug C _{maxFaSSIF} (µg/mL)	Total Drug AUC ₃₅₋₂₁₀ FaSSIF (min*µg/mL)	Total Drug C ₂₁₀ (µg/mL)	Increase in AUC of SDD over AUC of neat compound
25:75 compound of Formula (A-1) : HPMCAS-M SDD	81	90.2	8500	38.6	28.3
25:75 compound of Formula (A-1):HPMCP-HP55 SDD	12	258	22800	90.3	76.0
40:60 compound of Formula (A-1):HPMCP-HP55 SDD	17	103	11000	20.0	36.7
50:50 compound of Formula (A-1):HPMCP-HP55 SDD	9	45.7	5400	3.6	18.0
50:50 compound of Formula (A-1):HPMC E3LV SDD	9	34.9	4900	26.6	16.3

25:75 compound of Formula (A-1):Eudragit L100-55 SDD	14	98.7	9600	4.1	32.0
40:60 compound of Formula (A-1):Eudragit L100-55 SDD	66	151	22000	103	73.3
50:50 compound of Formula (A-1):Eudragit L100-55 SDD	15	180	22600	83.1	75.3
Neat compound of Formula (A-1)	4	2.9	300	1.1	NA

[0381] As shown in Table F-6, all SDDs provided significantly improved dissolution performance in FaSSIF and GB when compared to neat compound of Formula (A-1). 25:75 compound of Formula (A-1): HPMCP-HP55 showed 75-fold increase in solubility and afforded more stable solution in both FASSIF and GB, compared the neat compound of Formula (A-1). 40:60 compound of Formula (A-1):Eudragit L100-55 and 50:50 compound of Formula (A-1):Eudragit L100-55 also demonstrated significantly higher solubility and afforded more stable solution in both FASSIF and GB, compared the neat compound of Formula (A-1).

Example P-1. Preparation of polymorphic forms

[0382] In the experiments described in the present example and the next example, unless otherwise noted, drying was performed in a loosely capped vial, under vacuum at designated temperatures for certain time periods.

[0383] In the experiments described in the present example, fast evaporation (FE) was performed by preparing solutions in selected solvents, filtering the solutions through nylon or PVDF filters into clean glass vials, and allowing the solutions to evaporate at ambient temperature from uncapped vials.

[0384] In the experiments described in the present example and the next example, unless otherwise noted, fast cool (FC) was performed by removing the sample at elevated temperature from a heating plate and allowing the sample to cool to ambient temperature.

[0385] In the experiments described in the present example and the next example, unless otherwise noted, RH stress was performed by exposing the sample to 94% RH condition,

which was carried out by placing the solids into an uncapped clear glass vial inside a sealed container at the controlled condition. 94% RH was maintained by saturated KNO₃ aqueous solution (ASTM Standard E, 104-85, 1996).

[0386] In the experiments described in the present example and the next example, unless otherwise noted, slow evaporation (SE) was performed preparing solutions in selected solvents, filtering the solution through nylon or PVDF filters into clean glass vials, capping the vials with aluminum foil with a pinhole, and allowing the solution to evaporate.

[0387] In the experiments described in the present example and the next example, unless otherwise noted, vapor diffusion (VD) was performed by keeping a small vial containing solution of the compound of interest uncapped in a large container containing antisolvent. The larger container was capped and the anti-solvent vapor was allowed to diffuse into the solution.

[0388] Polymorph experiments were performed starting with as synthesized compound of Formula (A-1), employing solvent-based crystallization techniques with varying conditions of nucleation and growth to investigate kinetic conditions, including evaporation, cooling, slurring, vapor diffusion, and solvent/antisolvent precipitation. Only polymorphic Form A was obtained from these experiments. Details of the screening procedures and observations are summarized in Table P-1.

Table P-1

Solvent	Condition	XRPD Result
acetone	1. FE	Polymorphic Form A
acetone/ iBuOAc	1. iBuOAc suspension heated to 55 °C 2. added acetone at 55 °C 3. FC to RT 4. FE 5. added iBuOAc, stirred at RT, 5 h	Polymorphic Form A
acetone/ H ₂ O	1. H ₂ O added to acetone solution 2. dried under vacuum at RT, 1 d	Polymorphic Form A
ACN	1. suspension heated to 55 °C 2. FC to RT 3. kept at -10~-25 °C, 3 d	Polymorphic Form A
ACN/1-BuOH	1. 1-BuOH suspension heated to 55 °C 2. added ACN, 55 °C 3. FC to RT 4. FE (partial)	Polymorphic Form A

Solvent	Condition	XRPD Result
DMA/H ₂ O	1. H ₂ O added to DMA solution 2. stirred at RT, 1 d 3. stirred at 40 °C, 2 d 4. stirred at 50 °C, 1 d 5. added DMA, stirred at 50 °C, 2 d 6. added DMA, stirred at 50 °C, 1 d 7. added DMA, stirred at 50 °C, 1 d 8. FC to RT 9. kept at 2-8 °C, 8 h	Polymorphic Form A
DMF/H ₂ O	1. suspension heated to 55 °C 2. FC to RT 3. kept at -10~-25 °C, 5 d 4. FE under N ₂ purge 5. added H ₂ O, stirred at RT, 1 d 6. isolated solids washed by H ₂ O twice, dried under vacuum at RT for 8 h	Polymorphic Form A
DMSO/ nitromethane/ toluene	1. DMSO solution added to nitromethane 2. kept at -10~-25 °C, 3 d 3. FE under N ₂ purge 4. added nitromethane, stirred at RT, 1d 5. FE under N ₂ purge 6. added toluene, stirred at RT, 1 d	Polymorphic Form A
dioxane/ CPME	1. CPME suspension heated to 55 °C 2. added dioxane, 55 °C 3. FC to RT 4. kept at -10~-25 °C, 2 d 5. melted at RT, kept at 2-8 °C, 3 d 6. FE under N ₂ purge 7. added CPME, stirred at RT, 1 d	Polymorphic Form A
dioxane/ TAME	1. TAME added to dioxane solution 2. kept at -10~-25 °C, 3 d 3. FE under N ₂ purge 4. added TAME, stirred at RT, 5 h	Polymorphic Form A
EGEE/H ₂ O	1. EGEE suspension heated to 55 °C, filtered to H ₂ O at RT 2. stirred at RT, 3 h	Polymorphic Form A
EtOAc/ cyclohexane	1. suspension in EtOAc heated to 55 °C 2. FC to RT 3. VD w/ cyclohexane, RT 4. FE (partial)	Polymorphic Form A
EtOH	1. suspension heated to 55 °C 2. filtered, FC to RT 3. kept at -10~-25 °C, 3 d 4. FE (partial)	Polymorphic Form A
HFIPA/IPE	1. HFIPA solution SE 2. added IPE, stirred at RT, 1 d	Polymorphic Form A
MEK/hexane	1. hexane added to MEK solution	Polymorphic Form A

Solvent	Condition	XRPD Result
	2. heated to 50 °C	
MeOH	1. suspension heated to 55 °C 2. FC to RT 3. kept at -10~-25 °C, 3 d	Polymorphic Form A
2-MeTHF	1. SE	Polymorphic Form A
MIBK/toluene	1. MIBK suspension heated to 55 °C, filtered to toluene, RT 2. kept at -10~-25 °C, 3 d 3. FE under N ₂ purge 4. added toluene, stirred at RT, 5 h	Polymorphic Form A
NMP/toluene	1. toluene suspension heated to 55 °C 2. added NMP at 55 °C 3. FC to RT 4. kept at -10~-25 °C, 5 d 5. FE under N ₂ purge 6. added toluene, stirred at RT, 3 h	Polymorphic Form A
TFE	1. SE	Polymorphic Form A
TFE/1-PrOH	1. suspension heated to 55 °C 2. FC to RT 3. FE	Polymorphic Form A
THF/IPA	1. IPA suspension heated to 55 °C 2. added THF at 55 °C 3. FC to -10~-25 °C, and kept at -10~-25 °C, 3 d 4. FE (partial)	Polymorphic Form A
THF/methylcyclohexane	1. SE (partial)	Polymorphic Form A

* B/E: birefringence/extinction; agg.: aggregation.

[0389] Long-term slurry experiments were performed targeting stable forms, using as synthesized compound of Formula (A-1) as the starting material, in aqueous and organic solvents, at different temperatures. Only polymorphic Form A was obtained from these experiments, indicating that polymorphic Form A is likely the thermodynamically stable unsolvated form between 2-50 °C. Details of the experiment procedures and observations are summarized in Table P-2.

Table P-2

Solvent	Condition	XRPD Result
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anisole	50 °C, 2 weeks	Polymorphic Form A
55:45 dioxane/H ₂ O, aw=0.98	RT, 2 weeks	Polymorphic Form A
65:35 DMF/H ₂ O, aw=0.56		Polymorphic Form A
85:15 MeOH/H ₂ O, aw=0.39		Polymorphic Form A
EtOAc		Polymorphic Form A
MeOH		Polymorphic Form A
MIPK		Polymorphic Form A
30:70 THF/t-AmOH		Polymorphic Form A
75:25 CHCl ₃ /dipropyl ether	2-8 °C, 2 weeks	Polymorphic Form A

[0390] Polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) was prepared using H₂O and DMF. In one attempt, H₂O was added to a DMF solution of compound of Formula (A-1), resulting in precipitates with no birefringence/extinction. The solids were isolated and washed with H₂O, followed by vacuum drying. As determined by XRPD and shown in **FIG. 5**, middle trace, the post-dried solids however were a mixture of amorphous material (polymorphic Form C) and minor polymorphic Form A. In another attempt, a DMF solution of compound of Formula (A-1) was dried under nitrogen to a gel. This gel was stirred in H₂O briefly to yield a suspension. Solids were isolated and washed with H₂O, followed by vacuum drying for 1 day. As shown in **FIG. 5**, top trace, the final product was an X-ray amorphous material (polymorphic Form C). Details of preparation are summarized in Table P-3.

Table P-3

Solvent	Condition	XRPD Result
DMF/H ₂ O	1. H ₂ O added to DMF solution (~0.05 g of solids) 2. isolated solids washed by H ₂ O 3 times, dried under vacuum at RT for 30 min	amorphous + trace polymorphic Form A
	1. DMF solution (~0.6 g of solids) FE under N ₂ purge 2. added H ₂ O, stirred at RT for 10 min 3. isolated solids wash by H ₂ O 5 times, dried under vacuum at RT for 8 h	amorphous

Example P-2. Characterization of polymorphic forms

[0391] Sharp, well-resolved peaks by XRPD, as shown in **FIG. 2**, indicate that polymorphic Form A of compound of Formula (A-1) is a crystalline material. The observed peaks and prominent peaks are listed in Table III-1. Preferred orientation and particle statistic effects were not assessed. The XRPD pattern was successfully indexed and detailed crystallographic information is shown in Table P-4. The unit cell volume is consistent with an unsolvated form. Successful indexing of the pattern indicates that the sample is composed primarily or exclusively of a single crystalline phase.

Table P-4

Bravais Type	Primitive Monoclinic
a [Å]	15.172
b [Å]	20.506
c [Å]	9904
α [deg]	90
β [deg]	108.73
γ [deg]	90
Volume [Å ³ /cell]	2918.1
Chiral content?	Not specified
Extinction Symbol	P 1 2 ₁ /c 1
Space Group(s)	P2 ₁ /c (14)

[0392] The ¹H NMR of the polymorphic Form A was consistent with the structure of compound of Formula (A-1). Based on the spectrum, the polymorphic Form A contained 0.005~0.006 moles of DMF, indicated by the presence of DMF peaks at 2.89 and 2.73 ppm.

[0393] As determined by TGA and shown in **FIG. 3** top thermogram, the polymorphic Form A displayed a weight loss of 0.01% from 52- 150 °C, consistent with an unsolvated material. Apparent decomposition started at 316 °C.

[0394] As determined by DSC and shown in **FIG. 3** bottom thermogram, the polymorphic Form A showed a single endothermic peak at 194 °C, possibly due to melting.

[0395] As determined by DVS and shown in **FIG. 4**, the polymorphic Form A gained 0.095 wt. % from 5-95% RH and lost 0.097 wt. % from 95-5% RH. Therefore the polymorphic Form A exhibited low kinetic hygroscopicity. The post- DVS sample maintained the same form by XRPD.

[0396] As shown in **FIG. 5**, the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) prepared by slurring a gel from DMF in H₂O is substantially amorphous.

[0397] The ^1H NMR spectrum of the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) was consistent with the chemical structure and the spectrum of as synthesized compound of Formula (A-1). According to the presence of peaks at 2.89 and 2.73 ppm, the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) contained about 0.12 moles of DMF per mole of compound of Formula (A-1), corresponding to about 1.5 wt. %.

[0398] As shown in **FIG. 6**, the TGA thermogram of the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) displayed a weight loss of about 0.9% from 53-120 °C and an additional weight loss of about 1.1% from 120-200 °C, likely due to loss of residual solvents (H_2O and DMF). Apparent decomposition started at about 319 °C, similar to the result of polymorphic Form A (**FIG. 3**).

[0399] The observation of a glass transition (T_g) can be characteristic of the non-crystalline nature of a material. A T_g can be measured by TMDSC, in which the total heat flow signal can be separated into its thermodynamic (heat capacity) and kinetic components. Therefore, the T_g can typically be seen as a step change in the reversing signal. TMDSC was performed for the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1), and the reversing heat flow is presented in **FIG. 7**. A glass transition was observed at 85°C (ΔC_p 0.3 J/(g*K)). It should be noted that differences in solvent and/or water content within the sample can shift the temperature at which the glass transition occurs. An endothermic peak was observed at 191 °C, similar to the result observed for polymorphic Form A (**FIG. 3**). This endotherm was likely indicative of a melt and would suggest that the material may have crystallized at a temperature above the glass transition during the analysis.

[0400] By DVS, as shown in **FIG. 8**, the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) gained 1.13 wt. % from 5-95% RH, while it lost 1.57 wt. % from 95-5%. This hysteresis of 0.44 wt% was likely due to water in the sample at the start of the analysis. Based on the ^1H NMR spectrum, the as-generated the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) contained about 0.12 moles of DMF, corresponding to about 1.5 wt%, while the TGA thermogram displayed a weight loss of about 2.0% from 53-200 °C (**FIG. 6**). Therefore the water content was estimated as 0.5 wt%, consistent with the DVS hysteresis. The DMF in the sample of the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1), however, might influence the DVS result. The post-DVS sample remained amorphous as determined by XRPD.

