

CERTAIN CHEMICAL ENTITIES, COMPOSITIONS, AND METHODS**CROSS-REFERENCE TO RELATED APPLICATIONS**

[01] This application claims benefit of U.S. Provisional Patent Application No. 63/144,821, filed on February 2, 2021, which is incorporated herein by reference in its entirety.

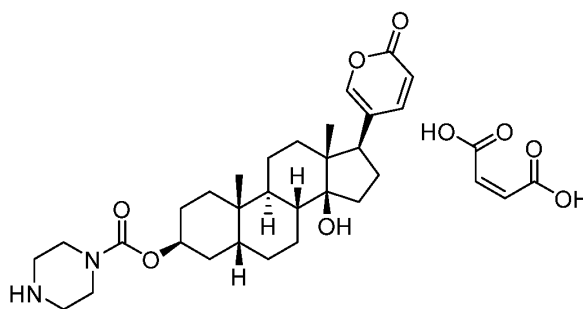
BACKGROUND OF THE INVENTION

[02] Cancer can be viewed as a breakdown in the communication between tumor cells and their environment, including their normal neighboring cells. Signals, both growth-stimulatory and growth-inhibitory, are routinely exchanged between cells within a tissue. Normally, cells do not divide in the absence of stimulatory signals, and likewise, will cease dividing in the presence of inhibitory signals. In a cancerous, or neoplastic state, a cell acquires the ability to "override" these signals and to proliferate under conditions in which normal cells would not grow.

[03] Cardiotonic steroids like digoxin and digitoxin are a class of naturally derived compounds that bind to and inhibit Na^+/K^+ -ATPase (sodium pump). Members of this family have been used for the treatment of heart failure and arrhythmia for many years. Recent findings have revealed that these compounds may be involved in the regulation of several important cellular processes. Several cardiotonic steroids such as digitoxin and oleandrin have shown inhibitory effect on the growth of human tumor cells.

SUMMARY OF THE INVENTION

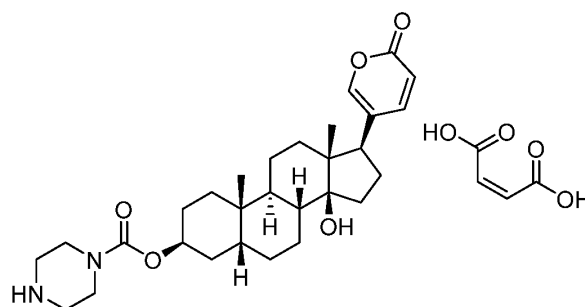
[04] In one aspect, the disclosure provides a compound that is (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

[05] In another aspect, the disclosure provides crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

[06] In some embodiments, the crystalline form is Crystalline Form I. In some embodiments, Crystalline Form I is characterized by:

- (a) an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;
 - (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**;
 - (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C;
 - (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C;
 - (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**;
 - (f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 3**;
 - (g) an unchanged XRPD after storage at 40 °C and 75% relative humidity (RH) for 6 months;
 - (h) an unchanged XRPD after storage at 25 °C and 60% relative humidity (RH) for 36 months;
- or
- (i) combinations thereof.

[07] In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some

embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $25.9 \pm 0.2^\circ$ 2- θ , $20.6 \pm 0.2^\circ$ 2- θ , and $14.8 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $27.8 \pm 0.2^\circ$ 2- θ , $25.2 \pm 0.2^\circ$ 2- θ , and $11.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least five peaks selected from $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , $10.3 \pm 0.2^\circ$ 2- θ , $25.9 \pm 0.2^\circ$ 2- θ , $20.6 \pm 0.2^\circ$ 2- θ , $14.8 \pm 0.2^\circ$ 2- θ , $27.8 \pm 0.2^\circ$ 2- θ , $25.2 \pm 0.2^\circ$ 2- θ , and $11.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at $13.8 \pm 0.1^\circ$ 2- θ , $19.5 \pm 0.1^\circ$ 2- θ , $10.3 \pm 0.1^\circ$ 2- θ , $25.9 \pm 0.1^\circ$ 2- θ , $20.6 \pm 0.1^\circ$ 2- θ , $14.8 \pm 0.1^\circ$ 2- θ , $27.8 \pm 0.1^\circ$ 2- θ , $25.2 \pm 0.1^\circ$ 2- θ , and $11.4 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**.

[08] In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C. In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C. In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**.

[09] In some embodiments, Crystalline Form I is characterized by a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 3**.

[10] In some embodiments, the crystalline form is Crystalline Form II. In some embodiments, Crystalline Form II is characterized by:

- (a) an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;
- (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**;
- (c) a differential scanning calorimetry (DSC) thermogram comprising:
 - i) an endotherm in the range of about 75-100 °C;
 - ii) an endotherm in the range of about 195-210 °C; and
 - iii) an endotherm in the range of 215-235 °C;
- (d) a differential scanning calorimetry (DSC) thermogram comprising
 - i) an endotherm with an onset of about 77 °C and a peak of about 94 °C;

- ii) an endotherm with an onset of about 202 °C and a peak of about 205 °C; and
- iii) an endotherm with an onset of about 220 °C and a peak of about 230 °C;
- (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**;
- (f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 6**;
- or
- (g) combinations thereof.

[11] In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , and $16.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least five peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at $14.3 \pm 0.1^\circ$ 2- θ , $20.1 \pm 0.1^\circ$ 2- θ , $15.2 \pm 0.1^\circ$ 2- θ , $18.4 \pm 0.1^\circ$ 2- θ , $26.2 \pm 0.1^\circ$ 2- θ , $16.4 \pm 0.1^\circ$ 2- θ , $20.9 \pm 0.1^\circ$ 2- θ , $25.0 \pm 0.1^\circ$ 2- θ , and $27.0 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**.

[12] In some embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising:

- i) an endotherm in the range of about 75-100 °C;
- ii) an endotherm in the range of about 195-210 °C; and
- iii) an endotherm in the range of 215-235 °C.

[13] In some embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising:

- i) an endotherm with an onset of about 77 °C and a peak of about 94 °C;
- ii) an endotherm with an onset of about 202 °C and a peak of about 205 °C; and

iii) an endotherm with an onset of about 220 °C and a peak of about 230 °C.

[14] In some embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**.

[15] In some embodiments, Crystalline Form II is characterized by a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 6**.

[16] In another aspect, the disclosure provides a pharmaceutical composition comprising crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate and at least one pharmaceutically acceptable excipient. In some embodiments, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some embodiments, the pharmaceutical composition is in the form of a solid form pharmaceutical composition. In some embodiments, the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a powder, a liquid, a suspension, a suppository, or an aerosol.

[17] In another aspect, the disclosure provides a packaged pharmaceutical composition comprising a pharmaceutical composition provided herein and instructions for using the composition to treat a subject suffering from cancer.

[18] In another aspect, the disclosure provides a method of treating a neoplasm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate provided herein, or the pharmaceutical composition provided herein. In some embodiments, the neoplasm is a cancer. In some embodiments, the cancer is head and neck cancer, brain cancer, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias, e.g., acute lymphocytic leukemia and acute

myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease. In some embodiments, the cancer is colorectal cancer. In some embodiments, the cancer is liver cancer. In some embodiments, the cancer is lung cancer. In some embodiments, the cancer is breast cancer. In some embodiments, the cancer is oral cancer. In some embodiments, the cancer is head and neck cancer. In some embodiments, the cancer is brain cancer.

[19] In another aspect, the disclosure provides a method of preparing Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate, wherein the method comprises:

- (a) contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid in a solvent to obtain a solution of the (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate; and
- (b) crystallizing the solution obtained in step (a) to obtain Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.

[20] In some embodiments, the solvent in step (a) comprises ethyl acetate, DCM, ethanol, or isopropanol. In some embodiments, the solvent in step (a) comprises ethanol. In some embodiments, step (a) is performed at a temperature of about 60-90 °C. In some embodiments, step (a) is performed at a temperature of about 70 °C. In some embodiments, step (a) is performed for a time of about 1-3 hours. In some embodiments, step (a) is performed for a time of about 1.5 hours.

[21] In some embodiments, step (b) comprises cooling the solution obtained in step (a) to room temperature. In some embodiments, step (b) comprises cooling the solution obtained in step (a) to a temperature of about 20-25 °C. In some embodiments, the method further comprises filtering the crystallized solution obtained in step (b) to obtain Crystalline Form I. In some embodiments, the method further comprises drying the obtained Crystalline Form I. In some embodiments, the drying is performed under vacuum at room temperature. In some embodiments, the drying is performed under vacuum at a temperature of about 20-25 °C.

[22] In another aspect, the disclosure provides a method of preparing Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate, wherein the method comprises:

- (a) contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid in a solvent to obtain a solution of the (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate; and
- (b) crystallizing the solution obtained in step (a) to obtain Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.

[23] In some embodiments, the solvent in step (a) comprises ethyl acetate, DCM, ethanol, or isopropanol. In some embodiments, the solvent in step (a) comprises isopropanol. In some embodiments, step (a) is performed at room temperature. In some embodiments, step (a) is performed at a temperature of about 20-25 °C.

[24] In some embodiments, step (b) comprises stirring the solution obtained in step (a) overnight.

[25] In some embodiments, the method further comprises filtering the crystallized solution obtained in step (b) to obtain Crystalline Form II. In some embodiments, the method further comprises drying the obtained Crystalline Form II. In some embodiments, the drying is performed under vacuum at 35 °C.

INCORPORATION BY REFERENCE

[26] All publications, patents, and patent applications mentioned in this specification are herein incorporated by reference in their entireties to the same extent as if each individual publication, patent, or patent application was specifically and individually indicated to be incorporated by reference.

DESCRIPTION OF THE DRAWINGS

[27] The novel features of the invention are set forth with particularity in the appended claims. An understanding of the features and advantages of the present invention may be obtained by reference to the following detailed description that sets forth illustrative embodiments, in which the principles of the invention are utilized, and the accompanying drawings of which:

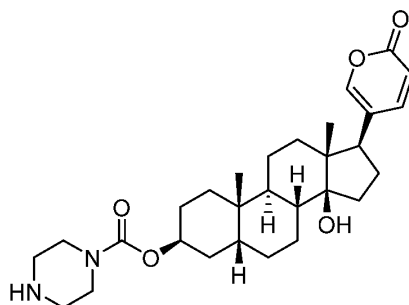
- [28] **Figure 1** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form I of Compound A maleate.
- [29] **Figure 2** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form I of Compound A maleate.
- [30] **Figure 3** shows the thermogravimetric analysis (TGA) pattern for Crystalline Form I of Compound A maleate.
- [31] **Figure 4** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form II of Compound A maleate.
- [32] **Figure 5** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form II of Compound A maleate.
- [33] **Figure 6** shows the thermogravimetric analysis (TGA) pattern for Crystalline Form II of Compound A maleate.
- [34] **Figure 7** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form I of Compound A maleate stored at 40 °C and 75% relative humidity (RH) for 6 months.
- [35] **Figure 8** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form I of Compound A maleate stored at 40 °C and 75% relative humidity (RH) for 6 months.
- [36] **Figure 9** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form I of Compound A maleate stored at 25 °C and 60% relative humidity (RH) for 36 months.
- [37] **Figure 10** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form I of Compound A maleate stored at 25 °C and 60% relative humidity (RH) for 36 months.

DETAILED DESCRIPTION OF THE INVENTION

[38] While small molecule inhibitors are often initially evaluated for their activity when dissolved in solution, solid state characteristics such as polymorphism are also important. Polymorphic forms of a drug substance can have different physical properties, including melting point, apparent solubility, dissolution rate, optical and mechanical properties, vapor pressure, and density. These properties can have a direct effect on the ability to process or manufacture a drug substance and the drug product. Moreover, differences in these properties can and often lead to different pharmacokinetics profiles for different polymorphic forms of a drug. Therefore, polymorphism is often an important factor under regulatory review of the ‘sameness’ of drug products from various manufacturers. For example, polymorphism has been evaluated in many multi-million dollar and even multi-billion dollar drugs, such as warfarin sodium, famotidine, and ranitidine. Polymorphism can affect the quality, safety, and/or efficacy of a drug product. Thus, there still remains a need for polymorphs of drug products. The present disclosure addresses this need and provides related advantages as well.

Compound A

[39] As used herein, Compound A refers to (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate, which has the chemical structure shown below:



Compound A.

[40] Compound A has been prepared previously (see, WO 2011/085641, U.S. Patent No. 8,334,376, U.S. Patent No. 8,993,550, U.S. Patent No. 9,399,659, U.S. Patent No. 9,814,735, U.S. Patent No. 10,179,141, U.S. Patent No. 10,471,078, and U.S. Patent Application No. 16/584,263).

[41] Disclosed herein is (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate).

[42] In some embodiments disclosed herein, Compound A maleate is crystalline.

[43] As used herein, “crystalline form,” “polymorph,” “Form,” and “form” may be used interchangeably herein, and are meant to include all crystalline and amorphous forms of the compound, including, for example, polymorphs, pseudopolymorphs, salts, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms, as well as mixtures thereof, unless a particular crystalline or amorphous form is referred to. Compounds of the present disclosure include crystalline and amorphous forms of those compounds, including, for example, polymorphs, pseudopolymorphs, solvates, hydrates, unsolvated polymorphs (including anhydrides), conformational polymorphs, and amorphous forms of the compounds, as well as mixtures thereof. In some embodiments, the crystalline form is a single solid state form, e.g., crystalline Form I.

I. Crystalline Forms of Compound A Maleate

[44] The polymorphs made according to the methods of the invention may be characterized by any methodology according to the art. For example, the polymorphs made according to the methods of the invention may be characterized by X-ray powder diffraction (XRPD), differential scanning calorimetry (DSC), thermogravimetric analysis (TGA), hot-stage microscopy, and/or

spectroscopy (e.g., Raman, solid state nuclear magnetic resonance (ssNMR), and infrared (IR)). In some embodiments, crystallinity of a solid form is determined by X-Ray Powder Diffraction (XRPD).

