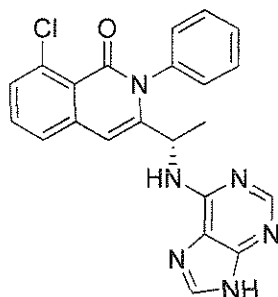


SUMMARY

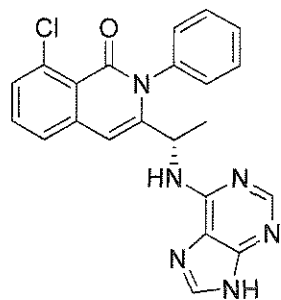
[0009] In one embodiment, provided herein are polymorphic forms of a compound of Formula (I):



(I),

herein referred to as Form A, Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), or a salt, solvate, or hydrate thereof; or a mixture of two or more thereof. In one embodiment, the polymorphic form of a compound of Formula (I) can be a crystalline form, a partially crystalline form, an amorphous form, or a mixture of crystalline form(s) and/or amorphous form(s).

[0009a] In one aspect, there is provided a compound of Formula (I):



Formula (I),

wherein the compound is polymorph Form C, Form B, Form D, Form E, Form F, Form G, Form H, Form I, or Form J of a compound of Formula (I), or a mixture of two or more thereof, wherein

polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$;

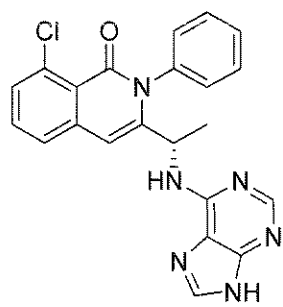
polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$;

polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$;

polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$; and

polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

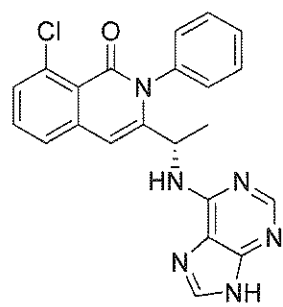
[0009b] In another aspect, there is provided a compound of Formula (I):



Formula (I).

wherein the compound is polymorph Form C of a compound of Formula (I), wherein the polymorph has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

[0009c] In another aspect, there is provided a compound of Formula (I):



Formula (I).

wherein the compound is:

(A) a mixture of two or more compounds of Formula (I), wherein the compounds of Formula (I) are selected from:

- i) polymorph Form C; and
- ii) at least one non-Form C polymorph selected from Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), optionally wherein the mixture is at least 50% by weight polymorph Form C; or

(B) a mixture of two or more compounds of Formula (I), wherein the compounds of Formula (I) are selected from:

- i) polymorph Form A; and
- ii) at least one non-Form A polymorph selected from Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I); wherein

polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;

polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$;

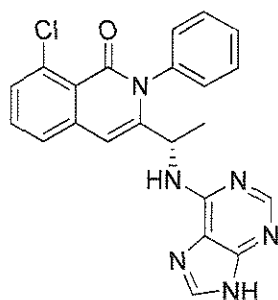
polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$;

polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$;

polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$; and

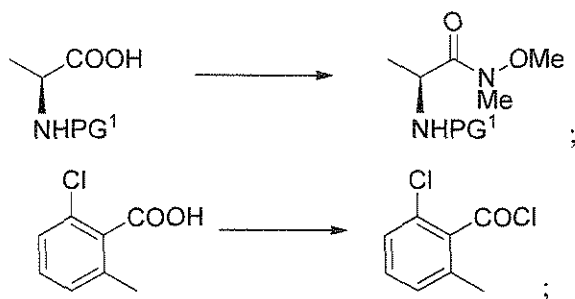
polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

[0010] In one embodiment, provided herein is a method of preparing a compound of Formula (I):



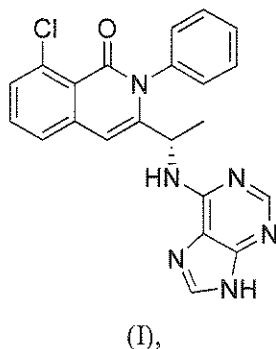
(I),

or a pharmaceutically acceptable salt, solvate, or hydrate thereof. In one embodiment, the method comprises any one, two, three, four, five, six, seven, or eight, or more of the following steps:



heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate.

[0011] In one embodiment, provided herein is a method of preparing a polymorph Form C of a compound of Formula (I):

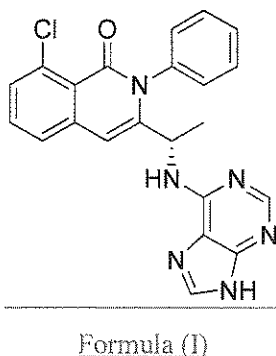


wherein the method comprises:

(i) exposing a composition comprising at least one non-Form C polymorph of a compound of Formula (I), or a salt, solvate, or hydrate thereof, to a non-anhydrous condition for a period of time sufficient to convert at least about 50% of the total amount of non-Form C polymorph(s) into Form C of a compound of Formula (I); and

(ii) recovering said polymorph Form C.

[0011a] In another aspect, there is provided a method of preparing polymorph Form C of a compound of Formula (I):



wherein the method comprises:

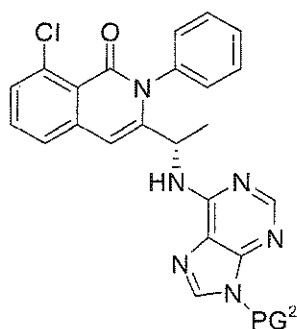
(i) exposing a composition comprising at least one non-Form C polymorph of a compound of Formula (I), to a non-anhydrous condition for a period of time sufficient to convert at least about 50% of the total amount of non-Form C polymorph(s) into Form C of a compound of Formula (I); and

(ii) recovering said polymorph Form C;

wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

[0012] In one embodiment, a non-anhydrous condition includes water, such as, in a form of water vapor and/or liquid water. In one embodiment, a non-anhydrous condition includes a solvent system comprising a non-water solvent and liquid water. In one embodiment, the non-water solvent is a water-miscible solvent. For example, liquid water can be present in an amount of about 1%, about 2%, about 3%, about 4%, about 5%, about 6%, about 7%, about 8%, about 9%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50% , about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, about 96%, about 97%, about 98%, about 99%, or about 100% by volume of the solvent system. In one embodiment, liquid water is present in an amount of between about 10% and about 50% by volume of the solvent system.

[0013] In one embodiment, a non-anhydrous condition includes a solvent system comprising water (*e.g.*, about 90% v/v) and isopropyl alcohol (*e.g.*, about 10% v/v). In one embodiment, a non-anhydrous condition includes a solvent system comprising water and ethanol. In one embodiment, a non-anhydrous condition includes a solvent system comprising water and a water-miscible solvent, such as, *e.g.*, C₁–C₄ alcohol, acetone, acetonitrile, among others. In one embodiment, a water-miscible solvent is an alcohol, such as, *e.g.*, methanol, ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, t-butanol, ethylene glycol, among others. In one embodiment, the ratio of water and water-miscible solvent in a solvent system provided herein is about 50:1, about 40:1, about 30:1, about 20:1, about 10:1, about 9:1, about 8:1, about 7:1, about 6:1, about 5:1,



(Ia),

wherein

PG² is a protecting group selected from methylsulfonyl, substituted methylsulfonyl, benzenesulfonyl, substituted benzenesulfonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, t-butoxycarbonyl, 1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, alkyl, substituted alkyl, t-butyltrimethylsilyl, triisopropylsilyl, allyl, benzyl, substituted benzyl, hydroxymethyl, methoxymethyl, diethoxymethyl, (2-chloroethoxy)methyl, t-butoxymethyl, t-butyltrimethylsilyloxymethyl, pivaloyloxymethyl, benzyloxymethyl, dimethylaminomethyl, 2-tetrahydropyranyl, substituted alkoxymethyl and substituted aryloxymethyl, and

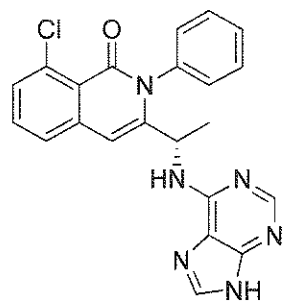
where substituents are selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, cycloalkoxy, heterocycloxy, aryloxy, heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate;

with one or more reagents to remove the protecting group PG² to form the compound of Formula (I); and

(ii) recovering polymorph Form C of the compound of Formula (I);

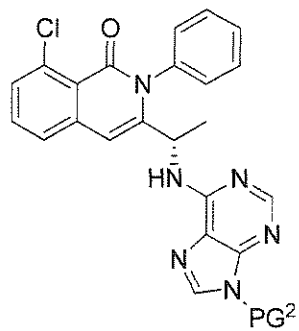
wherein at least one of steps (i) and (ii) occurs in a non-anhydrous condition.

