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(54) Title: AMORPHOUS CABAZITAXEL

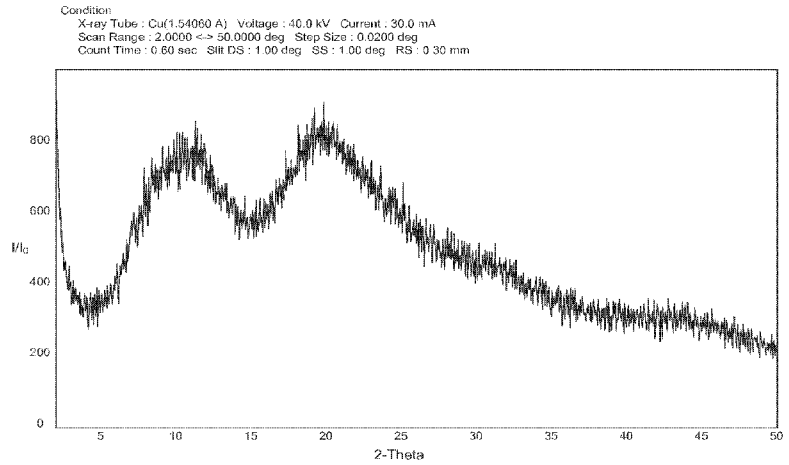


FIG. 2

(57) Abstract: The present invention is directed to an amorphous form of cabazitaxel, which can be prepared by dissolving a solid form of cabazitaxel in an organic solvent, and removing the organic solvent to dryness. The amorphous form of cabazitaxel is characterized by DSC as in FIG. 1 and/or X-ray powder diffraction pattern as in FIG. 2.

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AMORPHOUS CABAZITAXEL

FIELD OF THE INVENTION

The present disclosure relates to amorphous cabazitaxel and process of preparing it.

BACKGROUND OF THE INVENTION

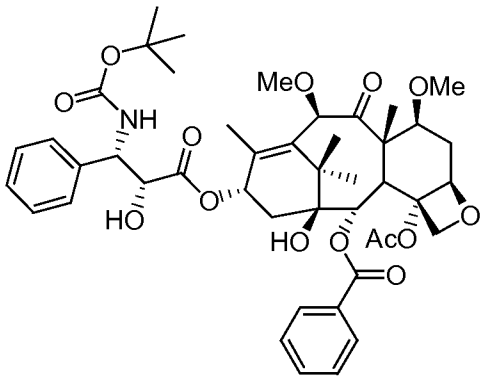
Taxoids are compounds derived from taxol (also referred to as paclitaxel), an isolated natural product and an important anticancer drug. Taxoids stabilize microtubules during mitosis to treat patients with different kinds of cancer (e.g. ovarian cancer, breast cancer and lung cancer).

Cabazitaxel is a semi-synthetic derivative of a natural taxoid 10-deacetylbaccatin III (10-DAB)) with potential anti-neoplastic activity. Cabazitaxel binds to and stabilizes tubulin, resulting in the inhibition of microtubule depolymerization and cell division, cell cycle arrest in the G2/M phase, and the inhibition of tumor cell proliferation. Unlike other taxane compounds, this agent is a poor substrate for the membrane-associated, multidrug resistance, P-glycoprotein (P-gp) efflux pump and may be useful for treating multidrug-resistant tumors. In addition, cabazitaxel penetrates the blood-brain barrier.

Cabazitaxel was developed by Sanofi-Aventis and was approved by FDA in 2010. JEVTANA® (cabazitaxel injection) is a microtubule inhibitor indicated in combination with prednisone for the treatment of patients with hormone-refractory metastatic prostate cancer previously treated with a docetaxel-containing treatment regimen.

The systematic (IUPAC) name of cabazitaxel is (1S,2S,3R,4S,7R,9S,10S,12R,15S)-4-(acetyloxy)-15-{[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoyl]oxy}-1-hydroxy-9,1

2-dimethoxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.03,10.04,7]heptadec-13-en-2-yl benzoate. Its chemical structure is shown below.



Cabazitaxel

BRIEF DESCRIPTION OF THE DRAWINGS

FIG. 1 shows a thermogram of differential scanning calorimetry (DSC) spectrum of amorphous cabazitaxel (Example 19).

FIG. 2 shows the X-ray powder diffraction pattern of amorphous cabazitaxel (Example 19).

