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.

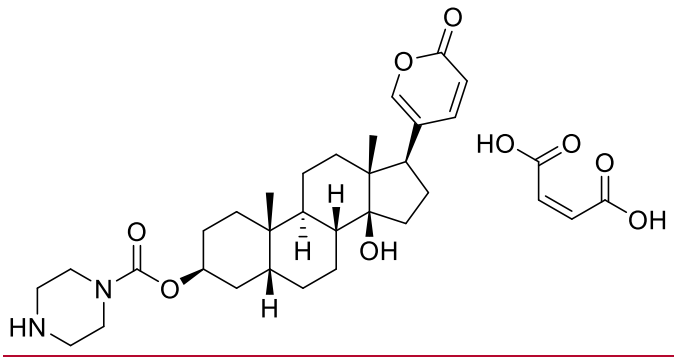
BACKGROUND OF THE INVENTION

[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~~

[03a] In an aspect of the present disclosure, there is provided 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):

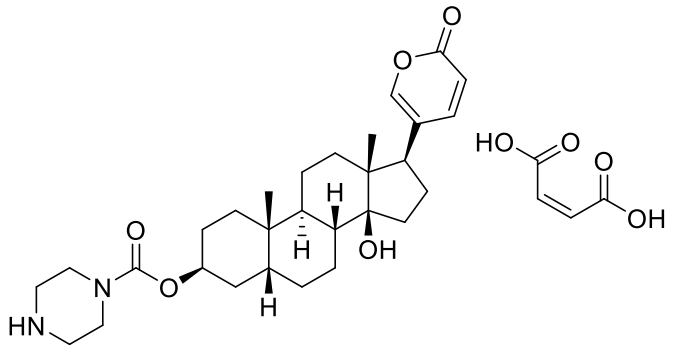


Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

[03b] In another aspect of the present disclosure, there is provided a 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.

[03c] In a further aspect of the present disclosure, there is provided 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 disclosed herein, and at least one pharmaceutically acceptable excipient.

[03d] In another aspect of the present disclosure, there is provided a packaged pharmaceutical composition comprising a pharmaceutical composition disclosed herein and instructions for using the composition to treat a subject suffering from cancer.

[03e] In a further aspect of the present disclosure, there is provided a use 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 disclosed herein, or the pharmaceutical composition disclosed herein, in the manufacture of a medicament for treating a neoplasm in a subject in need thereof.

[03f] In another aspect of the present disclosure, there is provided 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.

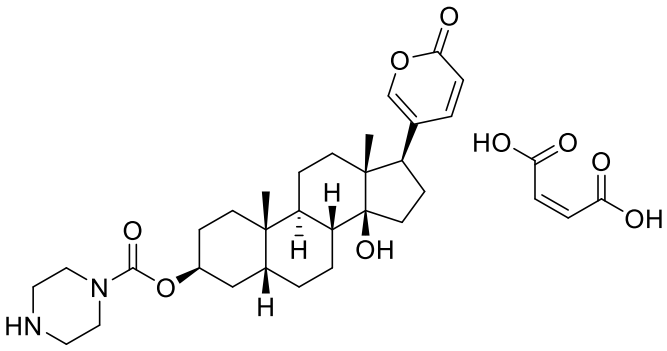
[03g] In a further aspect of the present disclosure, there is provided a method of preparing Crystalline Form II of (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate, wherein 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.

[03h] In another aspect of the present disclosure, there is provided a 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 disclosed herein, or the pharmaceutical composition disclosed herein, for use in therapy.

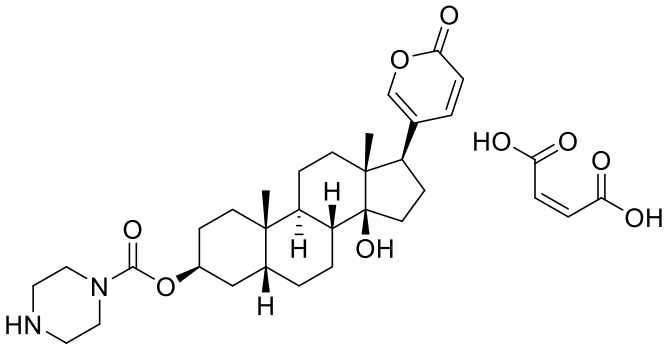
[04] In one ~~aspect~~example, the disclosure provides a compound that is (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



Compound A maleate,

or a pharmaceutically acceptable solvate or hydrate thereof.