[0401] The as-generated the polymorphic Form C (i.e. amorphous form) of compound of Formula (A-1) was used for crystallization experiments, as part of the polymorph screen (Table P-6). Common crystallization techniques were used including heat/RH stress, slurrying, evaporation, and solvent/anti-solvent addition. All samples exhibited partial or full crystallization to polymorphic Form A.

Table P-6

Solvent	Condition	XRPD Result
H ₂ O (elevated RH)	1. kept at 40 °C (closed vial), 5 d 2. kept at 60 °C/94% RH, 8 d	Polymorphic Form C (amorphous) + trace Polymorphic Form A
BTN/MTBE	1. slightly cloudy suspension stirred at RT, 3 d	Polymorphic Form A
BuOAc	1. suspension stirred at RT, 3 d	Polymorphic Form A
i-BuOH/IPE	1. suspension stirred at RT, 3 d	Polymorphic Form A
DCM/ cyclopentanol / H ₂ O	1. DCM solution SE 2. added cyclopentanol, stirred at RT, 1 d 3. added H ₂ O 4. FE under N ₂ purge	Polymorphic Form A
DME/H ₂ O	1. H ₂ O added to DME solution 2. stirred at RT, 3 h	Polymorphic Form A
ethylene glycol	1. suspension stirred at RT, 3 d 2. stirred at 50 °C, 1 d	Polymorphic Form A

Example P-3. Interrelationship investigation between Polymorphic Form A and Polymorphic Form B

[0402] To determine relative stability of polymorphic Form A and polymorphic Form B, competitive equilibration experiments were conducted in different solvent systems.

[0403] About 7mg of polymorphic Form A and 7mg of polymorphic Form B were added to 0.3-0.4mL of saturated solutions of selected solvents. Obtained suspensions were stirred at 5°C and 25°C for 1 week, respectively. Solid parts (wet cakes) were isolated by centrifugation filtration and investigated by XRPD. The results are summarized in Table P-7.

Table P-7. Interrelationship between Polymorphic Form A and B

Initial polymorphs: Polymorphic Form A and B		
Solvents	XRPD	
	5°C for 1 week	25°C for 1 week
MeOH	polymorphic Form B	polymorphic Form B
MEK	polymorphic Form B	polymorphic Form B
EA	polymorphic Form B	polymorphic Form B
2-MeTHF	polymorphic Form B	polymorphic Form B
ACN	polymorphic Form B	polymorphic Form B

Example P-4. Salt screening

[0404] Seven Class I bases, 2 Class II bases and 1 Class III base were selected to pursue potential salt opportunities. The selected counter ions for salt screening are summarized in Table P-8. Given consideration to the solubility of Compound of Formula (A-1) in various common solvents, ability of the solvents to dissolve counter ions, and solvent properties, ethanol, acetonitrile/water (90:10, v:v) and THF/water (90:10, v:v) were selected as screening solvents.

Table P-8. Counter ions used for salt screening

Nr.	Counter ions	pKa(s)*	M.W.	Class
1	NaOH	14	40.00	I
2	KOH	14	56.11	I
3	Mg(OH) ₂	11.4	58.33	I
4	Ca(OH) ₂	12.6, 11.57	74.10	I
5	L-Arginine	13.2, 9.09, 2.18	174.20	I
6	L-Lysine	10.79, 9.18, 2.16	146.19	I
7	Choline	>11	121.18	I
8	Betaine	12.16	117.15	II
9	Diethylamine	10.93	73.14	II
10	Zn(OH) ₂	14, 9.64	99.38	III

[0405] With the selected counter ions and solvents, slurry equilibration, cooling, slow evaporation, anti-solvent addition and salt metathesis were applied as screening methods.

[0406] As detailed below, seven crystalline salt hits were identified, including polymorphic Form IV, polymorphic Form V, polymorphic Form VIII, polymorphic Form X, polymorphic Form VI, polymorphic Form VII and polymorphic Form IX.

Slurry Equilibration

[0407] About 50mg of the polymorphic Form A and 1.05 or 2.05 equiv. of base were added into a screening solvent in a 2mL glass vial. Obtained mixtures were stirred at 50°C for 2 hours and then at 25°C for 2 days. Obtained suspensions were filtered through a 0.45µm nylon membrane filter by centrifugation at 14,000 rpm. After being dried at 50°C under vacuum for 2h, solids were analyzed by XRPD. Results are summarized in Table P-9.

Table P-9. Results of Slurry Equilibration

Counter ions	A	B	C
	EtOH	Acetonitrile/water (90:10, v:v)	THF/water (90:10, v:v)
N/A (free acid only)	polymorphic Form A	polymorphic Form A	Clear solution
NaOH (1.05 equiv.)	polymorphic Form IV	Clear solution	Clear solution
NaOH (2.05 equiv.)	polymorphic Form VIII	polymorphic Form X	Oil-like sample
KOH (1.05 equiv.)	polymorphic Form VII	Clear solution	Clear solution
KOH (2.05 equiv.)	polymorphic Form VII	polymorphic Form IX	Gel-like sample
Mg(OH) ₂ (1.05 equiv.)	polymorphic Form A + Mg(OH) ₂	polymorphic Form A + Mg(OH) ₂	A small amount of solids
Ca(OH) ₂ (1.05 equiv.)	polymorphic Form A + Ca(OH) ₂	Ca(OH) ₂ + extra peaks at 2 theta of 6.9°, 12.2°, 13.4°, 17.2°	A small amount of solids
L-Arginine (1.05 equiv.)	polymorphic Form A + L-arginine	polymorphic Form A + L-arginine	L-Arginine
L-Lysine (1.05 equiv.)	polymorphic Form A + L-lysine	polymorphic Form B	Clear solution
Choline (1.05 equiv.)	Clear solution	Clear solution	Clear solution
Betaine (1.05 equiv.)	polymorphic Form A	polymorphic Form B	Clear solution
Diethylamine (1.05 equiv.)	polymorphic Form A	polymorphic Form A	Clear solution
Zn(OH) ₂ (1.05 equiv.)	polymorphic Form A + Zn(OH) ₂	polymorphic Form A + Zn(OH) ₂	Zn(OH) ₂

Cooling

[0408] Clear solutions obtained in slurry equilibration experiments were cooled to 5°C to precipitate solids. Suspensions obtained after cooling were filtered through a 0.45µm nylon membrane filter by centrifugation at 14,000 rpm. After being dried at 50°C under vacuum for 2h, solids were analyzed by XRPD. Results are summarized in Table P-10.

Table P-10. Results of Cooling

Counter ions	A	B	C
	EtOH	Acetonitrile/water (90:10, v:v)	THF/water (90:10, v:v)
N/A (free acid only)	//	//	Clear solution
NaOH (1.05 equiv.)	//	polymorphic Form V	Clear solution
KOH (1.05 equiv.)	//	Clear solution	Clear solution
Mg(OH) ₂ (1.05 equiv.)	//	//	A small amount of solids
Ca(OH) ₂ (1.05 equiv.)	//	//	A small amount of solids
L-Lysine (1.05 equiv.)	//	//	Clear solution
Choline (1.05 equiv.)	Clear solution	Clear solution	Clear solution
Betaine (1.05 equiv.)	//	//	Clear solution
Diethylamine (1.05 equiv.)	//	//	Clear solution

//: experiment not carried out

Slow evaporation

[0409] Clear solutions obtained from cooling experiments were further treated by slow evaporation under ambient condition. Solids obtained by slow evaporation were dried at 50°C under vacuum for 2h and analyzed by XRPD. Results are summarized in Table P-11.

Table P-11. Results of Slow Evaporation

Counter ions	A	B	C
	EtOH	Acetonitrile/water (90:10, v:v)	THF/water (90:10, v:v)
N/A (free acid only)	//	//	Gel-like sample
NaOH (1.05 equiv.)	//	//	polymorphic Form V
KOH (1.05 equiv.)	//	polymorphic Form VI	Gel-like sample

Counter ions	A	B	C
	EtOH	Acetonitrile/water (90:10, v:v)	THF/water (90:10, v:v)
L-Lysine (1.05 equiv.)	//	//	Oil-like sample
Choline (1.05 equiv.)	Gel-like sample	Gel-like sample	Gel-like sample
Betaine (1.05 equiv.)	//	//	Oil-like sample
Diethylamine (1.05 equiv.)	//	//	Oil-like sample

//: experiment not carried out

Antisolvent Addition

[0410] Clear solutions obtained from cooling experiments were further treated by addition of anti-solvent. Suspensions obtained after anti-solvent addition were filtered through a 0.45µm nylon membrane filter by centrifugation at 14,000 rpm. After being dried at 50°C under vacuum for 2h, solids were analyzed by XRPD. Results are summarized in Table P-12.

Table P-12. Results of Anti-Solvent Addition

Counter ions	A	B	C
	EtOH	Acetonitrile/water (90:10, v:v)	THF/water (90:10, v:v)
	Heptane	MTBE	Heptane
N/A (free acid only)	//	//	polymorphic Form A
NaOH (1.05 equiv.)	//	//	Gel-like sample
KOH (1.05 equiv.)	//	polymorphic Form IX + polymorphic Form VI	Oil-like sample
L-Lysine (1.05 equiv.)	//	//	polymorphic Form A
Choline (1.05 equiv.)	Oil-like sample	Oil-like sample	Oil-like sample
Betaine (1.05 equiv.)	//	//	polymorphic Form A
Diethylamine (1.05 equiv.)	//	//	polymorphic Form A

//: experiment not carried out

Salt Metathesis

[0411] About 50mg of the polymorphic Form A and 1.0 equiv. of NaOH were weighted into a 2mL of glass vial. 1 mL of THF/water (2:3, v: v) was added to obtain a clear solution. After stirring at 25°C for about 10min, 0.5 equiv. of MgCl₂ was added. Obtained mixture was stirred at 25°C for about 1 day. Obtained suspension was filtered through a 0.45µm PVDF membrane filter by centrifugation at 14,000 rpm. Wet cake was analyzed by XRPD. The result indicated polymorphic Form A.

Characterization

[0412] The salt hits identified in salt screening were further characterized by DSC, TGA, ¹H-NMR, IC, and KF. Key results are summarized in Table P-13.

Table P-13. Characterization of Salt Hits

	polymorphic Form A	polymorphic Form B	polymorphic Form IV	polymorphic Form V
Counter ion Class	N/A	N/A	I	I
Preparation solvent	EA	ACN/water	EtOH	ACN/water
Purity	97.7%	98.7%	99.4%	99.2%
Crystallinity (by XRPD)	FIG. 2	FIG. 10	FIG. 14	FIG. 17
Melting onset (by DSC)	191.2°C	195.0°C FIG. 11	Endothermic peak from about 8°C melting T _{onset} @186.3°C FIG. 15	Dehydration T _{onset} @3°C, 68.9°C melting T _{onset} @203.1°C FIG. 18
Weight loss (by TGA)	0.2% @165°C, 0.5% @165-200°C	About 0.2% @80°C; 1.0% @80-180°C FIG. 12	About 0.7% @170°C FIG. 16	About 3.3% @48°C; 2.1% @48-100°C FIG. 19
Stoichiometric ratio (by IC)	N/A	N/A	Free acid: NaOH = 1:0.92	Free acid: NaOH=1:1.67
Residual solvent (by ¹ H-NMR)	0.6% EA by weight (0.04 equiv. by molar ratio)	0.3% ACN by weight (0.04 equiv. by molar ratio)	No detectable residual solvent	No detectable residual solvent

N/A: not applicable; //: experiment not carried out

	polymorphic Form VIII	polymorphic Form X	polymorphic Form VI	polymorphic Form VII	polymorphic Form IX
Counter ion Class	I	I	I	I	I

Preparation solvent	EtOH	ACN/water	ACN/Water	EtOH	ACN/water
Purity	98.6%	98.9%	97.5%	98.6%	99.4%
Crystallinity (by XRPD)	FIG. 26	FIG. 32	FIG. 20	FIG. 23	FIG. 29
Melting onset (by DSC, °C)	Endothermic T_{onset} @ 6°C, 88°C, 129.0°C, 172.8°C FIG. 27	Dehydration T_{onset} @ 24°C, 72.0°C, 95.7°C, 124.1°C FIG. 33	Dehydration from about: 3°C; endothermic T_{onset} @ 148.5°C FIG. 21	Endothermic peak from about 7°C desolvation T_{onset} @ 122.3°C, 151.5°C FIG. 24	Dehydration T_{onset} @ 31°C, 105°C FIG. 30
Weight loss (by TGA)	About 5.4% @ 140°C FIG. 28	About 11.9% @ 110°C FIG. 34	About 3.2% @ 100°C FIG. 22	Continuous weight loss FIG. 25	About 0.3% @ 40°C; 2.7% @ 40-75°C; 3.1% @ 75-170°C FIG. 31
Stoichiometric ratio (by ¹ H-NMR or IC)	Free acid: NaOH = 1:2.29	Free acid: NaOH = 1:2.37	Free acid: KOH = 1: 1.25	Free acid: KOH = 1:2.25	Free acid: KOH = 1:2.5
Residual solvent (by ¹ H-NMR)	7.6% EtOH by weight (1.1 equiv. by molar ratio)	No detectable residual solvent	No detectable residual solvent	7.0% EtOH by weight (1.0 equiv. by molar ratio)	0.06% ACN by weight (0.01equiv. by molar ratio)
Water content (by KF)	//	5.3% water by weight (1.9 equiv. by molar ratio)	//	//	5.8% water by weight (2.2 equiv. by molar ratio)

N/A: not applicable; //: experiment not carried out

[0413] Polymorphic Form X was placed at 25°C/92.5%RH in an open container, at 40°C/75%RH in an open container and at 60°C in a closed container for 1 week, after which polymorphic Form XI was obtained and further characterized by DSC, TGA, ¹H-NMR, IC, and KF.

