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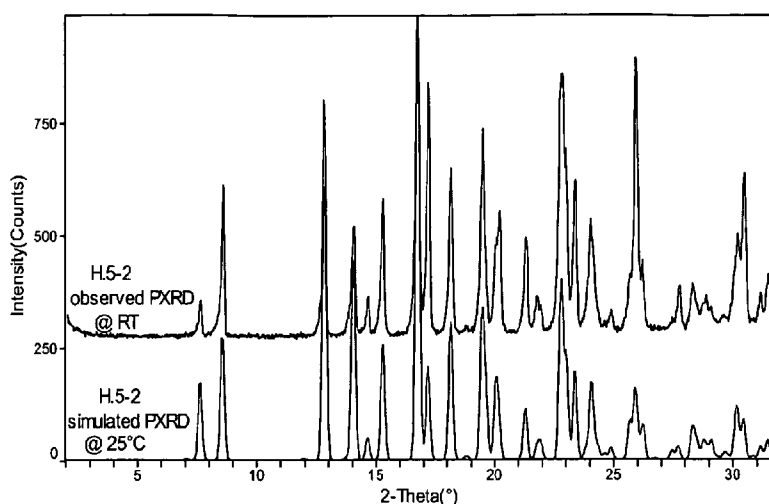
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[Continued on next page]

(54) Title: CRYSTALLINE FORMS OF (3 α , 4 β , 5 α , 7 β , 7 α)-4-(OCTAHYDRO-5-ETHYLSULFONAMIDO-4,7-DIMETHYL-1,3-DIOXO-4,7-EPOXY-2H-ISOINDOL-2-YL)-2-(TRIFLUOROMETHYL)BENZONITRILE AND METHOD OF PREPARATION

FIG. 1



(57) Abstract: Crystalline forms of (3 α ,4 β ,5 α ,7 β ,7 α)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile are provided. Also provided are at least one pharmaceutical composition comprising at least one crystalline form of (3 α ,4 β ,5 α ,7 β ,7 α)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile, at least one method of using at least one crystalline form of (3 α ,4 β ,5 α ,7 β ,7 α)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile to treat cancer and/or other proliferative diseases, and processes to prepare crystalline forms of (3 α ,4 β ,5 α ,7 β ,7 α)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile.

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**CRYSTALLINE FORMS OF (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(OCTAHYDRO-5-ETHYLSULFONAMIDO-4,7-DIMETHYL-1,3-DIOXO-4,7-EPOXY-2H-ISOINDOL-2-YL)-2-(TRIFLUOROMETHYL)BENZONITRILE AND
METHOD OF PREPARATION**

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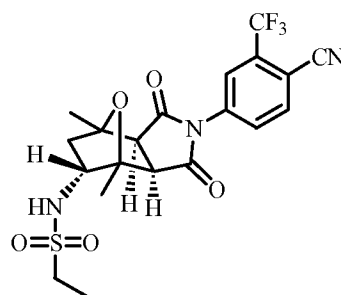
FIELD OF THE INVENTION

[0001] Disclosed are crystalline forms of (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile. Also disclosed are at least one pharmaceutical
10 composition comprising at least one crystalline form of (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile, at least one method of using at least one crystalline form of (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile to treat cancer and/or
15 other proliferative diseases, and processes to prepare crystalline forms of (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile.

BACKGROUND OF THE INVENTION

20 [0002] The androgen receptor (AR) is a key molecular target in the etiology and progression of prostate cancer. For example, androgens including, but not limited to, testosterone (T) and dihydrotestosterone (DHT), stimulate the growth of prostate cancer by binding to the AR. As a result, efforts have been undertaken to develop AR agonists and/or antagonists that are therapeutically effective in treating prostate
25 cancer.

[0003] (3 α ,4 β ,5 α ,7 β ,7 $\alpha\alpha$)-4-(octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile of Formula (I):



(I),

referred to herein as “Compound (I)”, has been found to be effective in treating cancer.

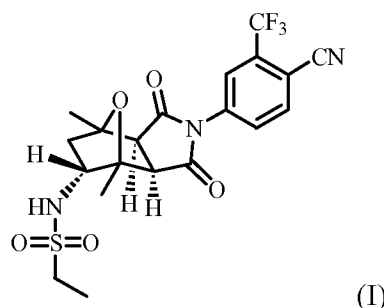
[0004] In at least one instance, Compound (I) was found to potentially bind to and
5 act as an antagonist and/or partial antagonist of the AR. Compound (I) and a process
for making Compound (I) are disclosed in Example 810 of U.S Patent 7,141,578 B1,
wherein said disclosure of Example 810 is hereby incorporated herein by reference.

[0005] In preparing a pharmaceutical composition of Compound (I), a form of the active ingredient is sought that has a balance of desired properties, such as, for example, dissolution rate, solubility, bioavailability, and/or storage stability. The particle shape and/or particle size are also important parameters that affect the release rate of the active ingredient and its bioavailability.

[0006] A difficulty regarding Compound (I) is that it has biological activity such that manufacturing processes involving an active ingredient with high biological activity may require the use of protective equipment to minimize or eliminate potential worker exposure. For an active ingredient with high biological activity, manufacturing processes are sought that minimize or avoid handling and processing the highly potent compound as a dry material and/or as a dry mixture. The present invention provides a form of Compound (I) that surprisingly affords a balance of properties sought in a pharmaceutical composition and can be manufactured as a moist or wet material.

SUMMARY OF THE INVENTION

[0007] Described herein is a first crystalline form of Compound (I):



(I)

comprising Form H.5-2.

[0008] Also described herein is a process for preparing Form H.5-2 comprising transforming a neat and/or a solvent-hydrate mixed form to afford Form H.5.2.

5 **[0009]** A second crystalline form of Compound (I) comprises Form N-4.

[0010] A third crystalline form of Compound (I) comprises Form SC-1.

[0011] Further described herein is at least one pharmaceutical composition comprising at least one crystalline form of Compound (I), at least one pharmaceutically acceptable carrier and/or diluent; and optionally at least one other anti-cancer agent.

10 **[0012]** Even further described herein is at least one method for treating at least one proliferative disease, comprising administering to a patient in need thereof, a therapeutically effect amount of Compound (I), wherein Compound (I) is provided in a crystalline form comprising Form H.5-2 and/or Form N-4; optionally administering either simultaneously or sequentially at least one other anti-cancer agent, and/or optionally administering either simultaneously or sequentially at least one other anti-cancer treatment.

BRIEF DESCRIPTION OF THE DRAWINGS

20 **[0013]** The invention is illustrated by reference to the accompanying drawings described below.

[0014] FIG. 1 shows observed (at room temperature (r.t.)) and simulated (at a Temperature (T) of about 25°C) powder x-ray diffraction (PXRD) patterns (CuK α λ =1.5418 Å) of the H.5-2 Form of Compound (I).

25 **[0015]** FIG. 2 shows observed (at r.t.) and simulated (at about 25°C) PXRD patterns (CuK α λ =1.5418 Å) of the N-4 Form of Compound (I).

- [0016] FIG. 3 shows observed (at r.t.) and simulated (at r.t.) PXRD patterns (CuK α λ =1.5418 Å) of the SC-1 Form of Compound (I).
- [0017] FIG. 4 shows a differential scanning calorimetry (DSC) thermogram of the H.5-2 Form of Compound (I).
- 5 [0018] FIG. 5 shows a DSC thermogram of the N-4 Form of Compound (I).
- [0019] FIG. 6 shows a DSC thermogram of the SC-1 Form of Compound (I).
- [0020] FIG. 7 shows a thermogravimetric analysis (TGA) thermogram of the H.5-2 Form of Compound (I).
- [0021] FIG. 8 shows a TGA thermogram of the N-4 Form of Compound (I).
- 10 [0022] FIG. 9 shows a TGA thermogram of the SC-1 Form of Compound (I).
- [0023] FIG. 10 shows the concentration versus time profile of Form N-4 in water and formation of Form H.5-2.

DETAILED DESCRIPTION OF THE INVENTION

- 15 [0024] The features and advantages of the invention may be more readily understood by those of ordinary skill in the art upon reading the following detailed description. It is to be appreciated that certain features of the invention that are, for clarity reasons, described above and below in the context of separate embodiments, may also be combined to form a single embodiment. Conversely, various features of
- 20 the invention that are, for brevity reasons, described in the context of a single embodiment, may also be combined so as to form sub-combinations thereof.
- [0025] The names used herein to characterize a specific form, e.g. “N-4” etc., are not to be limited so as to exclude any other substance possessing similar or identical physical and chemical characteristics, but rather such names are used as mere
- 25 identifiers that are to be interpreted in accordance with the characterization information presented herein.
- [0026] The definitions set forth herein take precedence over definitions set forth in any patent, patent application, and/or patent application publication incorporated herein by reference.
- 30 [0027] All numbers expressing quantities of ingredients, weight percentages, temperatures, and so forth that are preceded by the word “about” are to be understood as only approximations so that slight variations above and below the stated number

may be used to achieve substantially the same results as the stated number.

Accordingly, unless indicated to the contrary, numerical parameters preceded by the word “about” are approximations that may vary depending upon the desired properties sought to be obtained. At the very least, and not as an attempt to limit the application of the doctrine of equivalents to the scope of the claims, each numerical parameter should at least be construed in light of the number of reported significant digits and by applying ordinary rounding techniques.

[0028] All measurements are subject to experimental error and are within the spirit of the invention.

10 **[0029]** As used herein, “polymorphs” refer to crystalline forms having the same chemical structure but different spatial arrangements of the molecules and/or ions forming the crystals.

[0030] As used herein, “amorphous” refers to a solid form of a molecule and/or ion that is not crystalline. An amorphous solid does not display a definitive X-ray diffraction pattern with sharp maxima.

15 **[0031]** As used herein, the term “substantially pure” means the crystalline form of Compound (I) referred to contains at least about 90 wt.%, based on the weight of such crystalline form, of a form selected from Form H.5-2, Form N-4, and Form SC-1. The term “at least about 90 wt.%,” while not intending to limit the applicability of the doctrine of equivalents to the scope of the claims, includes, but is not limited to, for example, about 90, 90, about 91, 91, about 92, 92, about 93, 93, about 94, 94, about 20 95, 95, about 96, 96, about 97, 97, about 98, 98, about 99, 99, and about 100 wt. %, based on the weight of the crystalline form referred to. The remainder of the crystalline form of Compound (I) may comprise other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities that arise, for example, when the crystalline form is prepared.

25 **[0032]** For example, a crystalline form of Compound (I) may be deemed substantially pure if the crystalline form contains at least 90 wt. %, based on the weight of such crystalline form as measured by means that are at this time known and generally accepted in the art, of a Form selected from Form H.5-2, Form N-4, and 30 Form SC-1; and less than about 10 wt. %, based on the weight of such crystalline

form, of material comprising other Form(s) of Compound (I) and/or reaction impurities and/or processing impurities.

[0033] The presence of reaction impurities and/or processing impurities may be determined by analytical techniques known in the art, such as, for example,
5 chromatography, nuclear magnetic resonance spectroscopy, mass spectrometry, and/or infrared spectroscopy.

[0034] As used herein, the parameter “molecules/asymmetric unit” refers to the number of molecules of Compound (I) in the asymmetric unit.

[0035] As used herein, the unit cell parameter “molecules/unit cell” refers to the
10 number of molecules of Compound (I) in the unit cell.

[0036] When dissolved, the crystalline form of Compound (I) loses its crystalline structure, and is therefore referred to as a solution of Compound (I). At least one crystalline form of Compound (I) disclosed herein may be used to prepare at least one liquid formulation in which at least one crystalline form of Compound (I) is dissolved
15 and/or suspended.

[0037] By “therapeutically effective amount” is meant an amount that when administered either alone, or in combination with an additional therapeutic agent is effective to prevent, suppress, and/or ameliorate a disease and/or condition and/or the progression of a disease and/or condition.

20 [0038] Disclosed herein are crystalline forms of Compound (I).

Form H.5-2

[0039] A first crystalline form of Compound (I) comprises a hemihydrate crystalline form referred to herein as “Form H.5-2” or “H.5-2 Form”. The
25 hemihydrate Form H.5-2 comprises up to one molecule of water for each two molecules of Compound (I). For example, an H.5-2 Form may comprise less than one molecule of water for each two molecules of Compound (I). Alternatively, an H.5-2 Form may comprise one molecule of water for each two molecules of Compound (I).

[0040] In one embodiment, the H.5-2 Form is characterized by unit cell
30 parameters approximately equal to the following:

Cell dimensions: $a = 24.48 \text{ \AA}$
 $b = 7.23 \text{ \AA}$

$$c = 13.22 \text{ \AA}$$

$$\alpha = 90.0^\circ$$

$$\beta = 108.7^\circ$$

$$\gamma = 90.0^\circ$$

5 Space group: C2

Molecules of Compound (I)/asymmetric unit: 1

Volume = 554 $\text{\AA}^3$

Density (calculated) = 1.440 g/cm³,

wherein the unit cell parameters of Form H.5-2 are measured at a temperature of
10 about 25°C.

[0041] In another embodiment, the H.5-2 Form is characterized by a simulated powder x-ray diffraction (PXRD) pattern substantially in accordance with the pattern shown in Figure 1 and/or by an observed PXRD pattern substantially in accordance with the pattern shown in Figure 1.

15 **[0042]** In yet another embodiment, the H.5-2 Form is characterized by a PXRD pattern (CuK α λ =1.5418 $\text{\AA}$ at a temperature of about 25°C) comprising four or more, preferably five or more, 2 θ values selected from: 7.6 $\pm$ 0.2; 8.6 $\pm$ 0.2; 12.8 $\pm$ 0.2; 14.0 $\pm$ 0.2; 15.3 $\pm$ 0.2; 16.8 $\pm$ 0.2; 17.2 $\pm$ 0.2; 18.2 $\pm$ 0.2; 19.5 $\pm$ 0.2; and 20.1 $\pm$ 0.2, wherein the PXRD pattern of Form H.5-2 is measured at a temperature of about 25°C.

20 **[0043]** In yet an even further embodiment, the H.5-2 Form is characterized by fractional atomic coordinates substantially as listed in Table 1.