[0015a] In another aspect, there is provided a method of preparing polymorph Form C of a compound of Formula (I):



(I).

i) combining a compound of Formula (Ia):



wherein

PG² is a protecting group selected from methylsulfonyl, substituted methylsulfonyl, benzenesulfonyl, substituted benzenesulfonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, t-butoxycarbonyl, 1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, alkyl, substituted alkyl, t-butyl dimethylsilyl, triisopropylsilyl, allyl, benzyl, substituted benzyl, hydroxymethyl, methoxymethyl, diethoxymethyl, (2-chloroethoxy)methyl, t-butoxymethyl, t-butyl dimethylsiloxy methyl, pivaloyloxymethyl, benzyloxymethyl, dimethylaminomethyl, 2-tetrahydropyranyl, substituted alkoxy methyl and substituted aryloxymethyl, and

where substituents are selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, cycloalkoxy, heterocycloxy, aryloxy, heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate;

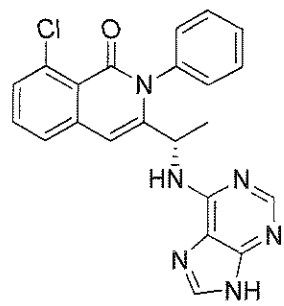
with one or more reagents to remove the protecting group PG² to form the compound of Formula (I); and

ii) recovering polymorph Form C of the compound of Formula (I);

wherein at least one of steps i) and ii) occurs in a non-anhydrous condition,

wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: 2θ = 10.4 ° (± 0.2°), 13.3 ° (± 0.2°), and 24.3 ° (± 0.2°).

[0015b] In another aspect, there is provided a method of preparing polymorph Form C of a compound of Formula (I):



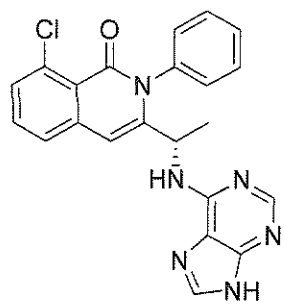
Formula (I)

comprising placing Form A in water or a water-containing solvent system, wherein

polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$; and

polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

[0015c] In another aspect, there is provided a method of preparing polymorph Form C of a compound of Formula (I):



Formula (I)

wherein the method comprises:

(i) preparing a first slurry of polymorph Form C in dichloromethane;

(ii) recovering the solids in the first slurry by filtration;

(iii) preparing a second slurry of the solids recovered in step ii) in a solvent system comprising water; and

(iv) recovering the solids in the second slurry by filtration to give polymorph Form C,

wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

[0016] In some embodiments, one or more reagents to remove the protecting group PG² includes, but is not limited to, acids such as HCl, HBr and TFA; carbonate bases, such as Na₂CO₃ and K₂CO₃; hydroxide bases, such as NaOH and KOH; lithium bases, such as methyl lithium, ethyl lithium, propyl lithium, n-butyl lithium, n-pentyl lithium, and n-hexyl lithium; oxidants such as ceric ammonium nitrate; hydrogenation conditions, such as cyclohexadiene/Pd black, and H₂/Pd on carbon; TBAF, and BF₃·Et₂O. In one embodiment, a non-anhydrous condition includes water, such as in a form of water vapor and/or liquid water. In one embodiment, a non-anhydrous condition includes a solvent system comprising a non-water solvent and liquid water, as described herein elsewhere.

trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, t-butoxycarbonyl, 1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, alkyl, substituted alkyl, t-butyldimethylsilyl, triisopropylsilyl, allyl, benzyl, substituted benzyl, hydroxymethyl, methoxymethyl, diethoxymethyl, (2-chloroethoxy)methyl, t-butoxymethyl, t-butyldimethylsiloxyethyl, pivaloyloxymethyl, benzyloxymethyl, dimethylaminomethyl, 2-tetrahydropyranyl, substituted alkoxymethyl and substituted aryloxymethyl, and

where substituents are selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, cycloalkoxy, heterocyclyloxy, aryloxy, heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate;

with one or more reagents to remove the protecting group PG² to form a compound of Formula (I); and

(ii) recovering polymorph Form A of the compound of Formula (I).

[0019] In some embodiments, step (ii) can include recrystallization of a compound of Formula (I), or a salt, solvate, or hydrate thereof, from a mono-solvent system, or from a multi-solvent system that does not contain both ethyl acetate and hexane. In certain embodiments, the method further comprises a step of dissolving a compound of Formula (I), or a salt, solvate, or hydrate thereof, in a mono-solvent system or a multi-solvent system, removing residual solid matter to yield a liquid solution, cooling said liquid solution at a rate to effect crystallization of Form A, and recovering Form A from the liquid solution.

[0020] In some embodiments, one or more reagents to remove the protecting group PG² includes, but is not limited to, acids such as HCl, HBr and TFA; carbonate bases, such as Na₂CO₃ and K₂CO₃; hydroxide bases, such as NaOH and KOH; lithium bases, such as methyl lithium, ethyl lithium, propyl lithium, n-butyl lithium, n-pentyl lithium, and n-hexyl lithium; oxidants such as ceric ammonium nitrate; hydrogenation conditions, such as cyclohexadiene/Pd black, and H₂/Pd on carbon; TBAF, and BF₃·Et₂O.

[0020a] In another aspect, there is provided a method of preparing a compound as defined above,

(A) wherein the compound of Formula (I) is polymorph Form B and the method comprises thermal conversion from a non-Form B polymorph to provide polymorph Form B; optionally

(B) wherein the compound of Formula (I) is polymorph Form D and the method comprises: fast cooling crystallization from a single solvent system selected from tetrahydrofuran, methyl ethyl ketone, dioxane, and dimethylformamide;

slow cooling crystallization from a single solvent system selected from tetrahydrofuran, methyl ethyl ketone, and dioxane;

slurrying Form C and/or Form E in methyl ethyl ketone;

slurrying a mixture of Form A, Form B and Form C in methyl ethyl ketone;

slurrying a mixture of Form B and Form D in methyl ethyl ketone;

fast cooling crystallization from a binary solvent system with tetrahydrofuran, dioxane, or DMF as the primary solvent and MTBE as the anti-solvent;

fast cooling crystallization from a binary solvent system with tetrahydrofuran, isopropanol, or DMF as the primary solvent and toluene as an anti-solvent;

fast cooling crystallization from a binary solvent system with tetrahydrofuran as the primary solvent and dichloromethane as the anti-solvent;

slow cooling crystallization from a binary solvent system with methyl ethyl ketone or DMF as the primary solvent and MTBE as the anti-solvent;

slow cooling crystallization from a binary solvent system with tetrahydrofuran or DME as the primary solvent and dichloromethane as the anti-solvent;

slow cooling crystallization from a binary solvent system with isopropanol, NMP, or DME as the primary solvent and toluene as the anti-solvent; or

crystallization from a multi-solvent system; optionally

(C) wherein the compound of Formula (I) is polymorph Form E and the method comprises:

slow cooling crystallization of Form A from a single solvent system with methanol;

fast or slow cooling crystallization from a binary solvent system with methanol as the primary solvent and water as the anti-solvent; or

crystallization from a multi-solvent system; optionally

(D) wherein the compound of Formula (I) is polymorph form F and the method comprises:

fast cooling crystallization from a binary solvent system with NMP as the primary solvent and MBTE as the anti-solvent;

slow cooling crystallization from a binary solvent system with NMP as the primary solvent and MBTE as the anti-solvent; or

crystallization from a multi-solvent system; optionally

(E) wherein the compound of Formula (I) is polymorph form G and the method comprises:

fast cooling crystallization from a binary solvent system with ethanol, isopropyl alcohol, or methanol as the primary solvent and MTBE as the anti-solvent; or

crystallization from a multi-solvent system; optionally

(F) wherein the compound of Formula (I) is polymorph form H and the method comprise:

slow cooling crystallization from a binary solvent system with dioxane as the primary solvent and MTBE as the anti-solvent; or

crystallization from a multi-solvent system; optionally

(G) wherein the compound of Formula (I) is polymorph form I and the method comprises:
slow cooling crystallization from a binary solvent system acetone, MEK, or dioxane as the primary
solvent and toluene as the anti-solvent; or

crystallization from a multi-solvent system; optionally
(H) wherein the compound of Formula (I) is polymorph form J and the method comprises:
slow cooling crystallization from a binary solvent system with DMF as the primary solvent and
toluene as the anti-solvent; or

crystallization from a multi-solvent system; wherein
polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta =$
 $10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;

polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$,
and $18.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$,
and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$,
and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$,
and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$,
and $24.6^\circ (\pm 0.2^\circ)$;

polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$,
and $19.0^\circ (\pm 0.2^\circ)$;

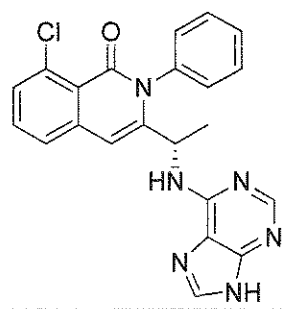
polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$,
and $14.1^\circ (\pm 0.2^\circ)$;

polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$,
and $24.5^\circ (\pm 0.2^\circ)$; and

polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$,
and $18.3^\circ (\pm 0.2^\circ)$.