[45] XRPD: Polymorphs according to the invention may be characterized by XRPD. The relative intensities of XRPD peaks can vary, depending upon the particle size, the sample preparation technique, the sample mounting procedure and the particular instrument employed. Moreover, instrument variation and other factors can affect the 2θ values. Therefore, the XRPD peak assignments can vary, for example by plus or minus about 0.2 degrees.

[46] DSC: Polymorphs according to the invention can also be identified by its characteristic DSC thermograms such as shown in **Figures 2, 5** etc. For DSC, it is known that the temperatures observed will depend upon the rate of temperature change as well as sample preparation technique and the particular instrument employed. Thus, the values reported herein relating to DSC thermograms can vary, for example by plus or minus about 4 °C.

[47] TGA: The polymorphic forms of the invention may also give rise to thermal behavior different from that of the amorphous material or another polymorphic form. Thermal behavior may be measured in the laboratory by thermogravimetric analysis (TGA) which may be used to distinguish some polymorphic forms from others. In one aspect, the polymorph may be characterized by thermogravimetric analysis.

[48] The polymorph forms of Compound A maleate are useful in the production of medicinal preparations and can be obtained by means of a crystallization process to produce crystalline and semi-crystalline forms or a solidification process to obtain the amorphous form. In various embodiments, the crystallization is carried out by either generating the desired compound (for example Compound A maleate) in a reaction mixture and isolating the desired polymorph from the reaction mixture, or by dissolving raw compound in a solvent, optionally with heat, followed by crystallizing/solidifying the product by cooling (including active cooling) and/or by the addition of an antisolvent for a period of time. The crystallization or solidification may be followed by drying carried out under controlled conditions until the desired water content is reached in the end polymorphic form.

[49] In various embodiments, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) are stable at room temperature. In some examples, the various polymorphs can be stored at room temperature for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, the various polymorphs can be stored at room temperature for a time period of at least about 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24

months, 30 months, or 36 months. In some examples, the various polymorphs can be stored at room temperature for a time period of more than about 36 months. In some examples, the various polymorphs can be stored at room temperature for a time period of 1-2 months, 1-3 months, 1-6 months, 1-9 months, 1-12 months, 1-18 months, 1-24 months, 1-30 months, 1-36 months, 2-3 months, 2-6 months, 2-9 months, 2-12 months, 2-18 months, 2-24 months, 2-30 months, 2-36 months, 3-6 months, 3-9 months, 3-12 months, 3-18 months, 3-24 months, 3-30 months, 3-36 months, 6-9 months, 6-12 months, 6-18 months, 6-24 months, 6-30 months, 6-36 months, 9-12 months, 9-18 months, 9-24 months, 9-30 months, 9-36 months, 12-18 months, 12-24 months, 12-30 months, 12-36 months, 18-24 months, 18-30 months, 18-36 months, 24-30 months, 24-36 months, or 30-36 months. In some examples, the various polymorphs can be stored at room temperature for a time period of at least 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, or 36 months.

[50] In various embodiments, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) are stable at temperatures above the room temperature and/or at high relative humidity (RH). In some examples, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) can be stored at about 40 °C at about 75% RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) can be stored at 40 °C and at about 75% RH for a time period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) can be stored at 40 °C and at about 75% RH for a time period of more than about 180 days. In some examples, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) can be stored at 40 °C and at about 75% RH for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26-60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days,

50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, the various polymorph Forms disclosed herein (e.g., Crystalline Form I and Crystalline Form II of Compound A maleate) can be stored at 40 °C at about 75% RH for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

Crystalline Form I of Compound A Maleate

[51] **Figure 1** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form I of Compound A maleate.

[52] **Figure 2** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form I of Compound A maleate.

[53] **Figure 3** shows the thermogravimetric analysis (TGA) pattern for Crystalline Form I of Compound A maleate.

[54] In one aspect, provided herein is Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate. Some embodiments provide a composition comprising Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate. In some embodiments, Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate is characterized as having:

- (a) an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;
- (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**;
- (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C;
- (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C;
- (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**;
- (f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 3**;

- (g) an unchanged XRPD after storage at 40 °C and 75% relative humidity (RH) for 6 months;
- (h) an unchanged XRPD after storage at 25 °C and 60% relative humidity (RH) for 36 months;
- or
- (i) combinations thereof.

[55] In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**.

[56] In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at $1.8 \pm 0.1^\circ$ 2- θ , $19.5 \pm 0.1^\circ$ 2- θ , and $10.3 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at about 13.8° 2- θ , about 19.5° 2- θ , and about 10.3° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[57] In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $25.9 \pm 0.2^\circ$ 2- θ , $20.6 \pm 0.2^\circ$ 2- θ , and $14.8 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $25.9 \pm 0.1^\circ$ 2- θ , $20.6 \pm 0.1^\circ$ 2- θ , and $14.8 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from about 25.9° 2- θ , about 20.6° 2- θ , and about 14.8° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[58] In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $27.8 \pm 0.2^\circ$ 2- θ , $25.2 \pm 0.2^\circ$ 2- θ , and $11.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $27.8 \pm 0.1^\circ$ 2- θ , $25.2 \pm 0.1^\circ$ 2- θ , and $11.4 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from about 27.8° 2- θ , about 25.2° 2- θ , and about 11.4° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

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$\pm 0.1^\circ$ 2- θ , and $11.4 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at about 13.8° 2- θ , about 19.5° 2- θ , about 10.3° 2- θ , about 25.9° 2- θ , about 20.6° 2- θ , about 14.8° 2- θ , about 27.8° 2- θ , about 25.2° 2- θ , and about 11.4° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[60] In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**. In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C. In some embodiments, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C.

[61] In some embodiments, Crystalline Form I is characterized by an endotherm at about 230-250 °C, 232-250 °C, 234-250 °C, 236-250 °C, 238-250 °C, 240-250 °C, 242-250 °C, 244-250 °C, 246-250 °C, 248-250 °C, 230-248 °C, 232-248 °C, 234-248 °C, 236-248 °C, 238-248 °C, 240-248 °C, 242-248 °C, 244-248 °C, 246-248 °C, 230-246 °C, 232-246 °C, 234-246 °C, 236-246 °C, 238-246 °C, 240-246 °C, 242-246 °C, 244-246 °C, 230-244 °C, 232-244 °C, 234-244 °C, 236-244 °C, 238-244 °C, 240-244 °C, 242-244 °C, 230-242 °C, 232-242 °C, 234-242 °C, 236-242 °C, 238-242 °C, 240-242 °C, 230-240 °C, 232-240 °C, 234-240 °C, 236-240 °C, 238-240 °C, 230-238 °C, 232-238 °C, 234-238 °C, 236-238 °C, 230-236 °C, 232-236 °C, 234-236 °C, 230-234 °C, 232-234 °C, or 230-232 °C in the DSC thermogram. In various embodiments, Crystalline Form I is characterized by an endotherm at about 230-240 °C in the DSC thermogram, for example about 230 °C, 231 °C, 232 °C, 233 °C, 234 °C, 235 °C, 236 °C, 237 °C, 238 °C, 239 °C, or 240 °C. In some embodiments, the melting point of Crystalline Form I is about 238 °C.

[62] In some embodiments, Crystalline Form I is characterized by a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 3**. In various embodiments, Crystalline Form I decomposes above a temperature of about 200 °C, about 250 °C, about 300 °C, about 350 °C, about 400 °C, about 450 °C, about 500 °C, about 550 °C or above 600 °C. In some examples, Crystalline Form I decomposes above a temperature of about 200 °C.

[63] In some embodiments, Crystalline Form I is characterized by an unchanged XRPD after storage at 40 °C and 75% relative humidity (RH) for 6 months. In some embodiments, Crystalline Form I is characterized by an XRPD substantially the same as shown in **Figure 7** after storage at 40 °C and 75% relative humidity (RH) for 6 months. In some embodiments, Crystalline Form I is characterized by an unchanged DSC after storage at 40 °C and 75%

relative humidity (RH) for 6 months. In some embodiments, Crystalline Form I is characterized by an DSC substantially the same as shown in **Figure 8** after storage at 40 °C and 75% relative humidity (RH) for 6 months.

[64] In some embodiments, Crystalline Form I is characterized by an unchanged XRPD after storage at 25 °C and 60% relative humidity (RH) for 36 months. In some embodiments, Crystalline Form I is characterized by an XRPD substantially the same as shown in **Figure 9** after storage at 25 °C and 60% relative humidity (RH) for 36 months. In some embodiments, Crystalline Form I is characterized by an unchanged DSC after storage at 25 °C and 60% relative humidity (RH) for 36 months. In some embodiments, Crystalline Form I is characterized by an DSC substantially the same as shown in **Figure 10** after storage at 25 °C and 60% relative humidity (RH) for 36 months.

[65] In various embodiments, Crystalline Form I is stable at room temperature. In some examples, Crystalline Form I can be stored at room temperature for extended period of time without significant chemical degradation or change in the crystalline form. In some examples, Crystalline Form I can be stored at room temperature for a time period of at least about 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, or 36 months. In some examples, Crystalline Form I can be stored at room temperature for a time period of more than about 36 months. In some examples, Crystalline Form I can be stored at room temperature for a time period of 1-2 months, 1-3 months, 1-6 months, 1-9 months, 1-12 months, 1-18 months, 1-24 months, 1-30 months, 1-36 months, 2-3 months, 2-6 months, 2-9 months, 2-12 months, 2-18 months, 2-24 months, 2-30 months, 2-36 months, 3-6 months, 3-9 months, 3-12 months, 3-18 months, 3-24 months, 3-30 months, 3-36 months, 6-9 months, 6-12 months, 6-18 months, 6-24 months, 6-30 months, 6-36 months, 9-12 months, 9-18 months, 9-24 months, 9-30 months, 9-36 months, 12-18 months, 12-24 months, 12-30 months, 12-36 months, 18-24 months, 18-30 months, 18-36 months, 24-30 months, 24-36 months, or 30-36 months. In some examples, Crystalline Form I can be stored at room temperature for a time period of at least 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, or 36 months.

[66] In various embodiments, Crystalline Form I is stable at temperatures above the room temperature and/or at high RH. In some examples, Crystalline Form I can be stored at about 40 °C at about 75% RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, Crystalline Form I can be stored at 40 °C and at about 75% RH for a time period of at least about 10 days, 30 days, 60 days, 90 days, 120 days, 150 days, or 180 days. In some examples, Crystalline Form I can be stored at 40 °C and at

about 75% RH for a time period of more than about 180 days. In some examples, Crystalline Form I can be stored at 40 °C and at about 75% RH for a time period of 10-14 days, 10-18 days, 10-22 days, 10-26 days, 10-30 days, 10-40 days, 10-50 days, 10-60 days, 10-90 days, 10-120 days, 10-150 days, 10-180 days, 14-18 days, 14-22 days, 14-26 days, 14-30 days, 14-40 days, 14-50 days, 14-60 days, 14-90 days, 14-120 days, 14-150 days, 14-180 days, 18-22 days, 18-26 days, 18-30 days, 18-40 days, 18-50 days, 18-60 days, 18-90 days, 18-120 days, 18-150 days, 18-180 days, 22-26 days, 22-30 days, 22-40 days, 22-50 days, 22-60 days, 22-90 days, 22-120 days, 22-150 days, 22-180 days, 26-30 days, 26-40 days, 26-50 days, 26-60 days, 26-90 days, 26-120 days, 26-150 days, 26-180 days, 30-40 days, 30-50 days, 30-60 days, 30-90 days, 30-120 days, 30-150 days, 30-180 days, 40-50 days, 40-60 days, 40-90 days, 40-120 days, 40-150 days, 40-180 days, 50-60 days, 50-90 days, 50-120 days, 50-150 days, 50-180 days, 60-90 days, 60-120 days, 60-150 days, 60-180 days, 90-120 days, 90-150 days, or 90-180 days. In some examples, Crystalline Form I can be stored at 40 °C at about 75% RH for a time period of at least 10 days, 14 days, 18 days, 22 days, 26 days, 30 days, 40 days, 50 days, 60 days, 90 days, 120 days, 150 days, or 180 days.

[67] In various embodiments, Crystalline Form I is stable at temperatures above the room temperature and/or at high RH. In some examples, Crystalline Form I can be stored at about 25 °C at about 60% RH for an extended period of time without significant chemical degradation or change in the crystalline form. In some examples, Crystalline Form I can be stored at 25 °C at about 60% RH for a time period of at least about 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, or 36 months. In some examples, Crystalline Form I can be stored at 25 °C at about 60% RH for a time period of more than about 36 months. In some examples, Crystalline Form I can be stored at 25 °C at about 60% RH for a time period of 1-2 months, 1-3 months, 1-6 months, 1-9 months, 1-12 months, 1-18 months, 1-24 months, 1-30 months, 1-36 months, 2-3 months, 2-6 months, 2-9 months, 2-12 months, 2-18 months, 2-24 months, 2-30 months, 2-36 months, 3-6 months, 3-9 months, 3-12 months, 3-18 months, 3-24 months, 3-30 months, 3-36 months, 6-9 months, 6-12 months, 6-18 months, 6-24 months, 6-30 months, 6-36 months, 9-12 months, 9-18 months, 9-24 months, 9-30 months, 9-36 months, 12-18 months, 12-24 months, 12-30 months, 12-36 months, 18-24 months, 18-30 months, 18-36 months, 24-30 months, 24-36 months, or 30-36 months. In some examples, Crystalline Form I can be stored at 25 °C at about 60% RH for a time period of at least 1 month, 2 months, 3 months, 6 months, 9 months, 12 months, 18 months, 24 months, 30 months, or 36 months.

Crystalline Form II of Compound A Maleate

[68] **Figure 4** shows the X-ray powder diffraction (XRPD) pattern for Crystalline Form II of Compound A maleate.

[69] **Figure 5** shows the differential scanning calorimetry (DSC) thermogram for Crystalline Form II of Compound A maleate.

[70] **Figure 6** shows the thermogravimetric analysis (TGA) pattern for Crystalline Form II of Compound A maleate.