Table 1: Fractional Atomic Coordinates of Form H.5-2

Calculated at a Temperature of about 25°C

Atom	X	Y	Z	Atom	X	Y	Z
S1	-0.0053	0.6723	-0.2585	C10	0.0980	1.0621	-0.0870
O1	0.1767	0.8595	0.0094	C11	0.1492	1.0595	0.5057
O2	0.2029	0.6785	0.3047	C12	0.1713	1.2377	0.5162
C1	0.1150	0.8765	-0.0354	C13	0.1687	0.7543	0.2298
N1	0.1487	0.9354	0.2355	C14	0.1000	0.7106	-0.1128
N2	0.0397	0.6506	-0.1402	C15	0.1755	1.3499	0.6078
C2	0.1596	1.0359	0.3326	C16	0.1895	1.3131	0.4350

O3	-0.0605	0.6342	-0.2487	C17	0.2415	0.6157	0.0997
C3	0.1054	0.9845	0.1420	O5	0.0049	0.8499	-0.2996
C4	0.1791	0.6726	0.0473	C18	0.0073	0.5163	-0.3468
C5	0.0960	0.8296	0.0627	F1	0.1028	0.8147	0.5630
C6	0.1431	0.9593	0.4132	F2	0.1697	0.9456	0.6783
C7	0.1454	0.5675	-0.0542	C19	0.1298	0.9769	0.5914
O4	0.0797	1.1308	0.1322	F3	0.0914	1.0773	0.6149
N3	0.1786	1.4437	0.6784	C20	-0.0053	0.3346	-0.3268
C8	0.1403	0.6794	0.1194	O6	0.0000	0.3889	0.0000
C9	0.1826	1.2126	0.3419	-	-	-	-

[0044] In a still further embodiment, the H.5-2 Form is characterized by a differential scanning calorimetry (DSC) thermogram substantially in accordance with that shown in Figure 4.

- 5 **[0045]** In still yet a further embodiment, the H.5-2 Form is characterized by a thermogravimetric analysis (TGA) thermogram having weight loss in the range of from about 1.8 to about 1.9 wt. %, based on the weight of the sample of Form H.5-2, upon being heated to a temperature of about 185°C.

- 10 **[0046]** In still another embodiment, the H.5-2 Form exhibits a TGA thermogram substantially the same as shown in Figure 7.

[0047] In still yet an even further embodiment, the first crystalline form of Compound (I) is substantially pure.

- 15 **[0048]** In still yet another embodiment, the first crystalline form of Compound (I) contains at least about 90 wt.%, preferably at least about 95 wt.%, and more preferably at least about 99 wt.%, based on weight of the first crystalline form, Form H.5-2.

- 20 **[0049]** In yet another embodiment, a substantially pure first crystalline form has substantially pure phase homogeneity with less than about 10%, preferably less than about 5%, and more preferably less than about 2% of the total peak area of the experimentally measured PXRD pattern arising from peaks that are absent from the simulated PXRD pattern. Most preferably, a substantially pure first crystalline form has substantially pure phase homogeneity with less than about 1% of the total peak

area of the experimentally measured PXRD pattern arising from peaks that are absent from the simulated PXRD pattern.

[0050] In another embodiment, the first crystalline form of Compound (I) consists essentially of Form H.5-2. The first crystalline form of this embodiment may
5 comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the first crystalline form, Form H.5-2.

[0051] In yet another embodiment, a pharmaceutical composition comprises Form H.5-2; and at least one pharmaceutically-acceptable carrier and/or diluent.

10 [0052] In still another embodiment, a pharmaceutical composition comprises a substantially pure first crystalline form; and at least one pharmaceutically-acceptable carrier and/or diluent.

[0053] In still an even further embodiment, a therapeutically effective amount of Form H.5-2 is combined with at least one pharmaceutically acceptable carrier and/or
15 diluent to provide at least one pharmaceutical composition.

[0054] Still yet a further embodiment provides a method for treating a proliferative disease comprising administering to a patient in need thereof a therapeutically effective amount of Compound (I), wherein Compound (I) is provided in a first crystalline form comprising Form H.5-2.

20 [0055] In one embodiment, the patient is a human.

[0056] In another embodiment, the proliferative disease is prostate cancer.

[0057] In an even further embodiment, the method comprises administering a first crystalline form of Compound (I) consisting essentially of Form H.5.2.

25 Form N-4

[0058] A second crystalline form of Compound (I) comprises a neat crystalline form referred to herein as "Form N-4" or "N-4 Form".

[0059] In one embodiment, the N-4 Form is characterized by unit cell parameters approximately equal to the following:

30 Cell dimensions: $a = 8.32 \text{ \AA}$
 $b = 11.70 \text{ \AA}$
 $c = 22.53 \text{ \AA}$

$$\alpha = 90.0^\circ$$

$$\beta = 90.0^\circ$$

$$\gamma = 90.0^\circ$$

Space group: $P2_12_12_1$

5 Molecules of Compound (I)/asymmetric unit: 1

Volume = $549 \text{ \AA}^3$

Density (calculated) = 1.427 g/cm^3 ,

wherein the unit cell parameters of Form N-4 are measured at a temperature of about 25°C .

10 **[0060]** In another embodiment, the N-4 Form is characterized by a simulated PXRD pattern substantially in accordance with the pattern shown in Figure 2 and/or by an observed PXRD pattern substantially in accordance with the pattern shown in Figure 2.

[0061] In yet another embodiment, the N-4 Form is characterized by a PXRD
15 pattern ($\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$ at a temperature of about 25°C) comprising four or more, preferably five or more, 2θ values ($\text{CuK}\alpha \lambda = 1.5418 \text{ \AA}$) selected from: 8.5 ± 0.2 ; 10.9 ± 0.2 ; 13.6 ± 0.2 ; 17.6 ± 0.2 ; 18.5 ± 0.2 ; 20.5 ± 0.2 ; and 21.9 ± 0.2 , wherein the PXRD pattern of Form N-4 is measured at a temperature of about 25°C .

[0062] In yet an even further embodiment, the N-4 Form is characterized by
20 fractional atomic coordinates substantially as listed in Table 2.

Table 2: Fractional Atomic Coordinates for Form N-4
Calculated at a Temperature of about 25°C

Atom	X	Y	Z	Atom	X	Y	Z
S1	-0.0153	0.3237	0.0377	F2	0.8633	0.5956	0.3741
O1	0.3424	0.5273	0.1745	C8	0.1852	0.3588	0.2011
O2	0.7898	0.5323	0.1702	C9	0.7990	0.4335	0.2927
O3	-0.0030	0.2261	0.0001	C10	0.5527	0.4603	0.1187
N1	0.1654	0.3527	0.0574	C11	0.3132	0.5456	0.0716
N2	0.6617	0.3718	0.2043	C12	0.5299	0.3018	0.1874
O4	-0.1119	0.3165	0.0903	C13	0.9275	0.2137	0.3067
O5	0.4999	0.2124	0.2114	C14	0.9011	0.4089	0.3403

C1	0.1979	0.4500	0.0968	F3	1.0999	0.5275	0.3788
C2	0.2882	0.4156	0.1548	C15	0.8283	0.2372	0.2588
C3	0.4327	0.5612	0.1220	C16	0.9413	0.5014	0.3819
C4	0.4486	0.3564	0.1361	C17	1.0588	0.2684	0.3989
C5	0.7661	0.3487	0.2528	N3	1.1292	0.2410	0.4401
C6	0.6820	0.4658	0.1658	C18	0.4953	0.6793	0.1290
C7	0.9624	0.2986	0.3479	C19	-0.0911	0.4397	-0.0044
F1	0.9212	0.4742	0.4384	C20	0.0076	0.4671	-0.0577

[0063] In a still further embodiment, the N-4 Form is characterized by a DSC thermogram substantially in accordance with that shown in Figure 5. The N-4 Form may be characterized by a melting point in the range of from about 182°C to about 189°C.

[0064] In still another embodiment, the N-4 Form is characterized by a TGA thermogram, wherein the N-4 Form experiences either no weight loss, or minimal weight loss upon being heated to a temperature of about 165°C.

[0065] In still an even further embodiment, the N-4 Form exhibits a TGA thermogram substantially the same as shown in Figure 8.

[0066] In still yet another embodiment, the second crystalline form of Compound (I) is substantially pure.

[0067] In still yet an even further embodiment, the second crystalline form of Compound (I) contains at least about 90 wt.%, preferably at least about 95 wt.%, and more preferably at least about 99 wt.%, based on weight of the second crystalline form, Form N-4.

[0068] In a still further embodiment, a substantially pure second crystalline form has substantially pure phase homogeneity with less than about 10%, preferably less than about 5%, and more preferably less than about 2% of the total peak area of the experimentally measured PXRD pattern arising from peaks that are absent from the simulated PXRD pattern. Most preferably, the substantially pure second crystalline form has substantially pure phase homogeneity with less than about 1% of the total peak area of the experimentally measured PXRD pattern arising from peaks that are absent from the simulated PXRD pattern.

[0069] In another embodiment, the second crystalline form of Compound (I) consists essentially of Form N-4. The second crystalline form of this embodiment may comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the second crystalline form, 5 Form N-4.

[0070] In yet another embodiment, a pharmaceutical composition comprises a second crystalline form; and at least one pharmaceutically-acceptable carrier and/or diluent.

[0071] In still another embodiment, a pharmaceutical composition comprises a 10 substantially pure second crystalline form; and at least one pharmaceutically-acceptable carrier and/or diluent.

[0072] In still an even further embodiment, a therapeutically effective amount of Form N-4 is combined with at least one pharmaceutically acceptable carrier and/or diluent to provide at least one pharmaceutical composition.

15 [0073] Still yet a further embodiment provides a method for treating a proliferative disease comprising administering to a patient in need thereof, a therapeutically effective amount of Compound (I), wherein Compound (I) is provided in a second crystalline form comprising Form N-4.

[0074] In one embodiment, the patient is a human.

20 [0075] In another embodiment, the proliferative disease is prostate cancer.

[0076] In an even further embodiment, the method comprises administering a second crystalline form of Compound (I) consisting essentially of Form N-4.

Form SC-1

25 [0077] A third crystalline form of Compound (I) comprises a hydrate-hemiacetic acid crystalline form referred to herein as "Form SC-1" or "SC-1 Form".

[0078] In one embodiment, the SC-1 Form is characterized by unit cell parameters approximately equal to the following:

30	Cell dimensions:	$a = 7.53 \text{ \AA}$
		$b = 12.21 \text{ \AA}$
		$c = 13.07 \text{ \AA}$
		$\alpha = 97.3^\circ$

$$\beta = 91.5^\circ$$

$$\gamma = 93.5^\circ$$

Space group: P1

Molecules of Compound (I)/asymmetric unit: 2

5 Volume = 594 Å³

Density (calculated) = 1.451 g/cm³,

wherein the unit cell parameters of Form SC-1 are measured at a temperature of about -40°C.

[0079] In one embodiment, the SC-1 Form is characterized by unit cell parameters
10 approximately equal to the following:

Cell dimensions:

$$a = 7.59 \text{ Å}$$

$$b = 12.21 \text{ Å}$$

$$c = 13.19 \text{ Å}$$

$$\alpha = 97.4^\circ$$

15 $\beta = 91.7^\circ$

$$\gamma = 93.6^\circ$$

Space group: P1

Molecules of Compound (I)/asymmetric unit: 2

Volume = 604 Å³

20 Density (calculated) = 1.429 g/cm³,

wherein the unit cell parameters of Form SC-1 are measured at a temperature of about 25°C.

[0080] In another embodiment, the SC-1 Form is characterized by a simulated
PXRD pattern substantially in accordance with the pattern shown in Figure 3 and/or
25 by a simulated PXRD pattern substantially in accordance with the pattern shown in
Figure 3.

[0081] In yet another embodiment, the SC-1 Form is characterized by a PXRD
pattern (CuKα λ=1.5418 Å at a temperature of about 25°C) comprising four or more,
preferably five or more, 2θ values (CuKα λ=1.5418 Å) selected from: 6.9±0.2,
30 7.4±0.2, 10.6±0.2, 11.8±0.2, 14.9±0.2, 15.2±0.2, 16.3±0.2, 17.7±0.2, 23.2±0.2, and
24.2±0.2, wherein the PXRD pattern of Form SC-1 is measured at a temperature of
about 25°C.

[0082] In yet an even further embodiment, the SC-1 Form is characterized by fractional atomic coordinates substantially as listed in Table 3.

Table 3: Fractional Atomic Coordinates for Form SC-1

5

Calculated at a Temperature of -40°C

Atom	X	Y	Z	Atom	X	Y	Z
S1	0.5177	0.4784	0.0888	N4	0.3305	0.6523	0.536
O1	0.6889	0.8617	0.1797	O8	0.1068	0.6838	0.4222
N1	0.8534	0.8536	0.4169	O9	0.7365	0.1682	0.2726
O2	1.0969	0.9483	0.3554	N5	0.4887	0.2682	0.3457
O3	0.6342	0.7213	0.4359	O10	0.5569	0.0921	0.4034
C1	0.845	0.7461	0.063	F4	0.3579	0.7595	0.9089
O4	0.3594	0.534	0.068	C21	0.4525	0.5741	0.5446
F1	0.7681	1.2317	0.7182	C22	0.3382	0.7577	0.5996
N2	0.8979	1.1002	0.9097	C23	0.349	0.758	0.7042
F2	0.8803	1.2402	0.5727	C24	0.3494	0.371	0.4962
C2	0.8617	0.9057	0.5206	C25	0.4195	0.4809	0.4588
C3	0.8736	1.0198	0.539	C26	0.2138	0.6237	0.4497
C4	0.9789	0.8759	0.342	C27	0.2566	0.5134	0.3984
C5	0.7763	0.724	0.275	C28	0.3262	0.2795	0.4019
C6	0.9392	0.7939	0.2469	C29	0.3519	0.954	0.6178
C7	0.6335	0.7507	0.1971	C30	0.1134	0.418	0.4128
C8	0.8801	1.0716	0.6399	C31	0.1617	0.3151	0.3445
C9	0.8719	0.8426	0.152	C32	0.3384	0.8538	0.5552
O5	0.5226	0.4266	0.1802	C33	0.3612	0.8597	0.7686
C10	0.7433	0.762	0.3825	C34	0.3641	0.9588	0.7242
N3	0.6851	0.5666	0.0909	C35	0.4378	0.3381	0.5903
C11	0.6703	0.6855	0.0921	C36	-0.0759	0.4432	0.4091
C12	0.4432	0.7469	0.2294	C37	0.4244	0.0731	0.2181
C13	0.8794	1.0058	0.7202	C38	0.4056	0.129	0.1233
C14	0.896	1.1928	0.6565	C39	0.3775	1.0655	0.7865

F3	1.0455	1.2329	0.706	C40	0.3692	0.8606	0.8823
C15	0.86	0.8438	0.6015	N6	0.3863	1.1505	0.8348
C16	0.866	0.894	0.7007	F5	0.237	0.9122	0.9255
C17	0.9641	0.9472	0.1245	F6	0.5143	0.9106	0.9245
C18	0.8879	1.0611	0.8254	O11	0.0126	0.4802	0.1372
C19	0.5544	0.3772	-0.0157	O12	0.9321	0.2538	0.1066
C20	0.5556	0.4193	-0.1149	O13	0.8403	0.4904	0.7029
S2	0.5661	0.1477	0.3155	C41	1.0849	0.5035	0.8133
O6	0.166	0.3938	0.5146	O14	0.9399	0.6531	0.7665
O7	0.5687	0.5837	0.6118	C42	0.9542	0.5552	0.7557

[0083] In a still further embodiment, the SC-1 Form is characterized by a DSC thermogram substantially in accordance with that shown in Figure 6.