10020b] In another aspect, there is provided a method of preparing a pharmaceutical composition
comprising:

mixing a compound of Formula (I);

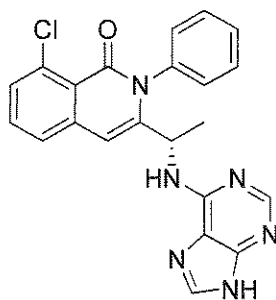


Formula (I).

with a pharmaceutically acceptable excipient or carrier; wherein the compound is polymorph Form C of a compound of Formula (I); and wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

[0020c] In another aspect, there is provided a pharmaceutical composition made by the method as defined above.

[0021] In one embodiment, provided herein is a composition comprising a compound of Formula (I):

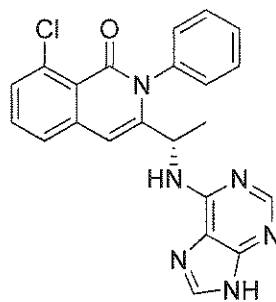


(I),

or a pharmaceutically acceptable salt, solvate, or hydrate thereof, and one or more pharmaceutically acceptable excipients.

[0021a] In another aspect, there is provided a pharmaceutical composition comprising a compound as defined above, and one or more pharmaceutically acceptable excipients.

[0021b] In another aspect, there is provided a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I):



Formula (I).

wherein the pharmaceutical composition comprises polymorph Form C of the compound of Formula (I) and one or more pharmaceutically acceptable excipients, wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

[0026] In other embodiments, the composition provided herein is a suspension comprising carboxymethyl cellulose and water. In one embodiment, the composition provided herein can further comprise one or more excipients, such as, *e.g.*, polysorbate, polyethyleneglycol, cyclodextrin, dextrose, *n*-methylpyrrolidone, pH buffers, dilute hydrochloric acid, polyoxyethylene esters of 12-hydroxystearic acid, or a mixture of two or more thereof. Other excipients that can be used in exemplary formulations include, but are not limited to, fillers such as lactose, mannitol, starch, sorbitol, sucrose, dicalcium phosphate, and microcrystalline cellulose; disintegrants such as croscarmellose sodium and sodium starch glycolate; glidants such as colloidal silicon dioxide, silicon dioxide, magnesium silicate, and talc; lubricants such as sodium stearyl fumarate and stearic acid; and surfactants such as sodium lauryl sulphate, sodium dodecyl sulphate, Tween® 80, and Lutrol®.

[0027] In one embodiment, the composition provided herein is used for the treatment of a PI3K-associated disorder (*e.g.*, a disease or disorder described herein elsewhere or known in the art). In one embodiment, the composition provided herein is used for inhibiting PI3K kinase activity. The efficacy of the compound of Formula (I) in these methods and others as disclosed herein has been described in, for example, US 2009/0312319.

[0028] In one embodiment, provided herein is a method of treating a PI3K-associated disorder (*e.g.*, a disorder or disease described herein elsewhere or known in the art), wherein the method comprises administering a polymorph of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to a subject in need thereof. In one embodiment, provided herein is a method of treating a PI3K-associated disorder, wherein the method comprises administering a polymorph of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or hydrate thereof, to a subject in need thereof. In one embodiment, provided herein is a method of treating a PI3K-associated disorder, wherein the method comprises administering a composition provided herein, to a subject in need thereof. In one embodiment, the method comprises administering a polymorph of a compound of Formula (I), or a pharmaceutically acceptable salt, solvate, or hydrate thereof, or a composition thereof, to a subject in need thereof, orally, parenterally, or topically. In one embodiment, the method comprises co-administering one or more additional therapeutic agent(s) or treating the subject with one or more additional therapy(ies) (*e.g.*, radiation therapy or surgery).

[0028a] In another aspect, there is provided the use of a compound as defined above, or a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

[0028b] In another aspect, there is provided the use of a compound as defined above, or a pharmaceutical composition as defined above, in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

DESCRIPTION OF THE DRAWINGS

[0029] FIG. 1 shows an X-ray powder diffraction (XRPD) for Polymorph Form A.

[0030] FIG. 2 shows an XRPD for Polymorph Form B.

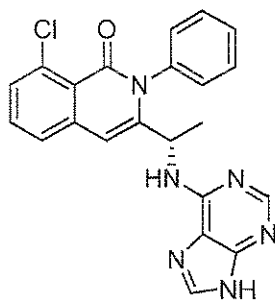
[0031] FIG. 3 shows an XRPD for Polymorph Form C.

[0032] FIG. 4 shows an XRPD for Polymorph Form D.

CLAIMS

WHAT IS CLAIMED IS:

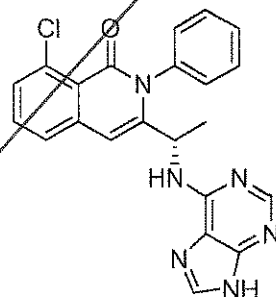
1. A compound of Formula (I):



Formula (I),

wherein the compound is polymorph Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), or a salt, solvate, or hydrate thereof; or a mixture of two or more thereof.

2. A mixture of two or more compounds of Formula (I):

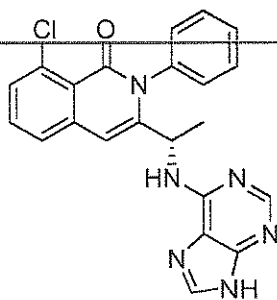


Formula (I),

wherein the compounds of Formula (I) are selected from:

- i) polymorph Form C, or a salt, solvate, or hydrate thereof; and
- ii) at least one non-Form C polymorph selected from Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), or a salt, solvate, or hydrate thereof.

- ~~3. A mixture of two or more compounds of Formula (I):~~



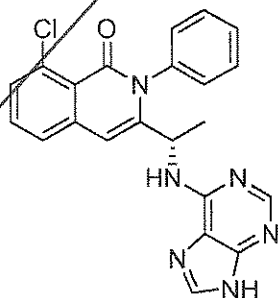
Formula (I),

wherein the compounds of Formula (I) are selected from:

- i) polymorph Form A, or a salt, solvate, or hydrate thereof; and
- ii) at least one non-Form A polymorph selected from Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), or a salt, solvate, or hydrate thereof.

4. A mixture according to claim 2, wherein the mixture is at least 50% by weight polymorph Form C, or a salt, solvate, or hydrate thereof.

5. Polymorph Form C of a compound of Formula (I):



Formula (I).

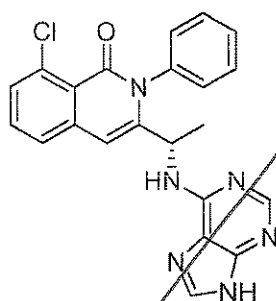
6. The polymorph according to claim 5, wherein the polymorph has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

7. The polymorph according to claim 6, further comprising at least one characteristic XRPD peak selected from $2\theta = 6.6^\circ (\pm 0.2^\circ)$ and $12.5^\circ (\pm 0.2^\circ)$.

8. The polymorph according to claim 5, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.6^\circ (\pm 0.2^\circ)$, $10.4^\circ (\pm 0.2^\circ)$, $12.5^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 8.8^\circ (\pm 0.2^\circ)$, $9.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.9^\circ (\pm 0.2^\circ)$, $19.8^\circ (\pm 0.2^\circ)$, $21.3^\circ (\pm 0.2^\circ)$, $23.6^\circ (\pm 0.2^\circ)$, $25.3^\circ (\pm 0.2^\circ)$, and $27.9^\circ (\pm 0.2^\circ)$.

9. The polymorph according to claim 5, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 3.

10. Polymorph Form B of a compound of Formula (I):



Formula (I).

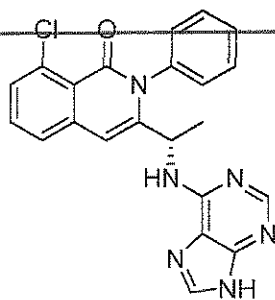
11. The polymorph according to claim 10, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$.

12. The polymorph according to claim 11, further comprising at least one characteristic XRPD peak selected from $2\theta = 14.0^\circ (\pm 0.2^\circ)$ and $15.0^\circ (\pm 0.2^\circ)$.