[0414] As shown in **FIG. 36**, polymorphic Form XI exhibits a dehydration event with an onset temperature T_{onset} at 6 °C, 71.1°C, 112.8°C, and 138.8°C. As shown in **FIG. 37**, polymorphic Form XI exhibits a weight loss of about 2.7% at about 64 °C, a weight loss of about 2.4% from 64 °C to about 100 °C, and a weight loss of 0.9% from about 100 °C to

about 140 °C. ¹H NMR indicated that there was not detectable residual solvent. IC indicated the stoichiometric ratio between free acid and NaOH is 1:2.35.

Example P-5. Scale-Up Preparation of Salts and Polymorphic Forms

[0415] Polymorphic Form B, polymorphic Form X, and polymorphic Form IX were scaled up successfully. These scale-up batches are the same polymorphs as those of the screening samples. In the preparation of mono-sodium salt, a new polymorph, polymorphic Form XII was obtained. Details are summarized below.

Polymorphic Form B

[0416] Polymorphic Form B was prepared following these steps:

- 1) 700mg of the polymorphic Form A was weighed into a 20mL glass vial. 6.2mL of ACN/water (9:1, v:v) was added into the vial at 50°C. After stirring for about 5 min, a clear solution was obtained.
- 2) About 3-5mg of polymorphic Form B seeds were added into above solution.
- 3) After stirring at 50°C for about 10 min, the clear solution was cooled to 25°C by natural cooling.
- 4) About 3-5mg of polymorphic Form B seeds were added into above solution.
- 5) After stirring at 25°C for about 5 min, the solution became cloudy and then gradually converted into a suspension.
- 6) After stirring at 25°C for about 2 days, solids were collected by centrifugation filtration and then dried at 50°C under vacuum for about 2 hours.
- 7) 425mg of the polymorphic Form B was obtained as an off-white solid in 60% yield.

[0417] Polymorphic Form B was also prepared following these steps:

- 1) Adding 2 g polymorphic Form A to a Crystallizer, then adding 18 ml solvent (ACN/Water=9/1, V/V) to form a mixture;
- 2) Heating the mixture of 1) to 50 °C for 10 min to dissolve solid;
- 3) Cooling the mixture to 25 °C and adding 5 mg polymorphic Form B as seed;
- 4) Heating the mixture to 50°C quickly and stir for 0.5 h, then cooling the mixture to 25 °C at 6 °C/h;
- 5) Filtering the suspension;
- 6) Drying the wet cake at 40°C vacuum oven.

[0418] Polymorphic Form B was also prepared using slurry experiments following these steps:

- 1) Putting 5 mg polymorphic Form B and 495 mg polymorphic Form A into 3 mL different solvents (MeOH, MEK, EA, 2-Me-THF, ACN);
- 2) Stirring the mixture at 25°C for 1 to 10 days.

[0419] The impact of residual ethyl acetate (EA) content on the slurry crystallization process was investigated. The results are also shown in Table P-A below.

Table P-A. Impact of EA on slurry experiments

Temperature	EA amount	Crystal form	Duration
25 °C	N/A	Form B	3 days
25 °C	0.3 wt. %	Form B	6 days
25 °C	1.0 wt. %	Form B	6 days

[0420] The impact of temperature on the slurry crystallization process was investigated. The results are shown in Table P-B below.

Table P-B. Results of slurry experiments

Temperature	MEK	Crystal form	Duration
25 °C	4 V	Form B	3 days
50 °C	4 V	Form B	24 h

[0421] The impact of purity of the compound of Formula (A-1) on the slurry crystallization process was then investigated. Different scale experiments (from 500 mg to 20 g) were conducted, and the procedure was the same with previous experiments, i.e., the excess Form A was suspended in 4 V MEK for transformation, and antisolvent HEP was added later to increase the yield. During this scale-up slurry experiments, Form A samples with varying purity level were tested, and the results are shown in Table P-C.

Table P-C. Impact of purity on slurry experiments

Purity	The biggest impurity of Form A	Crystal form	Duration
98.46%	RRT1.48=0.49	Form B	<24h
97.80%	RRT1.28=0.63	Form B	<24h
97.32%	RRT1.51=1.54	Form B	48h-72h
96.95%	RRT1.02=0.71	Form B	<24h
96.09%	RRT1.51=2.76	Form B	<24h
95.78%	RRT1.51=3.51	Form A	>72h

95.31%	RRT1.49=1.54	Form A	>72h
94.33%	RRT1.49=3.73	Form A	>72h
94.07%	RRT1.49=4.09	Form A	>72h

[0422] As shown in Table P-C, when the purity of Form A was below 96%, the final product was still Form A after slurry for more than 72h. Therefore, a starting material with Form A with > 96.09% purity can afford more optimized slurry experiment results.

[0423] Polymorphic Form B was also prepared at a large scale (60 g) following these steps:

- 1) Adding 53.75 g Compound of Formula (A-1) solid, 215 mL MEK and 1 wt.% Form B seed into 500 ml crystallizer, and keeping the temperature at 50 °C;
- 2) Sampling for PLM and XRPD at 24 h, 36 h or 48 h;
- 3) After completely transforming Form A to Form B, cooling the system to 25 °C within 5 h;
- 4) Adding 215 mL HEP within 4 h; and
- 5) Filtering the suspension, and drying the wet cake in vacuum oven at 40 °C for 48 h.

[0424] Following this 60 g scale preparation procedure, Form A was transformed to Form B completely at 24 h to 36 h. The dried solid of Form A had a purity of above 97 % as the starting material for this process. The final product after addition of anti-solvent HEP was still Form B. The results indicate the process is robust and can be transferred to larger scale production.

[0425] The process was further scaled up to 1.2 kg scale, and the final crystal form was Form B. 7 kg production also succeeded, which further verified the robustness of crystallization process.

Polymorphic Form X

[0426] Polymorphic Form X was prepared following these steps:

- 1) 400mg of the polymorphic Form A was weighed into a 20mL glass vial. 3.9mL of ACN/water (9:1, v: v) was added into the vial at 50°C. After stirring for about 5 min, a clear solution was obtained.
- 2) 61.6mg of sodium hydroxide (~2.05 equiv. by molar ratio) was weighed into a 2mL glass vial and 0.1mL of water was added under stirring at 50°C.
- 3) Then sodium hydroxide clear solution was added into free acid clear solution slowly under stirring at 50°C.
- 4) About 3-5mg of polymorphic Form X seeds were added into above solution.

- 5) After stirring at 50°C for about 10min, the solution became cloudy and then gradually converted into a suspension.
- 6) The suspension was cooled to 25°C by natural cooling and kept stirring at 25°C for about 5 days.
- 7) Solids were collected by centrifugation filtration and then dried at 50°C under vacuum for about 2 hours.
- 8) 350mg of the polymorphic Form X was obtained as a light yellow solid in 83% yield.

Polymorphic Form IX

[0427] Polymorphic Form IX was prepared following these steps:

- 1) 400mg of the polymorphic Form A was weighed into a 20mL glass vial. 3.9mL of ACN/water (9:1, v: v) was added into the vial at 50°C. After stirring for about 5 min, a clear solution was obtained.
- 2) 100.3mg of potassium hydroxide (~2.05 equiv. by molar ratio) was weighed into a 2mL glass vial and 0.1mL of water was added under stirring at 50°C.
- 3) Then potassium hydroxide clear solution was added into free acid clear solution slowly under stirring at 50°C.
- 4) About 3-5mg of polymorphic Form IX seeds were added into above solution.
- 5) After stirring at 50°C for about 10 min, the solution became cloudy and then gradually converted into a suspension.
- 6) The suspension was cooled to 25°C by natural cooling and kept stirring at 25°C for about 2 days.
- 7) Solids were collected by centrifugation filtration and then dried at 50°C under vacuum for about 2 hours.
- 8) 294mg of the polymorphic Form IX was obtained as a light yellow solid in 64% yield.

polymorphic Form XII

[0428] Polymorphic Form XII was prepared following these steps:

- 1) 400mg of the polymorphic Form A was weighed into a 20mL glass vial. 1mL of ethanol was added into the vial at 50°C. After stirring for about 5 min, a clear solution was obtained.

- 2) 31.3mg of sodium hydroxide (~1.05 equiv. by molar ratio) was weighed into a 4mL glass vial and 1.5mL of ethanol was added with stirring at 50°C. After stirring for about 10min, a clear solution was obtained.
- 3) Then sodium hydroxide clear solution was added into free acid clear solution slowly under stirring at 50°C.
- 4) About 3-5mg of polymorphic Form VI seeds were added into above solution.
- 5) After stirring at 50°C for about 10 min, the clear solution was cooled to 25°C by natural cooling.
- 6) About 3-5mg of polymorphic Form VI seeds added into above solution.
- 7) After stirring at 25°C for about 2 min, the solution became cloudy and then gradually converted into a suspension.
- 8) After stirring at 25°C for about 5 days, solids were collected by centrifugation filtration and then dried at 50°C under vacuum for about 2 hours.
- 9) 363mg of the polymorphic Form XII was obtained as a light yellow solid in 90% yield.

[0429] The newly identified polymorphic Form XII was characterized by DSC, TGA, ¹H-NMR, IC, and KF. Key results are summarized in Table P-14.

Table P-14. Characterization of polymorphic Form XII

Parameter	Method	Results
X-ray diffraction	XRPD, 3-40° (2 theta)	FIG. 38
Thermal events and enthalpy	DSC, 10°C/min	Desolvation onset: 135.1°C; Melting onset: 184.3°C; 201.2°C FIG. 39
Thermogravimetry	TGA, 10°C/min	0.3% @ 80°C; 7.3% @ 80-190°C FIG 40
Stoichiometric ratio	IC	Free acid: NaOH=1:1.07
Residual solvent(s)	¹ H-NMR (DMSO-d ₆)	7.3% EtOH by weight (1.08 equiv. by molar ratio)

Example P-6. Solubility of Salt Forms and Polymorphic Forms

Solubility test in aqueous media

[0430] Accurate 3.0mg or 4.0 mg of the polymorphic Form A, 3.0mg or 4.0mg of the polymorphic Form B, 4.6 mg of the polymorphic Form X and 5.0 mg of the polymorphic

Form IX was weighed into a 4mL glass vial, respectively. 1.5mL or 2 mL of solubility medium was added. The salt amount used is equivalent to 4mg anhydrous free acid. Obtained suspensions were stirred at 37°C at 400 rpm and sampled at 2 hours and at 24 hours. The samples were centrifuged at 37°C at 14,000 rpm for 5min. Supernatants were analyzed by UPLC and pH meter for solubility and pH value, respectively. Residual solids (wet cakes) from the 24 hours samples were also characterized by XRPD to determine physical form. The results are summarized in Table P-15.

Table P-15. Solubility in aqueous media

Solubility at 37°C, equilibration for 24 hours, LOQ: 0.3µg/mL									
Solubility media	Weight	Volume	Target concentration	Polymorphic Form A			Polymorphic Form B		
				Solubility (µg/mL)		XRPD of residual solid	Solubility (µg/mL)		XRPD of residual solid
				2h	24h (pH)		2h	24h (pH)	
Water	4mg	2mL	2mg/mL	<LOQ	0.3 (8.0)	Polymorphic Form A	0.6	1.2 (7.7)	Polymorphic Form B
FaSSGF, pH 1.6	4mg	2mL	2mg/mL	<LOQ	<LOQ (1.7)	Polymorphic Form A	<LOQ	<LOQ (1.6)	Polymorphic Form B
FaSSIF-v1, pH 6.5	4mg	2mL	2mg/mL	2.3	1.6 (6.4)	Polymorphic Form A	1.4	0.9 (6.5)	Polymorphic Form B
FeSSIF-v1, pH 5.0	4mg	2mL	2mg/mL	2.6	4.8 (4.9)	Polymorphic Form A	3.3	3.0 (5.0)	Polymorphic Form B
pH 1.0 HCl buffer	3mg	3mL	1mg/mL	<LOQ	<LOQ (1.0)	Polymorphic Form A	<LOQ	<LOQ (1.0)	Polymorphic Form B
pH 2.0 HCl buffer	3mg	3mL	1mg/mL	<LOQ	<LOQ (2.0)	Polymorphic Form A	<LOQ	<LOQ (1.98)	Polymorphic Form B
pH 3.0 Citrate buffer (100mM)	3mg	3mL	1mg/mL	<LOQ	<LOQ (3.0)	Polymorphic Form A	<LOQ	<LOQ (3.0)	Polymorphic Form B

pH 4.0 Citrate buffer (100mM)	3mg	3mL	1mg/ mL	<LO Q	<LOQ (4.0)	Polym orphic Form A	<LO Q	<LO Q (4.0)	Polymo rphic Form B
pH 5.0 Citrate buffer (100mM)	3mg	3mL	1mg/ mL	<LO Q	<LOQ (5.0)	Polym orphic Form A	<LO Q	<LO Q (4.9)	Polymo rphic Form B
pH 6.0 Phosphate buffer (50mM)	3mg	3mL	1mg/ mL	<LO Q	<LOQ (6.0)	Polym orphic Form A	<LO Q	<LO Q (5.9)	Polymo rphic Form B
pH 7.0 Phosphate buffer (50mM)	3mg	3mL	1mg/ mL	<LO Q	<LOQ (7.0)	Polym orphic Form A	<LO Q	<LO Q (7.2)	Polymo rphic Form B
pH 8.0 Phosphate buffer (50mM)	4mg	2mL	2mg/ mL	<LO Q	<LOQ (8.0)	Polym orphic Form A	<LO Q	<LO Q (8.0)	Polymo rphic Form B
pH 9.0 Alkaline borate buffer (50mM)	4mg	2mL	2mg/ mL	<LO Q	<LOQ (9.0)	Polym orphic Form A	<LO Q	<LO Q (9.0)	Polymo rphic Form B
pH 10.0 Alkaline borate buffer (50mM)	4mg	2mL	2mg/ mL	1.1	1.1 (10.0)	Polym orphic Form A	0.9	0.8 (10. 0)	Polymo rphic Form B
pH 11.0 Alkaline borate buffer (50mM)	4mg	2mL	2mg/ mL	3.6	8.5 (10.7)	Polym orphic Form A	4.4	3.1 (10. 8)	Polymo rphic Form B
pH 12.0 Alkaline borate buffer (50mM)	4mg	2mL	2mg/ mL	220. 9	327.8 (11.9)	Polym orphic Form A	141. 5	142. 8 (12. 0)	Polymo rphic Form B