[0084] In still yet a further embodiment, the SC-1 Form is characterized by a
5 TGA thermogram having weight loss in the range of from about 8 to about 9 wt. %, based on the weight of a sample of Form SC-1, upon being heated to a temperature of about 150°C.

[0085] In still another embodiment, the SC-1 Form exhibits a TGA thermogram substantially the same as shown in Figure 9.

10 **[0086]** In still yet an even further embodiment, the third crystalline form of Compound (I) is substantially pure.

[0087] In still yet another embodiment, the third crystalline form of Compound (I) contains at least about 90 wt.%, preferably at least about 95 wt.%, and more preferably at least about 99 wt.%, based on the weight of the third crystalline form,

15 Form SC-1.

[0088] In yet another embodiment, a substantially pure third crystalline form has substantially pure phase homogeneity with less than about 10%, preferably less than about 5%, and more preferably less than about 2% of the total peak area of the experimentally measured PXRD pattern arising from peaks that are absent from the
20 simulated PXRD pattern. Most preferably, a substantially pure third crystalline form has substantially pure phase homogeneity with less than about 1% of the total peak

area of the experimentally measured PXRD pattern arising from peaks that are absent from the simulated PXRD pattern.

[0089] In another embodiment, the third crystalline form of Compound (I) consists essentially of Form SC-1. The third crystalline form of this embodiment may
5 comprise at least about 90 wt. %, preferably at least about 95 wt. %, and more preferably at least about 99 wt. %, based on the weight of the third crystalline form, Form SC-1.

[0090] In yet another embodiment, a pharmaceutical composition comprises a third crystalline form; optionally at least one other component selected from, for
10 example, excipients and carriers; and optionally at least one other active pharmaceutical ingredient having at least one molecularly different active chemical entity.

[0091] In still another embodiment, a pharmaceutical composition comprises a substantially pure third crystalline form; optionally at least one other component
15 selected from, for example, excipients and carriers; and optionally at least one other active pharmaceutical ingredient having at least one molecularly different active chemical entity.

[0092] In still an even further embodiment, a therapeutically effective amount of Form SC-1 may be combined with at least one pharmaceutically acceptable carrier
20 and/or diluent to provide at least one pharmaceutical composition.

[0093] Still yet a further embodiment provides a method for treating a proliferative disease comprising administering to a patient in need thereof, a therapeutically effective amount of Compound (I), wherein Compound (I) is provided in a third crystalline form comprising Form SC-1.

25 [0094] In one embodiment, the patient is a human.

[0095] In an even further embodiment, the method comprises administering a third crystalline form of Compound (I) consisting essentially of Form SC-1.

Other Crystalline Forms of Compound (I)

30 [0096] Other crystalline forms of Compound (I) are listed in Table 4. Processes to prepare these forms are disclosed in copending United States Patent Application 60/xxx,xxx.

Table 4

Form	Water/Solvent	Comments
N-5	neat	contains large void; semistable at ambient conditions; can transform to N-4.
SA-1	1 H ₂ O/0.5 acetone	desolvates at about 60-70°C;
SA-6	1 H ₂ O/1 acetonitrile	desolvates and converts to Form N-5
SB-1	1 H ₂ O/0.5 ethanol	desolvates at about 69-90°C

Table 5 - Unit Cell Data for Other Crystalline Forms of Compound (I)

Form	a(Å)	b(Å)	c(Å)	$\alpha(^{\circ})$	$\beta(^{\circ})$	$\gamma(^{\circ})$	Z'	Space Group	Volume (Å ³)
N-5	17.19	7.47	17.82	90.0	98.4	90.0	2	P2 ₁	566
SA-1	7.60	12.21	13.29	97.3	91.7	93.6	2	P1	610
SA-6	22.73	15.29	13.46	90.0	90.0	90.0	2	P2 ₁ 2 ₁ 2 ₁	585
SB-1	7.53	12.28	13.19	97.6	92.4	93.3	2	P1	602
EA-3	24.89	7.67	14.06	90.0	90.0	90.0	1	P2 ₁ 2 ₁ 2 ₁	671
HAC-5	17.18	7.60	17.76	90.0	98.7	90.0	2	P2 ₁ 2 ₁ 2 ₁	573

^a Unit cell data at 25°C, except for Form SA-6 at -30°C.

5 ^b Z' = molecules of Compound (I)/asymmetric unit

[0097] Form N-4 and Form H.5-2 are surprisingly advantageous because they have a combination of properties that make them suitable for pharmaceutical drug production and administration of Compound (I) to a patient.

10 **[0098]** After the isolation of Compound (I) crystals from solution, the crystalline material is dried to remove excess solvent and/or water. The drying time can be reduced by heating at reduced pressure to speed the removal of excess solvent and/or water from the crystalline material. However, at drying conditions used in pharmaceutical production, such as, for example, at temperatures of about 60°C or

15 higher, Form SA-1, Form SA-6, and Form SB-1 were observed to undergo desolvation. Surprisingly, the hemihydrate Form H.5-2 was observed to not undergo dehydration when subjected to drying conditions of 60°C and approximately zero

percent relative humidity for a period of one hour. The neat forms are not subject to desolvation.

[0099] Administration of a Compound (I) as a solvated crystalline form, such as, Form SA-1 (acetone), Form SA-6 (acetonitrile), Form SB-1 (ethanol), Form EA-3
5 (ethyl acetate), and Form HAC-5 (acetic acid), includes the concomitant delivery of the solvent to the patient. Since certain solvents are unacceptable for administration to patients, solvated crystalline forms comprising unacceptable solvents cannot be employed for pharmaceutical drug delivery of Compound (I), although these crystalline forms can be usefully in processes to isolate and/or purify Compound (I).
10 Solvated crystalline forms comprising other solvents, such as ethanol or acetic acid, may be acceptable for certain routes of administration (e.g., oral administration) but these solvated crystalline forms of Compound (I) typically require more extensive testing to obtain regulatory approval than neat or hydrated forms.

[00100] A further requirement for the selection of a physical form for
15 pharmaceutical development is suitable chemical and physical stability, such as stability of the form during processing to the desired dosage form and/or stability during storage. Form N-4 and Form H.5.2 show suitable chemical and physical stability as indicated by testing at several different temperature and humidity conditions.

20 [00101] The neat form N-4 and the hemihydrate form H.5-2 have suitable bioavailability as indicated by their solubility in water.

Process for Preparing Form H.5-2

[00102] In one embodiment, a process is provided for preparing Form H.5-2 of
25 Compound (I), comprising: providing a neat form and/or a solvent-hydrate mixed form of Compound (I); and transforming said neat form and/or said solvent-hydrate mixed form to afford said Form H.5-2. Examples of solvent-hydrate mixed forms include, but are not limited to, Form SC-1, hydrate-hemiacetate Form SA-1, acetonitrile-hydrate Form SA-6, and hydrate-hemiethanolate Form SB-1. Form SA-1,
30 SA-6, and SB-1 are disclosed in a copending U.S. Patent Application 60/xxx,xxx and are incorporated herein by reference. In one process of this embodiment, the solvent-hydrate mixed form is transformed to Form H.5-2 by heating crystals of the solvent-

hydrate mixed forms to remove solvent and excess water. Suitable temperatures for heating the crystals include temperatures in the range of from about 30°C to about 155°C. Reduced pressure can be employed to remove solvent and/or excess water. In another process of this embodiment, a slurry is provided comprising i) particles of the
5 neat and/or solvent-hydrate mixed form and ii) water to afford Form H.5-2. The water can be added during preparation of the slurry and/or after slurry preparation. The slurry may be prepared by dispersing the neat and/or solvent-hydrate mixed form into a solvent or solvent-water mixture. Suitable solvents include solvents that are miscible with water including, for example, methanol, ethanol, and organic acids such
10 as acetic acid. The slurry may be subjected to mixing, for example, under high shear conditions. Suitable high shear conditions include a shear rate in the range of about 100 to about 300,000 s⁻¹, preferably from about 1000 to about 200,000 s⁻¹, and more preferably from about 5000 to about 100,000 s⁻¹. Other suitable high shear conditions for mixing devices using a rotator-stator configuration, such as a TURRAX®
15 homogenizer (IKA, Wilmington, NC), include shear frequencies in the range of from about 100 to about 500,000 s⁻¹, preferably from about 1000 to about 300,000 s⁻¹, and more preferably from about 5000 to about 300,000 s⁻¹. An example of a suitable process for preparing Form H.5-2 from a neat form and/or a solvent-hydrate mixed form is described in U.S. Patent Application Publication 2006/0160841 A1, which
20 discloses a process and apparatus for transforming a first polymorph of a chemical material into a second polymorph of the same material using a vessel connected to a re-circulation system, with the optional application of high shear mixing, the disclosure of which is incorporated herein in its entirety.

[00103] In a further embodiment, a process is provided for preparing Form H.5-2
25 of Compound (I), comprising: providing Form SC-1 of Compound (I); and transforming Form SC-1 to afford Form H.5-2. In one process of this embodiment, Form SC-1 is transformed by heating crystals of Form SC-1 to remove acetic acid and excess water, to afford the hemihydrate Form H.5-2. The crystals of Form SC-1 may be heated to a temperature in the range of from 30 to 155°C to remove acetic acid and
30 excess water, optionally under conditions of reduced pressure. In another process of this embodiment, a slurry is prepared comprising particles of Form SC-1 and water to afford Form H.5-2. The slurry may be prepared by adding water to a slurry

comprising Form SC-1 particles in acetic acid. The slurry may be subjected to mixing, for example, under high shear conditions, such as a shear rate in the range of about 100 to about 300,000 s⁻¹, preferably from about 1000 to about 200,000 s⁻¹, and more preferably from about 5000 to about 100,000 s⁻¹. The process can be conducted
5 at temperatures in which the aqueous phase of the slurry is a liquid with sufficiently low viscosity to allow mixing of the slurry, for example, temperatures in the range of from about 5°C to about 80°C, preferably from about 15°C to about 70°C, and more preferably from about 20°C to about 60°C.

[00104] The process of transforming a neat form and/or a solvent-hydrate mixed
10 form, preferably Form SC-1, to Form H.5-2 may be employed to prepare particles of Form H.5-2 having a particle size distribution characterized by a D₉₀ value of less than about 150 microns, preferably less than about 125 microns, and more preferably, less than about 100 microns. The D₉₀ value refers to a particle size defined by an equivalent spherical diameter for which 90% of the volume of particles are below this
15 particle size and 10% of the volume of particles are equal or bigger than this particle size. D₉₀ values may be determined by a suitable static laser light scattering technique. Further, the process may be employed to prepare particles of Form H.5-2 having a tabular or equant shape.

[00105] Further, the process of transforming a neat form and/or a solvent-hydrate
20 mixed form, preferably Form SC-1, to Form H.5-2 may be employed to prepare particles of Form H.5-2, wherein a substantial number of the particles of Form H.5-2 are characterized by shapes having axial dimension ratios of: width:length of about 1:1 to about 1:3; and thickness:width of about 1:1 to about 1:3. Examples of such shapes include equant and tabular shapes. In one embodiment, the process provides
25 particles of Form H.5-2 having a particle size distribution characterized by a D₉₀ value of less than about 150 microns, preferably less than about 125 microns, and more preferably, less than about 100 microns; wherein a substantial number of the particles are characterized by shapes having axial dimension ratios of: width:length of about 1:1 to about 1:3; and thickness:width of about 1:1 to about 1:3. The process may be
30 employed to prepare particles of Form H.5-2 having a tabular or equant shape.

[00106] In a further embodiment, the process comprises: providing a slurry comprising particles of Form SC-1 in acetic acid; adding water to the slurry; and

mixing the slurry during and/or after the addition of the water to afford particles of Form H.5-2. High shear mixing may be used to mix the slurry comprising the particles of Form SC-1 and water. The process of this embodiment may be employed to prepare particles of Form H.5-2 having a particle size characterized by a D_{90} value of less than about 150 microns, preferably less than about 125 microns, and more preferably, less than about 100 microns. The process of this embodiment may be employed to prepare particles of Form H.5-2, wherein a substantial number of the particles are characterized by shapes having axial dimension ratios of: width:length of about 1:1 to about 1:3; and thickness:width of about 1:1 to about 1:3.

10 **[00107]** In one embodiment, a composition is provided comprising particles of Form H.5-2, wherein the particles have a particle size characterized by a D_{90} value of less than about 150 microns, preferably less than about 125 microns, and more preferably, less than about 100 microns. The composition of this embodiment may be provided wherein a substantial number of the particles are characterized by shapes
15 having axial dimension ratios of: width:length of about 1:1 to about 1:3; and thickness:width of about 1:1 to about 1:3. The composition may optionally comprise other components, such as a pharmaceutically-acceptable carrier and/or diluent.