FIG.. 3 shows an infrared (IR) spectrum of amorphous cabazitaxel (Example 19).

DETAILED DESCRIPTION OF THE INVENTION

The present invention is directed to an amorphous form of cabazitaxel, which can be prepared by dissolving a solid form, e.g., a crystalline form, of cabazitaxel in an organic solvent, and removing the organic solvent to dryness.

An amorphous form, as used herein, refers to a solid without a shape. An amorphous solid is a solid that lacks the long-range order characteristic of a crystal. An amorphous solid is disordered and it does not have a single repeat unit like a crystal.

Method of Preparing an amorphous form of cabazitaxel

Crystalline forms of cabazitaxel can be purchased from several commercial sources, e.g., MedKoo Biosciences. Alternatively, a crystalline form of cabazitaxel can be prepared according to US2012/0149925, which is incorporated herein by reference in its entirety.

An amorphous form cabazitaxel can be prepared by a method comprising (a) dissolving a solid form of cabazitaxel in an organic solvent or a solvent mixture, and (b) removing the organic solvent or the solvent mixture to form the compound. Organic solvents suitable for this invention include C_{1-4} halogenated hydrocarbon, C_{1-4} alcohols, C_{3-5} ketone, C_{1-4} nitrile, C_{2-8} ether, or C_{3-7} ester. A suitable organic solvent or solvent mixture for example is dichloromethane, ethanol, methanol, acetone, acetonitrile, ethyl acetate, isopropyl acetate, isopropyl alcohol, diispropyl ether, diethyl ether, tetrahydrofuran, 1,2-dimethoxyethane, toluene, chloroform, dimethylformamide, dimethylsulfoxide, or a combination thereof.

The solvent or solvent mixture of the above method can be removed by evaporation, vacuum condensation, spray drying, or filtration and drying. In one embodiment, the solvent or solvent mixture is removed, for example, by vacuum condensation, at about 25 - 60°C, or about 25 - 45°C, and under a pressure is less than about 700 mm Hg, preferably less than about 300 or 100 mmHg. In another embodiment, the solvent or solvent mixture is removed by spray drying with nitrogen gas having an inlet temperature of about 50 - 150°C. In another embodiment, the solvent or solvent mixture is removed by drying under reduced pressure at about 40°C. The process of removing the solvent in general takes place quickly to avoid orderly crystal growth, in about 1-60 minutes, or 3-30 minutes, or 5-10 minutes.

The amorphous cabazitaxel can optionally be re-purified by re-dissolving the solid in a suitable organic solvent as describe above, followed by removing the solvent to dryness.

Characterization of Amorphous Cabazitaxel

The amorphous cabazitaxel can be characterized by the following analysis.

Thermal analysis: Two thermal analysis, thermogravimetric analysis (TGA) and differential scanning calorimetry (DSC) can be used. TGA measures the change in the mass of sample as the temperature is changed. The profile of the overall thermogravimetric weight loss versus temperature curve provides reliable indication of the phase and weight changes of the pharmaceutical compounds.

DSC examines the changes in physical properties of the pharmaceutical compound with temperature or time. During operation, DSC heats the test sample, measures heat flow between the test sample and its surrounding environment, and records a test thermogram of the test sample based on the measured heat flow. DSC provides information regarding the onset temperature, the endothermal maximum of melting, and the enthalpy of the compound.

Powder X-ray diffraction (PXRD): PXRD is used to characterize the solid state character of a compound.

High Performance Liquid Chromatography (HPLC): The content and/or purity of the amorphous cabazitaxel can be determined by HPLC method.

UV Spectroscopy: The UV spectroscopy can be used to perform qualitative analysis of the amorphous cabazitaxel.

Infrared (IR) Spectroscopy: Functional groups of the amorphous cabazitaxel can be determined by IR spectra based on their respective light transmittance.

Pharmaceutical Formulation

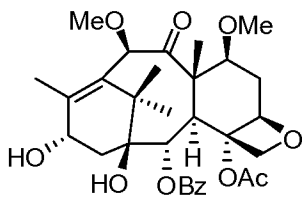
The present invention is directed to a pharmaceutical formulation comprising amorphous cabazitaxel and a pharmaceutically acceptable carrier. The pharmaceutical acceptable carriers

are in general those commonly used and generally recognized by person skilled in the art of pharmaceutical formulation.