[71] In one aspect, provided herein is Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate. Some embodiments provide a composition comprising Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate. In some embodiments, Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate is characterized as having:

- (a) an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;
- (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**;
- (c) a differential scanning calorimetry (DSC) thermogram comprising:
 - i) an endotherm in the range of about 75-100 °C;
 - ii) an endotherm in the range of about 195-210 °C; and
 - iii) an endotherm in the range of 215-235 °C;
- (d) a differential scanning calorimetry (DSC) thermogram comprising
 - i) an endotherm with an onset of about 77 °C and a peak of about 94 °C;
 - ii) an endotherm with an onset of about 202 °C and a peak of about 205 °C; and
 - iii) an endotherm with an onset of about 220 °C and a peak of about 230 °C;
- (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**;
- (f) a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 6**;
- or
- (g) combinations thereof.

[72] In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**.

[73] In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.1^\circ$ 2- θ , $20.1 \pm 0.1^\circ$ 2- θ , and $15.2 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at about 14.3° 2- θ , about 20.1° 2- θ , and about 15.2° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[74] In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , and $16.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $18.4 \pm 0.1^\circ$ 2- θ , $26.2 \pm 0.1^\circ$ 2- θ , and $16.4 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from about 18.4° 2- θ , about 26.2° 2- θ , and about 16.4° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[75] In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from $20.9 \pm 0.1^\circ$ 2- θ , $25.0 \pm 0.1^\circ$ 2- θ , and $27.0 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern further comprises at least one peak selected from about 20.9° 2- θ , about 25.0° 2- θ , and about 27.0° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[76] In some embodiments, the X-ray powder diffraction pattern comprises at least one peak selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least two peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray

wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least three peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least four peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least five peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least six peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least seven peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises at least eight peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at $14.3 \pm 0.1^\circ$ 2- θ , $20.1 \pm 0.1^\circ$ 2- θ , $15.2 \pm 0.1^\circ$ 2- θ , $18.4 \pm 0.1^\circ$ 2- θ , $26.2 \pm 0.1^\circ$ 2- θ , $16.4 \pm 0.1^\circ$ 2- θ , $20.9 \pm 0.1^\circ$ 2- θ , $25.0 \pm 0.1^\circ$ 2- θ , and $27.0 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some embodiments, the X-ray powder diffraction pattern comprises peaks at about 14.3° 2- θ , about 20.1° 2- θ , about 15.2° 2- θ , about 18.4° 2- θ , about 26.2° 2- θ , about 16.4° 2- θ , about 20.9° 2- θ , about 25.0° 2- θ , and about 27.0° 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

[77] In some embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**. In some

embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising: an endotherm in the range of about 75-100 °C; an endotherm in the range of about 195-210 °C; and an endotherm in the range of 215-235 °C. In some embodiments, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising: an endotherm with an onset of about 77 °C and a peak of about 94 °C; an endotherm with an onset of about 202 °C and a peak of about 205 °C; and an endotherm with an onset of about 220 °C and a peak of about 230 °C.

[78] In some embodiments, the Crystalline Form II is characterized by an endotherm in the range of about 70-100 °C, for example at about 70-100 °C, 70-95 °C, 70-90 °C, 70-85 °C, 70-80 °C, 70-75 °C, 75-100 °C, 75-95 °C, 75-90 °C, 75-85 °C, 75-80 °C, 80-100 °C, 80-95 °C, 80-90 °C, 80-85 °C, 85-100 °C, 85-95 °C, 85-90 °C, 90-100 °C, 90-95 °C, or 95-100 °C in the DSC thermogram. In some examples, the Crystalline Form II is characterized by an endotherm at about 94 °C in the DSC thermogram.

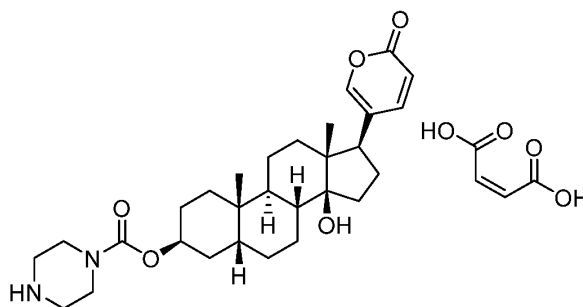
[79] In some embodiments, the Crystalline Form II is characterized by an endotherm in the range of about 190-220 °C, for example at about 190-220 °C, 190-215 °C, 190-210 °C, 190-205 °C, 190-200 °C, 190-195 °C, 195-220 °C, 195-215 °C, 195-210 °C, 195-205 °C, 195-200 °C, 200-220 °C, 200-215 °C, 200-210 °C, 200-205 °C, 205-220 °C, 205-215 °C, 205-210 °C, 210-220 °C, 210-215 °C, or 215-220 °C in the DSC thermogram. In some examples, the Crystalline Form II is characterized by an endotherm at about 205 °C in the DSC thermogram.

[80] In some embodiments, the Crystalline Form II is further characterized by an endotherm in the range of about 210-240 °C, for example at about 210-240 °C, 210-235 °C, 210-230 °C, 210-225 °C, 210-220 °C, 210-215 °C, 215-240 °C, 215-235 °C, 215-230 °C, 215-225 °C, 215-220 °C, 220-240 °C, 220-235 °C, 220-230 °C, 220-225 °C, 225-240 °C, 225-235 °C, 225-230 °C, 230-240 °C, 230-235 °C, or 235-240 °C in the DSC thermogram. In some examples, the Crystalline Form II is further characterized by an endotherm at about 230 °C in the DSC thermogram.

[81] In some embodiments, Crystalline Form II is characterized by a Thermogravimetric Analysis (TGA) pattern substantially the same as shown in **Figure 6**. In various embodiments, Crystalline Form II decomposes above a temperature of about 150 °C, about 200 °C, about 250 °C, about 300 °C, about 350 °C, about 400 °C, about 450 °C, about 500 °C, about 550 °C or above 600 °C. In some examples, Crystalline Form II decomposes above a temperature of about 150 °C.

II. Methods of Making Compound A Maleate and Polymorphic Forms Thereof

[82] In one aspect, the invention provides methods of making one or more polymorphs of Compound A maleate:



Compound A maleate.

[83] In some embodiments, Compound A maleate is prepared according to the examples herein.

[84] The polymorphs according to the invention are not limited by the starting materials used to produce Compound A or Compound A maleate.

[85] In one aspect, the invention is directed to methods of making polymorphs of Compound A maleate, or a pharmaceutically acceptable salt and/or solvate thereof, either by isolation of the desired polymorph as the first solid form after synthesis of Compound A maleate, or alternatively, by isolation of the desired polymorph as a transition from a prior solid form of Compound A maleate. Transitions from one form to another are within the scope of the invention because they can be an alternative manufacturing method for obtaining the form desired for the production of the medicinal preparations.

[86] Polymorphs of Compound A maleate, according to the methods of the invention can be selected from Crystalline Form I, Crystalline Form II, and mixtures thereof.

[87] Isolation and purification of the chemical entities and intermediates described herein can be performed, if desired, by any suitable separation or purification procedure such as, for example, filtration, extraction, crystallization, column chromatography, thin-layer chromatography or thick-layer chromatography, or a combination of these procedures. Specific illustrations of suitable separation and isolation procedures can be had by reference to the examples below. However, other equivalent separation or isolation procedures can also be used. Prior to crystallization, Compound A maleate may be isolated in about 50% chemical purity, 55% chemical purity, 60% chemical purity, 65% chemical purity, 70% chemical purity, 75% chemical purity, 80% chemical purity, 90% chemical purity, 91% chemical purity, 92% purity, 93% chemical purity, 94% chemical purity, 95% chemical purity, 96% chemical purity, 97% chemical purity, 98% chemical purity, 99% chemical purity, about 98% chemical purity, or about 100% chemical purity.

[88] In some embodiments, the crystalline forms disclosed herein are obtained by crystallizing Compound A maleate with a chemical purity of less than about 98%, less than about 97%, less than about 96%, less than about 95%, less than about 94%, less than about 93%, less than about 92%, less than about 91%, less than about 90%, less than about 89%, less than about 88%, less than about 87%, less than about 86%, less than about 85%, less than about 84%, less than about 83%, less than about 82%, less than about 81%, less than about 80%, less than about 78%, less than about 76%, less than about 74%, less than about 72%, or less than about 70%. In some embodiments, the crystalline forms are obtained by crystallizing Compound A maleate with a chemical purity in the range of about 70% to about 99%, 80% to about 96%, about 85% to about 96%, about 90% to about 96%, about 80% to 98%, about 85% to about 98%, about 90% to about 98%, about 92% to about 98%, about 94% to 98%, or about 96% to about 98%.

[89] In some embodiments, isolating the desired polymorph of Compound A maleate involves crystallization of crude reaction product from a mono-solvent system. In various embodiments, isolating the desired polymorph of Compound A maleate involves crystallization of crude product from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system.

[90] In some embodiments, the crystallization is carried out by generating the desired Compound A maleate in a reaction mixture and isolating the desired polymorph from the reaction mixture. In some embodiments, the reaction mixture is formed by adding maleic acid to a solution of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate to form dissolved (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate). In other embodiments, the reaction mixture is formed by dissolving Compound A maleate into a solvent.

Preparation of Crystalline Form I

[91] In some embodiments, the desired polymorph is Crystalline Form I of Compound A maleate, and the isolating step involves crystallization of crude reaction product from a mono-solvent system. In some embodiments, the desired polymorph is Crystalline Form I of Compound A maleate, and the isolating step involves crystallization of crude reaction product from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system. In some embodiments, the crude reaction product is formed by contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-

yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid to form dissolved (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate).

[92] In some embodiments, the desired polymorph is Crystalline Form I of Compound A maleate, and isolating Compound A maleate involves crystallization from a mono- or multi-solvent system, where the crystallization involves forming Compound A maleate *in situ* by contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid at a temperature above ambient temperature. In some examples, the reaction in the mono- or multi-solvent system is performed at a temperature of about 40-90 °C, 45-90 °C, 50-90 °C, 55-90 °C, 60-90 °C, 65-90 °C, 70-90 °C, 75-90 °C, 40-85 °C, 45-85 °C, 50-85 °C, 55-85 °C, 60-85 °C, 65-85 °C, 70-85 °C, 75-85 °C, 80-85 °C, 40-80 °C, 45-80 °C, 50-80 °C, 55-80 °C, 60-80 °C, 65-80 °C, 70-80 °C, 75-80 °C, 40-75 °C, 45-75 °C, 50-75 °C, 55-75 °C, 60-75 °C, 65-75 °C, 70-75 °C, 40-70 °C, 45-70 °C, 50-70 °C, 55-70 °C, 60-70 °C, 65-70 °C, 40-65 °C, 45-65 °C, 50-65 °C, 55-65 °C, 60-65 °C, 40-60 °C, 45-60 °C, 50-60 °C, 55-60 °C, 40-55 °C, 45-55 °C, 50-55 °C, 40-50 °C, or 45-50 °C.

[93] In some examples, the solvent comprises ethyl acetate, DCM, ethanol, or isopropanol. In some examples, the solvent comprises ethanol. In some embodiments, the solvent comprises ethanol and the reaction is performed at a temperature of about 65-75 °C. Any suitable amount of solvent can be used. In some embodiments, the amount of solvent (e.g., ethanol) used is from about 40-60 mL per gram of Compound A maleate. For example, in some embodiments, the amount of solvent used is 50 mL per gram of Compound A maleate. In some examples, the solvent comprises ethanol, the reaction is performed at a temperature of about 65-75 °C, and the amount of solvent is about 50 mL/g of Compound A maleate.

[94] In various embodiments, the crystallization further involves actively heating the solution containing the dissolved Compound A maleate, for example to a temperature of about 40-100 °C, 40-90 °C, 40-80 °C, 40-70 °C, 40-60 °C, 40-50 °C, 50-100 °C, 50-90 °C, 50-80 °C, 50-70 °C, 50-60 °C, 60-100 °C, 60-90 °C, 60-80 °C, 60-70 °C, 70-100 °C, 70-90 °C, 70-80 °C, 80-100 °C, or 80-90 °C. In some embodiments, the solution containing the dissolved Compound A maleate, is heated to a temperature of about 65-75 °C. In various embodiments, the solution containing the dissolved Compound A maleate is maintained at the heated temperature for a period of time, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h,

about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[95] In various embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound A maleate, for example to a temperature of about 0-40 °C, 0-30 °C, 0-20 °C, 0-10 °C, 10-40 °C, 10-30 °C, 10-20 °C, 20-40 °C, 20-30 °C, 20-10 °C, or 30 °C-40 °C. In some embodiments, the crystallization further involves actively cooling the heated solution containing the dissolved Compound A maleate to a temperature of about 20-30 °C. In various embodiments, the solution containing the dissolved Compound A maleate is further maintained at this lower temperature for a time period, for example for about 30 min, about 1 h, about 2 h, about 3 h, about 4 h, about 5 h, about 6 h, about 7 h, about 8 h, about 9 h, about 10 h, about 11 h, about 12 h, about 13 h, about 14 h, about 15 h, about 16 h, about 17 h, about 18 h, about 19 h, about 20 h, about 21 h, about 22 h, about 23 h, about 24 h or more.

[96] In various embodiments, the steps of active heating followed by active cooling are repeated multiple times, for example at least 2, at least 3, at least 4, at least 5, at least 6, at least 7, at least 8, at least 9, or at least 10 times. In some embodiments, the steps of active heating followed by active cooling are repeated 2, 3, 4, 5, 6, 7, 8, 9, or 10 times.

[97] In various embodiments, the crystallization further involves filtering the solution containing the obtained crystals of Compound A maleate. In some embodiments, the crystallization optionally involves washing the obtained crystals by a solvent, for example by the recrystallization solvent one or more times. In some embodiments, the crystallization optionally involves drying the obtained crystals, for example under vacuum at a temperature of about 20-30 °C.

[98] In some embodiments, the chemical purity of Crystalline Form I is greater than 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, the chemical purity of Crystalline Form I is greater than about 90%. In some embodiments, the chemical purity of Crystalline Form I is greater than about 95%. In some embodiments, the chemical purity of Crystalline Form I greater than about 99%. The chemical purity of Crystalline Form I may be measured by any available analytical technique, for example by HPLC analysis.