[00108] In a still different embodiment, a process is provided for preparing a hydrate crystalline form of Compound (I), comprising: providing a slurry comprising
20 a neat form and/or a solvent-hydrate mixed form of Compound (I) in solvent and/or water; and adding water to said slurry to afford said hydrate crystalline form, wherein said hydrate crystalline form is provided as particles having a particle size characterized by a D_{90} value of less than about 150 microns. A hydrate crystalline form of Compound (I) is a crystalline form of Compound (I) that comprises a
25 stoichiometric amount of water, and includes, for example, a hemihydrate form such as Form H.5-2. Suitable solvents include solvents that are miscible with water and in which Compound (I) is insoluble or slightly soluble, including, for example, organic acids such as acetic acid. The slurry may be subjected to mixing, for example, under high shear conditions, such as a shear rate in the range of about 100 to about 300,000
30 s^{-1} , preferably from about 1000 to about 200,000 s^{-1} , and more preferably from about 5000 to about 100,000 s^{-1} . The process can be conducted at temperatures in which the aqueous phase of the slurry is a liquid with sufficiently low viscosity to allow mixing

of the slurry, for example, temperatures in the range of from about 5°C to about 80°C, preferably from about 15°C to about 70°C, and more preferably from about 20°C to about 60°C. The process of this embodiment can be employed to prepared a hydrate crystalline form having a particle size characterized by a D₉₀ value of less than about 150 microns, preferably less than about 125 microns, and more preferably, less than about 100 microns. The process of this embodiment may be employed to prepare particles of Form H.5-2, wherein a substantial number of the particles are characterized by shapes having axial dimension ratios of: width:length of about 1:1 to about 1:3; and thickness:width of about 1:1 to about 1:3. Preferably, the solvent-hydrate mixed form is Form SC-1. Preferably, the hydrate crystalline form is Form H.5-2.

USE AND UTILITY

[00109] Compound (I) is useful for modulating the function of a nuclear hormone receptor specifically, the androgen receptor (AR). Compound (I) is useful to treat AR-associated conditions. In one embodiment, Compound (I) selectively modulates the androgen receptor within the NHR family.

[00110] Compound (I) may be used to treat a variety of medical conditions and/or disorders associated with the androgen receptor (AR) pathway. Compound (I) can modulate the function of the AR by antagonizing, and/or partially antagonizing the AR. In one embodiment, Compound (I) selectively modulates the function of the AR.

[00111] Medical conditions associated with the AR pathway include, but are not limited to, for example, benign prostate hyperplasia, hirsutism, acne, hyperpilosity, seborrhea, endometriosis, polycystic ovary syndrome, androgenic alopecia, adenomas and neoplasies of the prostate, benign or malignant tumor cells containing the androgen receptor, hypogonadism, osteoporosis, suppression of spermatogenesis, libido, cachexia, anorexia, androgen supplementation for age related decreased testosterone levels in men, prostate cancer, breast cancer, endometrial cancer, uterine cancer, hot flashes, and Kennedy's disease. For example, pan AR modulation is contemplated, with prostate selective AR modulation ("SARM") being particularly preferred, such as for the treatment of early stage prostate cancers. In one

embodiment, Compound (I) is used to treat prostate cancer by being employed as an antagonist or partial antagonist of the AR.

[00112] Compound (I) can be used to antagonize, preferably selectively antagonize, mutated ARs found, for example, in many tumor cell lines. Exemplary
5 mutated ARs, include, but are not limited to, those found in prostate tumor cell lines, such as, for example, LNCap (T877A mutation, *Biophys. Acta*, 187, 1052 (1990)); PCa2b (L701H & T877A mutations, *J. Urol.*, 162, 2192 (1999)); and CWR22 (H874Y mutation, *Mol. Endo.*, 11, 450 (1997)).

[00113] In one embodiment, a method for treating at least one proliferative disease
10 comprises administering to a patient in need of such treatment a therapeutically effective amount of Compound (I), wherein Compound (I) is provided in a crystalline form comprising at least one form selected from Form H.5-2 and Form N-4; optionally administering either simultaneously or sequentially at least one other anti-cancer agent, and optionally administering either simultaneously or sequentially at
15 least one other anti-cancer treatment. Preferably, in the method of this embodiment, Compound (I) is provided in Form H.5-2. Preferably, the proliferative disease is prostate cancer, breast cancer, endometrial cancer, or uterine cancer; and more preferably, prostate cancer.

[00114] In a further embodiment, a method for treating at least one proliferative
20 disease comprises administering to a patient in need of such treatment a therapeutically effective amount of Compound (I), wherein Compound (I) is provided in a crystalline form comprising Form H.5-2; optionally administering either simultaneously or sequentially at least one other anti-cancer agent, and optionally administering either simultaneously or sequentially at least one other anti-cancer
25 treatment. Preferably, the proliferative disease is prostate cancer, breast cancer, endometrial cancer, or uterine cancer; and more preferably, prostate cancer.

[00115] In another embodiment, the method for treating at least one proliferative disease involves providing Compound (I) in a substantially pure form.

[00116] The phrase “anti-cancer treatment” includes but is not limited to, for
30 example, radiation therapy and surgery, e.g. castration.

[00117] In another embodiment, a pharmaceutical composition comprises at least one crystalline form of Compound (I) comprising Form H.5-2 and/or Form N-4;

optionally at least one component selected from excipients and carriers; and optionally at least one other anti-cancer agent. Preferably, the pharmaceutical composition of this embodiment comprises Form H.5-2 .

[00118] The phrase “other anti-cancer agent” includes any known agent useful for treating cancer, preferably prostate cancer. In treating cancer, a combination of chemotherapeutic agents and/or other treatments (e.g., radiation therapy) is often advantageous. The other anti-cancer agent may have the same or different mechanism of action than the primary therapeutic agent. It may be especially useful to employ cytotoxic drug combinations wherein the two or more drugs being administered act in different manners or in different phased of the cell cycle, and/or where the two or more drugs have overlapping toxicities or side effects, and/or where the drugs being combined each has a demonstrated efficacy in treating the particular disease state manifested by the patient.

[00119] Accordingly, Form H.5-2 and/or Form N-4 of Compound (I) may be administered in combination with other anti-cancer agents and treatments useful in the treatment of cancer or other proliferative diseases. The invention herein further comprises use of Form H.5-2 and/or Form N-4 of Compound I in preparing medicaments for the treatment of cancer, and/or it comprises the packaging of the Form H.5-2 and/or Form N-4 of Compounds (I) herein together with instructions that the Compound (I) be used in combination with other anti-cancer agents and treatments for the treatment of cancer. The present invention further comprises combinations of Form H.5-2 and/or Form N-4 of Compound (I) and one or more additional agents in kit form, e.g., where they are packaged together or placed in separate packages to be sold together as a kit, or where they are packaged to be formulated together.

[00120] The other anti-cancer agents may be selected from any one or more of the following: alkylating agents (including nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimine derivatives, and triazenes); anti-angiogenics (including matrix metalloproteinase inhibitors); antimetabolites (including adenosine deaminase inhibitors, folic acid antagonists, purine analogues, and pyrimidine analogues); antibiotics or antibodies (including monoclonal antibodies, CTLA-4 antibodies, anthracyclines); aromatase inhibitors; cell-cycle response modifiers; enzymes;

farnesyl-protein transferase inhibitors; hormonal and antihormonal agents and steroids (including synthetic analogs, glucocorticoids, estrogens/anti-estrogens [e.g., SERMs], androgens/anti-androgens, progestins, progesterone receptor agonists, and luteinizing hormone-releasing [LHRH] agonists and antagonists); insulin-like growth factor

5 (IGF)/insulin-like growth factor receptor (IGFR) system modulators (including IGFR1 inhibitors); integrin-signaling inhibitors; kinase inhibitors (including multi-kinase inhibitors and/or inhibitors of Src kinase or Src/abl, cyclin dependent kinase [CDK] inhibitors, panHer, Her-1 and Her-2 antibodies, VEGF inhibitors, including anti-VEGF antibodies, EGFR inhibitors, mitogen-activated protein [MAP] inhibitors,

10 MEK inhibitors, Aurora kinase inhibitors, PDGF inhibitors, and other tyrosine kinase inhibitors or serine /threonine kinase inhibitors; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, and the naturally-occurring epothilones and their synthetic and semi-synthetic analogs; microtubule-binding, destabilizing agents (including vinca

15 alkaloids); topoisomerase inhibitors; prenyl-protein transferase inhibitors; platinum coordination complexes; signal transduction inhibitors; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors, and immune modulators.

[00121] Additionally, Compound (I) can be formulated or co-administered with

20 other therapeutic agents that are selected for their particular usefulness in addressing side effects associated with the aforementioned conditions. For example, Compound (I) may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H₁ and H₂ antihistaminics.

[00122] The above other therapeutic agents, when employed in combination with

25 Compound (I), can be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

[00123] In one embodiment, Form H.5-2 and/or Form N-4 of Compound (I) is used to treat cancer including, but not limited to, for example, carcinoma, including, for

30 example, that of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of

lymphoid lineage, such as, for example, leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell lymphoma, Hodgkins lymphoma, non-Hodgkins lymphoma, hairy cell lymphoma, and Burkett's lymphoma; hematopoietic tumors of myeloid lineage, such as, for example, acute and chronic
5 myelogenous leukemia, myelodysplastic syndrome, and promyelocytic leukemia; tumors of mesenchymal origin, including, for example, fibrosarcoma and rhabdomyosarcoma; tumors of the central and peripheral nervous system, including, for example, astrocytoma, neuroblastoma, glioma, and schwannomas; and other tumors, such as, for example, melanoma, seminoma, teratocarcinoma, osteosarcoma,
10 xeroderma pigmentosum, keratoacanthoma, thyroid follicular cancer, and Kaposi's sarcoma.

[00124] In another embodiment, Form H.5-2 and/or Form N-4 of Compound (I) is used to treat prostate cancer, breast cancer, uterine cancer, and/or endometrial cancer.

[00125] In another embodiment, Form H.5-2 and/or Form N-4 of Compound (I) is
15 used to treat prostate cancer.

[00126] In yet another embodiment, Form H.5-2 and/or Form N-4 of Compound (I) is used to treat adenomas and neoplasies of the prostate.

[00127] Form H.5-2 and/or Form N-4 of Compound (I) may be used, for example, in combination with known therapies for treating advanced metastatic prostate cancer
20 including, but not limited to, for example, "complete androgen ablation therapy" wherein tumor growth is inhibited by controlling the supply of androgen to the prostate tissues via chemical castration followed by the administration of at least one AR antagonist. Compound (I) can be employed as an AR antagonist in complete ablation therapy, alone or in combination with other AR antagonists such as
25 Flutamide, bicalutamide, Nilutamide, or Cyproterone acetate.

[00128] Form H.5-2 and/or Form N-4 of Compound (I) may further be employed adjuvant to surgery.

[00129] Form H.5-2 and/or Form N-4 of Compound (I) may be used, for example, either in combination with antibody therapy including, but not limited to, for example,
30 antibody therapy against PSCA, or in concert with vaccine/immune modulating agents used to treat cancer.

[00130] Form H.5-2 and/or Form N-4 of Compound (I) can be administered by any means suitable for the condition to be treated, which can depend on the need for site-specific treatment or quantity of Compound (I) to be delivered.

[00131] Any pharmaceutical composition contemplated herein can, for example, be delivered orally via any acceptable and suitable oral preparations. Exemplary oral preparations, include, but are not limited to, for example, tablets; troches; lozenges; aqueous or oily suspensions; dispersible powders or granules; emulsions; hard or soft capsules; syrups; and elixirs. Pharmaceutical compositions intended for oral administration can be prepared according to methods known in the art and can contain at least one agent selected from sweetening agents, flavoring agents, coloring agents, demulcents, antioxidants, and preserving agents.

[00132] Exemplary excipients include, but are not limited to, for example, inert diluents, such as, for example, calcium carbonate, sodium carbonate, lactose, calcium phosphate, and sodium phosphate; granulating and disintegrating agents, such as, for example, microcrystalline cellulose, sodium crosscarmellose, corn starch, and alginic acid; binding agents, such as, for example, starch, gelatin, polyvinyl-pyrrolidone, and acacia; and lubricating agents, such as, for example, magnesium stearate, stearic acid, and talc.

[00133] An aqueous suspension can be prepared, for example, by admixing at least one of Form H.5-2 and Form N-4 of Compound (I) with at least one excipient suitable for the manufacture of an aqueous suspension. Exemplary excipients suitable for the manufacture of an aqueous suspension, include, but are not limited to, for example, suspending agents, such as, for example, sodium carboxymethylcellulose or methylcellulose.

[00134] Oily suspensions can, for example, be prepared by suspending at least one of Form H.5-2 and Form N-4 of Compound (I) in either a vegetable oil, such as, for example, arachis oil; olive oil; sesame oil; and coconut oil; or in mineral oil, such as, for example, liquid paraffin.

[00135] Any pharmaceutical composition contemplated herein can, for example, also be delivered intravenously, subcutaneously, and/or intramuscularly via any pharmaceutically acceptable and suitable injectable form. Exemplary injectable forms include, but are not limited to, for example, sterile aqueous solutions comprising

acceptable vehicles and solvents, such as, for example, water, Ringer's solution, and isotonic sodium chloride solution; sterile oil-in-water microemulsions; and aqueous or oleaginous suspensions.

5 **[00136]** A sterile injectable oil-in-water microemulsion can, for example, be prepared by 1) dissolving at least one crystalline form of Compound (I) in an oily phase, such as, for example, a mixture of soybean oil and lecithin; 2) combining the Compound (I) containing oil phase with a water and glycerol mixture; and 3) processing the combination to form a microemulsion.

10 **[00137]** Any pharmaceutical composition contemplated herein can, for example, further be administered via any acceptable and suitable rectal preparation, including, but not limited to, for example, a suppository. A suppository can be prepared by mixing at least one crystalline form of Compound (I) with at least one suitable non-irritating excipient that is liquid at rectal temperatures but solid at a temperature below rectal temperature.

15 **[00138]** Any pharmaceutical composition contemplated herein can, for example, be administered via any acceptable and suitable topical preparations including, but not limited to, for example, creams; ointments; jellies; solutions; suspensions, transdermal patches; and intranasal inhalers. For purposes of this application, topical preparations include mouth washes and gargles.

20 **[00139]** Exemplary compositions for nasal aerosol or inhalation administration include solutions that may contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance absorption and/or bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

25 **[00140]** An "effective amount" of Compound (I) may be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for a mammal of from about 0.05 to about 300 mg/kg/day, preferably less than about 200 mg/kg/day, in a single dose or in 2 to 4 divided doses. The specific dose level and frequency of dosage for any particular subject, however, may be varied and generally depends on a variety of factors, including, but not limited to, for example, the bioavailability of
30 Compound (I) in the administered form; metabolic stability and length of action of Compound (I); species, age, body weight, general health, sex, and diet of the subject;

mode and time of administration; rate of excretion; drug combination; and severity of the particular condition.

[00141] In one embodiment, the patient is an animal.

[00142] In another embodiment, the patient is a mammalian species including, but not limited to, for example, humans and domestic animals, such as, for example, dogs, cats, and horses.