EXAMPLES

As used herein, "DMF" means dimethylformamide; "10-DAB" means 10-deacetylbaccatin III; "THF" means tetrahydrofuran.

Example 1. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by CsBr



C1

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen, and stirred for 20 minutes. Natural taxoid 10-deacetylbaccatin III (10-DAB) was obtained from Yung Shin Pharm. Ind. Co. LTD. (Taichung, Taiwan) or SM Herbal (India). 10-DAB (1 eq, 1 g)/Me_2SO_4 (10 eq, 1.74 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (yield : 50 %, 0.37 g, LC purity: 90%). ^1H NMR

(400 MHz, D^6-DMSO) δ 8.01 (d, J = 7.2 Hz, 2H), 7.66 (t, J = 7.4 Hz, 1H), 7.56 (t, J = 7.6 Hz, 2H), 5.37 (d, J = 7.2 Hz, 1H), 5.31 (d, J = 4.0 Hz, 1H), 4.97 (d, J = 8.4 Hz, 1H), 4.74 (s, 1H), 4.72-4.61 (m, 1H), 4.40 (s, 1H), 4.03 (dd, J = 8.2, 13.4 Hz, 2H), 3.81 (dd, J = 6.6, 10.6 Hz, 1H), 3.75 (d, J = 7.2 Hz, 1H), 3.29 (s, 3H), 3.21 (s, 3H), 2.74-2.62 (m, 1H), 2.20 (s, 3H), 2.17 (d, J = 8.4 Hz, 2H), 1.97 (s, 3H), 1.58-1.41 (m, 4H), 0.93 (s, 6H); ^{13}C NMR (100 MHz, D^6-DMSO) δ 205.5, 169.7, 165.2, 144.1, 133.3, 132.8, 130.2, 129.5, 128.7, 83.3, 82.8, 80.5, 80.1, 76.9, 75.3, 74.4, 66.2, 56.7, 56.5, 56.1, 47.1, 42.5, 31.8, 26.9, 22.4, 20.5, 15.2, 10.1.

Example 2. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by CsBr

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen and was stirred for 20 minutes. 10-DAB (1 eq, 1 g)/MeI (10 eq, 1.2 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 52%)

Example 3. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by CsBr

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen and was stirred for 20

minutes. 10-DAB (1 eq, 1 g)/$MePhSO_3Me$ (10 eq, 2.77 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 40%)

Example 4. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by CsBr

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen and was stirred for 20 minutes. 10-DAB (1 eq, 1 g)/CF_3SO_3Me (10 eq, 2.08 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 46%)

Example 5. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by a mixture of CsBr and KBr

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g)/KBr (0.1 eq, 0.02 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen and

was stirred 20 minutes. 10-DAB (1 eq, 1 g)/Me_2SO_4 (10 eq, 1.74 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 66%)

Example 6. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by a mixture of CsBr and $MgBr_2$

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g)/$MgBr_2$ (0.1 eq, 0.03 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen, and stirred for 20 minutes. 10-DAB (1 eq, 1 g)/Me_2SO_4 (10 eq, 1.74 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 74%).

Example 7. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by a mixture of CsBr and $ZnBr_2$

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g)/$ZnBr_2$ (0.1 eq, 0.04 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen, and

stirred for 20 minutes. 10-DAB (1 eq, 1 g)/Me_2SO_4 (10 eq, 1.74 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 17 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 44%).

Example 8. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) catalyzed by a mixture of CsBr and $CeCl_3$

A solution of sodium hydride (60%, 3 eq, 0.22 g)/CsBr (0.5 eq, 0.20 g)/$CeCl_3$ (0.1 eq, 0.05 g) was dissolved in co-solvent THF/DMF (2/1, 6 mL), cooled down to -20°C under nitrogen, and stirred for 20 minutes. 10-DAB (1 eq, 1 g)/Me_2SO_4 (10 eq, 1.74 mL) in THF/DMF (2/1, 6 mL) was added into the sodium hydride reaction mixture slowly. The reaction mixture was allowed to warm up to room temperature gradually. The reaction mixture was stirred for 2 hours until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with CH_2Cl_2 and water. After partition, the organic layer extracted with saturated $NaHCO_{3(aq)}$. It was concentrated and purification by recrystallization (CH_2Cl_2/Hexane) to yielded C1 as white solid (LC purity: 61%).