13. The polymorph according to claim 10, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $15.0^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.5^\circ (\pm 0.2^\circ)$, $12.7^\circ (\pm 0.2^\circ)$, $13.6^\circ (\pm 0.2^\circ)$, $14.2^\circ (\pm 0.2^\circ)$, $15.7^\circ (\pm 0.2^\circ)$, $19.0^\circ (\pm 0.2^\circ)$, $22.3^\circ (\pm 0.2^\circ)$, $24.2^\circ (\pm 0.2^\circ)$, $24.8^\circ (\pm 0.2^\circ)$, and $26.9^\circ (\pm 0.2^\circ)$.

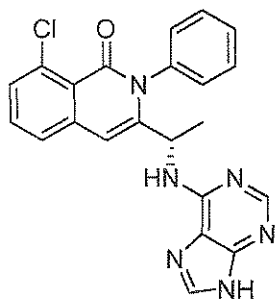
14. The polymorph according to claim 10, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 2.

15. Polymorph Form D of a compound of Formula (I):



Formula (I).

16. The polymorph according to claim 15, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$.
17. The polymorph according to claim 16, further comprising at least one characteristic XRPD peak selected from $2\theta = 9.2^\circ (\pm 0.2^\circ)$ and $18.3^\circ (\pm 0.2^\circ)$.
18. The polymorph according to claim 15, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.2^\circ (\pm 0.2^\circ)$, $11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, $18.3^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.8^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, $15.8^\circ (\pm 0.2^\circ)$, $16.2^\circ (\pm 0.2^\circ)$, $16.8^\circ (\pm 0.2^\circ)$, $18.9^\circ (\pm 0.2^\circ)$, $19.9^\circ (\pm 0.2^\circ)$, $20.0^\circ (\pm 0.2^\circ)$, $24.9^\circ (\pm 0.2^\circ)$, and $29.3^\circ (\pm 0.2^\circ)$.
19. The polymorph according to claim 15, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 4.
20. Polymorph Form E of a compound of Formula (I):



Formula (I).

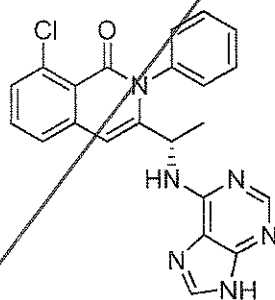
21. The polymorph according to claim 20, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$.

22. The polymorph according to claim 21, further comprising at least one characteristic XRPD peak selected from $2\theta = 12.7^\circ (\pm 0.2^\circ)$ and $13.9^\circ (\pm 0.2^\circ)$.

23. The polymorph according to claim 20, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, $12.7^\circ (\pm 0.2^\circ)$, $13.9^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 12.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, $14.3^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, $18.5^\circ (\pm 0.2^\circ)$, $22.0^\circ (\pm 0.2^\circ)$, $23.9^\circ (\pm 0.2^\circ)$, $24.1^\circ (\pm 0.2^\circ)$, and $26.4^\circ (\pm 0.2^\circ)$.

24. The polymorph according to claim 20, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 5.

25. Polymorph Form F of a compound of Formula (I):



Formula (I).

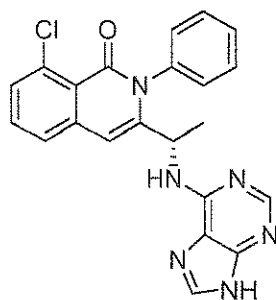
26. The polymorph according to claim 25, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$.

27. The polymorph according to claim 26, further comprising at least one characteristic XRPD peak selected from $2\theta = 14.0^\circ (\pm 0.2^\circ)$ and $19.2^\circ (\pm 0.2^\circ)$.

28. The polymorph according to claim 25, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $19.2^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 12.4^\circ (\pm 0.2^\circ)$, $16.1^\circ (\pm 0.2^\circ)$, $16.6^\circ (\pm 0.2^\circ)$, $17.1^\circ (\pm 0.2^\circ)$, $20.8^\circ (\pm 0.2^\circ)$, $21.5^\circ (\pm 0.2^\circ)$, $22.0^\circ (\pm 0.2^\circ)$, $24.3^\circ (\pm 0.2^\circ)$, $25.2^\circ (\pm 0.2^\circ)$, and $25.4^\circ (\pm 0.2^\circ)$.

29. The polymorph according to claim 25, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 6.

30. Polymorph Form G of a compound of Formula (I):



Formula (I).

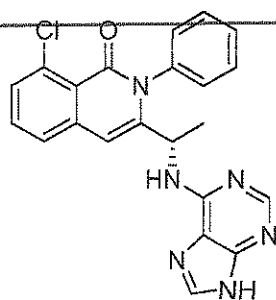
31. The polymorph according to claim 30, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$.

32. The polymorph according to claim 31, further comprising at least one characteristic XRPD peak selected from $2\theta = 10.6^\circ (\pm 0.2^\circ)$ and $19.6^\circ (\pm 0.2^\circ)$.

33. The polymorph according to claim 30, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, $10.6^\circ (\pm 0.2^\circ)$, $19.0^\circ (\pm 0.2^\circ)$, and $19.6^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 13.4^\circ (\pm 0.2^\circ)$, $15.0^\circ (\pm 0.2^\circ)$, $15.8^\circ (\pm 0.2^\circ)$, $17.8^\circ (\pm 0.2^\circ)$, $20.7^\circ (\pm 0.2^\circ)$, $21.2^\circ (\pm 0.2^\circ)$, $22.8^\circ (\pm 0.2^\circ)$, $23.8^\circ (\pm 0.2^\circ)$, $24.3^\circ (\pm 0.2^\circ)$, and $25.6^\circ (\pm 0.2^\circ)$.

34. The polymorph according to claim 30, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 7.

35. Polymorph Form H of a compound of Formula (I):



Formula (I).

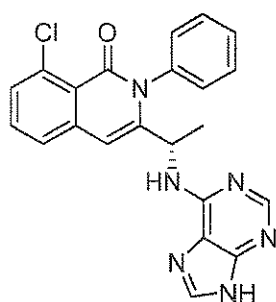
36. The polymorph according to claim 35, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$.

37. The polymorph according to claim 36, further comprising at least one characteristic XRPD peak selected from $2\theta = 17.3^\circ (\pm 0.2^\circ)$ and $18.53^\circ (\pm 0.2^\circ)$.

38. The polymorph according to claim 35, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, $14.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.5^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 7.1^\circ (\pm 0.2^\circ)$, $10.6^\circ (\pm 0.2^\circ)$, $11.3^\circ (\pm 0.2^\circ)$, $11.6^\circ (\pm 0.2^\circ)$, $16.2^\circ (\pm 0.2^\circ)$, $18.3^\circ (\pm 0.2^\circ)$, $18.8^\circ (\pm 0.2^\circ)$, $20.3^\circ (\pm 0.2^\circ)$, $21.7^\circ (\pm 0.2^\circ)$, and $24.7^\circ (\pm 0.2^\circ)$.

39. The polymorph according to claim 35, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 8.

40. Polymorph Form I of a compound of Formula (I):



Formula (I).

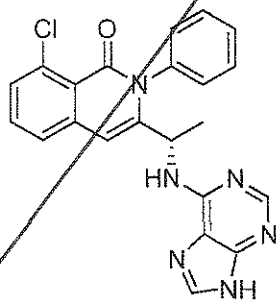
41. The polymorph according to claim 40, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$.

42. The polymorph according to claim 41, further comprising at least one characteristic XRPD peak selected from $2\theta = 11.4^\circ (\pm 0.2^\circ)$ and $14.2^\circ (\pm 0.2^\circ)$.

43. The polymorph according to claim 40, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $11.4^\circ (\pm 0.2^\circ)$, $14.2^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.2^\circ (\pm 0.2^\circ)$, $14.7^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.7^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $18.4^\circ (\pm 0.2^\circ)$, $21.4^\circ (\pm 0.2^\circ)$, $22.9^\circ (\pm 0.2^\circ)$, $29.1^\circ (\pm 0.2^\circ)$, and $34.1^\circ (\pm 0.2^\circ)$.

44. The polymorph according to claim 40, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 9.

45. Polymorph Form J of a compound of Formula (I):



Formula (I).

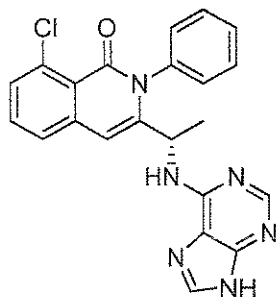
46. The polymorph according to claim 45, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

47. The polymorph according to claim 46, further comprising at least one characteristic XRPD peak selected from $2\theta = 16.4^\circ (\pm 0.2^\circ)$ and $17.9^\circ (\pm 0.2^\circ)$.