METHODS OF PREPARATION AND CHARACTERIZATION

[00143] Crystalline forms may be prepared by a variety of methods, including, but not limited to, for example, crystallization or recrystallization from a suitable solvent mixture; sublimation; growth from a melt; solid state transformation from another phase; crystallization from a supercritical fluid; and jet spraying. Techniques for crystallization or recrystallization of crystalline forms from a solvent mixture include, but are not limited to, for example, evaporation of the solvent; decreasing the temperature of the solvent mixture; crystal seeding a supersaturated solvent mixture of the compound and/or a salt from thereof; freeze drying the solvent mixture; and adding antisolvents (countersolvents) to the solvent mixture. High throughput crystallization techniques may be employed to prepare crystalline forms including polymorphs.

[00144] Crystals of drugs, including polymorphs, methods of preparation, and characterization of drug crystals are discussed in *Solid-State Chemistry of Drugs*, S.R. Byrn, R.R. Pfeiffer, and J.G. Stowell, 2nd Edition, SSCI, West Lafayette, Indiana (1999).

[00145] In a crystallization technique in which solvent is employed, the solvent(s) are typically chosen based on one or more factors including, but not limited to, for example, solubility of the compound; crystallization technique utilized; and vapor pressure of the solvent. Combinations of solvents may be employed. For example, the compound may be solubilized in a first solvent to afford a solution to which antisolvent is then added to decrease the solubility of the compound in the solution and precipitate the formation of crystals. An antisolvent is a solvent in which a compound has low solubility.

[00146] In one method that can be used in preparing crystals, a compound is suspended and/or stirred in a suitable solvent to afford a slurry, which may be heated to promote dissolution. The term "slurry", as used herein, means a saturated solution of the compound, wherein such solution may contain an additional amount of
5 compound to afford a heterogeneous mixture of compound and solvent at a given temperature.

[00147] Seed crystals may be added to any crystallization mixture to promote crystallization. Seeding may be employed to control growth of a particular polymorph and/or to control the particle size distribution of the crystalline product.
10 Accordingly, calculation of the amount of seeds needed depends on the size of the seed available and the desired size of an average product particle as described, for example, in "Programmed Cooling of Batch Crystallizers," J.W. Mullin and J. Nyvlt, *Chemical Engineering Science*, 1971,26, 369-377. In general, seeds of small size are needed to effectively control the growth of crystals in the batch. Seeds of small size
15 may be generated by sieving, milling, or micronizing large crystals, or by micro-crystallizing a solution. In the milling or micronizing of crystals, care should be taken to avoid changing crystallinity from the desired crystalline form (i.e., changing to an amorphous or other polymorphic form).

[00148] A cooled crystallization mixture may be filtered under vacuum and the
20 isolated solid product washed with a suitable solvent, such as, for example, cold recrystallization solvent. After being washed, the product may be dried under a nitrogen purge to afford the desired crystalline form. The product may be analyzed by a suitable spectroscopic or analytical technique including, but not limited to, for example, solid state nuclear magnetic resonance; differential scanning calorimetry
25 (DSC); and powder x-ray diffraction (PXRD) to assure the preferred crystalline form of the compound has been formed. The resulting crystalline form may be produced in an amount greater than about 70 wt. % isolated yield, based on the weight of the compound originally employed in the crystallization procedure, and preferably greater than about 90 wt. % isolated yield. Optionally, the product may be delumped by
30 being comilled or passed through a mesh screen.

[00149] Crystalline forms of Compound (I) including, but not limited to, for example, the Forms described herein, may be prepared directly from the reaction

medium produced via the final process step employed in preparing Compound (I). For example, crystalline form(s) of Compound (I) could be produced by employing a solvent or a mixture of solvents in the final process step employed in preparing Compound (I). Alternatively, crystalline forms of Compound (I) may be obtained by
5 distillation or solvent addition techniques. Suitable solvents for this purpose include, but are not limited to, for example, the aforementioned nonpolar and polar solvents, wherein polar solvents include, but are not limited to, for example, protic polar solvents, such as, for example, alcohols and aprotic polar solvents, such as, for example, ketones.

10 **[00150]** The presence of more than one crystalline form and/or polymorph in a sample may be determined by techniques, including, but not limited to, for example, PXRD and solid state nuclear magnetic resonance spectroscopy. For example, the presence of extra peaks when an experimentally measured PXRD pattern is compared to a simulated PXRD pattern may indicate more than one crystalline form and/or
15 polymorph in the sample. The simulated PXRD may be calculated from single crystal x-ray data. See, for example, Smith, D.K., "*A FORTRAN Program for Calculating X-Ray Powder Diffraction Patterns*," Lawrence Radiation Laboratory, Livermore, California, UCRL-7196 (April 1963).

[00151] Crystalline forms of Compound (I), including, but not limited to, those
20 described herein according to the invention may be characterized using a variety of techniques well known to person(s) of ordinary skill in the art. For example, the single x-ray diffraction technique may, under standardized operating conditions and temperatures, be used to characterize and distinguish crystalline form(s) of Compound (I). Such characterization may, for example, be based on unit cell measurements of a
25 single crystal of the desired form at a fixed analytical temperature. The approximate unit cell dimensions in Angstroms (Å), as well as the crystalline cell volume, space group, molecules per cell, and crystal density may be measured, for example, at a sample temperature of 25°C. A detailed description of unit cells is provided in Stout & Jensen, *X-Ray Structure Determination: A Practical Guide*, Macmillan Co., New
30 York (1968), Chapter 3, which is hereby incorporated herein by reference.

[00152] Additionally, the unique spatial arrangement of atoms in a crystalline lattice may be characterized according to the observed fractional atomic coordinates of such atoms.

5 [00153] Another means of characterizing the crystalline structure of the subject form is by PXRD analysis, the actual diffraction profile of such form is compared to a simulated profile representing pure powder material. Preferably, the actual and simulated profiles are both run at the same analytical temperature, and the subsequent measurements characterized as a series of 2θ values (usually four or more).

10 [00154] Other means of characterizing a crystalline form that may be used include, but are not limited to, for example, solid state nuclear magnetic resonance (NMR); DSC; thermography; gross examination of the crystalline or amorphous morphology; and combinations thereof.

[00155] At least one crystalline form of Compound (I) described herein was analyzed using at least one of the testing methods described hereinbelow.

15

Single Crystal X-Ray Measurements

[00156] Data was collected with a Bruker-Nonius CAD4 serial diffractometer (Bruker AXS, Inc., Madison, WI). Unit cell parameters were obtained through least-squares analysis of the experimental diffractometer settings of 25 high-angle
20 reflections. Intensities were measured using Cu K α radiation ($\lambda = 1.5418 \text{ \AA}$) at a constant temperature with the θ - 2θ variable scan technique and were corrected only for Lorentz-polarization factors. Background counts were collected at the extremes of the scan for half of the time of the scan. Alternately, single crystal data was collected with a Bruker-Nonius Kappa CCD 2000 system using Cu K α radiation ($\lambda = 1.5418$
25 $\text{\AA}$). Indexing and processing of the measured intensity data were carried out with the HKL2000 software package (Otwinowski, Z. and Minor, W., in *Macromolecular Crystallography*, eds. Carter, W.C. Jr. and Sweet, R.M., Academic Press, NY, 1997) in the Collect program suite (Collect: Data collection software, R. Hooft, Nonius B.V., 1998). When indicated, crystals were cooled in the cold stream of an Oxford
30 Cryosystems Cryostream Cooler (Oxford Cryosystems, Inc., Devens, MA) during data collection.

[00157] The structures were solved by direct methods and refined on the basis of observed reflections using either the SDP software package (SDP Structure Determination Package, Enraf-Nonius, Bohemia, NY) with minor local modifications or the crystallographic package maXus (maXus Solution and Refinement Software Suite: S. Mackay, C.J. Gilmore, C. Edwards, M. Tremayne, N. Stewart, and K. Shankland).

[00158] The derived atomic parameters (coordinates and temperature factors) were refined through full matrix least-squares. The function minimized in the refinements was $\sum_w (|F_o| - |F_c|)^2$. R is defined as $\sum ||F_o| - |F_c|| / \sum |F_o|$ while $R_w = [\sum_w (|F_o| - |F_c|)^2 / \sum_w |F_o|^2]^{1/2}$ where w is an appropriate weighting function based on errors in the observed intensities. Difference maps were examined at all stages of refinement. Hydrogen atoms were introduced in idealized positions with isotropic temperature factors, but no hydrogen parameters were varied.

[00159] Simulated PXRD patterns were generated from the single crystal atomic parameters at the data collection temperature, unless noted otherwise. (Yin, S.; Scaringe, R. P.; DiMarco, J.; Galella, M. and Gougoutas, J. Z., *American Pharmaceutical Review*, 2003, 6, 2, 80).

Powder X-Ray Diffraction (PXRD) Measurements – Method A

[00160] About 200 mg of the sample was packed by the backloading method into a Philips PXRD-sample holder. The sample holder was transferred to a Philips MPD unit (45 KV, 40 mA, Cu K α), and the data was subsequently collected at room temperature in the 2 to 32 2-theta range (continuous scanning mode, scanning rate 0.03 degrees/sec., auto divergence and anti scatter slits, receiving slit: 0.2 mm, sample spinner : ON)

Powder X-Ray Diffraction Measurements—Method B

[00161] PXRD data was obtained using a Bruker C2 GADDS. The radiation was Cu K α (40 KV, 50mA). The sample-detector distance was 15 cm. Powder samples were placed in sealed glass capillaries of 1mm or less in diameter, and the capillary was rotated during data collection. Data were collected for $3 \leq 2\theta \leq 35^\circ$ with a sample exposure time of at least about 2000 seconds. The resulting two-dimensional

diffraction arcs were integrated to create a traditional 1-dimensional PXRD pattern with a step size of 0.02 degrees 2θ in the range of 3 to 35 degrees 2θ .

Differential scanning calorimetry (DSC) (sealed pan)

- 5 **[00162]** DSC experiments were performed in a TA Instruments™ model Q1000 or 2920. The sample (about 2-6 mg) was weighed in a pinpricked hermetically sealed aluminum pan and, after being accurately recorded to a hundredth of a milligram, was transferred to the DSC. The instrument was purged with nitrogen gas at 50 mL/min. Data were collected between room temperature and about 350°C at a heating rate of about 10°C/min. The plot was made with the endothermic peaks pointing down.

Thermal gravimetric analysis (TGA) (sealed pan)

- 15 **[00163]** TGA experiments were performed in a TA Instruments™ model Q500 or 2950. The sample (about 10-30 mg) was placed in a pinpricked hermetically sealed aluminum pan on a platinum pan, both previously tared. The weight of the sample was measured accurately and recorded to a thousand of a milligram by the instrument. The furnace was purged with nitrogen gas at 100 mL/min. Data was collected between room temperature and about 350°C at a heating rate of about 10°C/min.

20 Particle Size Determination

- 25 **[00164]** Particle size measurements were performed using a Laser Light Scattering Instrument (LLS) Malvern Mastersizer 2000, Malvern Instruments, Worcestershire, UK. Samples were prepared by mixing about 40-60 mg of powder sample into about 3-5 ml of Tween80/water dispersion solution in a scintillation vial or test tube. The Tween 80/water solution was prepared by adding about 0.3 g of Tween 80 surfactant into 1 L of water. A portion of the sample dispersion was then introduced into Malvern Mastersizer measuring cell that was filled with water. The portion is limited by the instrument obscuration limits that are specified in Table 5. The instrument accessory and parameters are summarized in Table 5.

30

**Table 5: Method Conditions for Malvern Mastersizer 2000 with
Hydro S Sample Dispersion Unit Setup**

Accessory name	Hydro 2000S (A)
Analysis model	General purpose
Background time	10
Bubble removal	No
Calculation sensitivity	Normal
Dispersant name	Water
Dispersant refractive index	1.33
Irregular shape mode	On
Measurement time	10
Measurement repeat mode	Single
Obscuration range - lower	5
Obscuration range - upper	13
Obscuration filtering	On
Particle absorption index	0.1
Particle absorption index - blue	0.1
Particle refractive index	1.52
Particle refractive index - blue	1.52
Pump speed	2000
Result range	0.02 - 2000 micron
Ultrasonic level	0
Ultrasonic mode	Continuous from start
Ultrasonic stabilizing duration	10

5

EXAMPLES

Example 1: Hemihydrate Form H.5-2

[00165] Process A: A slurry was prepared by adding 0.3 grams of Compound (I) to 0.4 mL acetone at 50°C and then adding 6 mL of water. The slurry was maintained at 10 50°C for 1 hour and then cooled to 20°C over a period of 2 hours. The slurry solids

were filtered, washed with 1 mL of water, and allowed to dry under vacuum at 50°C overnight.

- [00166]** Process B: To a 250 mL 3-neck flask, which was equipped with a mechanical agitator and a sonication probe, was added 80 mL of water. A circulation bath was used to control the temperature of the water in the flask at 20°C. The agitation speed was 250 rpm and sonication power was 14 Watt. A solution was prepared by dissolving 5.06 grams of Compound (I) in 40 mL acetic acid at room temperature. The solution was added to the flask over 15 minutes. A slurry was formed rapidly during the addition. After the complete addition of the solution, sonication was shut off. The slurry was maintained at a temperature of 20°C for an additional 2 hours. Next, the slurry was filtered, washed with 50 mL of water, and the wet cake allowed to dry at 60° C under vacuum overnight. The weight of the dry cake was 4.76 grams (uncorrected yield: 94 M %).

- [00167]** PXRD: Method A

Example 2: Neat Form N-4

- [00168]** A solution was prepared by dissolving 0.2 grams of Compound (I) in 1.5 mL of boiling ethyl acetate. Hexanes were added dropwise until the solution became cloudy. The flask was slowly cooled to room temperature. White crystals precipitated from the solution. After being maintained at room temperature for one hour, the crystals were filtered and washed with cold diethyl ether.

PXRD: Method A

Example 3: Form SC-1

- [00169]** A solution was prepared by dissolving 25 gram of Compound (I) in 125 ml of glacial acetic acid. The slurry was agitated until the compound dissolved. Next, 625 ml of water was added over a period of 30 minutes from which crystals were obtained. The crystals were filtered and dried overnight in a vacuum oven at 50°C.

PXRD: Method B

Table 6

[00170] Characteristic diffraction peak positions (degrees $2\theta \pm 0.2$) at room temperature, based on a high quality pattern collected with a diffractometer ($\text{CuK}\alpha$) with a spinning capillary with 2θ calibrated with a NIST other suitable standard.