Solubility at 37°C, target concentration 2mg/mL (in free acid), equilibration for 24 hours, LOQ: 0.3µg/mL						
Solubility media	Polymorphic Form X			Polymorphic Form IX		
	Solubility (µg/mL)		XRPD of residual solid	Solubility (µg/mL)		XRPD of residual solid
	2h	24h (pH)		2h	24h (pH)	
pH 1.2 HCl buffer	<LOQ	<LOQ (1.3)	Polymorphic Form A	<LOQ	<LOQ (1.3)	Polymorphic Form A

Solubility at 37°C, target concentration 2mg/mL (in free acid), equilibration for 24 hours, LOQ: 0.3µg/mL						
	Polymorphic Form X			Polymorphic Form IX		
Solubility media	Solubility (µg/mL)		XRPD of residual solid	Solubility (µg/mL)		XRPD of residual solid
	2h	24h (pH)		2h	24h (pH)	
pH 4.5 acetate buffer (50mM)	<LOQ	<LOQ (4.7)	Polymorphic Form A + extra peak at 2 theta 8.9°	<LOQ	<LOQ (4.9)	Polymorphic Form A + extra peak at 2 theta 8.9°
pH 6.8 phosphate buffer (50mM)	<LOQ	<LOQ (7.1)	Polymorphic Form A	<LOQ	<LOQ (7.1)	Polymorphic Form A
Water	67.4	55.9 (11.6)	Polymorphic Form A	56.6	47.5 (11.5)	Polymorphic Form A
FaSSGF, pH 1.6	<LOQ	<LOQ (1.7)	Polymorphic Form A	<LOQ	<LOQ (1.8)	Polymorphic Form A
FaSSIF-v1, pH 6.5	2.3	1.0 (7.0)	Polymorphic Form A	2.7	1.2 (7.0)	Polymorphic Form A
FeSSIF-v1, pH 5.0	4.3	3.0 (5.1)	Polymorphic Form A + extra peak at 2 theta 8.9°	3.5	2.8 (5.2)	Polymorphic Form A + extra peak at 2 theta 8.9°

Solubility test in organic solvents

[0431] 11-200mg of the Polymorphic Form A or the Polymorphic Form B was equilibrated in 0.2-0.4mL of solvents at 25°C for 24 hours with a stirring bar on a magnetic stirring plate at a rate of 400rpm.

[0432] Obtained suspensions were filtered through a 0.45µm nylon membrane filter by centrifugation at 14,000rpm. Supernatants were analyzed by UPLC for solubility. Residual solids (wet cakes) were investigated by XRPD. Results are summarized in Table P-16.

Table P-16. Solubility test in organic solvent

Solubility at 25°C, equilibration for 24 hours, LOQ: 0.3µg/mL				
	Polymorphic Form A		Polymorphic Form B	
Solvents	Solubility (mg/mL)	XRPD	Solubility (mg/mL)	XRPD
Acetonitrile	37.3	Polymorphic Form A	24.2	Polymorphic Form B
Acetone	141.1	Polymorphic Form A	109.2	Polymorphic Form B
Dimethylacetamide	625.4	Polymorphic Form A	581.1	Polymorphic Form B
Dimethylformamide	640.5	Polymorphic Form A	587.0	Polymorphic Form B

Solubility at 25°C, equilibration for 24 hours, LOQ: 0.3µg/mL				
	Polymorphic Form A		Polymorphic Form B	
Solvents	Solubility (mg/mL)	XRPD	Solubility (mg/mL)	XRPD
Dimethylsulfoxide	>1000	//	>1000	//
Ethyl acetate	15.6	Polymorphic Form A	10.5	Polymorphic Form B
n-Heptane	0.7	Polymorphic Form A	<LOQ	Polymorphic Form B
Tetrahydrofuran	400.7	Polymorphic Form A	265.5	Polymorphic Form B
Ethanol	6.5	Polymorphic Form A	4.0	Polymorphic Form B
Methanol	17.0	Polymorphic Form A	10.7	Polymorphic Form B
Acetone/water (95:5, w:w)	184.8	Polymorphic Form A	147.0	Polymorphic Form B
Acetone/water (90:10, w:w)	179.1	Polymorphic Form A	122.7	Polymorphic Form B
Acetone/water (85:15, w:w)	127.5	Polymorphic Form A	94.0	Polymorphic Form B

Example S-1. Screening and preparation of salt forms

[0433] Free acid anhydrous form of compound of Formula (A-1) is prepared for salt form screening. Salt forms of compound of Formula (A-1) derived from inorganic or organic bases including NaOH, KOH, Mg(OH)₂, Ca(OH)₂, L-Arginine, L-Lysine, Choline, Betaine Diethylamine, and Zn(OH)₂ are screened using methods including slurry equilibration, cooling, slow evaporation, anti-solvent addition, and salt metathesis. Various solvents including methanol, ethanol, isopropanol, acetone, methyl ethyl ketone, ethyl acetate, acetonitrile, tetrahydrofuran, IPAc, anisole, dichloromethane, dimethylsulfoxide, dimethylformamide, or any combination thereof are also screened with respect to different counter ions. The salts forms obtained are further characterized by DCS, TGA, ¹H-NMR, IC, KF, and XRPD. Bulk stability, solubility, and hygroscopicity of the prepared salt forms are further measured and evaluated.

Biological Example B-1. Inhibition of KIF18A microtubule-dependent ATPase activity

[0434] Test compounds were plated in a 3× dilution scheme in a 384-well plate. Assay buffer: 80 mM PIPES (pH 6.9), 1 mM MgCl₂, 75 mM KCl, 1 mM EGTA, 1 mM DTT, 0.01% BSA, 0.005% Tween-20, 1 μM Taxol in H₂O. To 50 nL of compound in DMSO was added 2.5 μL of enzyme mix [4 nM hKIF18A (1-374) in assay buffer]. After incubation at room temperature for 30 min, 2.5 μL of microtubule mix was added [0.2 mg/mL pre-formed microtubules, 2.0 mM ATP in assay buffer], the plate was centrifuged for 30 s and then incubated at 28 °C for 60 min. 5 μL of Promega® ADP-Glo Max R1 was added, the plate was centrifuged for 30s, and the mixture incubated for 4 h at room temperature. 10 μL of Promega® ADP-Glo Max R2 was added, the plate centrifuged for 30 s, and incubated for 60 min at room temperature. Luminescence was measured with an Envision plate reader, and %Inhibition was calculated for each well as: $([\text{max} - \text{min}] - [\text{test} - \text{min}]) / [\text{max} - \text{min}]$. IC₅₀ values were calculated from concentration vs. % Inhibition data via a four-parameter variable slope model.

[0435] Table B-1 indicates that compounds as provided herein are potent inhibitors of KIF18a. As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) is 17 nM.

Table B-1

Compound	IC ₅₀ (μM)
Compound of Formula (A-1)	0.016
Compound of Formula (A-2)	0.011 (n=3) 0.0094 (n=10)
Compound of Formula (A-3)	0.012

Biological Example B-2. Binding kinetics to KIF18a-microtubule complex

[0436] Compound binding kinetics parameters (k_{on} and k_{off}) were determined by the method of global progress curve analysis (GPCA). KIF18A (0.25 nM) was incubated for up to 24 hr with serially diluted compound in the assay buffer containing 80mM PIPES, pH 6.9, 1 mM ATP, 0.1 mg/ml preformed microtubule from porcine brain (Cytoskeleton), 1 mM MgCl₂, 1μM Taxol, 75 mM KCl, 1 mM EGTA, 1 mM DTT, 0.01% BSA and 0.005% Tween-20. ADP product levels were determined by the Promega® ADP-Glo assay. The time/dose-dependent progress curves were then globally fit to a Michaelis-Menten kinetics model with

1-step slow binding inhibition to derive both on-rate k_{on} and off-rate k_{off} values (Zhang, R., Wong, K. (2017): “High performance enzyme kinetics of turnover, activation and inhibition for translational drug discovery”, *Expert Opinion on Drug Discovery*, 2017 Jan;12(1):17-37. doi: 10.1080/17460441.2017.1245721).

[0437] Results from the binding kinetics assay are summarized in Table B-2. The data in Table B-2 indicate that compounds as provided herein can achieve sub-nanomolar potency with small off-rates, or very long dissociation half-life ($\ln(2)/k_{off}$). As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) are: $k_{on} = 0.059 \text{ nM}^{-1}\text{h}^{-1}$; $k_{off} = 0.21 \text{ h}^{-1}$, dissociation $t_{1/2} = 4.1 \text{ h}$; $K_I = 3.4 \text{ nM}$.

Biological Example B-3. Cell Viability of KIF18a-sensitive cell lines

[0438] Cell lines were seeded as follows 24 hours before compound treatment: HCC15 (Korean Cell Line Bank) 600 cell/well, 95 μL of RPMI-1640 media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin and 10% FBS; NIH:OVCAR-3 (ATCC), 1000 cell/well, 95 μL of RPMI-1640 media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin, 0.01 mg/mL bovine insulin, and 20% FBS; JIMT-1 (Addexbio) 1000 cell/well, 95 μL of DMEM media supplemented with 100 units/mL penicillin, 100 units/mL streptomycin, and 10% FBS.

[0439] Test compounds were added to cells in a 20 $\times$ dilution scheme by adding 5 μL of serially diluted compound to the plate, and the treated cells were incubated for an additional 7 days in a 37 $^{\circ}\text{C}$, 5% CO_2 incubator. DMSO was used as the negative control (0% effect), and wells omitting cells were used as the positive control (100% effect). The cells were incubated for seven days, and cell viability determined via the Promega Cell Titre-Glo[®] Assay kit. Luminescence units were converted to ATP concentrations via an ATP standard curve (10 point, 2-fold dilution from 5 μM). %Inhibition was calculated for each well as: $([\text{max} - \text{min}] - [\text{test} - \text{min}]) / [\text{max} - \text{min}]$. IC_{50} values were calculated from concentration vs. %Inhibition data via a four-parameter variable slope model. Results from the biological assay are summarized in Table B-2.

[0440] Table B-3 indicates that compounds as provided herein potently inhibit cell growth or induce cell killing for KIF18a-sensitive cancer cell lines. As a comparison, the data for AMG650 (2-{6-azaspiro[2.5]octan-6-yl}-N-[2-(4,4-difluoropiperidin-1-yl)-6-

methylpyrimidin-4-yl]-4-(2-hydroxyethanesulfonamido)benzamide) are: HCC-15, 0.066 μM ; JIMT-1 0.13 μM ; NIH: OVCAR3 0.10 μM .

Table B-2

Compound	k_{on} ($\text{nM}^{-1}\text{h}^{-1}$) ^a	k_{off} (h^{-1}) ^b	disc. $t_{1/2}$ (h) ^c	K_{I} (nM) ^d
Compound of Formula (A-1)	0.054	0.018	40	0.34
Compound of Formula (A-2)	0.038	0.018	38	0.55
Compound of Formula (A-3)	0.049	0.014	48	0.29

Table B-3

Compound	HCC-15 IC_{50} (μM)	JIMT-1 IC_{50} (μM)	NIH-OVCAR3 IC_{50} (μM)
Compound of Formula (A-1)	0.0051	0.0040	0.0051
Compound of Formula (A-2)	0.011	0.0078	0.0097
Compound of Formula (A-3)	0.036		

Biological Example B-4. Assessment of *in vivo* Activity

[0441] OVCAR-3 (ATCC) tumor cells were maintained *in vitro* in RPMI-1640 medium supplemented with 20% fetal bovine serum, 0.01 mg/mL bovine insulin and 1% Anti-Anti at 37°C in an atmosphere of 5% CO_2 in air. HCC15 (DSMZ) tumor cells were maintained *in vitro* in RPMI 1640 medium supplemented with 10% fetal bovine serum and 1% Anti-Anti at 37°C in an atmosphere of 5% CO_2 in air.

[0442] The tumor cells were sub-cultured twice weekly. The cells growing in an exponential growth phase were harvested and counted for tumor inoculation.

[0443] Tumor cells (10×10^6) in 0.2 mL of PBS mixed with Matrigel (50:50) were inoculated subcutaneously on the right flank of each mouse. When the average tumor volume reached 110-175 mm^3 , animals were randomized into groups of 10 and treatment started. OVCAR-3 cells were implanted in Balb/C nude mice, and HCC15 cell were implanted in SCID Beige mice.

[0444] SDD samples of the compound of Formula (A-1) and the compound of Formula (A-2) were prepared respectively. The SDD sample for the compound of Formula (A-1) is 25:75 (w/w) the compound of Formula (A-1):HPMCAS-M. The SDD sample for the compound of Formula (A-2) is 25:75 (w/w) the compound of Formula (A-2):HPMCAS-M. The SDD

samples were dosed once or twice a day (12h) orally. Tumor Growth Inhibition (TGI) was calculated using the formula: $TGI (\%) = [1 - (T_N - T_0) / (V_N - V_0)] \times 100$; T_N is the average tumor volume of a treatment group at the indicated timepoint, T_0 is the average tumor volume of the treatment group on treatment day 0, V_N is the average tumor volume of the vehicle control group at the indicated timepoint, and V_0 is the average tumor volume of the vehicle group on treatment day 0. P value was calculated based on tumor size by One-Way ANOVA with GraphPad Prism 9.4.0 compared with the vehicle group, respectively. **** indicates $p < 0.0001$.

[0445] The tumor volume of vehicle- and compound-treated mice as a function of time after start of treatment and the results of treatments with selected compounds on SCID Beige mice or nude mice implanted with HCC15 or OVCAR-3 are shown in **FIGS. 9A-9E**. The TGI calculated for treatments with selected compounds are shown in in Table B-4.