[99] In various embodiments, Crystalline Form I is dry. In various embodiments, Crystalline Form I is non-solvated. In various embodiments, Crystalline Form I is non-hydrated. In various embodiments, Crystalline Form I is anhydrous.

Preparation of Crystalline Form II

[100] In some embodiments, the desired polymorph is Crystalline Form II of Compound A maleate, and the isolating step involves crystallization of crude reaction product from a mono-

solvent system. In some embodiments, the desired polymorph is Crystalline Form II of Compound A maleate, and the isolating step involves crystallization of crude reaction product from a binary, tertiary, or greater solvent system, collectively understood as a multi-solvent system. In some embodiments, the crude reaction product is formed by contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid to form dissolved (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate).

[101] In some embodiments, the desired polymorph is Crystalline Form II of Compound A maleate, and isolating Compound A maleate involves crystallization from a mono- or multi-solvent system, where the crystallization involves forming Compound A maleate *in situ* by contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid at a temperature above ambient temperature. In some examples, the reaction in the mono- or multi-solvent system is performed at a temperature of about 10-50 °C, 10-45 °C, 10-40 °C, 10-35 °C, 10-30 °C, 10-25 °C, 10-20 °C, 10-15 °C, 15-50 °C, 15-45 °C, 15-40 °C, 15-35 °C, 15-30 °C, 15-25 °C, 15-20 °C, 20-50 °C, 20-45 °C, 20-40 °C, 20-35 °C, 20-30 °C, 20-25 °C, 25-50 °C, 25-45 °C, 25-40 °C, 25-35 °C, 25-30 °C, 30-50 °C, 30-45 °C, 30-40 °C, 30-35 °C, 35-50 °C, 35-45 °C, 35-40 °C, 40-50 °C, 40-45 °C, or 45-50 °C.

[102] In some examples, the solvent comprises ethyl acetate, DCM, ethanol, or isopropanol. In some examples, the solvent comprises isopropanol. In some embodiments, the solvent comprises isopropanol and the reaction is performed at a temperature of about 20-30 °C. Any suitable amount of solvent can be used. In some embodiments, the amount of solvent (e.g., isopropanol) used is from about 80-100 mL per gram of Compound A maleate. For example, in some embodiments, the amount of solvent used is 90 mL per gram of Compound A maleate. In some examples, the solvent comprises isopropanol, the reaction is performed at a temperature of about 20-30 °C, and the amount of solvent is about 90 mL/g of Compound A maleate.

[103] In various embodiments, the crystallization further involves filtering the solution containing the obtained crystals of Compound A maleate. In some embodiments, the crystallization optionally involves washing the obtained crystals by a solvent, for example by the recrystallization solvent one or more times. In some embodiments, the crystallization optionally involves drying the obtained crystals, for example under vacuum at a temperature of about 30-40 °C.

[104] In some embodiments, the chemical purity of the Crystalline Form II is greater than 60%, 70%, 80%, 90%, 95%, or 99%. In some embodiments, the chemical purity of the Crystalline Form II is greater than about 90%. In some embodiments, the chemical purity of the Crystalline Form II is greater than about 95%. In some embodiments, the chemical purity of the Crystalline Form II greater than about 99%. The chemical purity of Crystalline Form II may be measured by any available analytical technique, for example by HPLC analysis.

III. Additional Definitions

[105] As used herein, “active agent” is used to indicate a chemical entity which has biological activity. In certain embodiments, an “active agent” is a compound having pharmaceutical utility. For example an active agent may be an anti-cancer therapeutic.

[106] As used herein, “modulation” refers to a change in activity as a direct or indirect response to the presence of a chemical entity as described herein, relative to the activity of in the absence of the chemical entity. The change may be an increase in activity or a decrease in activity, and may be due to the direct interaction of the compound with the target or due to the interaction of the compound with one or more other factors that in turn affect the target's activity. For example, the presence of the chemical entity may, for example, increase or decrease the target activity by directly binding to the target, by causing (directly or indirectly) another factor to increase or decrease the target activity, or by (directly or indirectly) increasing or decreasing the amount of target present in the cell or organism.

[107] As used herein, “therapeutically effective amount” of a chemical entity described herein refers to an amount effective, when administered to a human or non-human subject, to provide a therapeutic benefit such as amelioration of symptoms, slowing of disease progression, or prevention of disease.

[108] “Treating” or “treatment” encompasses administration of Compound A, or a pharmaceutically acceptable salt thereof, to a mammalian subject, particularly a human subject, in need of such an administration and includes (i) arresting the development of clinical symptoms of the disease, such as cancer, (ii) bringing about a regression in the clinical symptoms of the disease, such as cancer, and/or (iii) prophylactic treatment for preventing the onset of the disease, such as cancer.

[109] As used herein, a “pharmaceutically acceptable” component is one that is suitable for use with humans and/or animals without undue adverse side effects (such as toxicity, irritation, and allergic response) commensurate with a reasonable benefit/risk ratio.

[110] “Pharmaceutically acceptable salts” include, but are not limited to salts with inorganic acids, such as hydrochlorate, carbonate, phosphate, hydrogenphosphate, diphosphate,

hydrobromate, sulfate, sulfinate, nitrate, and like salts; as well as salts with an organic acid, such as malate, malonate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, gluconate, methanesulfonate, Tris (hydroxymethyl-aminomethane), p-toluenesulfonate, propionate, 2-hydroxyethylsulfonate, benzoate, salicylate, stearate, oxalate, pamoate, and alkanoate such as acetate, $\text{HOOC}-(\text{CH}_2)_n-\text{COOH}$ where n is 0-4, and like salts. Other salts include sulfate, methanesulfonate, bromide, trifluoroacetate, picrate, sorbate, benzilate, salicylate, nitrate, phthalate or morpholine. Pharmaceutically acceptable cations include, but are not limited to sodium, potassium, calcium, aluminum, lithium, and ammonium.

[111] In addition, if the compounds described herein are obtained as an acid addition salt, the free base can be obtained by basifying a solution of the acid salt. Conversely, if the product is a free base, an addition salt, particularly a pharmaceutically acceptable addition salt, may be produced by dissolving the free base in a suitable organic solvent and treating the solution with an acid, in accordance with conventional procedures for preparing acid addition salts from base compounds. Those skilled in the art will recognize various synthetic methodologies that may be used to prepare non-toxic pharmaceutically acceptable addition salts.

[112] As used herein, “subject” refers to a mammal that has been or will be the object of treatment, observation or experiment. The methods described herein can be useful in both human therapy and veterinary applications. In some embodiments, the subject is a human.

[113] The term “mammal” is intended to have its standard meaning, and encompasses humans, dogs, cats, sheep, and cows, for example.

[114] “Prodrugs” described herein include any compound that becomes Compound A when administered to a subject, e.g., upon metabolic processing of the prodrug. Similarly, “pharmaceutically acceptable salts” includes “prodrugs” of pharmaceutically acceptable salts. Examples of prodrugs include derivatives of functional groups, such as a carboxylic acid group, in Compound A. Exemplary prodrugs of a carboxylic acid group include, but are not limited to, carboxylic acid esters such as alkyl esters, hydroxyalkyl esters, arylalkyl esters, and aryloxyalkyl esters. Other exemplary prodrugs include lower alkyl esters such as ethyl ester, acyloxyalkyl esters such as pivaloyloxymethyl (POM), glycosides, and ascorbic acid derivatives. Other exemplary prodrugs include amides of carboxylic acids. A discussion of prodrugs is provided in T. Higuchi and V. Stella, *Pro-drugs as Novel Delivery Systems*, Vol. 14 of the A.C.S. Symposium Series, in Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association and Pergamon Press, 1987, and in *Design of Prodrugs*, ed. H. Bundgaard, Elsevier, 1985.

[115] The compounds disclosed herein can be used in different enriched isotopic forms, e.g., enriched in the content of ^2H , ^3H , ^{11}C , ^{13}C and/or ^{14}C . In one particular embodiment, the compound is deuterated at least one position. Such deuterated forms can be made by the procedure described in U.S. Patent Nos. 5,846,514 and 6,334,997. As described in U.S. Patent Nos. 5,846,514 and 6,334,997, deuteration can improve the efficacy and increase the duration of action of drugs.

[116] Deuterium substituted compounds can be synthesized using various methods such as described in: Dean, Dennis C.; Editor. Recent Advances in the Synthesis and Applications of Radiolabeled Compounds for Drug Discovery and Development. [In: Curr., Pharm. Des., 2000; 6(10)] 2000, 110 pp; George W.; Varma, Rajender S. The Synthesis of Radiolabeled Compounds via Organometallic Intermediates, Tetrahedron, 1989, 45(21), 6601-21; and Evans, E. Anthony. Synthesis of radiolabeled compounds, J. Radioanal. Chem., 1981, 64(1-2), 9-32.

[117] A “solvate” is formed by the interaction of a solvent and a compound. The term “compound” is intended to include solvates of compounds. Similarly, “pharmaceutically acceptable salts” includes solvates of pharmaceutically acceptable salts. Suitable solvates are pharmaceutically acceptable solvates, such as hydrates, including monohydrates and hemi-hydrates. Also included are solvates formed with the one or more crystallization solvents.

[118] Pharmaceutically acceptable forms of the compounds recited herein include pharmaceutically acceptable salts, chelates, non-covalent complexes, prodrugs, and mixtures thereof.

[119] A “chelate” is formed by the coordination of a compound to a metal ion at two (or more) points. The term “compound” is intended to include chelates of compounds. Similarly, “pharmaceutically acceptable salts” includes chelates of pharmaceutically acceptable salts.

[120] A “non-covalent complex” is formed by the interaction of a compound and another molecule wherein a covalent bond is not formed between the compound and the molecule. For example, complexation can occur through van der Waals interactions, hydrogen bonding, and electrostatic interactions (also called ionic bonding). Such non-covalent complexes are included in the term “compound”. Similarly, pharmaceutically acceptable salts include “non-covalent complexes” of pharmaceutically acceptable salts.

[121] When ranges are used herein for physical properties, such as molecular weight, or chemical properties, such as chemical formulae, all combinations and sub combinations of ranges and specific embodiments therein are intended to be included.

[122] The term “about” when referring to a number or a numerical range means that the number or numerical range referred to is an approximation within experimental variability (or

within statistical experimental error), and thus the number or numerical range may vary from, for example, between 1% and 15% of the stated number or numerical range. In some instances of numerical ranges, “about” means $\pm 10\%$.

[123] As used herein, “significant” refers to any detectable change that is statistically significant in a standard parametric test of statistical significance such as Student's T-test, where $p < 0.05$.

[124] As used herein, “cancer” refers to all types of cancer or neoplasm or malignant tumors found in mammals, including carcinomas and sarcomas. Examples of cancer are cancer of the brain, breast, cervix, colon, head & neck, kidney, lung, non-small cell lung, melanoma, mesothelioma, ovary, sarcoma, stomach, uterus and Medulloblastoma.

IV. Methods of Use

[125] The polymorphs described herein may be used in treating a variety of neoplasms, including malignant and benign tumors, as well as cancers. Cancers that can be prevented and/or treated by the polymorphs, compositions, and methods described herein include, but are not limited to, human sarcomas and carcinomas, e.g., carcinomas, e.g., colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, thyroid cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma, angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wilms' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, Langerhans cell histiocytosis (LCH), Erdheim-Chester disease (ECD), leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease. Benign tumors that can be prevented and/or treated by the polymorphs, compositions, and methods described herein include, but are not limited to, craniopharyngioma.

[126] In some embodiments, the polymorphs described herein are used for the treatment of cancers of the

- i. digestive system including, without limitation, the esophagus, stomach, small intestine, colon (including colorectal), liver & intrahepatic bile duct, gallbladder & other biliary, pancreas, and other digestive organs;
- ii. respiratory system, including without limitation, larynx, lung & bronchus, and other respiratory organs;
- iii. skin;
- iv. thyroid;
- v. breast;
- vi. genital system, including without limitation, uterine cervix, ovary, and prostate;
- vii. urinary system, including without limitation, urinary bladder and kidney and renal pelvis; and
- viii. oral cavity & pharynx, including without limitation, tongue, mouth, pharynx, and other oral cavity.

[127] In some embodiments, the polymorphs described herein are used for the treatment of colon cancer, liver cancer, lung cancer, melanoma, thyroid cancer, breast cancer, ovarian cancer, oral cancer, head and neck cancer, and brain cancer.

[128] The polymorphs described herein may also be used in conjunction with other well-known therapeutic agents that are selected for their particular usefulness against the condition that is being treated. For example, the polymorphs described herein may be useful in combination with at least one additional anti-cancer and/or cytotoxic agents. Further, the polymorphs described herein may also be useful in combination with other inhibitors of parts of the signaling pathway that links cell surface growth factor receptors to nuclear signals initiating cellular proliferation.