H.5-2	N-4	SC-1
7.6	8.5	6.9
8.6	10.9	7.4
12.8	13.6	10.6
14.0	17.6	11.8
15.3	18.5	14.9
16.8	20.5	15.2
17.2	21.9	16.3
18.2	-	17.7
19.5	-	23.2
20.1	-	24.2

5

Example 4: Crystallization Process to Prepare Form H.5-2 from Form SC-1

- [00171]** Compound I in crystalline Form H.5-2 was prepared from Form SC-1 by a two-stage batch crystallization process. The two-stage batch crystallization process was conducted in a 1-liter glass vessel equipped with an overhead stirrer and a
- 10 recirculation loop. The recirculation loop included an integrated Ultra-TURRAX[®] homogenizer (IKA[®] model UTL-25, Wilmington, NC), an inline Raman spectrometer (Kaiser Optical Systems, Inc. model RXN1, Baltimore, MD), and an inline Lasentec[™] particle size analyzer (Mettler-Toledo Autochem model Lasentec FBRM D600L, Redmond, WA).
- 15 **[00172]** An acetic acid solution of Compound I was prepared in the vessel by dissolving 25 g of Compound I in 75 mL glacial acetic acid (3 mL/g), heating the solution to 30°C until the solution was homogeneous, and then allowing the acetic acid solution to cool to 20°C. Next, water (319 mL) was metered to the acetic acid solution over 15 minutes, resulting in the formation of crystalline material (Form SC-
- 20 1). The contents of the vessel was passed through the recirculation loop with the TURRAX[®] homogenizer operating at 13,500 rpm and 70 mL/min for a period of one

hour. Next, the contents of the vessel was heated to a temperature of 50°C over a period of an hour and then maintained at 50°C for a period of approximately two hours. Transformation of the crystalline material to the hemihydrate crystalline form was monitored by the inline Raman spectrometer (a peak change from 1440 cm⁻¹ to 1430 cm⁻¹) and offline pXRD. Next, the contents of the vessel was allowed to cool to 20°C over 30 minutes. The resulting slurry was filtered using a 15 cm Buchner funnel with filter paper and the wet cake was washed with 150 mL of water. The filtration of the mother liquor and cake washes were each done within one minute, yielding an average flux rate of approximately 3000 L/m²*hr. The wet cake was dried at 50°C under reduced pressure (5-6.2 kPa) until the water content of the crystalline material was approximately 2.5 wt%, as measured by a Karl Fischer titrator, to afford 22 g (90 M%) of Form H.5-2 of Compound I.

Example 5: Direct Crystallization Process to Prepare Form H.5-2

[00173] Compound I in crystalline Form H.5-2 was prepared by a direct crystallization process. A 1-liter glass vessel was equipped with a sonicator (VCX 750, Sonics and Materials, Inc., Newtown, CT), Lasentec™ FBRM D600L inline particle size analyzer (Mettler-Toledo Autochem model, Redmond, WA) and an overhead stirrer. Two feed vessels were set up to pump solutions to the crystallizer. A 20-liter glass receiving vessel was equipped with overhead agitation and a vacuum source. This vessel was connected to the crystallizer with tubing. The tubing was attached to the top of the crystallizer and set at a level of 600 ml.

[00174] Solution 1 was prepared in a 5-liter glass feed vessel by dissolving 700 g of Compound I into approximately 2.8 L of acetic acid at room temperature. In the second feed vessel, 16 L of water was added. A seed slurry was prepared in the 1-liter crystallizer by mixing 1 g of Compound I (as Form H.5-2) in approximately 600 mL of a water and acetic acid (4:1 ratio) mixture and added to the crystallizer. Vigorous agitation was initiated and the sonication power was set to 40 watts.

[00175] In a continuous manner, water (~100 mL/min) and the Solution 1 (~25 mL/min) were slowly metered to the crystallizer over 150 minutes, resulting in the formation of crystalline material (Form SC-1). As the feed solution entered the crystallizer, the resulting slurry was continuously withdrawn to the 20-liter receiving

vessel by vacuum. Next, the contents of the receiving vessel were held at a temperature of 20–25°C.

[00176] The resulting slurry was filtered using a 15-cm diameter Buchner funnel with filter paper and the wet cake was washed twice with 1500 mL of water. The filtration of the mother liquor and cake washes required approximately 30 minutes, yielding an average flux rate of approximately 2000 L/m²*hr. The wet cake was dried at 50°C under reduced pressure (5-6.2 kPa) until the water content was approximately 2.5 wt % as measured by a Karl Fischer titration to afford 645 g (99 M%) of Form H.5-2 of Compound I.

10

Table 7
Comparison of H.5-2 Crystals Prepared by Direct Crystallization and Recrystallization from Form SC-1

	Recrystallization from Form SC-1 (Example 4)	Direct Crystallization (Example 5)
Crystal Habit	tabular	needle
Filtration Time	10 minutes	7.5 hours
Drying Time	20 hours	>50 hours
Agglomeration	no observed agglomeration	some agglomeration observed

Comparison batches conducted at approximately one-kilogram scale.

15

Example 6: Evaluations of Form H.5-2 and Form N-4

a) Solid-State Chemical Stability

[00177] The solid-state stabilities of Form H.5-2 and Form N-4 were evaluated at test conditions of 5°C, 25°C/60% relative humidity (RH), 40°C/75% RH, and 50°C for four weeks. No significant chemical degradation was observed for these forms at the test conditions.

20

b) Solid-State Physical Stability

[00178] A sample of Form H.5-2 was stored at 25°C/11% RH and a sample of Form N-4 was stored at 25°C/85% RH for several weeks. No changes in either form was observed.

25

[00179] Samples of Form N-4 that contained minor amounts of Form H.5-2 were stored at 40°C/65% RH and 60°/75%RH. The stored samples were found to transform to Form H.5-2.

c) Aqueous Solubilities

5 [00180] The aqueous solubility of Form H.5-2 was determined to be 32.4 µg/ml at room temperature.

[00181] The equilibrium solubility of Form N-4 in water could not be measured due to formation of Form H.5-2. Figure 10 shows the concentration versus time profile of Form N-4 in water. The apparent solubility of Form N-4 at room
10 temperature was estimated to be approximately 58 µg/ml. Form N-4 converted to Form H.5-2 within 3 hours.

d) In Vivo Exposure

[00182] Pharmacokinetic studies in dogs (n=3) were conducted at a dose of 2 mg/kg for Form H.5-2 and Form N-4. The forms were administered as dry blend
15 capsules (Form H.5-2 or Form N-4/lactose monohydrate/microcrystalline cellulose PH 101). The particles sizes (D₉₀) of the two forms were 22 µm and 25 µm for Form H.5-2 and Form H-4, respectively.

	C _{max} (µM)	AUC (µM*h)
Form H.5-2	14 ± 2	279 ± 65
Form N-4	34 ± 2	558 ± 34

Example 7: Antitumor Activity of Compound (I)

20 [00183] The antitumor activity of Compound (I) was evaluated in the CWR22 Human Prostate Xenograft Assay according to the general procedure described in U.S. Patent 7,141,578, wherein said disclosure is hereby incorporated herein by reference. Compound (I) was administered qd orally for 37 consecutive days to BALB/c athymic (nu/nu) mice. Compound (I) was administered as a dosing solution in PEG
25 400:Tween-80 (80:20) and stored in sealed glass dark vials at ambient temperature. The tumor fragments were implanted subcutaneously into the mice and treatments were initiated when the subcutaneous tumors reached a median size between 100-200 mm³. Tumor size was measured twice weekly. A control group of mice were administered the control vehicle of PEG 400:Tween-80 (80:20).

Treatment	Dose (mg/kg)	% TGI [*]	T-C (1000 mm ³) ^{**}
Compound (I)	10	60	18
Compound (I)	30	81	22
Compound (I)	90	97	36
Control Vehicle	-	-	-

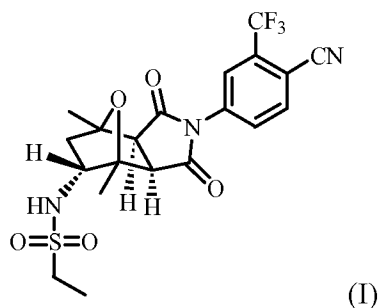
^{*} % TGI = tumor growth inhibition of treated groups over control group at the end of treatment.

^{**} T-C = [time in days for the median tumor size of treated group (T) to reach 1000 mm³] minus [the time in day for the median tumor size of the control group (C) to reach 1000 mm³].

CLAIMS

What is claimed is:

1. A crystalline form of Compound (I):



comprising hemihydrate Form H.5-2.

2. The crystalline form according to Claim 1 consisting essentially of said Form H.5-2.

3. The crystalline form according to Claim 1, wherein said crystalline form is substantially pure.

4. The crystalline form according to Claim 1, wherein at least about 90 wt.% of said crystalline form is comprised of Form H.5-2.

5. The crystalline form according to Claim 1, wherein said Form H.5-2 is characterized by a simulated powder x-ray diffraction pattern substantially as shown in Figure 1.

6. The crystalline form according to Claim 1, wherein said Form H.5-2 is characterized by an observed powder x-ray diffraction pattern substantially as shown in Figure 1.

7. The crystalline form according to Claim 1, wherein said Form H.5-2 is characterized by a powder x-ray diffraction pattern comprising four or more 2θ values (CuK α $\lambda=1.5418$ Å) selected from: 7.6 ± 0.2 , 8.6 ± 0.2 , 12.8 ± 0.2 , 14.0 ± 0.2 , 15.3 ± 0.2 ,

16.8±0.2, 17.2±0.2, 18.2±0.2, 19.5±0.2, and 20.1±0.2, wherein the powder x-ray diffraction pattern of said crystalline form is measured at a temperature of about 25°C.

8. The crystalline form according to Claim 1, wherein said Form H.5-2 is
5 characterized by a powder x-ray diffraction pattern comprising five or more 2θ values (CuKα λ=1.5418 Å) selected from: 7.6±0.2, 8.6±0.2, 12.8±0.2, 14.0±0.2, 15.3±0.2, 16.8±0.2, 17.2±0.2, 18.2±0.2, 19.5±0.2, and 20.1±0.2, wherein the powder x-ray diffraction pattern of said crystalline form is measured at a temperature of about 25°C.

10 9. The crystalline form according to Claim 1, wherein said Form H.5-2 is characterized by unit cell parameters substantially equal to the following:

cell dimensions: a = 24.48 Å

b = 7.23 Å

c = 13.22 Å

15 α = 90.0°

β = 108.7°

γ = 90.0°

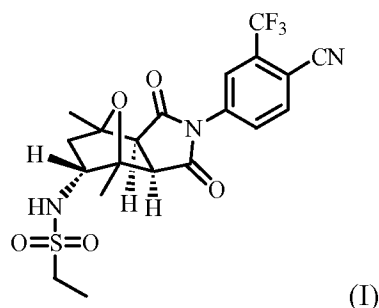
space group: C2

molecules of Compound (I)/asymmetric unit: 1,

20 wherein the unit cell parameters of said crystalline form are measured at a temperature of about 25°C.

10. The crystalline form according to Claim 1, wherein said Form H.5-2 is characterized by a thermogravimetric analysis thermogram having weight loss in the
25 range of from about 1.8 to about 1.9 weight % upon heating to a temperature of about 185°C.

11. A composition comprising particles of Compound (I):



wherein said particles comprise Form H.5-2 of Compound (I); and said particles have a particle size characterized by a D₉₀ value of less than about 150 microns.

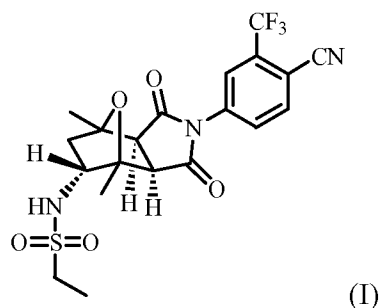
- 5 12. The composition according to claim 11 wherein a substantial number of said particles of Form H.5-2 have shapes characterized by axial dimension ratios of:
width:length of about 1:1 to about 1:3; and
thickness:width of about 1:1 to about 1:3.

- 10 13. The composition according to claim 12 wherein said particles consist essentially of said Form H.5-2.

14. The composition according to claim 11 further comprising a pharmaceutically-acceptable carrier and/or diluent.

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15. A process for preparing Form H.5-2 of Compound (I):



comprising:

- a) providing a neat form and/or a solvent-hydrate mixed form of Compound (I); and
20 b) transforming said neat form and/or said solvent hydrate mixed form to afford said Form H.5-2.

16. The process of claim 15 wherein said solvent-hydrate mixed form is Form SC-1.

17. The process of claim 16 wherein in step b), said Form SC-1 is
5 transformed by heating to afford said Form H.5-2.

18. The process of claim 16 wherein Form SC-1 is provided as a slurry comprising particles of said Form SC-1 in acetic acid and water.

19. The process of claim 18 wherein in step b), water is added to said slurry to afford particles of Form H.5-2.

20. The process of claim 19 wherein in step b), said slurry is subjected to high shear mixing during and/or after addition of said water.

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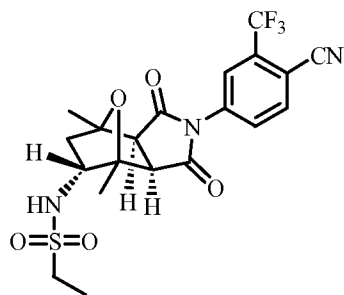
21. The process of claim 20 wherein said particles of Form H.5-2 have a particle size characterized by a D_{90} value of less than about 150 microns.

22. The process of claim 21, wherein a substantial number of said particles of
20 Form H.5-2 have shapes characterized by axial dimension ratios of:

width:length of about 1:1 to about 1:3; and

thickness:width of about 1:1 to about 1:3.

23. A composition comprising Form H.5-2 of Compound (I):

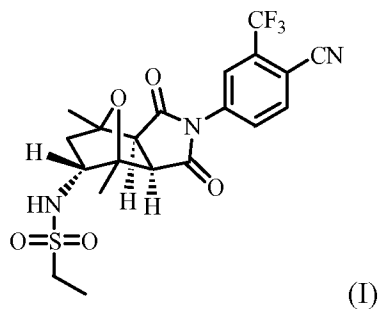


(I)

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prepared according to the process of Claim 15.