[05] In another ~~aspect~~example, 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 ~~embodiment~~examples, the crystalline form is Crystalline Form I. In some ~~embodiment~~examples, Crystalline Form I is characterized by:

(a) an X-ray powder diffraction pattern comprising peaks at 13.8 ± 0.2° 2-θ, 19.5 ± 0.2° 2-θ, and 10.3 ± 0.2° 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 ~~embodiment~~examples, Crystalline Form I is characterized by an X-ray powder diffraction pattern comprising peaks at 13.8 ± 0.2° 2-θ, 19.5 ± 0.2° 2-θ, and 10.3 ± 0.2° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some

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

[08] In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~examples, Crystalline Form I is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 2**.

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

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

(a) an X-ray powder diffraction pattern comprising peaks at 14.3 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, and 15.2 ± 0.2° 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 ~~embodiment~~examples, Crystalline Form II is characterized by an X-ray powder diffraction pattern comprising peaks at 14.3 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, and 15.2 ± 0.2° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some ~~embodiment~~examples, the X-ray powder diffraction pattern further comprises at least one peak selected from 18.4 ± 0.2° 2-θ, 26.2 ± 0.2° 2-θ, and 16.4 ± 0.2° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some ~~embodiment~~examples, the X-ray powder diffraction pattern further comprises at least one peak selected from 20.9 ± 0.2° 2-θ, 25.0 ± 0.2° 2-θ, and 27.0 ± 0.2° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some ~~embodiment~~examples, the X-ray powder diffraction pattern comprises at least five peaks selected from 14.3 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, 15.2 ± 0.2° 2-θ, 18.4 ± 0.2° 2-θ, 26.2 ± 0.2° 2-θ, 16.4 ± 0.2° 2-θ, 20.9 ± 0.2° 2-θ, 25.0 ± 0.2° 2-θ, and 27.0 ± 0.2° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some ~~embodiment~~examples, the X-ray powder diffraction pattern comprises peaks at 14.3 ± 0.1° 2-θ, 20.1 ± 0.1° 2-θ, 15.2 ± 0.1° 2-θ, 18.4 ± 0.1° 2-θ, 26.2 ± 0.1° 2-θ, 16.4 ± 0.1° 2-θ, 20.9 ± 0.1° 2-θ, 25.0 ± 0.1° 2-θ, and 27.0 ± 0.1° 2-θ, as measured by X-ray powder diffraction using an X-ray wavelength of 1.54179 Å. In some ~~embodiment~~examples, Crystalline Form II is characterized by an X-ray powder diffraction pattern substantially the same as shown in **Figure 4**.

[12] In some ~~embodiment~~examples, 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 ~~embodiment~~examples, 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 ~~embodiment~~example**s**, Crystalline Form II is characterized by a differential scanning calorimetry (DSC) thermogram substantially the same as shown in **Figure 5**.

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

[16] In another ~~aspect~~example, 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 ~~embodiment~~example**s**, the pharmaceutical composition is formulated for administration to a mammal by oral administration. In some ~~embodiment~~example**s**, the pharmaceutical composition is in the form of a solid form pharmaceutical composition. In some ~~embodiment~~example**s**, 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~~example, 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~~example, 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 ~~embodiment~~example**s**, the neoplasm is a cancer. In some ~~embodiment~~example**s**, 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. In some ~~embodiment~~examples, the cancer is colorectal cancer. In some ~~embodiment~~examples, the cancer is liver cancer. In some ~~embodiment~~examples, the cancer is lung cancer. In some ~~embodiment~~examples, the cancer is breast cancer. In some ~~embodiment~~examples, the cancer is oral cancer. In some ~~embodiment~~examples, the cancer is head and neck cancer. In some ~~embodiment~~examples, the cancer is brain cancer.

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

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

[22] In another ~~aspect~~example, 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 ~~embodiment~~examples, the solvent in step (a) comprises ethyl acetate, DCM, ethanol, or isopropanol. In some ~~embodiment~~examples, the solvent in step (a) comprises isopropanol. In some ~~embodiment~~examples, step (a) is performed at room temperature. In some ~~embodiment~~examples, step (a) is performed at a temperature of about 20-25 °C.

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

[25] In some ~~embodiment~~examples, the method further comprises filtering the crystallized solution obtained in step (b) to obtain Crystalline Form II. In some ~~embodiment~~examples, the method further comprises drying the obtained Crystalline Form II. In some ~~embodiment~~examples, 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.