[129] Such known anti-cancer and/or cytotoxic agents that may be used in combination with the polymorphs described herein include:

- (i) other antiproliferative/antineoplastic drugs and combinations thereof, as used in medical oncology, such as alkylating agents (for example cis-platin, oxaliplatin, carboplatin, cyclophosphamide, nitrogen mustard, melphalan, chlorambucil, busulphan, temozolamide and nitrosoureas); antimetabolites (for example gemcitabine and antifolates such as fluoropyrimidines like 5-fluorouracil and tegafur, raltitrexed, methotrexate, cytosine arabinoside, and hydroxyurea); antitumor antibiotics (for example anthracyclines like adriamycin, bleomycin, doxorubicin, daunomycin, epirubicin, idarubicin, mitomycinC,

dactinomycin and mithramycin); antimetabolic agents (for example vinca alkaloids like vincristine, vinblastine, vindesine and vinorelbine and taxoids like taxol and taxotere and polokinas inhibitors); and topoisomerase inhibitors (for example epipodophyllotoxins like etoposide and teniposide, amsacrine, topotecan and camptothecin);

(ii) cytostatic agents such as antioestrogens (for example tamoxifen, fulvestrant, toremifene, raloxifene, droloxifene and idoxifene), antiandrogens (for example bicalutamide, flutamide, nilutamide and cyproterone acetate), LHRH antagonists or LHRH agonists (for example goserelin, leuprorelin and buserelin), progestogens (for example megestrol acetate), aromatase inhibitors (for example as anastrozole, letrozole, vorazole and exemestane) and inhibitors of 5 α -reductase such as finasteride;

(iii) anti-invasion agents [for example c-Src kinase family inhibitors like 4-(6-chloro-2,3-methylenedioxyanilino)-7-[2-(4-methylpiperazin-1-yl)ethoxy]-5-tetrahydropyran-4-yloxyquinazoline (AZD0530; International Patent Application WO 01/94341), *N*-(2-chloro-6-methylphenyl)-2-[6-[4-(2-hydroxyethyl)piperazin-1-yl]-2-methylpyrimidin-4-ylamino]thiazole-5-carboxamide (dasatinib, BMS-354825; J. Med. Chem., 2004, 47, 66586661) and bosutinib (SK1-606), and metalloproteinase inhibitors like marimastat, inhibitors of urokinase plasminogen activator receptor function or antibodies to Heparanase];

(iv) inhibitors of growth factor function: for example such inhibitors include growth factor antibodies and growth factor receptor antibodies (for example the anti-erbB2 antibody trastuzumab [HerceptinTM], the anti-EGFR antibody panitumumab, the anti-erbB 1 antibody cetuximab [Erbix, C225] and any growth factor or growth factor receptor antibodies disclosed by Stem *et al.* Critical reviews in oncology/haematology, 2005, Vol. 54, pp 11-29); such inhibitors also include tyrosine kinase inhibitors, for example inhibitors of the epidermal growth factor family (for example EGFR family tyrosine kinase inhibitors such as *N*-(3-chloro-4-fluorophenyl)-7-methoxy-6-(3-morpholinopropoxy)quinazolin-4-amine (gefitinib, ZD1839), *N*-(3-ethynylphenyl)-6,7-bis(2-methoxyethoxy)quinazolin-4-amine (erlotinib, OSI-774) and 6-acrylamido-*N*-(3-chloro-4-fluorophenyl)-7-(3-morpholinopropoxy)-quinazolin-4-amine (CI 1033), erbB2 tyrosine kinase inhibitors such as lapatinib); inhibitors of the hepatocyte growth factor family; inhibitors of the insulin growth factor family; inhibitors of the platelet-derived growth factor family such as imatinib and/or nilotinib (AMN107); inhibitors of serine/threonine kinases (for example Ras/Raf signalling inhibitors such as farnesyl transferase inhibitors, for example sorafenib (BAY 43-9006), tipifarnib (RI15777) and lonafarnib (SCH66336)), inhibitors of cell signalling through MEK and/or AKT kinases, c-kit inhibitors, abl kinase inhibitors, P13 kinase inhibitors, Plt3 kinase inhibitors, CSF-1R kinase inhibitors, IGF receptor (insulin like

growth factor) kinase inhibitors; aurora kinase inhibitors (for example AZD1152, PH739358, VX-680, MLN8054, R763, MP235, MP529, VX-528 and AX39459) and cyclin dependent kinase inhibitors such as CDK2 and/or CDK4 inhibitors;

(v) antiangiogenic agents such as those which inhibit the effects of vascular endothelial growth factor, [for example the anti-vascular endothelial cell growth factor antibody bevacizumab (Avastin™) and for example, a VEGF receptor tyrosine kinase inhibitor such as vandetanib(ZD6474), vatalanib (PTK787), sunitinib (SU11248), axitinib (AG-013736), pazopanib (GW 786034) and 4-{4-fluoro-2-methylindol-5-yloxy)-6-methoxy-7-(3pyrrolidin-1-ylpropoxy)quinazoline (AZD2171; Example 240 within WO 00/47212), compounds such as those disclosed in International Patent Applications WO 97/22596, WO 97/30035, WO 97/32856 and WO 98/13354 and compounds that work by other mechanisms (for example linomide, inhibitors of integrin α_3 function and angiostatin));

(vi) vascular damaging agents such as Combretastatin A4 and compounds disclosed in International Patent Applications WO 99/02166, WO 00/40529, WO 00/41669, WO 01/92224, WO 02/04434 and WO 02/08213;

(vii) an endothelin receptor antagonist, for example zibotentan (ZD4054) or atrasentan;

(viii) antisense therapies, for example those which are directed to the targets listed above, such as ISIS 2503, an anti-ras antisense;

(ix) gene therapy approaches, including for example approaches to replace aberrant genes such as aberrant p53 or aberrant BRCA1 or BRCA2, GDEPT (gene-directed enzyme pro-drug therapy) approaches such as those using cytosine deaminase, thymidine kinase or a bacterial nitroreductase enzyme and approaches to increase subject tolerance to chemotherapy or radiotherapy such as multi-drug resistance gene therapy; and

(x) immunotherapy approaches, including for example ex-vivo and in-vivo approaches to increase the immunogenicity of subject's tumor cells, such as transfection with cytokines such as interleukin 2, interleukin 4 or granulocyte-macrophage colony stimulating factor, approaches to decrease T-cell energy, approaches using transfected immune cells such as cytokine-transfected dendritic cells, approaches using cytokine-transfected tumor cell lines and approaches using anti-idiotypic antibodies.

[130] In certain embodiments, the at least one polymorph of Compound A is administered in combination with one or more agents chosen from paclitaxel, bortezomib, dacarbazine, gemcitabine, trastuzumab, bevacizumab, capecitabine, docetaxel, erlotinib, aromatase inhibitors,

such as AROMASIN™ (exemestane), and estrogen receptor inhibitors, such as FASLODEX™ (fulvestrant).

[131] When a polymorph of Compound A is administered into a human subject, the daily dosage will normally be determined by the prescribing physician with the dosage generally varying according to the age, weight, and response of the individual subject, as well as the severity of the subject's symptoms.

[132] In one exemplary application, a suitable amount of at least one polymorph of Compound A is administered to a mammal undergoing treatment for cancer, for example, breast cancer. Administration typically occurs in an amount of between about 0.01 mg/kg of body weight to about 100 mg/kg of body weight per day (administered in single or divided doses), such as at least about 0.1 mg/kg of body weight per day. A particular therapeutic dosage can include, e.g., from about 0.01 mg to about 1000 mg of the polymorph of Compound A, such as including, e.g., from about 1 mg to about 1000 mg. The quantity of the at least one polymorph of Compound A in a unit dose of preparation may be varied or adjusted from about 0.1 mg to 1000 mg, such as from about 1 mg to 300 mg, for example 10 mg to 200 mg, according to the particular application. The amount administered will vary depending on the particular IC₅₀ value of the at least one polymorph of Compound A used and the judgment of the attending clinician taking into consideration factors such as health, weight, and age. In combinational applications in which the at least one polymorph of Compound A described herein is not the sole active ingredient, it may be possible to administer lesser amounts of the at least one polymorph of Compound A and still have therapeutic or prophylactic effect.

[133] In some embodiments, the pharmaceutical preparation is in unit dosage form. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the polymorph of Compound A, e.g., an effective amount to achieve the desired purpose.

[134] The actual dosage employed may be varied depending upon the requirements of the subject and the severity of the condition being treated. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the at least one polymorph of Compound A. Thereafter, the dosage is increased by small amounts until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day if desired.

[135] The amount and frequency of administration of the at least one polymorph of Compound A, and if applicable other chemotherapeutic agents and/or radiation therapy, will be regulated

according to the judgment of the attending clinician (physician) considering such factors as age, condition and size of the subject as well as severity of the disease being treated.

[136] The chemotherapeutic agent and/or radiation therapy can be administered according to therapeutic protocols well known in the art. It will be apparent to those skilled in the art that the administration of the chemotherapeutic agent and/or radiation therapy can be varied depending on the disease being treated and the known effects of the chemotherapeutic agent and/or radiation therapy on that disease. Also, in accordance with the knowledge of the skilled clinician, the therapeutic protocols (e.g., dosage amounts and times of administration) can be varied in view of the observed effects of the administered therapeutic agents (i.e., antineoplastic agent or radiation) on the subject, and in view of the observed responses of the disease to the administered therapeutic agents.

[137] Also, in general, the at least one polymorph of Compound A need not be administered in the same pharmaceutical composition as a chemotherapeutic agent, and may, because of different physical and chemical characteristics, be administered by a different route. For example, the polymorphs/compositions may be administered orally to generate and maintain good blood levels thereof, while the chemotherapeutic agent may be administered intravenously. The determination of the mode of administration and the advisability of administration, where possible, in the same pharmaceutical composition, is well within the knowledge of the skilled clinician. The initial administration can be made according to established protocols known in the art, and then, based upon the observed effects, the dosage, modes of administration and times of administration can be modified by the skilled clinician.

[138] The particular choice of polymorph (and where appropriate, chemotherapeutic agent and/or radiation) will depend upon the diagnosis of the attending physicians and their judgment of the condition of the subject and the appropriate treatment protocol.

[139] The one or more polymorphs of Compound A (and where appropriate chemotherapeutic agent and/or radiation) may be administered concurrently (e.g., simultaneously, essentially simultaneously or within the same treatment protocol) or sequentially, depending upon the nature of the proliferative disease, the condition of the subject, and the actual choice of chemotherapeutic agent and/or radiation to be administered in conjunction (i.e., within a single treatment protocol) with the one or more polymorphs/composition.

[140] In combinational applications and uses, the one or more polymorphs/composition and the chemotherapeutic agent and/or radiation need not be administered simultaneously or essentially simultaneously, and the initial order of administration of the one or more polymorphs/composition, and the chemotherapeutic agent and/or radiation, may not be

important. Thus, the at least one polymorph of Compound A may be administered first followed by the administration of the chemotherapeutic agent and/or radiation; or the chemotherapeutic agent and/or radiation may be administered first followed by the administration of the at least one polymorph of Compound A. This alternate administration may be repeated during a single treatment protocol. The determination of the order of administration, and the number of repetitions of administration of each therapeutic agent during a treatment protocol, is well within the knowledge of the skilled physician after evaluation of the disease being treated and the condition of the subject. For example, the chemotherapeutic agent and/or radiation may be administered first, and then the treatment continued with the administration of the at least one polymorph of Compound A followed, where determined advantageous, by the administration of the chemotherapeutic agent and/or radiation, and so on until the treatment protocol is complete.

[141] Thus, in accordance with experience and knowledge, the practicing physician can modify each protocol for the administration of a polymorph of Compound A/composition for treatment according to the individual subject's needs, as the treatment proceeds.

[142] The attending clinician, in judging whether treatment is effective at the dosage administered, will consider the general well-being of the subject as well as more definite signs such as relief of disease-related symptoms, inhibition of tumor growth, actual shrinkage of the tumor, or inhibition of metastasis. Size of the tumor can be measured by standard methods such as radiological studies, e.g., CAT or MRI scan, and successive measurements can be used to judge whether or not growth of the tumor has been retarded or even reversed. Relief of disease-related symptoms such as pain, and improvement in overall condition can also be used to help judge effectiveness of treatment.

V. Compositions and Formulations

[143] The disclosure provides compositions, including pharmaceutical compositions, comprising one or more crystalline forms of the present invention.

[144] In various embodiments, the ratio of desired crystalline form such as Crystalline Form I to all other crystalline forms in a composition is greater than about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or more w/w. In other embodiments, the ratio of Crystalline Form II to all other polymorphs is greater than about 1:1, 2:1, 3:1, 4:1, 5:1, 6:1, 7:1, 8:1, 9:1, or more w/w.

[145] In some embodiments, the one or more polymorphs of Compound A are formulated into pharmaceutical compositions. In specific embodiments, pharmaceutical compositions are formulated in a conventional manner using one or more physiologically acceptable carriers comprising excipients and auxiliaries which facilitate processing of the active compounds/polymorphs into preparations which can be used pharmaceutically. Proper

formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are used as suitable to formulate the pharmaceutical compositions described herein: *Remington: The Science and Practice of Pharmacy*, Nineteenth Ed (Easton, Pa.: Mack Publishing Company, 1995); Hoover, John E., *Remington's Pharmaceutical Sciences*, Mack Publishing Co., Easton, Pennsylvania 1975; Liberman, H.A. and Lachman, L., Eds., *Pharmaceutical Dosage Forms*, Marcel Decker, New York, N.Y., 1980; and *Pharmaceutical Dosage Forms and Drug Delivery Systems*, Seventh Ed. (Lippincott Williams & Wilkins 1999).

[146] Provided herein are pharmaceutical compositions comprising one or more polymorphs of Compound A and a pharmaceutically acceptable diluent(s), excipient(s), or carrier(s). In certain embodiments, the one or more polymorphs of Compound A are administered as pharmaceutical compositions in which the one or more polymorphs, are mixed with other active ingredients, as in combination therapy. Encompassed herein are all combinations of actives set forth in the combination therapies section below and throughout this disclosure. In specific embodiments, the pharmaceutical compositions include one or more polymorphs of Compound A.

[147] A pharmaceutical composition, as used herein, refers to a mixture of one or more polymorphs of Compound A with other chemical components, such as carriers, stabilizers, diluents, dispersing agents, suspending agents, thickening agents, and/or excipients. In certain embodiments, the pharmaceutical composition facilitates administration of the polymorphs to an organism. In some embodiments, in practicing the methods of treatment or use provided herein, therapeutically effective amounts of one or more polymorphs of Compound A are administered in a pharmaceutical composition to a mammal having a disease or condition to be treated. In specific embodiments, the mammal is a human. In certain embodiments, therapeutically effective amounts vary depending on the severity of the disease, the age and relative health of the subject and other factors. The one or more polymorphs of Compound A described herein are used singly or in combination with one or more therapeutic agents as components of mixtures.

[148] In one embodiment, one or more polymorphs of Compound A are formulated in an aqueous solution. In specific embodiments, the aqueous solution is selected from, by way of example only, a physiologically compatible buffer, such as Hank's solution, Ringer's solution, or physiological saline buffer. In other embodiments, one or more polymorphs of Compound A are formulated for transmucosal administration. In specific embodiments, transmucosal formulations include penetrants that are appropriate to the barrier to be permeated. In still other embodiments wherein the one or more polymorphs described herein are formulated for other parenteral injections, appropriate formulations include aqueous or nonaqueous solutions. In

specific embodiments, such solutions include physiologically compatible buffers and/or excipients.