24. A process for preparing a hydrate crystalline form of Compound (I):



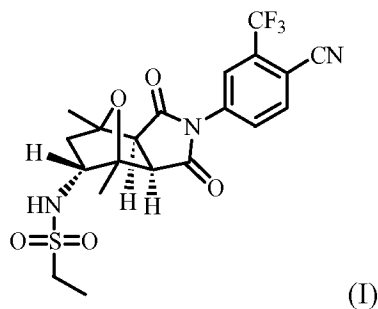
comprising:

- a) providing a slurry comprising a neat form and/or a solvent-hydrate mixed form of Compound (I) in solvent and/or water; and
- b) adding water to said slurry to afford said hydrate crystalline form, wherein said hydrate crystalline form is provided as particles having a particle size characterized by a D_{90} value of less than about 150 microns.

25. The process of claim 24 wherein in step b), said slurry is subjected to high shear mixing during and/or after addition of said water.

26. The process of claim 25 wherein a substantial number of said particles have shapes characterized by axial dimension ratios of:
width:length of about 1:1 to about 1:3; and
thickness:width of about 1:1 to about 1:3.

27. A crystalline form of Compound (I):



comprising Form N-4.

28. The crystalline form according to Claim 27 consisting essentially of said

Form N-4.

29. The crystalline form according to Claim 27, wherein said crystalline form is substantially pure.

5

30. The crystalline form according to Claim 27, wherein at least about 90 wt.% of said crystalline form is comprised of Form N-2.

31. The crystalline form according to Claim 27, wherein said Form N-4 is characterized by a powder x-ray diffraction pattern comprising four or more 2θ values (CuK α $\lambda=1.5418$ Å) selected from: 8.5 ± 0.2 , 10.9 ± 0.2 , 13.6 ± 0.2 , 17.6 ± 0.2 , 18.5 ± 0.2 , 20.5 ± 0.2 , and 21.9 ± 0.2 , wherein the powder x-ray diffraction pattern of said crystalline form is measured at a temperature of about 25°C.

32. The crystalline form according to Claim 27, wherein said Form N-4 is characterized by unit cell parameters substantially equal to the following:

cell dimensions:	$a = 8.32$ Å
	$b = 11.70$ Å
	$c = 22.53$ Å
	$\alpha = 90.0^\circ$
	$\beta = 90.0^\circ$
	$\gamma = 90.0^\circ$

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space group: $P2_12_12_1$

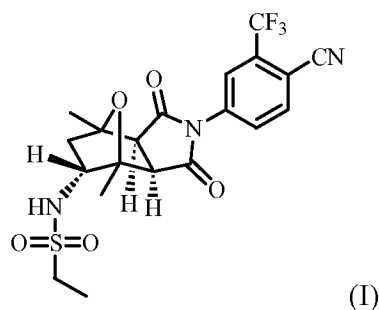
molecules of Compound (I)/asymmetric unit: 1,

wherein the unit cell parameters of said crystalline form are measured at a temperature of about 25°C.

33. The crystalline form according to Claim 27, wherein said Form N-4 is characterized by a melting point in the range of from about 182°C to about 189°C.

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34. A crystalline form of Compound (I):



comprising hydrate-hemiacetic acid Form SC-1.

35. The crystalline form according to Claim 34 consisting essentially of the
5 Form SC-1.

36. The crystalline form according to Claim 34, wherein said crystalline form
is substantially pure.

10 37. The crystalline form according to Claim 34, wherein at least about 90
wt.% of said crystalline form is comprised of Form SC-1.

38. The crystalline form according to Claim 34, wherein said Form SC-1 is
characterized by a simulated powder x-ray diffraction pattern substantially as shown
15 in Figure 3.

39. The crystalline form according to Claim 34, wherein said Form SC-1 is
characterized by an observed powder x-ray diffraction pattern substantially as shown
in Figure 3.

20 40. The crystalline form according to Claim 34, wherein said Form SC-1 is
characterized by a powder x-ray diffraction pattern comprising four or more 2θ values
(CuK α $\lambda=1.5418$ Å) selected from: 6.9 ± 0.2 , 7.4 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 14.9 ± 0.2 ,
 15.2 ± 0.2 , 16.3 ± 0.2 , 17.7 ± 0.2 , 23.2 ± 0.2 , and 24.2 ± 0.2 , wherein the PXRD pattern of
25 Form SC-1 is measured at a temperature of about 25°C.

41. The crystalline form according to Claim 34, wherein said Form SC-1 is

characterized by a powder x-ray diffraction pattern comprising five or more 2θ values (CuK α $\lambda=1.5418$ Å) selected from: 6.9 ± 0.2 , 7.4 ± 0.2 , 10.6 ± 0.2 , 11.8 ± 0.2 , 14.9 ± 0.2 , 15.2 ± 0.2 , 16.3 ± 0.2 , 17.7 ± 0.2 , 23.2 ± 0.2 , and 24.2 ± 0.2 , wherein the PXRD pattern of Form SC-1 is measured at a temperature of about 25°C.

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42. The crystalline form according to Claim 34, wherein said Form SC-1 is characterized by unit cell parameters substantially equal to the following:

cell dimensions: $a = 7.53$ Å
 $b = 12.21$ Å
 $c = 13.07$ Å
 $\alpha = 97.3^\circ$
 $\beta = 91.5^\circ$
 $\gamma = 93.5^\circ$

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space group: P1

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molecules of Compound (I)/asymmetric unit: 2

wherein the unit cell parameters of Form SC-1 are measured at a temperature of about -40°C.

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43. The crystalline form according to Claim 34, wherein said Form SC-1 is characterized by a thermogravimetric analysis thermogram having weight loss in the range of from about 8 to about 9 weight % upon heating to a temperature of about 150°C.

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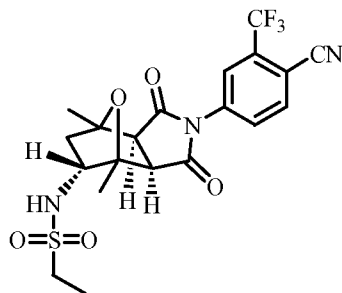
44. A pharmaceutical composition comprising at least one crystalline form of Compound (I) selected from Form H.5-2 and Form N-4; and at least one pharmaceutically acceptable carrier and/or diluent.

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45. The pharmaceutical composition according to Claim 44, wherein said crystalline form of Compound (I) comprises Form H.5-2.

46. The pharmaceutical composition according to Claim 45, wherein said crystalline form is in a substantially pure form.

47. A method for treating a proliferative disease, comprising administering a therapeutically effect amount of Compound (I)



(I)

5 to a patient in need thereof, wherein said Compound (I) is provided in a crystalline form comprising Form H.5-2 and/or Form N-4.

48. The method of Claim 47, wherein said proliferative disease is prostate cancer.

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49. The method of claim 48, wherein the at least one form is Form H.5-2.

50. The method of claim 49, wherein the crystalline form is in a substantially pure form.

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51. The method of claim 48, wherein the at least one form is Form N-4.

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FIG. 1

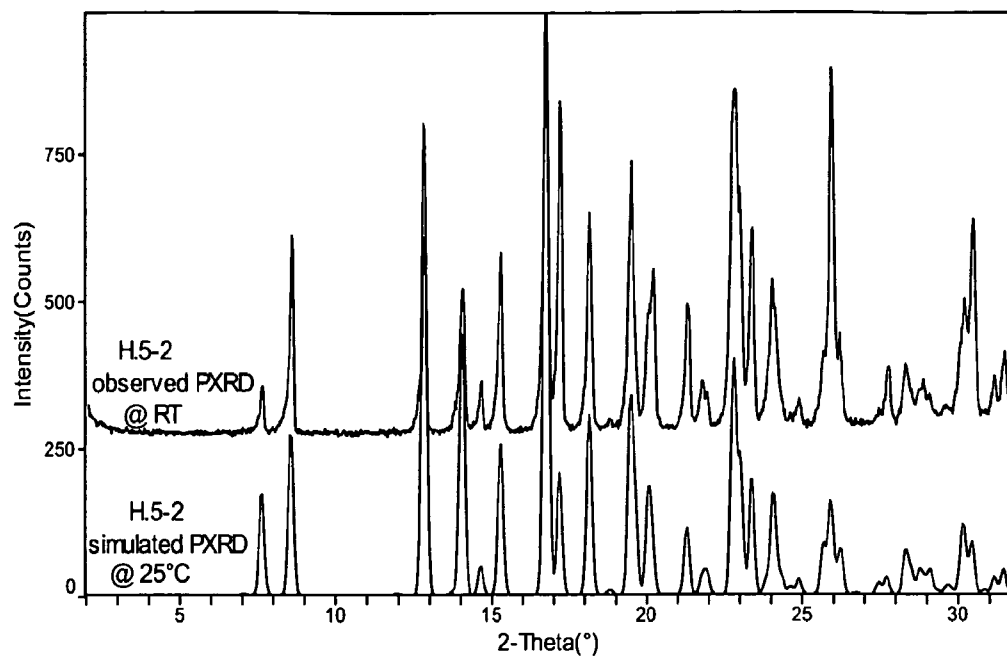
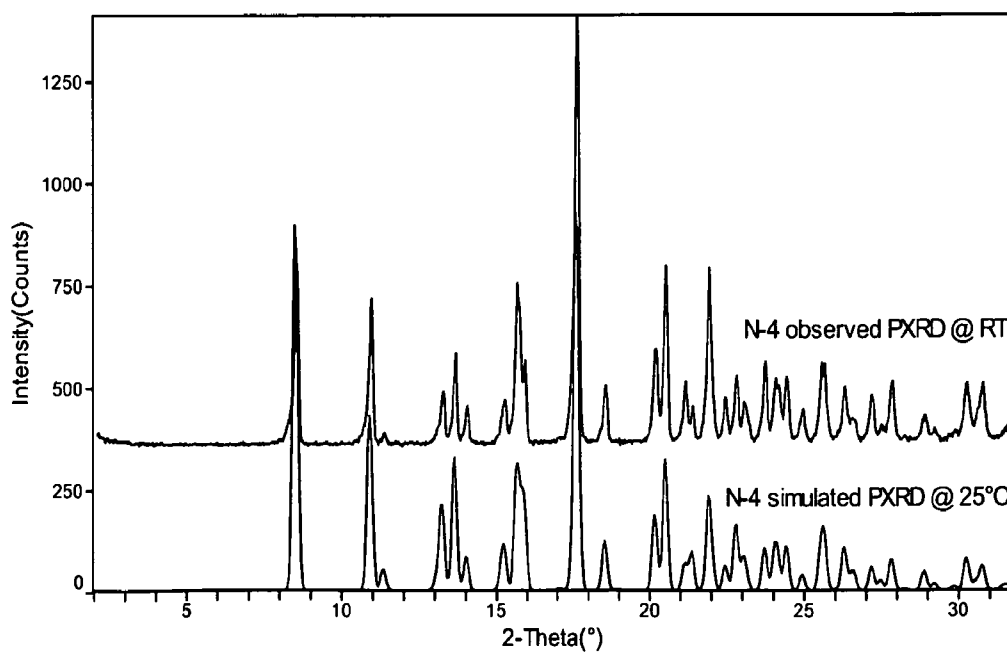


FIG. 2



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FIG. 3

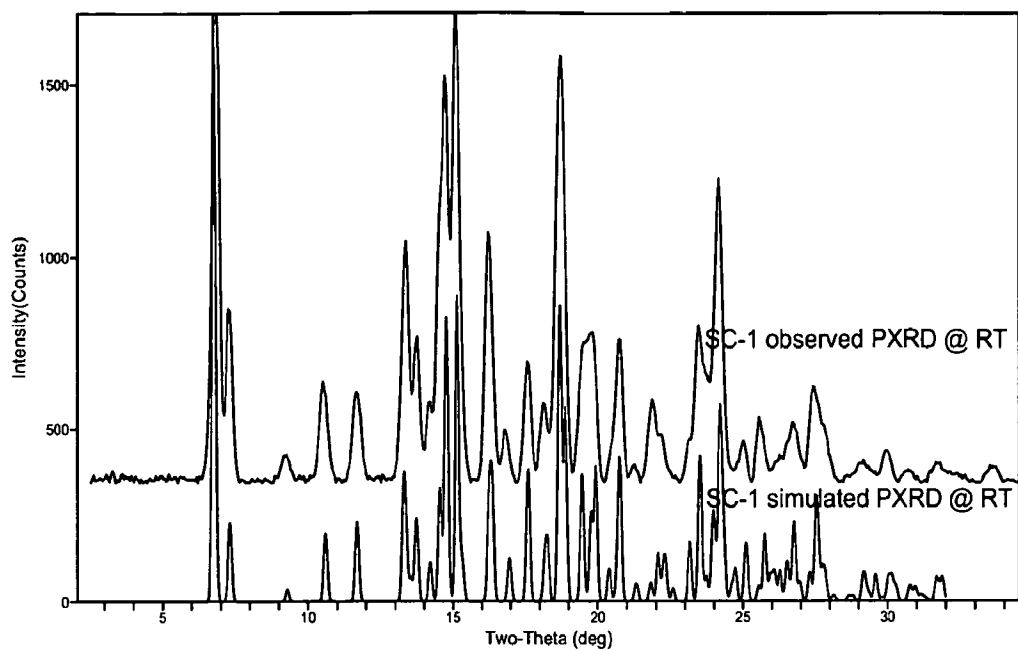
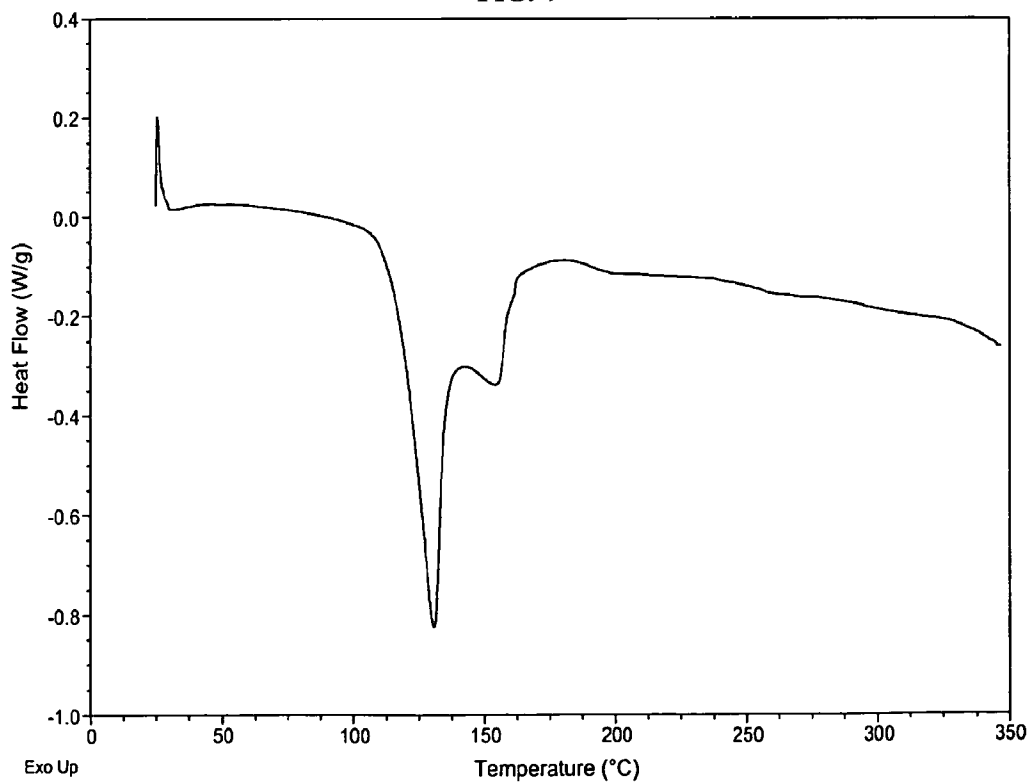