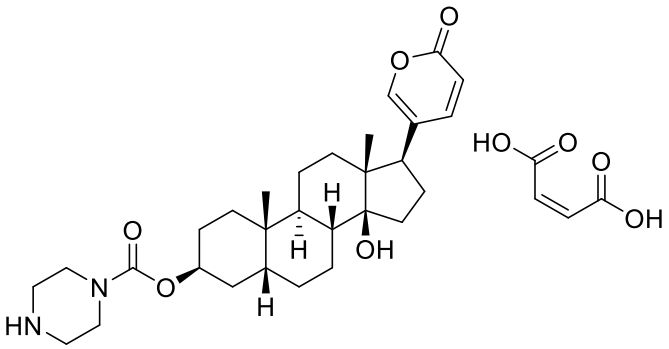
DESCRIPTION OF THE DRAWINGS

[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:

CLAIMS

WHAT IS CLAIMED IS:

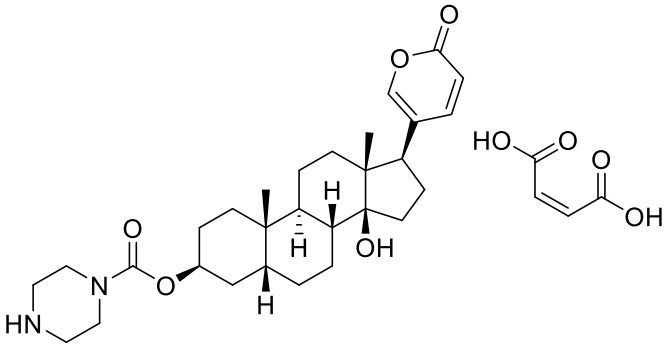
1. A compound that is (3*S*,5*R*,8*R*,9*S*,10*S*,13*R*,14*S*,17*R*)-14-hydroxy-10,13-dimethyl-17-(2-oxo-2*H*-pyran-5-yl)hexadecahydro-1*H*-cyclopenta[*a*]phenanthren-3-yl piperazine-1-carboxylate maleate (Compound A maleate):



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 ± 0.2° 2-θ, 19.5 ± 0.2° 2-θ, and 10.3 ± 0.2° 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 ± 0.2° 2-θ, 19.5 ± 0.2° 2-θ, and 10.3 ± 0.2° 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 ± 0.2° 2-θ, 20.6 ± 0.2° 2-θ, and 14.8 ± 0.2° 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 ± 0.2° 2-θ, 25.2 ± 0.2° 2-θ, and 11.4 ± 0.2° 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 ± 0.2° 2-θ, 19.5 ± 0.2° 2-θ, 10.3 ± 0.2° 2-θ, 25.9 ± 0.2° 2-θ, 20.6 ±

0.2° 2-θ, 14.8 ± 0.2° 2-θ, 27.8 ± 0.2° 2-θ, 25.2 ± 0.2° 2-θ, and 11.4 ± 0.2° 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 ± 0.1° 2-θ, 19.5 ± 0.1° 2-θ, 10.3 ± 0.1° 2-θ, 25.9 ± 0.1° 2-θ, 20.6 ± 0.1° 2-θ, 14.8 ± 0.1° 2-θ, 27.8 ± 0.1° 2-θ, 25.2 ± 0.1° 2-θ, and 11.4 ± 0.1° 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 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, and 15.2 ± 0.2° 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 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, and 15.2 ± 0.2° 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 ± 0.2° 2-θ, 26.2 ± 0.2° 2-θ, and 16.4 ± 0.2° 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 ± 0.2° 2-θ, 25.0 ± 0.2° 2-θ, and 27.0 ± 0.2° 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 ± 0.2° 2-θ, 20.1 ± 0.2° 2-θ, 15.2 ± 0.2° 2-θ, 18.4 ± 0.2° 2-θ, 26.2 ± 0.2° 2-θ, 16.4 ± 0.2° 2-θ, 20.9 ± 0.2° 2-θ, 25.0 ± 0.2° 2-θ, and 27.0 ± 0.2° 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 ± 0.1° 2-θ, 20.1 ± 0.1° 2-θ, 15.2 ± 0.1° 2-θ, 18.4 ± 0.1° 2-θ, 26.2 ± 0.1° 2-θ, 16.4 ± 0.1° 2-θ, 20.9 ± 0.1° 2-θ, 25.0 ± 0.1° 2-θ, and 27.0 ± 0.1° 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:
    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.
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:
    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.

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~~ Use 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, in the manufacture of a medicament for treating a neoplasm in a subject in need thereof.
33. The ~~method~~use of claim 32, wherein the neoplasm is a cancer.
34. The ~~method~~use 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~~use of claim 33 or claim 34, wherein the cancer is colorectal cancer.
36. The ~~method~~use of claim 33 or claim 34, wherein the cancer is liver cancer.
37. The ~~method~~use of claim 33 or claim 34, wherein the cancer is lung cancer.
38. The ~~method~~use of claim 33 or claim 34, wherein the cancer is breast cancer.
39. The ~~method~~use of claim 33 or claim 34, wherein the cancer is oral cancer.
40. The ~~method~~use of claim 33 or claim 34, wherein the cancer is head and neck cancer.
41. The ~~method~~use 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.

64. 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, for use in therapy.