48. The polymorph according to claim 45, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $16.4^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $17.9^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.4^\circ (\pm 0.2^\circ)$, $10.1^\circ (\pm 0.2^\circ)$, $10.7^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $14.3^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.9^\circ (\pm 0.2^\circ)$, $19.9^\circ (\pm 0.2^\circ)$, $24.0^\circ (\pm 0.2^\circ)$, and $24.7^\circ (\pm 0.2^\circ)$.

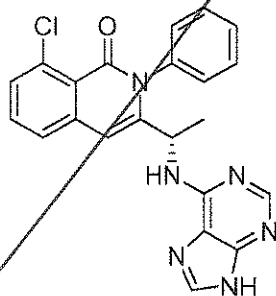
49. The polymorph according to claim 45, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 10.

50. A substantially amorphous compound of Formula (I):



Formula (I).

51. A method of preparing polymorph Form C of a compound of Formula (I):



Formula (I)

wherein the method comprises:

(i) exposing a composition comprising at least one non-Form C polymorph of a compound of Formula (I), or a salt, solvate, or hydrate thereof, to a non-anhydrous condition for a period of time sufficient to convert at least about 50% of the total amount of non-Form C polymorph(s) into Form C of a compound of Formula (I); and

(ii) recovering said polymorph Form C.

52. The method according to claim 51, wherein the non-anhydrous condition includes liquid water.

53. The method according to claim 52, wherein the non-anhydrous condition includes a water-miscible solvent and liquid water solvent system.

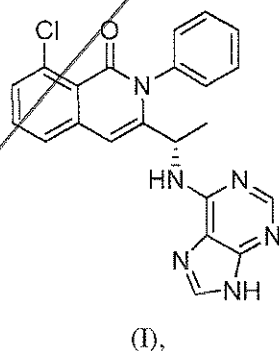
54. The method of claim 53, wherein the liquid water is present in an amount selected from about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, and about 100% by volume of the solvent system.

55. The method of claim 54, wherein said liquid water is present in an amount between about 85% to about 95% by volume of the solvent system.

56. The method of claim 51, wherein the one or more non-Form C polymorphs are selected from the group consisting of Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, amorphous form, or a salt, solvate, or hydrate thereof, and mixtures thereof.

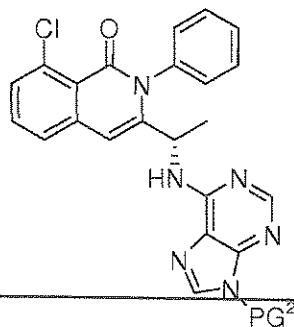
57. The method of claim 56, wherein the one or more non-Form C polymorphs comprise at least about 50% by weight polymorph Form A.

58. A method of preparing polymorph Form C of a compound of Formula (I):



wherein the method comprises:

i) combining a compound of Formula (Ia):



(Ia),

wherein

PG² is a protecting group selected from methylsulfonyl, substituted methylsulfonyl, benzenesulfonyl, substituted benzenesulfonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, 2,2,2-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, t-butoxycarbonyl, 1-adamantylloxycarbonyl, 2-adamantylloxycarbonyl, alkyl, substituted alkyl, t-butyldimethylsilyl, triisopropylsilyl, allyl, benzyl, substituted benzyl, hydroxymethyl, methoxymethyl, diethoxymethyl, (2-chloroethoxy)methyl, t-butoxymethyl, t-butyldimethylsiloxymethyl, pivaloyloxymethyl, benzyloxymethyl, dimethylaminomethyl, 2-tetrahydropyranyl, substituted alkoxymethyl and substituted aryloxymethyl, and

where substituents are selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, cycloalkoxy, heterocycloxy, aryloxy, heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate;

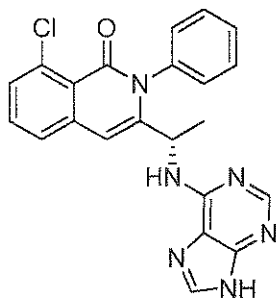
with one or more reagents to remove the protecting group PG² to form the compound of Formula (I); and

ii) recovering polymorph Form C of the compound of Formula (I);

wherein at least one of steps i) and ii) occurs in a non-anhydrous condition.

59. The method according to claim 58, wherein the one or more reagents to remove the protecting group PG² is selected from HCl, HBr, TFA, Na₂CO₃ and K₂CO₃, NaOH, KOH, methyl lithium, ethyl lithium, propyl lithium, n-butyl lithium, n-pentyl lithium, n-hexyl lithium, ceric ammonium nitrate, cyclohexadiene/Pd black, H₂/Pd on carbon, TBAF, and BF₃·Et₂O.

60. A method of preparing polymorph Form C of a compound of Formula (I):



Formula (I)

wherein the method comprises:

(i) preparing a first slurry of polymorph Form C in dichloromethane;

(ii) recovering the solids in the first slurry by filtration;

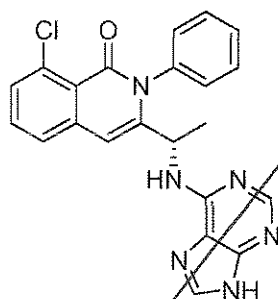
- (iii) preparing a second slurry of the solids recovered in step ii) in water; and
 (iv) recovering the solids in the second slurry by filtration to give polymorph Form C.

61. A pharmaceutical composition comprising

- i) a compound according to claim 1 or 50,
- ii) a mixture according to any one of claims 2-4, or
- iii) a polymorph according to any one of claims 5-49,

and one or more pharmaceutically acceptable excipients.

62. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I):



Formula (I),

wherein the pharmaceutical composition comprises polymorph Form C of the compound of Formula (I), or its pharmaceutically acceptable salts, solvates and hydrates thereof, and one or more pharmaceutically acceptable excipients.

63. The pharmaceutical composition according to claim 62, wherein the pharmaceutical composition further comprises at least one non-Form C polymorph selected from Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), or a salt, solvate, or hydrate thereof.

64. The pharmaceutical composition according to claim 63, wherein the pharmaceutical composition comprises polymorph Form C and polymorph Form A in a ratio of greater than about 9:1 Form C:Form A.

65. The pharmaceutical composition according to claim 62, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable excipients selected from silicified microcrystalline cellulose, lactose, mannitol, starch, sorbitol, sucrose, dicalcium phosphate, microcrystalline cellulose, croscopolone, croscarmellose sodium, and sodium starch glycolate, silicon dioxide, silicon dioxide,

~~magnesium silicate, talc, magnesium stearate, sodium stearyl fumarate, stearic acid, sodium lauryl sulphate, sodium dodecyl sulphate, Tween® 80, and Lutrol®.~~

66. A method of treating a PI3K mediated disorder in a subject, the method comprising administering a therapeutically effective amount of:

- i) a compound according to claim 1 or 50,
- ii) a mixture according to any one of claims 2-4,
- iii) a polymorph according to any one of claims 5-49, or
- iv) a pharmaceutical composition according to any one of claims 61-65

to said subject.

67. The method of claim 66, wherein the disorder is cancer, an inflammatory disease or an auto-immune disease.

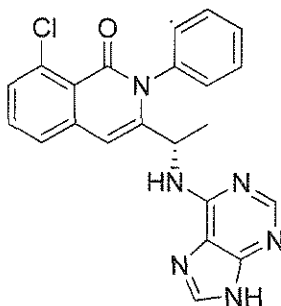
68. Use of:

- i) a compound according to claim 1 or 50,
- ii) a mixture according to any one of claims 2-4,
- iii) a polymorph according to any one of claims 5-49, or
- iv) a pharmaceutical composition according to any one of claims 61-65

~~in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.~~

CLAIMS

1. A compound of Formula (I):



Formula (I),

wherein the compound is polymorph Form C, Form B, Form D, Form E, Form F, Form G, Form H, Form I, or Form J of a compound of Formula (I), or a mixture of two or more thereof, wherein

polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$;

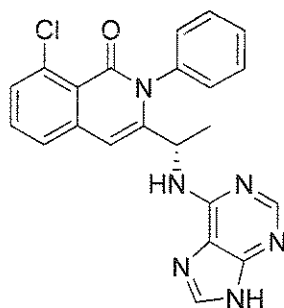
polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$;

polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$;

polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$; and

polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

2. A compound of Formula (I):

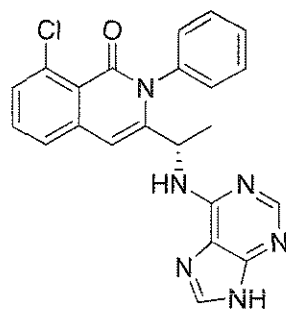


Formula (I),

wherein the compound is polymorph Form C of a compound of Formula (I), wherein the polymorph has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