Table B-4

Compound	Model	Subfigure	Dose	TGI
25:75 compound of Formula (A-1): HPMCAS-M	HCC15	9C	10 mg/kg BID PO	61 ± 10%
	HCC15	9C	30 mg/kg BID PO	89 ± 7%
	HCC15	9C	60 mg/kg BID PO	94 ± 5%
	OVCAR3	9D	10 mg/kg BID PO	60 ± 17%
	OVCAR3	9D	30 mg/kg BID PO	111 ± 1%
	OVCAR3	9D	60 mg/kg BID PO	112 ± 1%
	OVCAR3	9E	30 mg/kg QD PO	104 ± 7%
	OVCAR3	9E	60 mg/kg QD PO	109 ± 2%
	OVCAR3	9E	30 mg/kg BID PO	110 ± 1%
25:75 compound of Formula (A-2): HPMCAS-M	HCC15	9A	10 mg/kg BID PO	30 ± 15%
	HCC15	9A	30 mg/kg BID PO	72 ± 6%
	HCC15	9A	60 mg/kg BID PO	82 ± 9%
	OVCAR3	9B	10 mg/kg QD PO	24 ± 26%
	OVCAR3	9B	30 mg/kg QD PO	72 ± 17%
	OVCAR3	9B	60 mg/kg QD PO	82 ± 10%

Biological Example B-5. Pharmacokinetics of the 50:50 compound of Formula (A-1):Eudragit L100-55 SDD following oral administration to Male CD-1 Mice

[0446] The pharmacokinetic (PK) profile of 50:50 compound of Formula (A-1):Eudragit L100-55 SDD was first tested and evaluated in Male CD-1 Mice following oral administration (PO). The study design is shown in Table B-5.

Table B-5

Number/Sex	Sample	Dose (mg/kg)	Conc. (mg/mL)	Dose Volume (mL/kg)	Vehicle	Route
21/Male	50:50 compound of Formula (A-1):Eudragit L100-55 SDD	50	5	10	0.5% methylcellulose 400cp	PO

[0447] The 50:50 compound of Formula (A-1):Eudragit L100-55 SDD was provided as a neat powder and stored at 2-8 °C before the PK profile study. On the morning of dose administration, the 50:50 compound of Formula (A-1):Eudragit L100-55 SDD was dissolved in an appropriate amount of vehicle(s) to achieve the desired concentration. Prior to starting the formulation, the approximate dosing volume of water was added to the container and a Q.S. line was marked. The water was discarded. A small amount of the vehicle (0.5% methylcellulose (MC) (400cp) in water) was added to the container and stirred continuously. The appropriate amount of 50:50 compound of Formula (A-1):Eudragit L100-55 SDD was slowly be added to the stirring vehicle. After all the 50:50 compound of Formula (A-1):Eudragit L100-55 SDD was added, the vehicle was added until the formulation reaches the Q.S. line. Homogenization and/or room temperature (18-26 °C) water bath sonication was used (if necessary) to achieve a white homogeneous suspension. The formulations was stirred continuously throughout dosing.

[0448] Blood samples were collected for pharmacokinetic (PK) analysis at 0.25, 0.5, 1, 2, 4, 8, and 24 hours post dose. Samples were collected from 3 animals/group/time point as a terminal cardiac stick while anesthetized with inhaled isoflurane. Blood samples were kept on wet ice until centrifuged at settings of 2000 × g for 10 minutes at ~ 5°C within 1 h of collection. Plasma was directly transferred to cryovials and stored at -70°C±10-°C until shipment.

[0449] The collected blood samples were analyzed using a qualified bioanalytical method. PK analysis was performed to include, at a minimum: T_{max}, C_{max}, AUC₀₋₂₄, T_{max} (median) and T_{max} (range). The plasma concentration data are shown in Table B-6. The plasma PK parameter summary data are shown in Table B-7.

Table B-6. Mean Concentration Versus Time Summary of 50:50 compound of Formula (A-1):Eudragit L100-55 SDD Following a Single PO Gavage Dose to Male CD-1 Mice

Group	Dose (mg/kg)	Time (hr)	N	Mean (ng/mL)	SD (ng/mL)
1	50	0.25	3	3460	234
		0.50	3	7940	1530

		1.00	3	10300	2040
		2.00	3	8800	941
		4.00	3	7690	2540
		8.00	3	5330	159
		24.00	0	<LLOQ	N/A

Table B-7. Plasma 50:50 compound of Formula (A-1):Eudragit L100-55 SDD Parameter
Summary Following a Single PO Gavage Dose to Male CD-1 Mice

Animal	Sample	dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	T _{1/2} (h)	AUC ₀₋₂₄ (hr*ng/mL)
mouse	50:50 compound of Formula (A-1):Eudragit L100-55 SDD	50	1	10300	8.17	58200

[0450] Following similar procedures, PK profiles of neat compounds disclosed herein, and various SDD formulations in mouse were determined. Detailed dosing parameters and PK parameters are shown in Table B-8.

Table B-8

Vehicle	Sample	dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	T _{1/2} (h)	AUC _{last} (hr*ng/mL)	AUC _{inf} (hr*ng/mL)	MR T _{last} (h)	MR T _{inf} (h)
0.5% MC+1% Tween 80 in water	Neat Compound of Formula (A-2)	10	1	19.1	6.88	189	205	6.79	8.9
5% TPGS+0.5% MC 400 in water	Neat Compound of Formula (A-2)	10	1	70.4	4.04	481	488	5.08	5.44
5% TPGS+0.5% MC 400 in water	Neat Compound of Formula (A-3)	10	2	1010	2.49	6550	6560	4.73	4.75
5% TPGS+0.5%MC(400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	30	0.5	5580	2.2	64000	64000	5.47	5.48
5% TPGS+0.5%MC(400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	100	4	17500	1.97	212000	212000	5.81	5.82
5% TPGS+0.5%MC	25:75 Compound of Formula (A-1):	300	2	22200	3.38	322000	325000	6.28	6.44

C(400cp) in water	HPMCAS-M SDD								
5% TPGS+0.5% MC 400 in water	25:75 Compound of Formula (A-2): PVP VA64 SDD	10	1	3090	1.97	19400	19400	3.95	3.96
5% TPGS+0.5% MC 400 in water	25:75 Compound of Formula (A-2): PVP VA64 SDD	30	1	8170	2.11	54400	54500	4.09	4.1
5% TPGS+0.5% MC 400 in water	25:75 Compound of Formula (A-2): HPMCAS-M SDD	30	2	8460	1.82	63400	63400	4.63	4.63
5% TPGS+0.5% MC 400 in water	25:75 Compound of Formula (A-2): Eudragit L55 SDD	30	2	8340	1.74	67600	67600	4.61	4.61

TPGS: tocophersolan; MRT: Mean Residence Time

[0451] PK profiles of various SDD formulations when orally administered to mouse were further measured and the results are summarized in Table B-9.

Table B-9

Day	Sex	Wt% of the SDD polymer	C _{max} (ng/mL)	AUC (h·ng/mL)
1	Female	25:75 the compound of Formula (A-1) : HPMCAS	7,400	48,600
14	Female	25:75 the compound of Formula (A-1) : HPMCAS	10,200	53,200
1	Male	25:75 the compound of Formula (A-1) : HPMCAS	7,960	48,200
14	Male	25:75 the compound of Formula (A-1) : HPMCAS	7,880	24,800
1	Male	50:50 the compound of Formula (A-1) : Eudragit L55	9,930	35,300
7	Male	50:50 the compound of Formula (A-1) : Eudragit L55	12,700	62,400
1	Male	40:60 the compound of Formula (A-1) : HPMCP-HP55	13900	63,400
7	Male	40:60 the compound of Formula (A-1) : HPMCP-HP55	14,200	62,300

[0452] As shown in Table B-8 and Table B-9, the oral PK profiles of neat compound of Formula (A-2), and (A-3) were poor in typical suspension formulation. All suitable SDD formulations comprising the compound of Formula (A-1), (A-2) or (A-3) showed significantly improved bioavailability compared to corresponding neat compounds.

Biological Example B-6. Pharmacokinetics of the compound of Formula (A-1) following oral administration to rat

[0453] PK profiles of neat compounds described herein and SDD formulations when orally administered to rat under different dosages were determined. Detailed dosing parameters and PK parameters are shown in Table B-10.

Table B-10

Vehicle	Sample	dose (mg/kg)	T _{max} (h)	C _{max} (ng/mL)	T _{1/2} (h)	AUC _{last} (hr*ng/mL)	AUC _{inf} (h*ng/mL)	MRT _{last} (h)	MRT _{inf} (h)
5% TPGS+0.5%MC (400cp) in water	Neat Compound of Formula (A-1)	10	1.67	59.2	3.68	306	439	3.61	6.02
5% TPGS+0.5%MC (400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	10	4	683	2.46	6920	6930	5.55	5.59
5% TPGS+0.5%MC(400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	30	3.33	2820	2.11	34700	34700	6.15	6.16
5% TPGS+0.5%MC(400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	100	5.33	5220	1.99	69800	74800	6.36	6.2
5% TPGS+0.5%MC(400cp) in water	25:75 Compound of Formula (A-1): HPMCAS-M SDD	300	5.33	9380	2.24	128000	111000	6.41	6.27
5% TPGS+0.5%MC 400 in water	25:75 Compound of Formula (A-2): HPMCAS-M SDD	10	3.33	400	4.89	2800	3260	5.04	6.84
5% TPGS+0.5%MC 400 in water	25:75 Compound of Formula (A-2): HPMCAS-M SDD	30	2	1610	2.24	14900	14900	5.42	5.44
5% TPGS+0.5%MC 400 in water	25:75 Compound of Formula (A-2): HPMCAS-M SDD	100	2.67	3630	1.81	34400	34400	5.38	5.39

[0454] As shown in Table B-10, the oral PK profile of neat compound of Formula (A-1) was poor in typical suspension formulation. All suitable SDD formulations comprising the compound of Formula (A-1) showed similarly improved bioavailability compared to neat compound of Formula (A-1). These SDD formulations also showed similar C_{max} , AUC, and half-life of the compound of Formula (A-1). The SDD formulations comprising the compound of Formula (A-2) exhibited high bioavailability as well. The loading of the compound of Formula (A-1) or (A-2) in SDD formulations was achieved up to 50%. The data also demonstrated that TPGS was not required to achieve satisfying exposure of the compound of Formula (A-1).

Biological Example B-7. Human PK parameters following oral administration of SDD formulation

[0455] The pharmacokinetic (PK) profile of the compound of Formula (A-1) after oral administration of the SDD formulations of the compound of Formula (A-1) was extrapolated based on rat and dog data to human subject and the details are summarized in Table B-11. The human PK profile is consistent with oral administration and high target engagement with Q.D. or B.I.D. dosing.

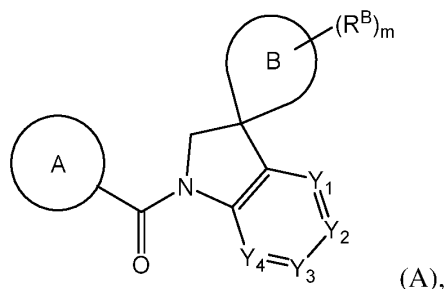
Table B-11

Predicted Parameter	Method and Rationale	Value
CL_p (mL/min/kg)	Geo mean of 6 allometric methods	2.3
V_{ss} (L/kg)	Geo mean of 9 allometric methods	0.97
Oral F (%)	$F = f_a * f_g * f_h$	74
k_a (hr^{-1})	$k_a = 1/MAT = 1/(MRT_{PO} - MRT_{IV})$, based on rat and dog	0.24
$t_{1/2}$ (hrs)	$t_{1/2} = \ln 2 * V_{dss} / CL$, assuming 1-cpt	4.9
$C_{max,ss}$ (μM)	$C_{max,ss} = (F * e^{-k_e T_{max}} * dose) / V_{ss}$, where $T_{max} = (\ln(k_a/k_e)) / (k_a - k_e)$	2.7 (0.52)
T_{max} (hrs)	$T_{max} = \ln(k_a/k_e) / (k_a - k_e)$	5.4
$AUC_{0-\tau,ss}$ ($\mu M * hr$)	$AUC_{ss} = C_{av,ss} * \tau$	40.8 (7.77)
R_{AC}	$R_{AC} = 1 / (1 - e^{(-k_e * t)})$	1.0 (1.2)

CLAIMS

1. A solid pharmaceutical formulation, comprising:

(1) a compound of Formula (A):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C₃₋₁₀ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and

(2) a pharmaceutically acceptable polymer.

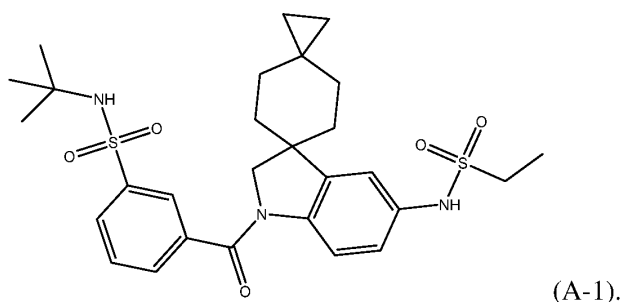
2. The formulation of claim 1, wherein the pharmaceutically acceptable polymer comprises hydroxypropylmethylcellulose acetate succinate (HPMCAS), hydroxypropyl methylcellulose phthalate (HPMCP), hydroxypropyl methylcellulose (HPMC), or methacrylic acid-ethyl acrylate copolymer, or any combination thereof.
3. The formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable polymer comprises HPMCAS.
4. The formulation of claim 3, wherein the HPMCAS is HPMCAS-M.
5. The formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable polymer comprises HPMCP.
6. The formulation of claim 5, wherein the HPMCP is HPMCP-HP55.
7. The formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable polymer comprises HPMC.

8. The formulation of claim 7, wherein the HPMC is HPMC E3LV.
9. The formulation of claim 1 or claim 2, wherein the pharmaceutically acceptable polymer comprises methacrylic acid-ethyl acrylate copolymer.
10. The formulation of claim 9, wherein the methacrylic acid-ethyl acrylate copolymer is methacrylic acid-ethyl acrylate copolymer (1:1).
11. The formulation of any one of claims 1-10, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of from about 20:80 to about 90:10.
12. The formulation of any one of claims 1-11, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of from about 25:75 to about 70:30.
13. The formulation of any one of claims 1-12, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of about 25:75.
14. The formulation of any one of claims 1-12, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of about 40:60.
15. The formulation of any one of claims 1-12, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of about 50:50.
16. The formulation of any one of claims 1-12, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of about 60:40.
17. The formulation of any one of claims 1-12, wherein the formulation has a weight ratio of the compound of Formula (A), or pharmaceutically acceptable salt thereof, to the pharmaceutically acceptable polymer of about 70:30.