[149] In another embodiment, the polymorphs described herein are formulated for oral administration. The polymorphs of Compound A are formulated by combining the polymorphs with, e.g., pharmaceutically acceptable carriers or excipients. In various embodiments, the polymorphs described herein are formulated in oral dosage forms that include, by way of example only, tablets, powders, pills, dragees, capsules, liquids, gels, syrups, elixirs, slurries, suspensions and the like.

[150] In certain embodiments, pharmaceutical preparations for oral use are obtained by mixing one or more solid excipient with one or more of the polymorphs described herein, optionally grinding the resulting mixture, and processing the mixture of granules, after adding suitable auxiliaries, if desired, to obtain tablets or dragee cores. Suitable excipients are, in particular, fillers such as sugars, including lactose, sucrose, mannitol, or sorbitol; cellulose preparations such as: for example, maize starch, wheat starch, rice starch, potato starch, gelatin, gum tragacanth, methylcellulose, microcrystalline cellulose, hydroxypropylmethylcellulose, sodium carboxymethylcellulose; or others such as: polyvinylpyrrolidone (PVP or povidone) or calcium phosphate. In specific embodiments, disintegrating agents are optionally added. Disintegrating agents include, by way of example only, cross-linked croscarmellose sodium, polyvinylpyrrolidone, agar, or alginic acid or a salt thereof such as sodium alginate.

[151] In one embodiment, dosage forms, such as dragee cores and tablets, are provided with one or more suitable coating. In specific embodiments, concentrated sugar solutions are used for coating the dosage form. The sugar solutions, optionally contain additional components, such as by way of example only, gum arabic, talc, polyvinylpyrrolidone, carbopol gel, polyethylene glycol, and/or titanium dioxide, lacquer solutions, and suitable organic solvents or solvent mixtures. Dyestuffs and/or pigments are also optionally added to the coatings for identification purposes. Additionally, the dyestuffs and/or pigments are optionally utilized to characterize different combinations of active compound doses.

[152] In certain embodiments, therapeutically effective amounts of at least one of the polymorphs described herein is formulated into other oral dosage forms. Oral dosage forms include push-fit capsules made of gelatin, as well as soft, sealed capsules made of gelatin and a plasticizer, such as glycerol or sorbitol. In specific embodiments, push-fit capsules contain the active ingredients in admixture with one or more filler. Fillers include, by way of example only, lactose, binders such as starches, and/or lubricants such as talc or magnesium stearate and, optionally, stabilizers. In other embodiments, soft capsules, contain one or more active

compound that is dissolved or suspended in a suitable liquid. Suitable liquids include, by way of example only, one or more fatty oil, liquid paraffin, or liquid polyethylene glycol. In addition, stabilizers are optionally added.

[153] In other embodiments, therapeutically effective amounts of at least one of the polymorphs described herein are formulated for buccal or sublingual administration. Formulations suitable for buccal or sublingual administration include, by way of example only, tablets, lozenges, or gels. In still other embodiments, the polymorphs described herein are formulated for parental injection, including formulations suitable for bolus injection or continuous infusion. In specific embodiments, formulations for injection are presented in unit dosage form (e.g., in ampoules) or in multi-dose containers. Preservatives are, optionally, added to the injection formulations. In still other embodiments, the pharmaceutical composition of a polymorph of Compound A is formulated in a form suitable for parenteral injection as sterile suspension, solution or emulsion in oily or aqueous vehicles. Parenteral injection formulations optionally contain formulatory agents such as suspending, stabilizing and/or dispersing agents. In specific embodiments, pharmaceutical formulations for parenteral administration include aqueous solutions of the active polymorphs in water-soluble form. In additional embodiments, suspensions of the active polymorphs are prepared as appropriate oily injection suspensions. Suitable lipophilic solvents or vehicles for use in the pharmaceutical compositions described herein include, by way of example only, fatty oils such as sesame oil, or synthetic fatty acid esters, such as ethyl oleate or triglycerides, or liposomes. In certain specific embodiments, aqueous injection suspensions contain substances which increase the viscosity of the suspension, such as sodium carboxymethyl cellulose, sorbitol, or dextran. Optionally, the suspension contains suitable stabilizers or agents which increase the solubility of the polymorphs to allow for the preparation of highly concentrated solutions. Alternatively, in other embodiments, the active ingredient is in powder form for constitution with a suitable vehicle, e.g., sterile pyrogen-free water, before use.

[154] In still other embodiments, the one or more polymorphs of Compound A are administered topically. The one or more polymorphs described herein are formulated into a variety of topically administrable compositions, such as solutions, suspensions, lotions, gels, pastes, medicated sticks, balms, creams or ointments. Such pharmaceutical compositions optionally contain solubilizers, stabilizers, tonicity enhancing agents, buffers and preservatives.

[155] In yet other embodiments, the one or more polymorphs of Compound A are formulated for transdermal administration. In specific embodiments, transdermal formulations employ transdermal delivery devices and transdermal delivery patches and can be lipophilic emulsions

or buffered, aqueous solutions, dissolved and/or dispersed in a polymer or an adhesive. In various embodiments, such patches are constructed for continuous, pulsatile, or on demand delivery of pharmaceutical agents. In additional embodiments, the transdermal delivery of the one or more polymorphs of Compound A is accomplished by means of iontophoretic patches and the like. In certain embodiments, transdermal patches provide controlled delivery of the one or more polymorphs of Compound A. In specific embodiments, the rate of absorption is slowed by using rate-controlling membranes or by trapping the compound within a polymer matrix or gel. In alternative embodiments, absorption enhancers are used to increase absorption.

Absorption enhancers or carriers include absorbable pharmaceutically acceptable solvents that assist passage through the skin. For example, in one embodiment, transdermal devices are in the form of a bandage comprising a backing member, a reservoir containing the compound optionally with carriers, optionally a rate controlling barrier to deliver the compound to the skin of the host at a controlled and predetermined rate over a prolonged period of time, and means to secure the device to the skin.

[156] In other embodiments, the one or more polymorphs of Compound A are formulated for administration by inhalation. Various forms suitable for administration by inhalation include, but are not limited to, aerosols, mists or powders. Pharmaceutical compositions of the polymorphs of Compound A are conveniently delivered in the form of an aerosol spray presentation from pressurized packs or a nebuliser, with the use of a suitable propellant (e.g., dichlorodifluoromethane, trichlorofluoromethane, dichlorotetrafluoroethane, carbon dioxide or other suitable gas). In specific embodiments, the dosage unit of a pressurized aerosol is determined by providing a valve to deliver a metered amount. In certain embodiments, capsules and cartridges of, such as, by way of example only, gelatin for use in an inhaler or insufflator are formulated containing a powder mix of the compound and a suitable powder base such as lactose or starch.

[157] In still other embodiments, the one or more polymorphs of Compound A are formulated in rectal compositions such as enemas, rectal gels, rectal foams, rectal aerosols, suppositories, jelly suppositories, or retention enemas, containing conventional suppository bases such as cocoa butter or other glycerides, as well as synthetic polymers such as polyvinylpyrrolidone, PEG, and the like. In suppository forms of the compositions, a low-melting wax such as, but not limited to, a mixture of fatty acid glycerides, optionally in combination with cocoa butter is first melted.

[158] In certain embodiments, pharmaceutical compositions are formulated in any conventional manner using one or more physiologically acceptable carriers comprising

excipients and auxiliaries which facilitate processing of the active polymorphs into preparations which can be used pharmaceutically. Proper formulation is dependent upon the route of administration chosen. Any pharmaceutically acceptable techniques, carriers, and excipients are optionally used as suitable. Pharmaceutical compositions comprising the one or more polymorphs of Compound A are manufactured in a conventional manner, such as, by way of example only, by means of conventional mixing, dissolving, granulating, dragee-making, levigating, emulsifying, encapsulating, entrapping or compression processes.

[159] Pharmaceutical compositions include at least one pharmaceutically acceptable carrier, diluent or excipient and at least one polymorph of Compound A described herein as an active ingredient. The active ingredient is in free-acid or free-base form, or in a pharmaceutically acceptable salt form. All tautomers of the compounds described herein are included within the scope of the compounds presented herein. Additionally, the compounds described herein encompass unsolvated as well as solvated forms with pharmaceutically acceptable solvents such as water, ethanol, and the like. The solvated forms of the compounds presented herein are also considered to be disclosed herein. In addition, the pharmaceutical compositions optionally include other medicinal or pharmaceutical agents, carriers, adjuvants, such as preserving, stabilizing, wetting or emulsifying agents, solution promoters, salts for regulating the osmotic pressure, buffers, and/or other therapeutically valuable substances.

[160] Methods for the preparation of compositions, comprising the one or more polymorphs of Compound A described herein include formulating the polymorphs with one or more inert, pharmaceutically acceptable excipients or carriers to form a solid, semi-solid or liquid. Solid compositions include, but are not limited to, powders, tablets, dispersible granules, capsules, cachets, and suppositories. Liquid compositions include solutions in which a compound is dissolved, emulsions comprising a compound, or a solution containing liposomes, micelles, or nanoparticles comprising a compound as disclosed herein. Semi-solid compositions include, but are not limited to, gels, suspensions and creams. The form of the pharmaceutical compositions described herein include liquid solutions or suspensions, solid forms suitable for solution or suspension in a liquid prior to use, or as emulsions. These compositions also optionally contain minor amounts of nontoxic, auxiliary substances, such as wetting or emulsifying agents, pH buffering agents, and so forth.

[161] In some embodiments, a pharmaceutical composition comprising at least one polymorph of Compound A illustratively takes the form of a liquid where the agents are present in solution, in suspension or both. Typically when the composition is administered as a solution or suspension a first portion of the agent is present in solution and a second portion of the agent is

present in particulate form, in suspension in a liquid matrix. In some embodiments, a liquid composition includes a gel formulation. In other embodiments, the liquid composition is aqueous.

[162] In certain embodiments, useful aqueous suspension contain one or more polymers as suspending agents. Useful polymers include water-soluble polymers such as cellulosic polymers, e.g., hydroxypropyl methylcellulose, and water-insoluble polymers such as cross-linked carboxyl-containing polymers. Certain pharmaceutical compositions described herein comprise a mucoadhesive polymer, selected for example from carboxymethylcellulose, carbomer (acrylic acid polymer), poly(methylmethacrylate), polyacrylamide, polycarbophil, acrylic acid/butyl acrylate copolymer, sodium alginate and dextran.

[163] Useful pharmaceutical compositions also, optionally, include solubilizing agents to aid in the solubility of a polymorph of Compound A. The term “solubilizing agent” generally includes agents that result in formation of a micellar solution or a true solution of the agent. Certain acceptable nonionic surfactants, for example polysorbate 80, are useful as solubilizing agents, as can ophthalmically acceptable glycols, polyglycols, e.g., polyethylene glycol 400, and glycol ethers.

[164] Furthermore, useful pharmaceutical compositions optionally include one or more pH adjusting agents or buffering agents, including acids such as acetic, boric, citric, lactic, phosphoric and hydrochloric acids; bases such as sodium hydroxide, sodium phosphate, sodium borate, sodium citrate, sodium acetate, sodium lactate and tris-hydroxymethylaminomethane; and buffers such as citrate/dextrose, sodium bicarbonate and ammonium chloride. Such acids, bases and buffers are included in an amount required to maintain pH of the composition in an acceptable range.

[165] Additionally, useful compositions also, optionally, include one or more salts in an amount required to bring osmolality of the composition into an acceptable range. Such salts include those having sodium, potassium or ammonium cations and chloride, citrate, ascorbate, borate, phosphate, bicarbonate, sulfate, thiosulfate or bisulfite anions; suitable salts include sodium chloride, potassium chloride, sodium thiosulfate, sodium bisulfite and ammonium sulfate.

[166] Other useful pharmaceutical compositions optionally include one or more preservatives to inhibit microbial activity. Suitable preservatives include mercury-containing substances such as merfen and thiomersal; stabilized chlorine dioxide; and quaternary ammonium compounds such as benzalkonium chloride, cetyltrimethylammonium bromide and cetylpyridinium chloride.

[167] Still other useful compositions include one or more surfactants to enhance physical stability or for other purposes. Suitable nonionic surfactants include polyoxyethylene fatty acid glycerides and vegetable oils, e.g., polyoxyethylene (60) hydrogenated castor oil; and polyoxyethylene alkylethers and alkylphenyl ethers, e.g., octoxynol 10, octoxynol 40.

[168] Still other useful compositions include one or more antioxidants to enhance chemical stability where required. Suitable antioxidants include, by way of example only, ascorbic acid and sodium metabisulfite.

[169] In certain embodiments, aqueous suspension compositions are packaged in single-dose non-reclosable containers. Alternatively, multiple-dose reclosable containers are used, in which case it is typical to include a preservative in the composition.

[170] In alternative embodiments, other delivery systems for hydrophobic pharmaceutical compounds are employed. Liposomes and emulsions are examples of delivery vehicles or carriers useful herein. In certain embodiments, organic solvents such as *N*-methylpyrrolidone are also employed. In additional embodiments, the polymorphs described herein are delivered using a sustained-release system, such as semipermeable matrices of solid hydrophobic polymers containing the therapeutic agent. Various sustained-release materials are useful herein. In some embodiments, sustained-release capsules release the polymorphs for a few weeks up to over 100 days. Depending on the chemical nature and the biological stability of the therapeutic reagent, additional strategies for protein stabilization are employed.

[171] In certain embodiments, the formulations described herein comprise one or more antioxidants, metal chelating agents, thiol containing compounds and/or other general stabilizing agents. Examples of such stabilizing agents, include, but are not limited to: (a) about 0.5% to about 2% w/v glycerol, (b) about 0.1% to about 1% w/v methionine, (c) about 0.1% to about 2% w/v monothioglycerol, (d) about 1 mM to about 10 mM EDTA, (e) about 0.01% to about 2% w/v ascorbic acid, (f) 0.003% to about 0.02% w/v polysorbate 80, (g) 0.001% to about 0.05% w/v. polysorbate 20, (h) arginine, (i) heparin, (j) dextran sulfate, (k) cyclodextrins, (l) pentosan polysulfate and other heparinoids, (m) divalent cations such as magnesium and zinc; or (n) combinations thereof.