3. The compound of claim 2, further comprising at least one characteristic XRPD peak selected from $2\theta = 6.6^\circ (\pm 0.2^\circ)$ and $12.5^\circ (\pm 0.2^\circ)$.
4. The compound of claim 2, wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.6^\circ (\pm 0.2^\circ)$, $10.4^\circ (\pm 0.2^\circ)$, $12.5^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 8.8^\circ (\pm 0.2^\circ)$, $9.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.9^\circ (\pm 0.2^\circ)$, $19.8^\circ (\pm 0.2^\circ)$, $21.3^\circ (\pm 0.2^\circ)$, $23.6^\circ (\pm 0.2^\circ)$, $25.3^\circ (\pm 0.2^\circ)$, and $27.9^\circ (\pm 0.2^\circ)$.
5. The compound according to claim 2, wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 3.
6. The compound of claim 2, wherein the polymorph has an endothermic peak at about 203°C .
7. The compound of claim 2, wherein the polymorph has an endothermic peak at about 206°C or about 208°C .
8. The compound of claim 2, wherein the polymorph has an endothermic peak in the range of about 203°C to about 208°C , and at least one peak selected from an exothermic peak in the range of about 251°C to about 254°C , and an endothermic peak in the range of about 281°C to about 283°C .
9. The compound of claim 2, wherein the polymorph has an endothermic peak at about 208°C , an exothermic peak at about 254°C , and an endothermic peak at about 283°C .

10. The compound of any one of claims 6-9, wherein the endothermic and exothermic peaks are determined by Differential Scanning Calorimetry (DSC).
11. The compound of claim 10, wherein ramp rate of the DSC is about 10 °C/min.
12. The compound of claim 2, which is a hydrate.
13. A compound of Formula (I):



Formula (I),

wherein the compound is:

- (A) a mixture of two or more compounds of Formula (I), wherein the compounds of Formula (I) are selected from:
 - i) polymorph Form C; and
 - ii) at least one non-Form C polymorph selected from Form A, Form B, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I), optionally wherein the mixture is at least 50% by weight polymorph Form C; or
 - (B) a mixture of two or more compounds of Formula (I), wherein the compounds of Formula (I) are selected from:
 - i) polymorph Form A; and
 - ii) at least one non-Form A polymorph selected from Form B, Form C, Form D, Form E, Form F, Form G, Form H, Form I, Form J, or an amorphous form of a compound of Formula (I);
- wherein

polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;

polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$;

polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$;

polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$;

polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$; and

polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

14. The compound of claim 1, which is polymorph Form B of a compound of Formula (I), optionally,

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 14.0^\circ (\pm 0.2^\circ)$ and $15.0^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $15.0^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.5^\circ (\pm 0.2^\circ)$, $12.7^\circ (\pm 0.2^\circ)$, $13.6^\circ (\pm 0.2^\circ)$, $14.2^\circ (\pm 0.2^\circ)$, $15.7^\circ (\pm 0.2^\circ)$, $19.0^\circ (\pm 0.2^\circ)$, $22.3^\circ (\pm 0.2^\circ)$, $24.2^\circ (\pm 0.2^\circ)$, $24.8^\circ (\pm 0.2^\circ)$, and $26.9^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 2.

15. The compound of claim 1, which is polymorph Form D of a compound of Formula (I), optionally,

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 9.2^\circ (\pm 0.2^\circ)$ and $18.3^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.2^\circ (\pm 0.2^\circ)$, $11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, $18.3^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.8^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, $15.8^\circ (\pm 0.2^\circ)$, $16.2^\circ (\pm 0.2^\circ)$, $16.8^\circ (\pm 0.2^\circ)$, $18.9^\circ (\pm 0.2^\circ)$, $19.9^\circ (\pm 0.2^\circ)$, $20.0^\circ (\pm 0.2^\circ)$, $24.9^\circ (\pm 0.2^\circ)$, and $29.3^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 4.

16. The compound of claim 1, which is polymorph Form E of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 12.7^\circ (\pm 0.2^\circ)$ and $13.9^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, $12.7^\circ (\pm 0.2^\circ)$, $13.9^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 12.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, $14.3^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, $18.5^\circ (\pm 0.2^\circ)$, $22.0^\circ (\pm 0.2^\circ)$, $23.9^\circ (\pm 0.2^\circ)$, $24.1^\circ (\pm 0.2^\circ)$, and $26.4^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 5.

17. The compound of claim 1, which is polymorph Form F of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 14.0^\circ (\pm 0.2^\circ)$ and $19.2^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $19.2^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 12.4^\circ (\pm 0.2^\circ)$, $16.1^\circ (\pm 0.2^\circ)$, $16.6^\circ (\pm 0.2^\circ)$, $17.1^\circ (\pm 0.2^\circ)$, $20.8^\circ (\pm 0.2^\circ)$, $21.5^\circ (\pm 0.2^\circ)$, $22.0^\circ (\pm 0.2^\circ)$, $24.3^\circ (\pm 0.2^\circ)$, $25.2^\circ (\pm 0.2^\circ)$, and $25.4^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 6.

18. The compound of claim 1, which is polymorph Form G of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 10.6^\circ (\pm 0.2^\circ)$ and $19.6^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, $10.6^\circ (\pm 0.2^\circ)$, $19.0^\circ (\pm 0.2^\circ)$, and $19.6^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 13.4^\circ (\pm 0.2^\circ)$, $15.0^\circ (\pm 0.2^\circ)$, $15.8^\circ (\pm 0.2^\circ)$, $17.8^\circ (\pm 0.2^\circ)$, $20.7^\circ (\pm 0.2^\circ)$, $21.2^\circ (\pm 0.2^\circ)$, $22.8^\circ (\pm 0.2^\circ)$, $23.8^\circ (\pm 0.2^\circ)$, $24.3^\circ (\pm 0.2^\circ)$, and $25.6^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 7.

19. The compound of claim 1, which is polymorph Form H of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 17.3^\circ (\pm 0.2^\circ)$ and $18.53^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, $14.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.5^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 7.1^\circ (\pm 0.2^\circ)$, $10.6^\circ (\pm 0.2^\circ)$, $11.3^\circ (\pm 0.2^\circ)$, $11.6^\circ (\pm 0.2^\circ)$, $16.2^\circ (\pm 0.2^\circ)$, $18.3^\circ (\pm 0.2^\circ)$, $18.8^\circ (\pm 0.2^\circ)$, $20.3^\circ (\pm 0.2^\circ)$, $21.7^\circ (\pm 0.2^\circ)$, and $24.7^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 8.

20. The compound of claim 1, which is polymorph Form I of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 11.4^\circ (\pm 0.2^\circ)$ and $14.2^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $11.4^\circ (\pm 0.2^\circ)$, $14.2^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.2^\circ (\pm 0.2^\circ)$, $14.7^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.7^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $18.4^\circ (\pm 0.2^\circ)$, $21.4^\circ (\pm 0.2^\circ)$, $22.9^\circ (\pm 0.2^\circ)$, $29.1^\circ (\pm 0.2^\circ)$, and $34.1^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 9.

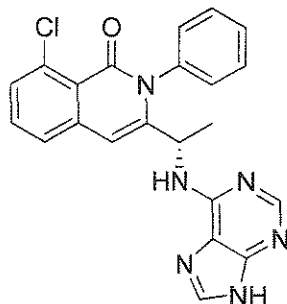
21. The compound of claim 1, which is polymorph Form J of a compound of Formula (I), optionally:

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$, optionally further comprising at least one characteristic XRPD peak selected from $2\theta = 16.4^\circ (\pm 0.2^\circ)$ and $17.9^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $16.4^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, $17.9^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$, in combination with at least one XRPD peak selected from $2\theta = 9.4^\circ (\pm 0.2^\circ)$, $10.1^\circ (\pm 0.2^\circ)$, $10.7^\circ (\pm 0.2^\circ)$, $14.0^\circ (\pm 0.2^\circ)$, $14.3^\circ (\pm 0.2^\circ)$, $15.5^\circ (\pm 0.2^\circ)$, $16.9^\circ (\pm 0.2^\circ)$, $19.9^\circ (\pm 0.2^\circ)$, $24.0^\circ (\pm 0.2^\circ)$, and $24.7^\circ (\pm 0.2^\circ)$; or

wherein the polymorph has substantially all peaks in its XRPD pattern as shown in Figure 10.

22. A method of preparing polymorph Form C of a compound of Formula (I):



Formula (I)

wherein the method comprises:

(i) exposing a composition comprising at least one non-Form C polymorph of a compound of Formula (I), to a non-anhydrous condition for a period of time sufficient to convert at least about 50% of the total amount of non-Form C polymorph(s) into Form C of a compound of Formula (I); and

(ii) recovering said polymorph Form C;

wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

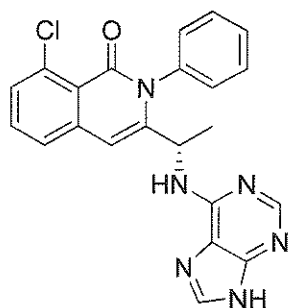
23. The method of claim 22, wherein the non-anhydrous condition includes liquid water.