FIG. 4



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FIG. 5

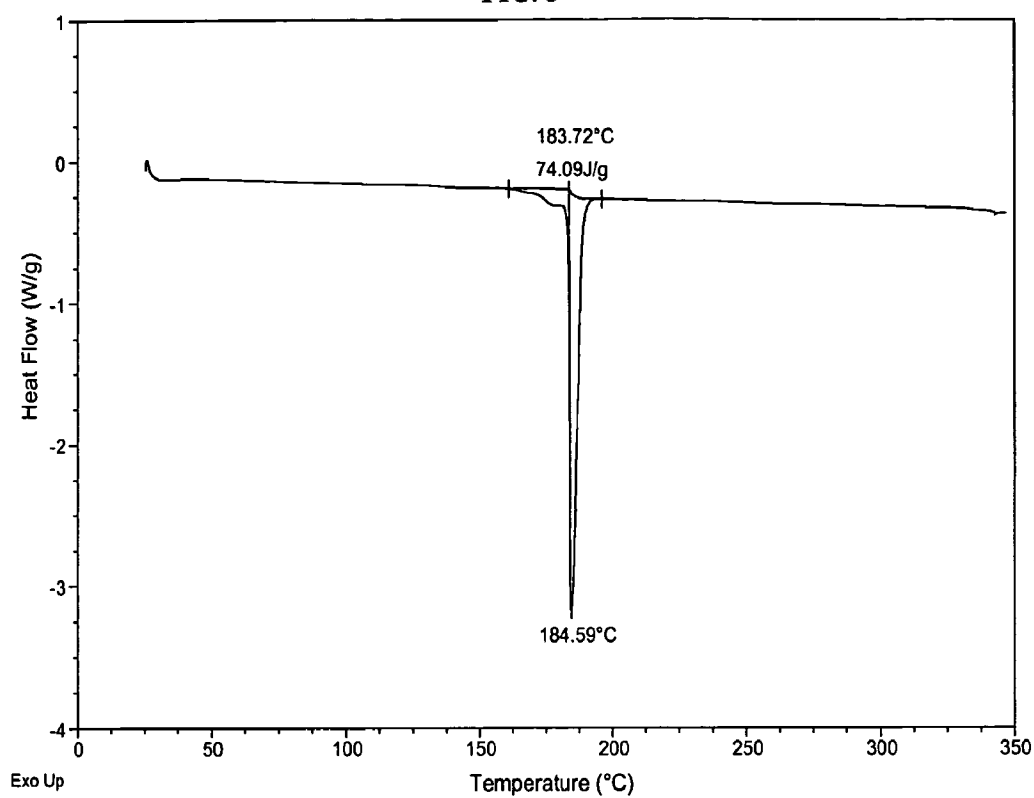
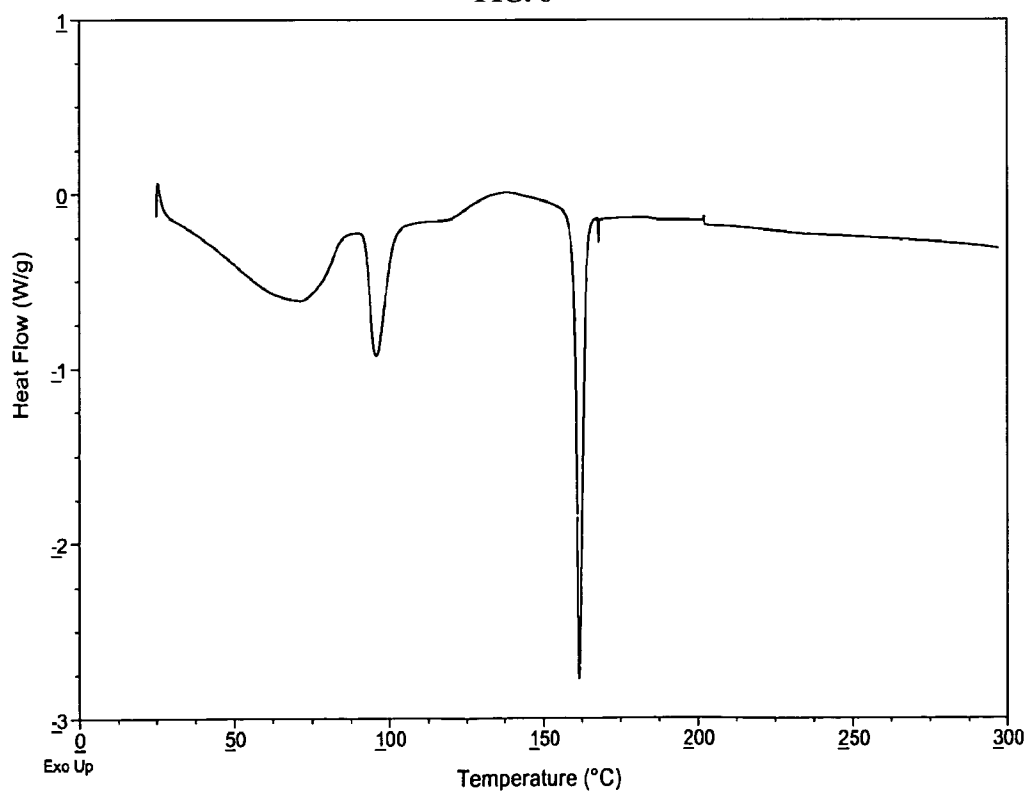


FIG. 6



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FIG. 7

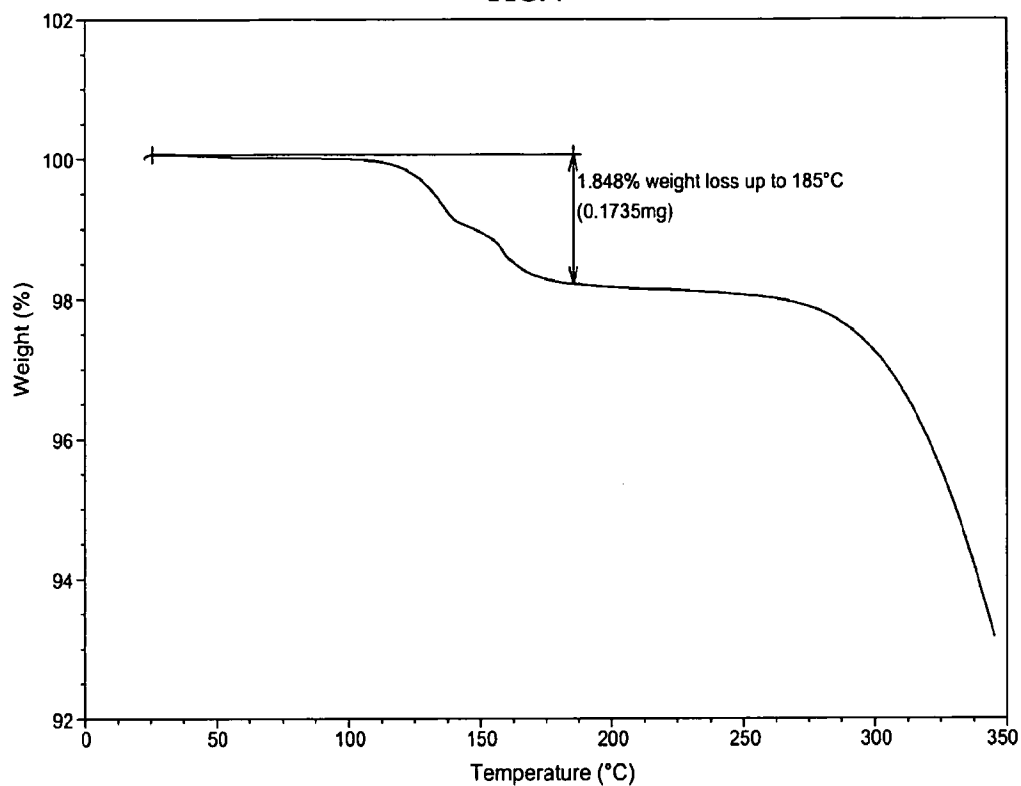
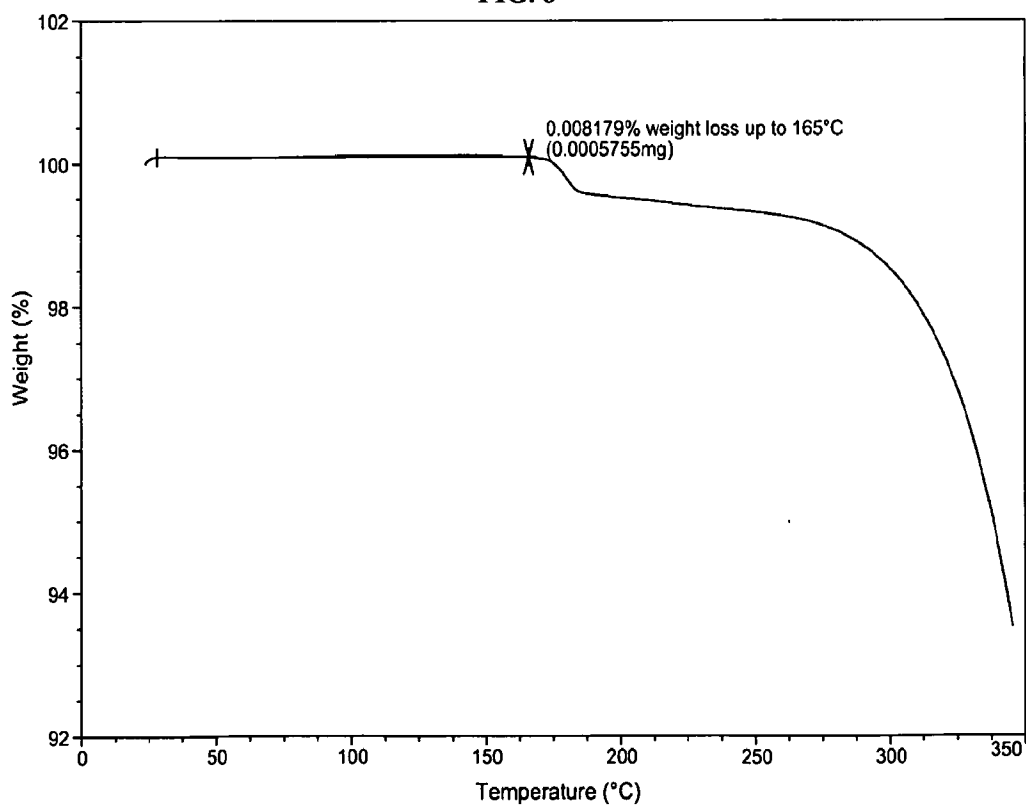


FIG. 8



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FIG. 9

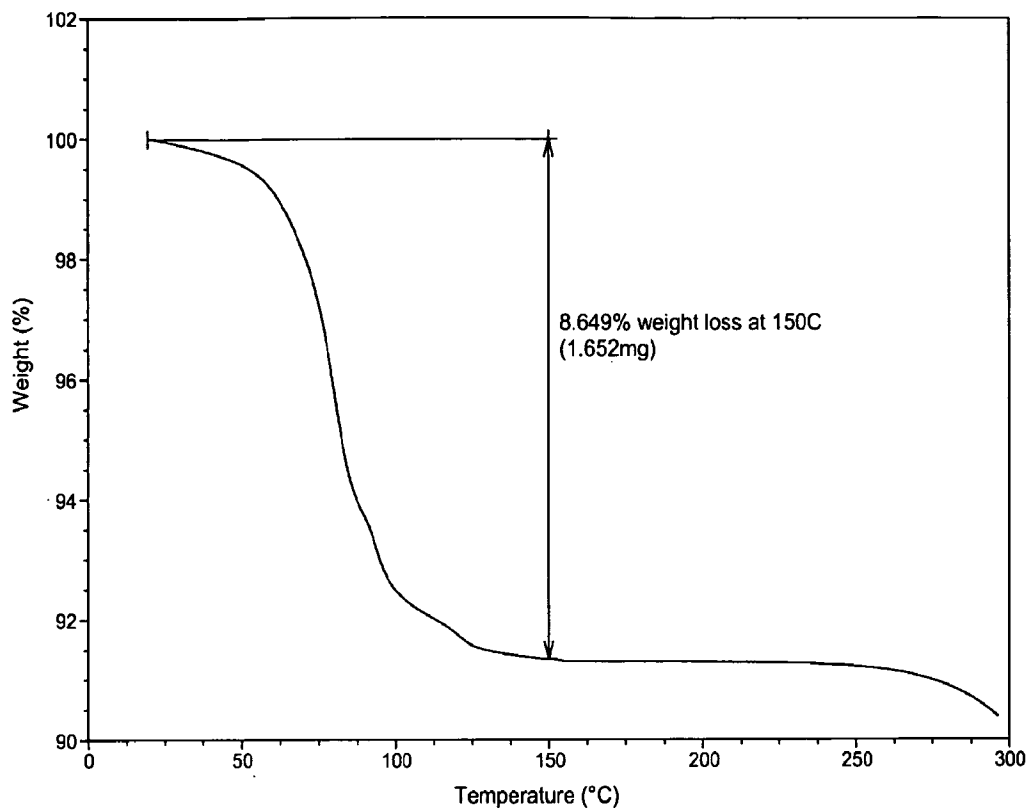


FIG. 10