VI. Routes of Administration

[172] Suitable routes of administration include, but are not limited to, oral, intravenous, rectal, aerosol, parenteral, ophthalmic, pulmonary, transmucosal, transdermal, vaginal, otic, nasal, and topical administration. In addition, by way of example only, parenteral delivery includes intramuscular, subcutaneous, intravenous, intramedullary injections, as well as intrathecal, direct intraventricular, intraperitoneal, intralymphatic, and intranasal injections.

[173] In certain embodiments, a polymorph of Compound A is administered in a local rather than systemic manner, for example, via injection of the polymorph directly into an organ, often in a depot preparation or sustained release formulation. In specific embodiments, long acting formulations are administered by implantation (for example subcutaneously or intramuscularly) or by intramuscular injection. Furthermore, in other embodiments, the drug is delivered in a targeted drug delivery system, for example, in a liposome coated with organ-specific antibody. In such embodiments, the liposomes are targeted to and taken up selectively by the organ. In yet other embodiments, a polymorph of Compound A is provided in the form of a rapid release formulation, in the form of an extended release formulation, or in the form of an intermediate release formulation. In yet other embodiments, a polymorph of Compound A is administered topically.

VII. Kits/Articles of Manufacture

[174] For use in the therapeutic applications described herein, kits and articles of manufacture are also provided. In some embodiments, such kits comprise a carrier, package, or container that is compartmentalized to receive one or more containers such as vials, tubes, and the like, each of the container(s) comprising one of the separate elements to be used in a method described herein. Suitable containers include, for example, bottles, vials, syringes, and test tubes. The containers are formed from a variety of materials such as glass or plastic.

[175] The articles of manufacture provided herein contain packaging materials. Packaging materials for use in packaging pharmaceutical products include those found in, e.g., U.S. Pat. Nos. 5,323,907, 5,052,558 and 5,033,252. Examples of pharmaceutical packaging materials include, but are not limited to, blister packs, bottles, tubes, inhalers, pumps, bags, vials, containers, syringes, bottles, and any packaging material suitable for a selected formulation and intended mode of administration and treatment. For example, the container(s) includes one or more polymorphs described herein, optionally in a composition or in combination with another agent as disclosed herein. The container(s) optionally have a sterile access port (for example the container is an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). Such kits optionally comprising a compound with an identifying description or label or instructions relating to its use in the methods described herein.

[176] For example, a kit typically includes one or more additional containers, each with one or more of various materials (such as reagents, optionally in concentrated form, and/or devices) desirable from a commercial and user standpoint for use of a compound described herein. Non-limiting examples of such materials include, but not limited to, buffers, diluents, filters, needles, syringes; carrier, package, container, vial and/or tube labels listing contents and/or instructions

for use, and package inserts with instructions for use. A set of instructions will also typically be included. A label is optionally on or associated with the container. For example, a label is on a container when letters, numbers or other characters forming the label are attached, molded or etched into the container itself, a label is associated with a container when it is present within a receptacle or carrier that also holds the container, e.g., as a package insert. In addition, a label is used to indicate that the contents are to be used for a specific therapeutic application. In addition, the label indicates directions for use of the contents, such as in the methods described herein. In certain embodiments, the pharmaceutical composition is presented in a pack or dispenser device which contains one or more unit dosage forms containing a compound provided herein. The pack for example contains metal or plastic foil, such as a blister pack. Or, the pack or dispenser device is accompanied by instructions for administration. Or, the pack or dispenser is accompanied with a notice associated with the container in form prescribed by a governmental agency regulating the manufacture, use, or sale of pharmaceuticals, which notice is reflective of approval by the agency of the form of the drug for human or veterinary administration. Such notice, for example, is the labeling approved by the U.S. Food and Drug Administration for prescription drugs, or the approved product insert. In some embodiments, compositions containing a polymorph of Compound A formulated in a compatible pharmaceutical carrier are prepared, placed in an appropriate container, and labeled for treatment of an indicated condition.

EXAMPLES

[177] The following examples serve to more fully describe the manner of using the invention. These examples are presented for illustrative purposes and should not serve to limit the true scope of the invention.

[178] In carrying out the procedures of the methods described herein, it is of course to be understood that references to particular buffers, media, reagents, cells, culture conditions and the like are not intended to be limiting, but are to be read so as to include all related materials that one of ordinary skill in the art would recognize as being of interest or value in the particular context in which that discussion is presented. For example, it is often possible to substitute one buffer system or culture medium for another and still achieve similar, if not identical, results. Those of skill in the art will have sufficient knowledge of such systems and methodologies so as to be able, without undue experimentation, to make such substitutions as will optimally serve their purposes in using the methods and procedures disclosed herein.

[179] The polymorphs described herein can be synthesized utilizing techniques well known in the art from commercially available starting materials and reagents. For example, the polymorphs described herein can be prepared as illustrated below with reference to the examples and reaction schemes.

[180] Bufalin can be obtained from the skin glands of *Bufo gargarizans* or *B. melanostictus* toads and is commercially available, *e.g.* from Sigma-Aldrich Corp. (St. Louis, MO). Other reagents are commercially available, *e.g.* from Sigma-Aldrich Corp., or can be readily prepared by those skilled in the art using commonly employed synthetic methodology.

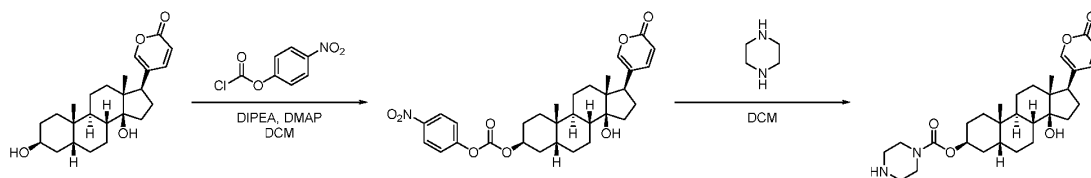
[181] The polymorphs described herein may be prepared in substantially pure form, typically by standard chromatographic methods, prior to formulation in a pharmaceutically acceptable form.

[182] The following abbreviations and terms have the indicated meanings throughout:

AcOH	=	acetic acid
Boc	=	tert-butoxycarbonyl
c-	=	cyclo
DCC	=	dicyclohexylcarbodiimide
DCM	=	dichloromethane
DIPEA	=	N,N-diisopropylethylamine
DMAP	=	4-dimethylaminopyridine
EDC	=	1-ethyl-3-(3-dimethylaminopropyl) carbodiimide
eq	=	equivalent(s)

Et	=	ethyl
EtOAc or EA	=	ethyl acetate
EtOH	=	ethanol
g	=	gram
h or hr	=	hour
HBTU	=	O-(benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	=	hydroxybenzotriazole
HPLC	=	high pressure liquid chromatography
i-	=	iso
kg or Kg	=	kilogram
L or l	=	liter
LC/MS	=	LCMS = liquid chromatography-mass spectrometry
LRMS	=	low resolution mass spectrometry
m/z	=	mass-to-charge ratio
Me	=	methyl
MeOH	=	methanol
mg	=	milligram
min	=	minute
mL	=	milliliter
mmol	=	millimole
n-	=	normal
NaOAc	=	sodium acetate
PE	=	petroleum ether
Ph	=	phenyl
Prep	=	preparative
quant.	=	quantitative
RP-HPLC	=	reverse phase-high pressure liquid chromatography
rt or RT	=	room temperature
s-	=	sec- = secondary
t-	=	tert- = tertiary
THF	=	tetrahydrofuran
TLC	=	thin layer chromatography
UV	=	ultraviolet

Example 1: Preparation of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate (Compound A)



[183] Step 1: To a solution of bufalin (60 mg, 0.15 mmol) and DMAP (16.8 mg, 0.15 mmol) in CH₂Cl₂ (10 mL) was added DIPEA (77.5 mg, 0.6 mmol) and 4-nitrophenyl carbonochloridate (60.6 mg, 0.3 mmol). The mixture was stirred at 37 °C for 16 h and then purified via preparative TLC (PE/EA=1:1) to afford (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 4-nitrophenyl carbonate as a white solid (72 mg, 87.1%).

[184] Step 2: To a solution of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl 4-nitrophenyl carbonate (29 mg, 0.054 mmol) in CH₂Cl₂ was added piperazine (46.4 mg, 0.54 mmol). The resultant mixture was stirred at rt for 16 h and then purified via preparative TLC to afford (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate (18.6 mg, 69.2%) as a white solid. LRMS (M+H⁺) *m/z* 499.5. ¹H NMR (CD₃OD, 400 MHz) δ 7.90 (dd, *J* = 9.6, 2.4 Hz, 1H), 7.33 (m, 1H), 6.18 (d, *J* = 9.6 Hz, 1H), 4.89 (m, 1H), 3.41 (m, 4H), 2.77-2.80 (m, 4H), 2.44-2.48 (m, 1H), 1.08-2.15 (m, 21H), 0.88 (s, 3H), 0.62 (s, 3H).

Example 2. Preparation of Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate)

[185] A solution of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate (2.4 g, 4.81 mmol) in EtOH (120 mL) was stirred at 70 °C for 1 h. A solution of maleic acid in EtOH (21.6 mL, 0.25 M) was slowly added with stirring. The mixture was stirred at 70 °C for about 1.5 h. The suspension was cooled to room temperature and stirred for 15-16 h. The precipitate was filtered, washed with EtOH and dried under vacuum at room temperature to afford

Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.

Example 3. Preparation of Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate)
[186] (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate (1 g, 2 mmol) was dissolved into 90 mL of isopropyl alcohol (IPA) at room temperature. A solution of maleic acid (0.252 g, 2.2 mmol) in IPA (5 mL) was added. The mixture was stirred overnight at room temperature. The precipitate was filtered and washed twice with IPA, and dried in a vacuum oven at 35°C overnight to afford Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.

Example 4. X-Ray Powder Diffraction (XRPD)

[187] X-ray powder diffraction (XRPD) patterns were obtained on a Bruker D8 Advance. A CuK source (=1.54179 angstrom) operating minimally at 40 kV and 40 mA scans each sample between 3 and 40 degrees 2-theta. The scanning rate is 10 degrees 2-theta per minute and the sample rotation speed is 15 revolutions per minute.

[188] The XRPD pattern obtained for Crystalline Form I of Compound A maleate is summarized in **Table 1** and **Figure 1**.

Table 1.

Peak #	Angle (° 2-θ)	Intensity (%)	Peak #	Angle (° 2-θ)	Intensity (%)
1	3.443	18.2	13	18.404	2.4
2	6.902	5	14	19.547	66.8
3	9.708	5.3	15	20.572	12.1
4	10.297	16.5	16	20.789	9.7
5	11.421	5.4	17	22.327	2.2
6	13.789	100	18	22.667	2.6
7	14.262	3.3	19	24.062	3.8
8	14.814	8.1	20	24.3	3
9	15.17	3.6	21	25.208	7.7
10	16.581	2.4	22	25.938	14.9
11	17.3	2.1	23	27.515	5
12	18.143	3	24	27.752	8

Peak #	Angle (° 2-θ)	Intensity (%)
25	28.762	2.4
26	30.496	2.4

Peak #	Angle (° 2-θ)	Intensity (%)
27	32.759	5.5
28	36.49	2.3

[189] The XRPD pattern obtained for Crystalline Form II of Compound A maleate is summarized in **Table 2** and **Figure 4**.

Table 2.

Peak #	Angle (° 2-θ)	Intensity (%)
1	3.601	43.7
2	6.808	14.7
3	9.511	13.6
4	10.539	12.2
5	11.579	8.8
6	13.871	29
7	14.345	100
8	15.231	41.2
9	16.435	33.7
10	16.869	16.4
11	18.408	38
12	19.671	25.5
13	20.065	62.5
14	20.933	24.2
15	21.844	10.6
16	23.32	12.7

Peak #	Angle (° 2-θ)	Intensity (%)
17	24.031	13
18	24.56	9.3
19	24.997	21.8
20	26.24	34
21	27.047	19.2
22	28.132	11.7
23	28.865	13.1
24	29.257	11.7
25	30.679	9.4
26	31.104	7.7
27	31.556	8.7
28	31.879	9.8
29	32.867	11.9
30	33.998	7.2
31	34.529	6.3
32	37.349	6

Example 5. Thermogravimetric Analysis (TGA)

[190] Thermogravimetric analysis was carried out on a TA Instrument TGA unit (Q5000IR). Samples were heated in platinum pans from ambient to 300 °C at 10 °C/min. The TGA pattern obtained for Crystalline Form I of Compound A maleate is shown in **Figure 3**. The TGA pattern obtained for Crystalline Form II of Compound A maleate is shown in **Figure 6**.

[191] The TGA patterns obtained for Crystalline Forms of Compound A maleate are summarized in the following table:

Polymorph	TGA Patterns
Crystalline Form I	0.31% w/w loss from 31.4 °C to 190.2 °C
Crystalline Form II	1.44% w/w loss from 33.7 °C to 122.6 °C

Example 6. Differential Scanning Calorimetry (DSC)

[192] Differential scanning calorimetry analysis was carried out on a TA Instrument DSC unit (TA Q2000). Samples were heated in non-hermetic aluminum pans from ambient to 260 °C at 10 °C/min. The DSC thermogram obtained for Crystalline Form I of Compound A maleate is summarized in **Figure 2**. The DSC thermogram obtained for Crystalline Form II of Compound A maleate is summarized in **Figure 5**.