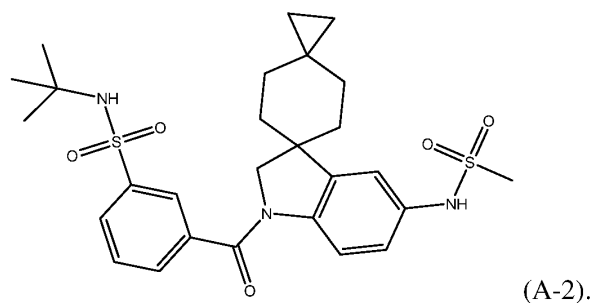
18. The formulation of any one of claims 1-2, 5-6, and 11-13, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCP-HP55 in a weight ratio of about 25:75.
19. The formulation of any one of claims 1-2, 5-6, 11, 12, and 14, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCP-HP55 in a weight ratio of about 40:60.
20. The formulation of any one of claims 1-2, 5-6, 11, 12, and 15, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCP-HP55 in a weight ratio of about 50:50.
21. The formulation of any one of claims 1-2, 5-6, 11, 12, and 16, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCP-HP55 in a weight ratio of about 60:40.
22. The formulation of any one of claims 1-2, 5-6, 11, 12, and 17, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCP-HP55 in a weight ratio of about 70:30.
23. The formulation of any one of claims 1-2, 9-10, and 11-13, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and methacrylic acid-ethyl acrylate copolymer (1:1) in a weight ratio of about 25:75.
24. The formulation of any one of claims 1-2, 9-10, 11, 12, and 14, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and methacrylic acid-ethyl acrylate copolymer (1:1) in a weight ratio of about 40:60.
25. The formulation of any one of claims 1-2, 9-10, 11, 12, and 15, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and methacrylic acid-ethyl acrylate copolymer (1:1) in a weight ratio of about 50:50.
26. The formulation of any one of claims 1-2, 9-10, 11, 12, and 16, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and methacrylic acid-ethyl acrylate copolymer (1:1) in a weight ratio of about 60:40.

27. The formulation of any one of claims 1-2, 9-10, 11, 12, and 17, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and methacrylic acid-ethyl acrylate copolymer (1:1) in a weight ratio of about 70:30.
28. The formulation of any one of claims 1-4 or 11-13, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCAS in a weight ratio of about 25:75.
29. The formulation of any one of claims 1-4, 11, 12, and 14, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCAS in a weight ratio of about 40:60.
30. The formulation of any one of claims 1-4, 11, 12, and 15, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCAS in a weight ratio of about 50:50.
31. The formulation of any one of claims 1-4, 11, 12, and 16, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCAS in a weight ratio of about 60:40.
32. The formulation of any one of claims 1-4, 11, 12, and 17, wherein the formulation comprises a compound of Formula (A), or pharmaceutically acceptable salt thereof, and HPMCAS in a weight ratio of about 70:30.
33. The formulation of any one of claims 1-32, wherein ring B is cyclohexyl.
34. The formulation of any one of claims 1-33, wherein the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form cyclopropyl.
35. The formulation of any one of claims 1-34, wherein ring A is C_{6-14} aryl substituted with one $-S(O)_2NR^{a14}R^{a15}$ group.
36. The formulation of any one of claims 1-35, wherein Y^2 is CR^{C2} , and CR^{C2} is $-NR^{c5}S(O)_2R^{c6}$.

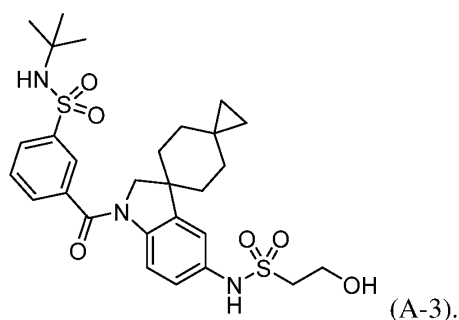
37. The formulation of any one of claims 1-36, wherein ring A is C₆₋₁₄ aryl substituted with one -S(O)₂NR^{a14}R^{a15} group, and Y² is CR^{C2}, and CR^{C2} is -NR^{c5}S(O)₂R^{c6}.
38. The formulation of any one of claims 1-37, wherein ring A is C₆₋₁₄ aryl substituted with one -S(O)₂NR^{a14}R^{a15} group, wherein R^{a14} is H and R^{a15} is C₁₋₆ alkyl; and Y² is CR^{C2}, CR^{C2} is -NR^{c5}S(O)₂R^{c6}, wherein R^{c6} is C₁₋₆ alkyl optionally substituted with one -OH group.
39. The formulation of any one of claims 1-38, wherein the compound of Formula (A) is a compound of Formula (A-1):



40. The formulation of any one of claims 1-38, wherein the compound of Formula (A) is a compound of Formula (A-2):

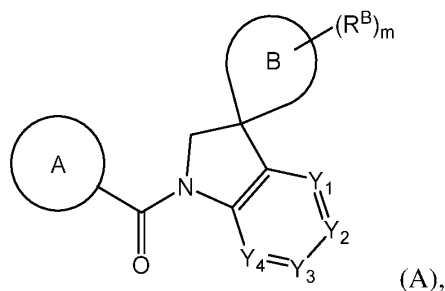


41. The formulation of any one of claims 1-38, wherein the compound of Formula (A) is a compound of Formula (A-3):



42. The formulation of any one of claims 1-41, wherein the compound of Formula (A) is in substantially amorphous form.

43. A solid formulation comprising a compound of Formula (A):



or a pharmaceutically acceptable salt thereof, wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀ cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1}-R^{a22} are each independently hydrogen, C₁₋₆ alkyl, C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, C₃₋₁₀ cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C₆₋₁₄ aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C₁₋₆ alkyl), C₂₋₆ alkenyl, C₃₋₁₀ cycloalkyl, -S(C₁₋₆ alkyl), =CR^{1a1}R^{1a2}, and C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the

group consisting of halo, -OH, and -O(C₁₋₆ alkyl), wherein R^{1a1} and R^{1a2} are each independently hydrogen or C₁₋₆ alkyl;

ring B is C₅₋₇ cycloalkyl, C₅₋₇ cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C₃₋₇ cycloalkyl;

Y¹ is N or CR^{C1};

Y² is N or CR^{C2};

Y³ is N or CR^{C3};

Y⁴ is N or CR^{C4};

wherein no more than three of Y¹, Y², Y³, and Y⁴ are N;

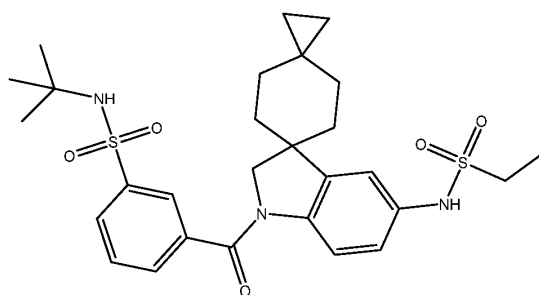
R^{C1}-R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

R^{c1}-R^{c18} are each independently hydrogen, C₃₋₁₀ cycloalkyl, or C₁₋₆ alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH; and

wherein the formulation is effective to provide a maximum plasma concentration (C_{max}) of the compound of Formula (A), or a pharmaceutically acceptable salt thereof, in a human subject of from about 1.5 μmol/mL to about 5.0 μmol/mL.

44. The formulation of claim 43, wherein the formulation is effective to achieve an area under a plasma concentration-time curve (AUC₀₋₂₄) of the compound of Formula (A) in a human subject from about 10 μmol·hr/mL to about 100 μmol·hr/mL from about 0 hour to about 24 hours after administration of the formulation to the subject.

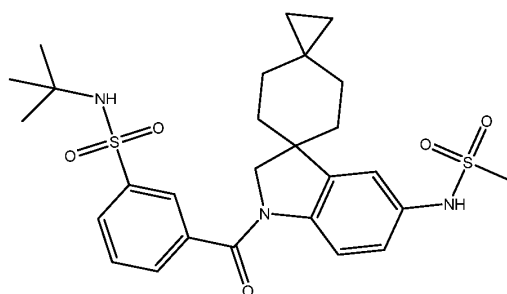
45. The formulation of claim 43 or 44, wherein the compound of Formula (A), or a pharmaceutically acceptable salt thereof, is a compound of Formula (A-1):



(A-1),

or a pharmaceutically acceptable salt thereof.

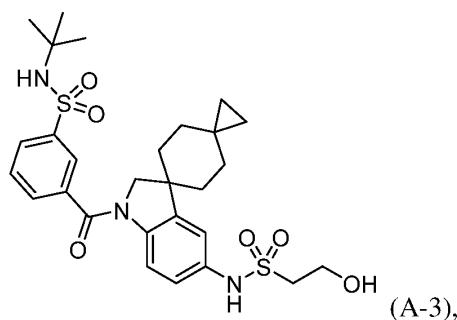
46. The formulation of claim 43 or 44, wherein the compound of Formula (A), or a pharmaceutically acceptable salt thereof, is a compound of Formula (A-2):



(A-2),

or a pharmaceutically acceptable salt thereof.

47. The formulation of claim 43 or 44, wherein the compound of Formula (A), or a pharmaceutically acceptable salt thereof, is a compound of Formula (A-3):



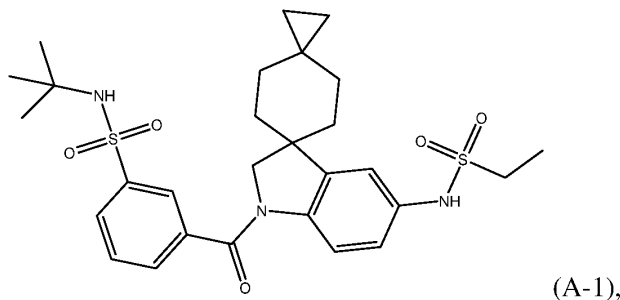
(A-3),

or a pharmaceutically acceptable salt thereof.

48. The formulation of any one of claims 43-47, wherein the formulation is administered to the subject without food.

49. The formulation of any one of claims 1-48, wherein the formulation is a spray-dried dispersion.

50. A crystalline form of a compound of Formula (A-1):



or a pharmaceutically acceptable salt thereof.

51. The crystalline form of claim 50, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 13.54 ± 0.20 , 17.89 ± 0.20 , 18.39 ± 0.20 , 19.39 ± 0.20 , and 19.73 ± 0.20 degrees.

52. The crystalline form of claim 51, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 15.46 ± 0.20 and 17.29 ± 0.20 degrees.

53. The crystalline form of claims 51 or 52, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 8.61 ± 0.20 and 15.04 ± 0.20 degrees.

54. The crystalline form of any one of claims 50-53, characterized by having an XRPD pattern substantially as shown in **FIG. 2**.

55. The crystalline form of any one of claims 50-54, characterized by having an endotherm onset at $188 \pm 2^\circ\text{C}$, as determined by DSC.

56. The crystalline form of any one of claims 50-55, characterized by having an endotherm peak at $194 \pm 2^\circ\text{C}$, as determined by DSC.

57. The crystalline form of any one of claims 50-56, characterized by having a DSC graph substantially as shown in **FIG. 3**.

58. The crystalline form of any one of claims 50-57, characterized by having a weight loss of $0.01 \pm 0.005\%$ between $52-150^{\circ}\text{C}$, as determined by TGA.
59. The crystalline form of any one of claims 50-58, characterized by having an apparent decomposition at $316 \pm 5^{\circ}\text{C}$, as determined by TGA.
60. The crystalline form of any one of claims 50-59, characterized by having a TGA graph substantially as shown in **FIG. 3**.
61. The crystalline form of any one of claims 50-60, characterized by having a weight gain of $0.095 \pm 0.005\%$ from 5% RH to 95% RH, as determined by DVS.
62. The crystalline form of any one of claims 50-61, characterized by having a weight loss of $0.097 \pm 0.005\%$ from 95% RH to 5% RH, as determined by DVS.
63. The crystalline form of any one of claims 50-62, characterized by having a DVS graph substantially as shown in **FIG. 4**.
64. The crystalline form of claim 50, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 15.62 ± 0.20 , 16.60 ± 0.20 , 19.87 ± 0.20 , 20.11 ± 0.20 , and 25.76 ± 0.20 degrees.
65. The crystalline form of claim 64, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 17.50 ± 0.20 and 21.13 ± 0.20 degrees.
66. The crystalline form of claims 64 or 65, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 8.23 ± 0.20 and 11.72 ± 0.20 degrees.
67. The crystalline form of any one of claims 50 or 64-66, characterized by having an XRPD pattern substantially as shown in **FIG. 10**.
68. The crystalline form of any one of claims 50 or 64-67, characterized by having an endotherm onset at $196 \pm 2^{\circ}\text{C}$, as determined by DSC.
69. The crystalline form of any one of claims 50 or 64-68, characterized by having an endotherm peak at $197 \pm 2^{\circ}\text{C}$, as determined by DSC.

70. The crystalline form of any one of claims 50 or 64-69, characterized by having a DSC graph substantially as shown in **FIG. 11**.
71. The crystalline form of any one of claims 50 or 64-70, characterized by having a weight loss of $0.05 \pm 0.01\%$ between 25 and 100°C , as determined by TGA.
72. The crystalline form of any one of claims 50 or 64-71, characterized by having a weight loss of $0.10 \pm 0.05\%$ between 100 and 180°C , as determined by TGA.
73. The crystalline form of any one of claims 50 or 64-72, characterized by having a TGA graph substantially as shown in **FIG. 12**.
74. The crystalline form of any one of claims 50 or 64-73, characterized by having a weight gain of $0.030\% \pm 0.005\%$ from 0.1% RH to 95% RH, as determined by DVS.
75. The crystalline form of any one of claims 50 or 64-74, characterized by having a weight loss of $0.050\% \pm 0.005\%$ from 95 % RH to 0.1% RH, as determined by DVS.
76. The crystalline form of any one of claims 50 or 64-75, characterized by having a DVS graph substantially as shown in **FIG. 13**.
77. The crystalline form of any one of claims 50-76, comprising a compound of Formula (A-1).
78. The crystalline form of claim 50, comprising a mono-sodium salt of the compound of Formula (A-1).
79. The crystalline form of claim 78, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 7.66 ± 0.20 , 8.45 ± 0.20 , 11.64 ± 0.20 , 17.92 ± 0.20 , and 22.82 ± 0.20 degrees.
80. The crystalline form of claim 79, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 16.91 ± 0.20 and 17.13 ± 0.20 degrees.
81. The crystalline form of claims 78 or 79, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.60 ± 0.20 and 18.34 ± 0.20 degrees.