24. The method of claim 23, wherein the non-anhydrous condition includes a water-miscible solvent and liquid water solvent system.

25. The method of claim 24, wherein the liquid water is present in an amount selected from about 1%, about 5%, about 10%, about 15%, about 20%, about 25%, about 30%, about 35%, about 40%, about 45%, about 50%, about 55%, about 60%, about 65%, about 70%, about 75%, about 80%, about 85%, about 90%, about 95%, and about 100% by volume of the solvent system.

26. The method of claim 25, wherein said liquid water is present in an amount between about 85% to about 95% by volume of the solvent system.

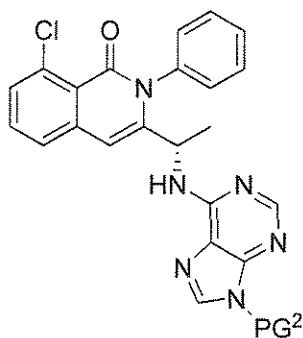
27. A method of preparing polymorph Form C of a compound of Formula (I):



(I),

wherein the method comprises:

i) combining a compound of Formula (Ia):



(Ia),

wherein

PG² is a protecting group selected from methylsulfonyl, substituted methylsulfonyl, benzenesulfonyl, substituted benzenesulfonyl, benzyloxycarbonyl, substituted benzyloxycarbonyl, 2,2,2,-trichloroethoxycarbonyl, 2-trimethylsilylethoxycarbonyl, t-butoxycarbonyl, 1-adamantyloxycarbonyl, 2-adamantyloxycarbonyl, alkyl, substituted alkyl, t-butyldimethylsilyl, triisopropylsilyl, allyl, benzyl, substituted benzyl, hydroxymethyl, methoxymethyl, diethoxymethyl, (2-chloroethoxy)methyl, t-butoxymethyl, t-butyldimethylsiloxyethyl, pivaloyloxymethyl, benzyloxymethyl, dimethylaminomethyl, 2-tetrahydropyranyl, substituted alkoxymethyl and substituted aryloxymethyl, and

where substituents are selected from alkyl, heteroalkyl, alkenyl, alkynyl, cycloalkyl, heterocyclyl, aryl, arylalkyl, heteroaryl, heteroarylalkyl, alkoxy, cycloalkoxy, heterocycloxy, aryloxy, heteroaryloxy, amido, amino, acyl, acyloxy, alkoxycarbonyl, ester, ether, thio, sulfinyl, sulfonyl, sulfonamido, halo, cyano, hydroxyl, nitro, phosphate, urea, carbamate, and carbonate;

with one or more reagents to remove the protecting group PG² to form the compound of Formula (I); and

ii) recovering polymorph Form C of the compound of Formula (I);

wherein at least one of steps i) and ii) occurs in a non-anhydrous condition,

wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks:

$2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

28. The method of claim 27, wherein step (i) occurs in a non-anhydrous condition.

29. The method of claim 27, wherein step (ii) involves addition of an anti-solvent either with or without a cooling step to cause precipitation of Form C.

30. The method of claim 29, wherein the anti-solvent comprises water.

31. The method of claim 27, wherein the one or more reagents to remove the protecting group PG² is selected from acids, carbonate bases, hydroxide bases, lithium bases, oxidants, hydrogenation reagents, TBAF, and BF₃·Et₂O.

32. The method of claim 31, wherein the one or more reagents to remove the protecting group PG² is selected from HCl, HBr, TFA, Na₂CO₃, K₂CO₃, NaOH, KOH, methyl lithium, ethyl lithium, propyl lithium, n-butyl lithium, n-pentyl lithium, n-hexyl lithium, ceric ammonium nitrate, cyclohexadiene/Pd black, H₂/Pd on carbon, TBAF, and BF₃·Et₂O.

33. The method of claim 31, wherein the reagent to remove the protecting group PG² is an acid and PG² is 2-tetrahydropyranyl.

34. The method of claim 33, wherein the acid is HCl, HBr, TFA, perchloric acid, sulfuric acid, nitric acid, or phosphoric acid.

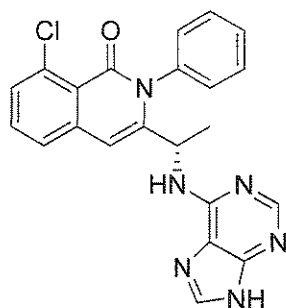
35. The method of claim 34, wherein the acid is HCl.

36. The method of claim 33, further comprising adjusting pH of the reaction mixture after step (i) to from about 8 to about 9.

37. The method of claim 36, wherein the pH is adjusted by adding a hydroxide base.

38. The method of claim 37, wherein the hydroxide base is NH₄OH.

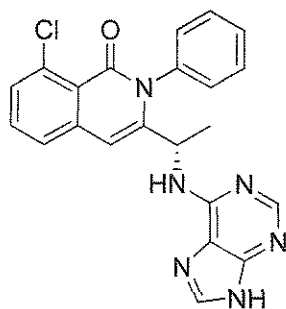
39. The method of claim 33, wherein the removal of the protecting group PG² occurs in an alcoholic solvent.
40. The method of claim 39, wherein the alcoholic solvent is MeOH, EtOH, PrOH, or iPrOH.
41. The method of claim 27, wherein PG² is 2-tetrahydropyranyl and the method comprises:
- (i) combining the compound of Formula (Ia) with HCl in a solvent of EtOH and water to form the compound of Formula (I);
 - (ii) adjusting pH of the reaction mixture after step (i) to from about 8 to about 9 by adding NH₄OH; and
 - (iii) recovering polymorph Form C.
42. A method of preparing polymorph Form C of a compound of Formula (I):



Formula (I)

- comprising placing Form A in water or a water-containing solvent system, wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$; and polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.
43. The method of claim 42, wherein the solvent system comprises water and isopropanol.
44. The method of claim 42, wherein Form A is placed in water or a water-containing solvent system to form a slurry for about 18-24 hours.
45. The method of claim 42, wherein Form A is placed in water or a water-containing solvent system to form a slurry for from less than about an hour to about 24 hours.
46. The method of claim 42, wherein Form A is prepared by re-slurrying one or more non-Form A polymorph(s) in an anhydrous solvent.

47. The method of claim 46, wherein the anhydrous solvent is chloroform, dichloromethane, isopropyl alcohol, ethanol, or a mixture thereof.
48. The method of claim 47, wherein the anhydrous solvent is dichloromethane.
49. The method of claim 46, wherein the one or more non-Form A polymorph(s) is Form C.
50. A method of preparing polymorph Form C of a compound of Formula (I):

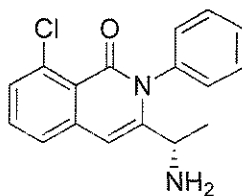


Formula (I)

wherein the method comprises:

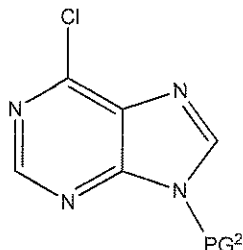
- (i) preparing a first slurry of polymorph Form C in dichloromethane;
 - (ii) recovering the solids in the first slurry by filtration;
 - (iii) preparing a second slurry of the solids recovered in step ii) in a solvent system comprising water; and
 - (iv) recovering the solids in the second slurry by filtration to give polymorph Form C,
- wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

51. The method of claim 50, wherein the solids recovered in the first slurry is Form A, wherein Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.
52. The method of claim 50, wherein the second slurry further comprises isopropanol.
53. The method of claim 27, wherein compound of Formula (Ia) is prepared by combining compound 9 of the formula:



9

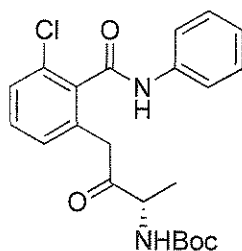
with a protected chloropurine compound of the formula:



in the presence of Et₃N in an alcoholic solvent selected from MeOH, EtOH, PrOH, and iPrOH.

54. The method of claim 53, wherein PG² is 2-tetrahydropyranyl.

55. The method of claim 53, wherein compound 9 is prepared by converting a compound 8 of the formula:

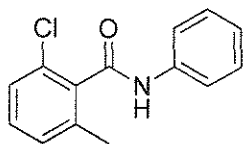


8

in the presence of an acid selected from trifluoroacetic acid and methanesulfonic acid in a solvent selected from methanol, isopropyl alcohol, anisole, and THF, or a mixture thereof.