Example 9. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) by $(Naphthalene)^- \cdot Li^+$ and catalyzed with CsBr

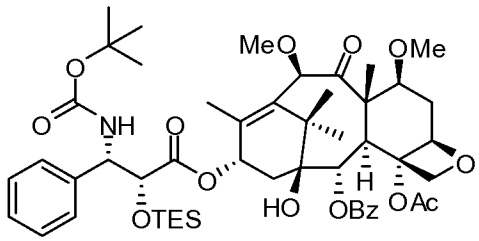
Lithium (3.0 eq, 40 mg) and naphthalene (3.3 eq, 780 mg) in anhydrous THF (11 mL) was stirred under nitrogen at 25 °C for 16 hr, then cooled to -78°C. The solution of 10-DAB (1 eq, 1

g) and Me_2SO_4 (10 eq, 1.74 mL) in anhydrous THF (9 mL) was added into mixture of $(Naphthalene)^-\bullet Li^+$ and CsBr (0.5 eq, 200 mg) slowly. The reaction mixture was returned gradually to room temperature. After stirred for 6.5h, the starting material was consumed. The mixture was quenched by 10% AcOH/THF and then extracted with CH_2Cl_2 and H_2O. The organic layer was dried by rotavapor to obtain the crude C1 (HPLC purity: 22%). (*Tetrahedron, 66*, 871, 2010; *Tetrahedron lett., 39*, 4183, 1998)

Example 10. Preparation of 7,10-di-methoxy-10-deacetylbaccatin (III) (C1) by $(Naphthalene)^- \cdot Li^+$ and catalyzed with KBr

Lithium (3.0 eq, 40 mg) and naphthalene (3.3 eq, 780 mg) in anhydrous THF (11 mL) was stirred under nitrogen at 25 °C for 16 hr, then cooled to -78 °C. The solution of 10-DAB (1 eq, 1 g) and Me_2SO_4 (10 eq, 1.74 mL) in anhydrous THF (9 mL) was added into mixture of $(Naphthalene)^-\bullet Li^+$, and KBr (0.5 eq, 110 mg) slowly. The reaction mixture was returned gradually to room temperature. After stirred for 6.5h, the starting material was consumed. The mixture was quenched by 10% AcOH/THF and then extracted with CH_2Cl_2 and H_2O. The organic layer was dried by rotavapor to obtain the crude C1 (HPLC purity: 10%). (*Tetrahedron, 66*, 871, 2010; *Tetrahedron lett., 39*, 4183, 1998)

Example 11. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of LiBr



C2

A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15°C under nitrogen. And then 7,10-di-methoxy-10-DAB C1 (1 eq, 200 mg) dissolved in 2 mL THF was added into the sodium hydride mixture. And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (2.5 eq, 329 mg) and LiBr (0.5 eq, 15 mg) in 2 mL THF slowly. The reaction mixture was stirred 2 hours at -15~20°C until the reaction was complete. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (LC purity: 58%); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.10 (d, J = 7.2 Hz, 2H), 7.58 (t, J = 7.4 Hz, 1H), 7.47 (t, J = 7.6 Hz, 2H), 7.37 (t, J = 7.4 Hz, 2H), 7.32-7.27 (m, 3H), 6.29 (t, J = 8.6 Hz, 1H), 5.65 (d, J = 7.2 Hz, 1H), 5.49 (d, J = 9.6 Hz, 1H), 5.27 (d, J = 10.0 Hz, 1H), 5.00 (d, J = 7.6 Hz, 1H), 4.80 (s, 1H), 4.55 (s, 1H), 4.25 (dd, J = 8.4, 52.0 Hz, 2H), 3.94-3.83 (m, 2H), 3.45 (s, 3H), 3.30 (s, 3H), 2.76-2.65 (m, 1H), 2.53 (s, 3H), 2.41-2.14 (m, 2H), 1.95 (s, 3H), 1.85-1.74 (m, 2H), 1.72 (s, 3H), 1.68 (s, 1H), 1.33 (s, 9H), 1.24 (s, 3H), 1.20 (s, 3H), 0.78 (t, J = 7.8 Hz, 9H), 0.49-0.28 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 171.7, 170.0, 166.9, 155.2, 139.4, 138.9, 135.0, 133.5, 130.1, 129.2, 128.6, 128.5, 127.7, 126.4, 84.1, 82.4, 81.5, 80.6, 79.8, 78.9,

76.4, 75.2, 74.8, 71.6, 57.2, 57.0, 56.7, 47.2, 43.3, 35.2, 31.9, 28.1, 26.6, 22.9, 21.2, 14.3, 10.3, 6.5, 4.2.