82. The crystalline form of any one of claims 50 or 78-81, characterized by having an XRPD pattern substantially as shown in **FIG. 14**.
83. The crystalline form of any one of claims 50 or 78-82, characterized by having an endotherm onset at $186\pm 2^{\circ}\text{C}$, as determined by DSC.
84. The crystalline form of any one of claims 50 or 78-83, characterized by having an endotherm peak at $190\pm 2^{\circ}\text{C}$, as determined by DSC.
85. The crystalline form of any one of claims 50 or 78-84, characterized by having a DSC graph substantially as shown in **FIG. 15**.
86. The crystalline form of any one of claims 50 or 78-85, characterized by having a weight loss of $0.7\%\pm 0.1\%$ between 25°C and 170°C , as determined by TGA.
87. The crystalline form of any one of claims 50 or 78-86, characterized by having a TGA graph substantially as shown in **FIG. 16**.
88. The crystalline form of claim 78, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 14.19 ± 0.20 , 17.44 ± 0.20 , 17.70 ± 0.20 , and 18.14 ± 0.20 degrees.
89. The crystalline form of claim 88, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 18.61 ± 0.20 and 27.38 ± 0.20 degrees.
90. The crystalline form of claims 88 or 89, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 16.87 ± 0.20 and 21.64 ± 0.20 degrees.
91. The crystalline form of any one of claims 50, 78, or 88-90, characterized by having an XRPD pattern substantially as shown in **FIG. 38**.
92. The crystalline form of any one of claims 50, 78, or 88-91, characterized by having an endotherm peak at $166\pm 2^{\circ}\text{C}$, as determined by DSC.
93. The crystalline form of any one of claims 50, 78, or 88-92, characterized by having an endotherm peak at $192\pm 2^{\circ}\text{C}$, as determined by DSC.

94. The crystalline form of any one of claims 50, 78, or 88-93, characterized by having an endotherm peak at 208 ± 2 °C, as determined by DSC.
95. The crystalline form of any one of claims 50, 78, or 88-94, characterized by having a DSC graph substantially as shown in **FIG. 39**.
96. The crystalline form of any one of claims 50, 78, or 88-95, characterized by having a weight loss of $0.3\% \pm 0.1\%$ between 25 °C and 80 °C, as determined by TGA.
97. The crystalline form of any one of claims 50, 78, or 88-96, characterized by having a weight loss of $7.3\% \pm 0.1\%$ between 80 °C and 190 °C, as determined by TGA.
98. The crystalline form of any one of claims 50, 78, or 88-97, characterized by having a TGA graph substantially as shown in **FIG. 40**.
99. The crystalline form of claim 78, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.85 ± 0.20 , 11.74 ± 0.20 , 17.14 ± 0.20 , and 18.92 ± 0.20 degrees.
100. The crystalline form of claim 99, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 18.51 ± 0.20 and 20.95 ± 0.20 degrees.
101. The crystalline form of claims 99 or 100, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 16.64 ± 0.20 and 24.73 ± 0.20 degrees.
102. The crystalline form of any one of claims 50, 78, or 99-101, characterized by having an XRPD pattern substantially as shown in **FIG. 49**.
103. The crystalline form of any one of claims 50, 78, or 99-102, characterized by having an endotherm peak at 183 ± 2 °C, as determined by DSC.
104. The crystalline form of any one of claims 50, 78, or 99-103, characterized by having a DSC graph substantially as shown in **FIG. 50**.
105. The crystalline form of any one of claims 50, 78, or 99-104, characterized by having a weight loss of $0.7\% \pm 0.1\%$ between 30 °C and 120 °C, as determined by TGA.

106. The crystalline form of any one of claims 50, 78, or 99-105, characterized by having a weight loss of $8.0\% \pm 0.1\%$ between 120 °C and 180 °C, as determined by TGA.
107. The crystalline form of any one of claims 50, 78, or 99-106, characterized by having a weight loss of $4.2\% \pm 0.1\%$ between 180 °C and 230 °C, as determined by TGA.
108. The crystalline form of any one of claims 50, 78, or 99-107, characterized by having a TGA graph substantially as shown in **FIG. 51**.
109. The crystalline form of claim 50, comprising a di-sodium salt of the compound of Formula (A-1).
110. The crystalline form of claims 50 or 109, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.39 ± 0.20 , 6.89 ± 0.20 , 16.32 ± 0.20 , 17.01 ± 0.20 , and 22.82 ± 0.20 degrees.
111. The crystalline form of claim 110, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 12.50 ± 0.20 and 16.52 ± 0.20 degrees.
112. The crystalline form of claims 100 or 111, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.48 ± 0.20 and 14.34 ± 0.20 degrees.
113. The crystalline form of any one of claims 50 or 109-112, characterized by having an XRPD pattern substantially as shown in **FIG. 17**.
114. The crystalline form of any one of claims 50 or 109-113, characterized by having an endotherm peak at 60 ± 2 °C, as determined by DSC.
115. The crystalline form of any one of claims 50 or 109-114, characterized by having an endotherm peak at 212 ± 2 °C, as determined by DSC.
116. The crystalline form of any one of claims 50 or 109-115, characterized by having a DSC graph substantially as shown in **FIG. 18**.
117. The crystalline form of any one of claims 50 or 109-116, characterized by having a weight loss of $3.3\% \pm 0.5\%$ between 25 °C and 48 °C as determined by TGA.

118. The crystalline form of any one of claims 50 or 109-117, characterized by having a weight loss of $2.1\% \pm 0.5\%$ between 48 °C and 100 °C as determined by TGA.
119. The crystalline form of any one of claims 50 or 109-118, characterized by having a TGA graph substantially as shown in **FIG. 19**.
120. The crystalline form of claims 50 or 109, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 5.26 ± 0.50 , 8.80 ± 0.50 , 16.75 ± 0.50 , and 17.72 ± 0.50 degrees.
121. The crystalline form of claim 120, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 9.28 ± 0.50 and 10.47 ± 0.50 degrees.
122. The crystalline form of claims 120 or 121, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 8.37 ± 0.50 and 21.32 ± 0.50 degrees.
123. The crystalline form of any one of claims 50, 109, or 120-122, characterized by having an XRPD pattern substantially as shown in **FIG. 26**.
124. The crystalline form of any one of claims 50, 109, or 120-123, characterized by having a DSC graph substantially as shown in **FIG. 27**.
125. The crystalline form of any one of claims 50, 109, or 120-124, characterized by having a weight loss of $5.4\% \pm 0.1\%$ between 25 °C and 140 °C as determined by TGA.
126. The crystalline form of any one of claims 50, 109, or 120-125, characterized by having a TGA graph substantially as shown in **FIG. 28**.
127. The crystalline form of claims 50 or 109, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.03 ± 0.20 , 7.66 ± 0.20 , 12.04 ± 0.20 , and 18.73 ± 0.20 degrees.
128. The crystalline form of claim 127, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 12.93 ± 0.20 and 18.97 ± 0.20 degrees.
129. The crystalline form of claims 127 or 128, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 19.91 ± 0.20 and 24.62 ± 0.20 degrees.

130. The crystalline form of any one of claims 50, 109 or 127-129, characterized by having an XRPD pattern substantially as shown in **FIG. 32**.
131. The crystalline form of any one of claims 50, 109 or 127-130, characterized by having an endotherm peak at 52 ± 2 °C, as determined by DSC.
132. The crystalline form of any one of claims 50, 109 or 127-131, characterized by having an endotherm peak at 84 ± 2 °C, as determined by DSC.
133. The crystalline form of any one of claims 50, 109 or 127-132, characterized by having an endotherm peak at 104 ± 2 °C, as determined by DSC.
134. The crystalline form of any one of claims 50, 109 or 127-133, characterized by having an endotherm peak at 128 ± 2 °C, as determined by DSC.
135. The crystalline form of any one of claims 50, 109 or 127-134, characterized by having a DSC graph substantially as shown in **FIG. 33**.
136. The crystalline form of any one of claims 50, 109 or 127-135, characterized by having a weight loss of $11.9\% \pm 3.0\%$ between 30 °C and 110 °C as determined by TGA.
137. The crystalline form of any one of claims 50, 109 or 127-136, characterized by having a TGA graph substantially as shown in **FIG. 34**.
138. The crystalline form of claims 50 or 109, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.07 ± 0.20 , 6.84 ± 0.20 , 12.07 ± 0.20 , 18.75 ± 0.20 , and 19.96 ± 0.20 degrees.
139. The crystalline form of claim 138, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 18.10 ± 0.20 and 20.47 ± 0.20 degrees.
140. The crystalline form of claims 138 or 139, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 7.70 ± 0.20 and 13.63 ± 0.20 degrees.
141. The crystalline form of any one of claims 50, 109 or 138-140, characterized by having an XRPD pattern substantially as shown in **FIG. 41**.

142. The crystalline form of any one of claims 50, 109 or 138-141, characterized by having an endotherm peak at 73 ± 2 °C, as determined by DSC.
143. The crystalline form of any one of claims 50, 109 or 138-142, characterized by having an endotherm peak at 99 ± 2 °C, as determined by DSC.
144. The crystalline form of any one of claims 50, 109 or 138-143, characterized by having an endotherm peak at 120 ± 2 °C, as determined by DSC.
145. The crystalline form of any one of claims 50, 109 or 138-144, characterized by having a DSC graph substantially as shown in **FIG. 42**.
146. The crystalline form of any one of claims 50, 109 or 138-145, characterized by having a weight loss of $0.6\% \pm 0.5\%$ between 30 °C and 48 °C as determined by TGA.
147. The crystalline form of any one of claims 50, 109 or 138-146, characterized by having a weight loss of $4.1\% \pm 0.5\%$ between 48 °C and 81 °C as determined by TGA.
148. The crystalline form of any one of claims 50, 109 or 138-147, characterized by having a weight loss of $2.7\% \pm 0.5\%$ between 81 °C and 140 °C as determined by TGA.
149. The crystalline form of any one of claims 50, 109 or 138-148, characterized by having a TGA graph substantially as shown in **FIG. 43**.
150. The crystalline form of any one of claims 50, 109 or 138-149, characterized by having a weight gain of $60\% \pm 5\%$ from 1% RH to 95% RH, as determined by DVS.
151. The crystalline form of any one of claims 50, 109 or 138-150, characterized by having a weight loss of $58\% \pm 5\%$ from 95% RH to 1% RH, as determined by DVS.
152. The crystalline form of any one of claims 50, 109 or 138-150, characterized by having a DVS graph substantially as shown in **FIG. 44**.
153. The crystalline form of claims 50 or 109, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 66.93 ± 0.50 , 20.10 ± 0.50 , 32.35 ± 0.50 , and 37.94 ± 0.50 degrees.

154. The crystalline form of claim 153, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.86 ± 0.50 and 17.26 ± 0.50 degrees.
155. The crystalline form of claims 153 or 154, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 20.80 ± 0.50 and 32.53 ± 0.50 degrees.
156. The crystalline form of any one of claims 50, 109 or 153-155, characterized by having an XRPD pattern substantially as shown in **FIG. 35**.
157. The crystalline form of any one of claims 50, 109 or 153-156, characterized by having a DSC graph substantially as shown in **FIG. 36**.
158. The crystalline form of any one of claims 50, 109 or 153-157, characterized by having a weight loss of $2.7\% \pm 0.1\%$ between $25\text{ }^{\circ}\text{C}$ and $64\text{ }^{\circ}\text{C}$ as determined by TGA.
159. The crystalline form of any one of claims 50, 109 or 153-158, characterized by having a weight loss of $2.4\% \pm 0.1\%$ between $65\text{ }^{\circ}\text{C}$ and $100\text{ }^{\circ}\text{C}$ as determined by TGA.
160. The crystalline form of any one of claims 50, 109 or 153-159, characterized by having a weight loss of $0.9\% \pm 0.1\%$ between $100\text{ }^{\circ}\text{C}$ and $140\text{ }^{\circ}\text{C}$ as determined by TGA.
161. The crystalline form of any one of claims 50, 109 or 153-160, characterized by having a TGA graph substantially as shown in **FIG. 37**.
162. The crystalline form of claim 50, comprising a mono-potassium salt of the compound of Formula (A-1).
163. The crystalline form of claim 50 or 162, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 13.48 ± 0.20 , 16.62 ± 0.20 , and 16.62 ± 0.20 degrees.
164. The crystalline form of claim 163, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 12.25 ± 0.20 and 19.69 ± 0.20 degrees.
165. The crystalline form of claims 163 or 164, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 11.21 ± 0.20 and 24.83 ± 0.20 degrees.
166. The crystalline form of any one of claims 50 or 162-165, characterized by having an XRPD pattern substantially as shown in **FIG. 20**.