56. The method of claim 55, wherein the acid is trifluoroacetic acid.

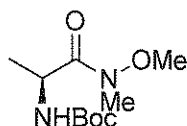
57. The method of claim 55, wherein compound 8 is prepared by combining compound 7 of the formula:



7

with n-hexyl lithium, and

adding compound 2 of the formula:



2

wherein compound 2 is previously combined with isopropyl Grignard.

58. The method of claim 57, wherein the combination formed after adding compound 2 is added to a solution of anisole and isobutyric acid.

59. A method of preparing a compound of claim 1,

(A) wherein the compound of Formula (I) is polymorph Form B and the method comprises thermal conversion from a non-Form B polymorph to provide polymorph Form B; optionally

(B) wherein the compound of Formula (I) is polymorph Form D and the method comprises:

fast cooling crystallization from a single solvent system selected from tetrahydrofuran, methyl ethyl ketone, dioxane, and dimethylformamide;

slow cooling crystallization from a single solvent system selected from tetrahydrofuran, methyl ethyl ketone, and dioxane;

slurrying Form C and/or Form E in methyl ethyl ketone;

slurrying a mixture of Form A, Form B and Form C in methyl ethyl ketone;

slurrying a mixture of Form B and Form D in methyl ethyl ketone;

fast cooling crystallization from a binary solvent system with tetrahydrofuran, dioxane, or DMF as the primary solvent and MTBE as the anti-solvent;

fast cooling crystallization from a binary solvent system with tetrahydrofuran, isopropanol, or DMF as the primary solvent and toluene as an anti-solvent;

fast cooling crystallization from a binary solvent system with tetrahydrofuran as the primary solvent and dichloromethane as the anti-solvent;

slow cooling crystallization from a binary solvent system with methyl ethyl ketone or DMF as the primary solvent and MTBE as the anti-solvent;

slow cooling crystallization from a binary solvent system with tetrahydrofuran or DME as the primary solvent and dichloromethane as the anti-solvent;

slow cooling crystallization from a binary solvent system with isopropanol, NNP, or DME as the primary solvent and toluene as the anti-solvent; or

crystallization from a multi-solvent system; optionally

- (C) wherein the compound of Formula (I) is polymorph Form E and the method comprises:
- slow cooling crystallization of Form A from a single solvent system with methanol;
 - fast or slow cooling crystallization from a binary solvent system with methanol as the primary solvent and water as the anti-solvent; or
 - crystallization from a multi-solvent system; optionally
- (D) wherein the compound of Formula (I) is polymorph form F and the method comprises:
- fast cooling crystallization from a binary solvent system with NMP as the primary solvent and MBTE as the anti-solvent;
 - slow cooling crystallization from a binary solvent system with NMP as the primary solvent and MBTE as the anti-solvent; or
 - crystallization from a multi-solvent system; optionally
- (E) wherein the compound of Formula (I) is polymorph form G and the method comprises:
- fast cooling crystallization from a binary solvent system with ethanol, isopropyl alcohol, or methanol as the primary solvent and MTBE as the anti-solvent; or
 - crystallization from a multi-solvent system; optionally
- (F) wherein the compound of Formula (I) is polymorph form H and the method comprise:
- slow cooling crystallization from a binary solvent system with dioxane as the primary solvent and MTBE as the anti-solvent; or
 - crystallization from a multi-solvent system; optionally
- (G) wherein the compound of Formula (I) is polymorph form I and the method comprises:
- slow cooling crystallization from a binary solvent system acetone, MEK, or dioxane as the primary solvent and toluene as the anti-solvent; or
 - crystallization from a multi-solvent system; optionally
- (H) wherein the compound of Formula (I) is polymorph form J and the method comprises:
- slow cooling crystallization from a binary solvent system with DMF as the primary solvent and toluene as the anti-solvent; or
 - crystallization from a multi-solvent system; wherein
- polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks:
 $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$;
- polymorph Form A has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $12.2^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$;

polymorph Form B has the following characteristic XRPD peaks: $2\theta = 7.9^\circ (\pm 0.2^\circ)$, $13.4^\circ (\pm 0.2^\circ)$, and $23.4^\circ (\pm 0.2^\circ)$;

polymorph Form D has the following characteristic XRPD peaks: $2\theta = 11.4^\circ (\pm 0.2^\circ)$, $17.4^\circ (\pm 0.2^\circ)$, and $22.9^\circ (\pm 0.2^\circ)$;

polymorph Form E has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.3^\circ (\pm 0.2^\circ)$, and $24.4^\circ (\pm 0.2^\circ)$;

polymorph Form F has the following characteristic XRPD peaks: $2\theta = 9.6^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $24.6^\circ (\pm 0.2^\circ)$;

polymorph Form G has the following characteristic XRPD peaks: $2\theta = 6.7^\circ (\pm 0.2^\circ)$, $9.5^\circ (\pm 0.2^\circ)$, and $19.0^\circ (\pm 0.2^\circ)$;

polymorph Form H has the following characteristic XRPD peaks: $2\theta = 8.9^\circ (\pm 0.2^\circ)$, $9.2^\circ (\pm 0.2^\circ)$, and $14.1^\circ (\pm 0.2^\circ)$;

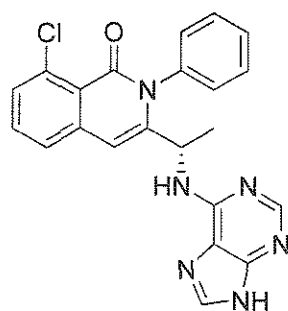
polymorph Form I has the following characteristic XRPD peaks: $2\theta = 9.7^\circ (\pm 0.2^\circ)$, $19.3^\circ (\pm 0.2^\circ)$, and $24.5^\circ (\pm 0.2^\circ)$; and

polymorph Form J has the following characteristic XRPD peaks: $2\theta = 9.1^\circ (\pm 0.2^\circ)$, $17.3^\circ (\pm 0.2^\circ)$, and $18.3^\circ (\pm 0.2^\circ)$.

60. A pharmaceutical composition comprising a compound of any one of claims 1–21, and one or more pharmaceutically acceptable excipients.

61. The pharmaceutical composition of claim 60, further comprising an amorphous form of a compound of Formula (I).

62. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I):



Formula (I),

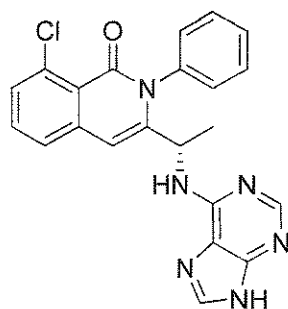
wherein the pharmaceutical composition comprises polymorph Form C of the compound of Formula (I) and one or more pharmaceutically acceptable excipients, wherein polymorph Form C has the

following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

63. A pharmaceutical composition comprising a compound of any one of claims 2–12, and one or more pharmaceutically acceptable excipients.

64. The pharmaceutical composition of claim 63, further comprising an amorphous form of a compound of Formula (I).

65. A method of preparing a pharmaceutical composition comprising:
mixing a compound of Formula (I):



Formula (I),

with a pharmaceutically acceptable excipient or carrier; wherein the compound is polymorph Form C of a compound of Formula (I); and wherein polymorph Form C has the following characteristic X-ray Powder Diffraction (XRPD) peaks: $2\theta = 10.4^\circ (\pm 0.2^\circ)$, $13.3^\circ (\pm 0.2^\circ)$, and $24.3^\circ (\pm 0.2^\circ)$.

66. A pharmaceutical composition made by the method of claim 65.

67. The pharmaceutical composition of claim 62 or method of claim 65, wherein the pharmaceutical composition comprises one or more pharmaceutically acceptable excipients selected from silicified microcrystalline cellulose, lactose, mannitol, starch, sorbitol, sucrose, dicalcium phosphate, microcrystalline cellulose, croscopovidone, croscarmellose sodium, and sodium starch glycolate, silicon dioxide, magnesium silicate, talc, magnesium stearate, sodium stearyl fumarate, stearic acid, sodium lauryl sulphate, sodium dodecyl sulphate, and polyoxyethylene sorbitan monooleate.

68. The pharmaceutical composition of claim 62 or method of claim 65, wherein the pharmaceutical composition is solid form or liquid form.

69. Use of a compound of any one of claims 1–21, or a pharmaceutical composition of any one of claims 60–64, in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

70. Use of a compound of any one of claims 2–12, or a pharmaceutical composition of any one of claims 62–64, in the manufacture of a medicament for the treatment of a PI3K mediated disorder in a subject.

71. The use of claim 70, wherein the disorder is cancer, an inflammatory disease or an auto-immune disease.

72. The use of claim 71, wherein the disorder is cancer.

73. The use of claim 72, wherein the cancer is leukemia or lymphoma.