[193] The DSC thermograms obtained for Crystalline Forms of Compound A maleate are summarized in the following table:

Polymorph	DSC Thermogram Characteristic Peaks
Crystalline Form I	endotherm with an onset of about 234 °C and a peak of about 238 °C
Crystalline Form II	three endotherms with: an onset of about 77 °C and a peak of about 94 °C; an endotherm with an onset of about 202 °C and a peak of about 205 °C; and an endotherm with an onset of about 220 °C and a peak of about 230 °C

Example 7. Stability Tests of Crystalline Form I

[194] Crystalline Form I was not changed after storage at 40 °C/75%RH for 6 months, or storage at 25 °C/60% RH for 36 months. The results of Crystalline Form I in accelerated and long-term stability tests are shown in **Table 3** and **Figures 7-10**.

Table 3.

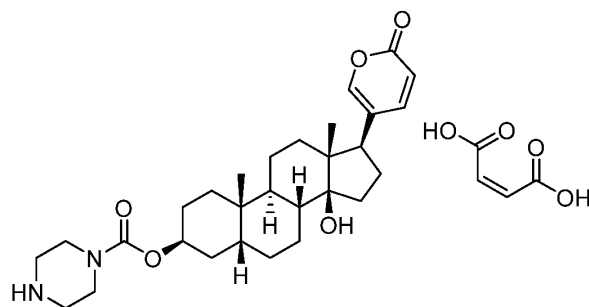
Conditions	Time points	Appearance	Purity	DSC	XRPD
40°C / 75%RH (open)	0 month	White powder	99.86%	233.84 °C	Form I
	6 months	White powder	99.91%	234.28 °C	Form I
25°C / 60%RH (open)	0 month	White powder	99.86%	233.84 °C	Form I
	12 months	White powder	99.87%	234.41 °C	Form I
	24 months	White powder	99.91%	232.9 °C	Form I
	36 months	White powder	100.00%	233.6 °C	Form I

[195] While some embodiments have been shown and described, various modifications and substitutions may be made thereto without departing from the spirit and scope of the invention. For example, for claim construction purposes, it is not intended that the claims set forth hereinafter be construed in any way narrower than the literal language thereof, and it is thus not intended that exemplary embodiments from the specification be read into the claims. Accordingly, it is to be understood that the present invention has been described by way of illustration and not limitations on the scope of the claims.

CLAIMS

WHAT IS CLAIMED IS:

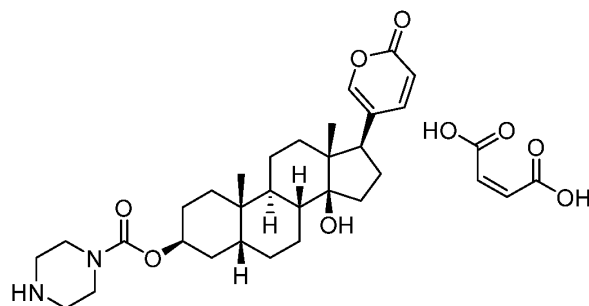
1. A compound that is (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

2. Crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

3. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 2, wherein the crystalline form is Crystalline Form I.
4. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 3, wherein Crystalline Form I is characterized by:
 - (a) an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;

- (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**;
 - (c) a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C;
 - (d) a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C;
 - (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**;
 - (f) a Thermogravimetric Analysis (TGA) thermogram substantially the same as shown in **Figure 3**;
 - (g) an unchanged XRPD after storage at 40 °C and 75% relative humidity (RH) for 6 months;
 - (h) an unchanged XRPD after storage at 25 °C and 60% relative humidity (RH) for 36 months;
 - or
 - (i) combinations thereof.
5. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 3 or claim 4, wherein Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , and $10.3 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
 6. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 5, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from $25.9 \pm 0.2^\circ$ 2- θ , $20.6 \pm 0.2^\circ$ 2- θ , and $14.8 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
 7. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 5 or claim 6, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from $27.8 \pm 0.2^\circ$ 2- θ , $25.2 \pm 0.2^\circ$ 2- θ , and $11.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
 8. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 5, wherein the X-ray powder diffraction pattern comprises at least five peaks selected from $13.8 \pm 0.2^\circ$ 2- θ , $19.5 \pm 0.2^\circ$ 2- θ , $10.3 \pm 0.2^\circ$ 2- θ , $25.9 \pm 0.2^\circ$ 2- θ , $20.6 \pm$

0.2° 2- θ , $14.8 \pm 0.2^\circ$ 2- θ , $27.8 \pm 0.2^\circ$ 2- θ , $25.2 \pm 0.2^\circ$ 2- θ , and $11.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

9. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 5, wherein the X-ray powder diffraction pattern comprises peaks at $13.8 \pm 0.1^\circ$ 2- θ , $19.5 \pm 0.1^\circ$ 2- θ , $10.3 \pm 0.1^\circ$ 2- θ , $25.9 \pm 0.1^\circ$ 2- θ , $20.6 \pm 0.1^\circ$ 2- θ , $14.8 \pm 0.1^\circ$ 2- θ , $27.8 \pm 0.1^\circ$ 2- θ , $25.2 \pm 0.1^\circ$ 2- θ , and $11.4 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
10. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 3 to 9, wherein Crystalline Form I is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 1**.
11. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 3 to 10, wherein Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm in the range of about 230-240 °C.
12. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 3 to 11, wherein Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram comprising an endotherm with an onset of about 234 °C and a peak of about 238 °C.
13. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 3 to 12, wherein Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**.
14. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 3 to 13, wherein Crystalline Form I is characterized by a Thermogravimetric Analysis (TGA) thermogram substantially the same as shown in **Figure 3**.

15. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 2, wherein the crystalline form is Crystalline Form II.
16. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 15, wherein Crystalline Form II is characterized by:
- (a) an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å;
 - (b) an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**;
 - (c) a differential scanning calorimetry (DSC) thermogram comprising:
 - i) an endotherm in the range of about 75-100 °C;
 - ii) an endotherm in the range of about 195-210 °C; and
 - iii) an endotherm in the range of 215-235 °C;
 - (d) a differential scanning calorimetry (DSC) thermogram comprising
 - i) an endotherm with an onset of about 77 °C and a peak of about 94 °C;
 - ii) an endotherm with an onset of about 202 °C and a peak of about 205 °C; and
 - iii) an endotherm with an onset of about 220 °C and a peak of about 230 °C;
 - (e) a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**;
 - (f) a Thermogravimetric Analysis (TGA) thermogram substantially the same as shown in **Figure 6**;
 - or
 - (g) combinations thereof.
17. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 15 or claim 16, wherein Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , and $15.2 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
18. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 17, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , and $16.4 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.

19. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 17 or claim 18, wherein the X-ray powder diffraction pattern further comprises at least one peak selected from $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
20. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 17, wherein the X-ray powder diffraction pattern comprises at least five peaks selected from $14.3 \pm 0.2^\circ$ 2- θ , $20.1 \pm 0.2^\circ$ 2- θ , $15.2 \pm 0.2^\circ$ 2- θ , $18.4 \pm 0.2^\circ$ 2- θ , $26.2 \pm 0.2^\circ$ 2- θ , $16.4 \pm 0.2^\circ$ 2- θ , $20.9 \pm 0.2^\circ$ 2- θ , $25.0 \pm 0.2^\circ$ 2- θ , and $27.0 \pm 0.2^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
21. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of claim 17, wherein the X-ray powder diffraction pattern comprises peaks at $14.3 \pm 0.1^\circ$ 2- θ , $20.1 \pm 0.1^\circ$ 2- θ , $15.2 \pm 0.1^\circ$ 2- θ , $18.4 \pm 0.1^\circ$ 2- θ , $26.2 \pm 0.1^\circ$ 2- θ , $16.4 \pm 0.1^\circ$ 2- θ , $20.9 \pm 0.1^\circ$ 2- θ , $25.0 \pm 0.1^\circ$ 2- θ , and $27.0 \pm 0.1^\circ$ 2- θ , as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å.
22. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 15 to 21, wherein Crystalline Form II is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**.
23. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 15 to 22, wherein Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising:
- an endotherm in the range of about 75-100 °C;
 - an endotherm in the range of about 195-210 °C; and
 - an endotherm in the range of 215-235 °C.
24. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 15 to 23, wherein Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram comprising:
- an endotherm with an onset of about 77 °C and a peak of about 94 °C;
 - an endotherm with an onset of about 202 °C and a peak of about 205 °C; and

- iii) an endotherm with an onset of about 220 °C and a peak of about 230 °C.
25. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 15 to 24, wherein Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**.
26. The crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 15 to 25, wherein Crystalline Form II is characterized by a Thermogravimetric Analysis (TGA) thermogram substantially the same as shown in **Figure 6**.
27. A pharmaceutical composition comprising crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 2 to 26, and at least one pharmaceutically acceptable excipient.
28. The pharmaceutical composition of claim 27, wherein the pharmaceutical composition is formulated for administration to a mammal by oral administration.
29. The pharmaceutical composition of claim 27 or claim 28, wherein the pharmaceutical composition is in the form of a solid form pharmaceutical composition.
30. The pharmaceutical composition of any one of claims 27 to 29, wherein the pharmaceutical composition is in the form of a tablet, a pill, a capsule, a powder, a liquid, a suspension, a suppository, or an aerosol.
31. A packaged pharmaceutical composition comprising a pharmaceutical composition of any one of claims 27 to 30 and instructions for using the composition to treat a subject suffering from cancer.
32. A method of treating a neoplasm in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of the crystalline (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate of any one of claims 2 to 26, or the pharmaceutical composition of any one of claims 27 to 30.
33. The method of claim 32, wherein the neoplasm is a cancer.
34. The method of claim 33, wherein the cancer is head and neck cancer, brain cancer, colon carcinoma, pancreatic cancer, breast cancer, ovarian cancer, prostate cancer, fibrosarcoma, myxosarcoma, liposarcoma, chondrosarcoma, osteogenic sarcoma, chondroma,

angiosarcoma, endotheliosarcoma, lymphangiosarcoma, lymphangioendotheliosarcoma, synovioma, mesothelioma, Ewing's tumor, leiomyosarcoma, rhabdomyosarcoma, squamous cell carcinoma, basal cell carcinoma, adenocarcinoma, sweat gland carcinoma, sebaceous gland carcinoma, papillary carcinoma, papillary adenocarcinomas, cystadenocarcinoma, medullary carcinoma, bronchogenic carcinoma, renal cell carcinoma, hepatoma, bile duct carcinoma, choriocarcinoma, seminoma, embryonal carcinoma, Wiims' tumor, cervical cancer, testicular tumor, lung carcinoma, small cell lung carcinoma, bladder carcinoma, epithelial carcinoma, glioma, astrocytoma, medulloblastoma, craniopharyngioma, ependymoma, pinealoma, hemangioblastoma, acoustic neuroma, oligodendroglioma, meningioma, melanoma, neuroblastoma, retinoblastoma, leukemias, e.g., acute lymphocytic leukemia and acute myelocytic leukemia (myeloblastic, promyelocytic, myelomonocytic, monocytic and erythroleukemia); chronic leukemia (chronic myelocytic (granulocytic) leukemia and chronic lymphocytic leukemia); and polycythemia vera, lymphoma (Hodgkin's disease and non-Hodgkin's disease), multiple myeloma, Waldenstrom's macroglobulinemia, and heavy chain disease.

35. The method of claim 33 or claim 34, wherein the cancer is colorectal cancer.
36. The method of claim 33 or claim 34, wherein the cancer is liver cancer.
37. The method of claim 33 or claim 34, wherein the cancer is lung cancer.
38. The method of claim 33 or claim 34, wherein the cancer is breast cancer.
39. The method of claim 33 or claim 34, wherein the cancer is oral cancer.
40. The method of claim 33 or claim 34, wherein the cancer is head and neck cancer.
41. The method of claim 33 or claim 34, wherein the cancer is brain cancer.
42. A method of preparing Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate, wherein the method comprises:
 - (a) contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid in a solvent to obtain a solution of the (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate; and
 - (b) crystallizing the solution obtained in step (a) to obtain Crystalline Form I of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-

yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.

43. The method of claim 42, wherein the solvent in step (a) comprises ethyl acetate, DCM, ethanol, or isopropanol.
44. The method of claim 42 or claim 43, wherein the solvent in step (a) comprises ethanol.
45. The method of any one of claims 42 to 44, wherein step (a) is performed at a temperature of about 60-90 °C.
46. The method of any one of claims 42 to 45, wherein step (a) is performed at a temperature of about 70 °C.
47. The method of any one of claims 41 to 45, wherein step (a) is performed for a time of about 1-3 hours.
48. The method of any one of claims 42 to 47, wherein step (a) is performed for a time of about 1.5 hours.
49. The method of any one of claims 42 to 48, wherein step (b) comprises cooling the solution obtained in step (a) to room temperature.
50. The method of any one of claims 42 to 48, wherein step (b) comprises cooling the solution obtained in step (a) to a temperature of about 20-25 °C.
51. The method of any one of claims 42 to 50, further comprising filtering the crystallized solution obtained in step (b) to obtain Crystalline Form I.
52. The method of any one of claims 42 to 51, further comprising drying the obtained Crystalline Form I.
53. The method of claim 52, wherein the drying is performed under vacuum at room temperature.
54. The method of claim 52, wherein the drying is performed under vacuum at a temperature of about 20-25 °C.
55. A method of preparing Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate, wherein the method comprises:
 - (a) contacting (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate with maleic acid in a solvent to obtain a solution of the (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate; and

- (b) crystallizing the solution obtained in step (a) to obtain Crystalline Form II of
(3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate.
56. The method of claim 55, wherein the solvent in step (a) comprises ethyl acetate, DCM, ethanol, or isopropanol.
57. The method of claim 55 or claim 56, wherein the solvent in step (a) comprises isopropanol.
58. The method of any one of claims 55 to 57, wherein step (a) is performed at room temperature.
59. The method of any one of claims 55 to 57, wherein step (a) is performed at a temperature of about 20-25 °C.
60. The method of any one of claims 55 to 59, wherein step (b) comprises stirring the solution obtained in step (a) overnight.
61. The method of any one of claims 55 to 60, further comprising filtering the crystallized solution obtained in step (b) to obtain Crystalline Form II.
62. The method of any one of claims 55 to 61, further comprising drying the obtained Crystalline Form II.
63. The method of claim 62, wherein the drying is performed under vacuum at 35 °C.