167. The crystalline form of any one of claims 50 or 162-166, characterized by having an endotherm peak at 39 ± 5 °C, as determined by DSC.
168. The crystalline form of any one of claims 50 or 162-167, characterized by having an endotherm peak at 156 ± 5 °C, as determined by DSC.
169. The crystalline form of any one of claims 50 or 162-168, characterized by having a DSC graph substantially as shown in **FIG. 21**.
170. The crystalline form of any one of claims 50 or 162-169, characterized by having a weight loss of $3.2\%\pm 0.1\%$ between 25 °C and 100 °C, as determined by TGA.
171. The crystalline form of any one of claims 50 or 162-170, characterized by having a TGA graph substantially as shown in **FIG. 22**.
172. The crystalline form of claim 50, comprising a di-potassium salt of the compound of Formula (A-1).
173. The crystalline form of claim 50 or 172, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 5.84 ± 0.50 , 5.91 ± 0.50 , 9.21 ± 0.50 , and 18.56 ± 0.50 degrees.
174. The crystalline form of claim 173, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 15.56 ± 0.50 and 19.02 ± 0.50 degrees.
175. The crystalline form of claims 173 or 174, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.56 ± 0.50 and 25.27 ± 0.50 degrees.
176. The crystalline form of any one of claims 50, or 172-175, characterized by having an XRPD pattern substantially as shown in **FIG. 23**.
177. The crystalline form of any one of claims 50 or 172-176, characterized by having an endotherm peak at 70 ± 10 °C, as determined by DSC.
178. The crystalline form of any one of claims 50 or 172-177, characterized by having a DSC graph substantially as shown in **FIG. 24**.

179. The crystalline form of any one of claims 50 or 172-178, characterized by having a substantially continuous weight loss between 25 °C and 300 °C, as determined by TGA.
180. The crystalline form of any one of claims 50 or 172-179, characterized by having a TGA graph substantially as shown in **FIG. 25**.
181. The crystalline form of claim 50 or 172, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.66 ± 0.20 , 17.43 ± 0.20 , 19.31 ± 0.20 , and 23.72 ± 0.20 degrees.
182. The crystalline form of claim 181, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.12 ± 0.20 and 19.99 ± 0.20 degrees.
183. The crystalline form of claims 181 or 182, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 18.82 ± 0.20 and 22.76 ± 0.20 degrees.
184. The crystalline form of any one of claims 50, 172, or 181-183, characterized by having an XRPD pattern substantially as shown in **FIG. 29**.
185. The crystalline form of any one of claims 50, 172, or 181-184, characterized by having an endotherm peak at 83 ± 2 °C, as determined by DSC.
186. The crystalline form of any one of claims 50, 172, or 181-185, characterized by having a DSC graph substantially as shown in **FIG. 30**.
187. The crystalline form of any one of claims 50, 172, or 181-186, characterized by having a weight loss of $0.3\%\pm0.1\%$ between 25 °C and 40 °C, as determined by TGA.
188. The crystalline form of any one of claims 50, 172, or 181-187, characterized by having a weight loss of $2.7\%\pm0.1\%$ between 40 °C and 75 °C, as determined by TGA.
189. The crystalline form of any one of claims 50, 172, or 181-188, characterized by having a weight loss of $3.1\%\pm0.1\%$ between 75 °C and 170 °C, as determined by TGA.
190. The crystalline form of any one of claims 50, 172, or 181-189, characterized by having a TGA graph substantially as shown in **FIG. 31**.

191. The crystalline form of claim 50 or 172, characterized by having an XRPD pattern comprising peaks at angles 2-theta of 6.65 ± 0.20 , 17.42 ± 0.20 , 19.30 ± 0.20 , and 23.75 ± 0.20 degrees.
192. The crystalline form of claim 191, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 20.00 ± 0.20 and 22.78 ± 0.20 degrees.
193. The crystalline form of claims 191 or 192, characterized by having an XRPD pattern comprising additional peaks at angles 2-theta of 13.13 ± 0.20 and 18.82 ± 0.20 degrees.
194. The crystalline form of any one of claims 50, 172, or 191-193, characterized by having an XRPD pattern substantially as shown in **FIG. 45**.
195. The crystalline form of any one of claims 50, 172, or 191-194, characterized by having an endotherm peak at 86 ± 2 °C, as determined by DSC.
196. The crystalline form of any one of claims 50, 172, or 191-195, characterized by having a DSC graph substantially as shown in **FIG. 46**.
197. The crystalline form of any one of claims 50, 172, or 191-196, characterized by having a weight loss of 0.7% or $0.7\% \pm 0.1\%$ between 25 °C and 42 °C, as determined by TGA.
198. The crystalline form of any one of claims 50, 172, or 191-197, characterized by having a weight loss of $6.0\% \pm 0.1\%$ between 42 °C and 94 °C, as determined by TGA.
199. The crystalline form of any one of claims 50, 172, or 191-198, characterized by having a TGA graph substantially as shown in **FIG. 47**.
200. The crystalline form of any one of claims 50, 172, or 191-199, characterized by having a weight gain of $62\% \pm 5\%$ from 1% RH to 95% RH, as determined by DVS.
201. The crystalline form of any one of claims 50, 172, or 191-200, characterized by having a weight loss of $70\% \pm 5\%$ from 95% RH to 1% RH, as determined by DVS.
202. The crystalline form of any one of claims 50, 172, or 191-201, characterized by having a DVS graph substantially as shown in **FIG. 48**.

203. A method of inhibiting KIF18A comprising contacting a cell with an effective amount of (i) a formulation of any one of claims 1-49, or (ii) a crystalline form of any one of claims 50-202.

204. A method of treating a disease or condition mediated by KIF18A in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of (i) a formulation of any one of claims 1-49, or (ii) a crystalline form of any one of claims 50-202.

205. A method of treating cancer in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of (i) a formulation of any one of claims 1-49, or (ii) a crystalline form of any one of claims 50-202.

206. The method of claim 205, wherein the cancer is selected from the group consisting of carcinomas, cancer of the anus, bladder, breast, colon, small intestine, appendix, kidney, renal pelvis, ureter, urothelium, liver, lung, pleura, esophagus, head and neck, nasopharynx, oropharynx, hypopharynx, oral cavity, larynx, biliary tract, gall-bladder, ovary, testicle, germ cell, uterus, pancreas, stomach, cervix, thyroid, prostate, salivary gland, or skin, hematopoietic tumors of lymphoid lineage, hematopoietic tumors of myeloid lineage, hematopoietic tumors of any lineage, myeloma, tumors of mesenchymal origin including sarcomas, tumors of the central and peripheral nervous system, tumor of neuroendocrine origin, tumor of endocrine origin, small cell tumors, tumors of unknown primary, other tumors comprising retinoblastoma, melanoma, seminoma, teratocarcinoma, osteosarcoma, and other cancer-related disorders that are a consequence of cancer presence or progression.

207. A method of preparing the formulation of any one of claims 1-49, wherein the process comprises spray-drying a solution of a compound of Formula (A), or a pharmaceutically acceptable salt thereof, and a polymer to obtain an amorphous solid dispersion of the compound of Formula (A), or a pharmaceutically acceptable salt thereof.

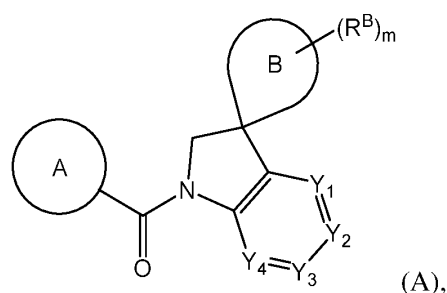
208. The method of claim 207, wherein the solution of a compound of Formula (A) comprises dichloromethane and alcohol.

209. The method of claim 207 or claim 208, wherein the solution of a compound of Formula (A) comprises dichloromethane and methanol.

210. The method of any one of claims 207-209, wherein the solution of a compound of Formula (A) comprises dichloromethane and methanol in a weight ratio of about 87:13.

211. A method of preparing the crystalline form of any one of claims 50-202, comprising forming a mixture of the compound of Formula (A), or a pharmaceutically acceptable salt thereof, and a solvent selected from the group consisting of acetone, isobutyl acetate, water, acetone nitrile, 1-butanol, dimethylacetamide, N,N-dimethylformamide, nitromethane, toluene, dimethyl sulfoxide, dioxane, cyclopentyl methyl ether, tert-amyl methyl ether, 2-ethoxyethanol, ethyl acetate, ethanol, hexafluoroisopropanol, diisopropyl ether, methyl ethyl ketone, hexane, methanol, 2-methyltetrahydrofuran, N-methyl-2-pyrrolidone, 2,2,2-trifluoroethanol, 1-propanol, isopropanol alcohol, methylcyclohexane, tetrahydrofuran, anisole, methyl isopropyl ketone, dipropyl ether, chloroform, tert-amyl alcohol, and any mixture thereof.

212. A method of preparing a substantially amorphous form of a compound of Formula (A):



comprising (1) forming a mixture of a compound of Formula (A) and a solvent selected from the group consisting of N,N-dimethylformamide (DMF), water, and mixtures thereof; (2) isolating solid from the mixture of (1); (3) washing the solid of (2) with water; and (4) drying the solid of (3) at room temperature; wherein:

ring A is C₆₋₁₄ aryl or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, C₁₋₆ alkyl, 3- to 10-membered heterocycloalkyl, -NR^{a1}C(O)NR^{a2}R^{a3}, -NR^{a4}C(O)OR^{a5}, -NR^{a6}R^{a7}, -N=S(O)R^{a8}R^{a9}, -OR^{a10}, -S(O)R^{a11}, -S(O)(NR^{a12})R^{a13}, -S(O)₂NR^{a14}R^{a15}, -S(O)₂R^{a16}, -(CR^{a17}R^{a18})₀₋₁C(O)NR^{a19}R^{a20}, -SR^{a21}, -C(O)R^{a22}, and C₁₋₆ alkyl substituted with one or more substituents independently selected from the group consisting of -OH, cyano, C₃₋₁₀

cycloalkyl, and 3- to 10-membered heterocycloalkyl optionally substituted with one or more halo;

R^{a1} - R^{a22} are each independently hydrogen, C_{1-6} alkyl, C_{2-6} alkenyl, C_{3-10} cycloalkyl, C_{3-10} cycloalkenyl, 3- to 10-membered heterocycloalkyl, 3- to 10-membered heterocycloalkenyl, C_{6-14} aryl, or 5- to 12-membered heteroaryl, each optionally substituted with one or more substituents independently selected from the group consisting of halo, cyano, -OH, -O(C_{1-6} alkyl), C_{2-6} alkenyl, C_{3-10} cycloalkyl, -S(C_{1-6} alkyl), =CR^{la1}R^{la2}, and C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo, -OH, and -O(C_{1-6} alkyl), wherein R^{la1} and R^{la2} are each independently hydrogen or C_{1-6} alkyl;

ring B is C_{5-7} cycloalkyl, C_{5-7} cycloalkenyl, or 5- to 7-membered heterocycloalkyl wherein one or two of the ring atoms are each oxygen and the remaining ring atoms are each carbon;

m is 2;

the two R^B groups are attached to the same carbon atom on ring B and are taken together with the carbon atom to which they are attached to form C_{3-7} cycloalkyl;

Y^1 is N or CR^{C1};

Y^2 is N or CR^{C2};

Y^3 is N or CR^{C3};

Y^4 is N or CR^{C4};

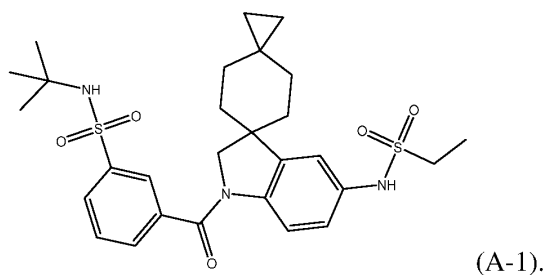
wherein no more than three of Y^1 , Y^2 , Y^3 , and Y^4 are N;

R^{C1} - R^{C4} are each independently hydrogen, halo, cyano, -OH, -NO₂, -C(O)NR^{c1}R^{c2}, -NR^{c3}R^{c4}, -NR^{c5}S(O)₂R^{c6}, -P(O)R^{c7}R^{c8}, -N=S(O)R^{c9}R^{c10}, -S(O)(NR^{c11})R^{c12}, -S(O)₂R^{c13}, -NR^{c14}C(O)OR^{c15}, -NR^{c16}S(O)₂(CH₂)₁₋₆NR^{c17}C(O)R^{c18}, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH;

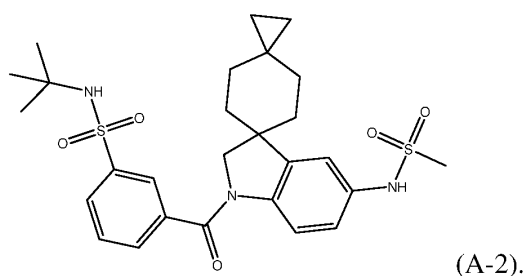
R^{c1} - R^{c18} are each independently hydrogen, C_{3-10} cycloalkyl, or C_{1-6} alkyl optionally substituted with one or more substituents independently selected from the group consisting of halo and -OH.

213. The method of claim 212, wherein the solvent is a mixture of DMF and water.

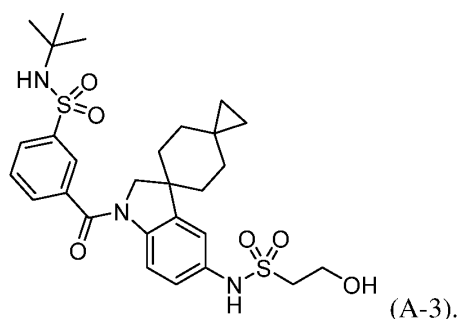
214. The method of claim 212 or 213, wherein the compound of Formula (A) is a compound of Formula (A-1):



215. The method of claims 212 or 213, wherein the compound of Formula (A) is a compound of Formula (A-2):



216. The method of claims 212 or 213, wherein the compound of Formula (A) is a compound of Formula (A-3):



217. The method of claims 205 or 206, wherein the cancer is associated with chromosomal instability.

218. The method of claim 205 or 217, wherein the cancer is selected from the group consisting of advanced solid tumor, high grade serous adenocarcinoma of ovary, squamous non-small-cell lung cancer, triple negative breast cancer, gastric adenocarcinoma, colorectal adenocarcinoma, esophageal squamous cell carcinoma, esophageal adenocarcinoma, gastroesophageal junction adenocarcinoma, transitional cell carcinoma of bladder, head and

neck squamous cell carcinoma, ovarian carcinosarcoma, uterine carcinosarcoma, uterine serous carcinoma, and endometrium cancer.

219. The method of any one of claims 205, 206, 217, or 218, wherein the (i) a formulation of any one of claims 1-49, or (ii) a crystalline form of any one of claims 50-202 is administered to the subject in 28-day cycles.