Example 12. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of $MgBr_2$

A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15°C under nitrogen. And then 7,10-di-methoxy-10-DAB C1 (1 eq, 200 mg) dissolved in 2 mL THF was added into the sodium hydride mixture, And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (2.5 eq, 329 mg) and $MgBr_2$ (0.5 eq, 32 mg) in 2 mL THF slowly. The reaction mixture was stirred for 2 hours at -15~20 °C until the reaction was complete. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (LC purity: 79%).

Example 13. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of CsBr

A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15oC under nitrogen. And 7,10-di-methoxy-10-DAB C1 (1 eq, 200 mg) dissolved in 2 mL THF was added into the sodium hydride mixture, And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (2.5 eq, 329 mg)

and CsBr (0.5 eq, 37 mg) in 2 mL THF slowly. The reaction mixture was stirred for 1.5 hours at -15~20°C until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (LC purity: 85%).

Example 14. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of $CeCl_3$

A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15oC under nitrogen. And then 7,10-di-methoxy-10-DAB C1 (1 eq, 200 mg) dissolved in 2 mL THF was added into the sodium hydride mixture, And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (β-lactam, 2.5 eq, 329 mg) and $CeCl_3$ (0.5 eq, 43 mg) in 2 mL THF slowly. The reaction mixture was stirred for 2.5 hours at -15~20°C until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (LC purity: 87%).

Example 15. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of KBr

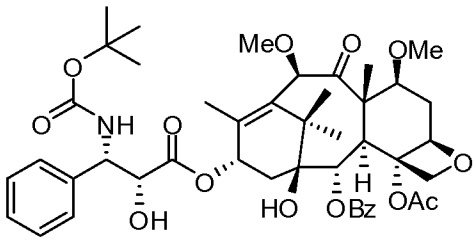
A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15oC under nitrogen. And then 7,10-di-methoxy-10-DAB C1 (1 eq, 200 mg) dissolved

in 2 mL THF was added into the sodium hydride mixture. And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (2.5 eq, 329 mg) and KBr (0.5 eq, 20 mg) in 2 mL THF slowly. The reaction mixture was for stirred 2.5 hours at -15~20°C until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (LC purity: 72%).

Example 16. Preparation of 1-hydroxy-7β,10β-di-methoxy-9-oxo-5β,20-epoxytax-11-ene-2α,4,13α-triyl 4-acetate 2-benzoate 13-{(2*R*,3*S*)-3-[(*tert*-butoxycarbonyl)amino]- 2-trethylsilyloxy-3-phenylpropanoate} (C2) by the catalyst of $FeCl_3$

A solution of sodium hydride (60 %, 8 eq, 112 mg) was dissolved in 2 mL THF and cooled down to -15°C under nitrogen. And then 7,10-di-methoxy-10-DAB (1 eq, 200 mg) dissolved in 2 mL THF was added into the sodium hydride mixture, And then was added the mixture of (3R,4S)-tert-butyl-2-oxy-4-phenyl-3-(triethylsilyloxy)azetidine-1-carboxylate (2.5 eq, 329 mg) and $FeCl_3$ (0.5 eq, 28 mg) in 2 mL THF slowly. The reaction mixture was stirred for 2.5 hours at -15~20°C until the reaction was completed. The mixture was quenched with 10 % AcOH/THF, and extracted with ethylacetate and water. The organic layer was dried by rotavapor to obtain the crude C2 (Yield: 45%, LC purity: 95%).

Example 17. Preparation of (1S,2S,3R,4S,7R,9S,10S,12R,15S)-4-(acetyloxy)-15-{[(2R,3S)-3-{[(tert-butoxy)carbonyl]amino}-2-hydroxy-3-phenylpropanoyl]oxy}-1-hydroxy-9,12-dimethoxy-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.$0^{3,10}$.$0^{4,7}$]heptadec-13-en-2-yl benzoate (Cabazitaxel)



Cabazitaxel

The C2 (490 mg, 1eq) was dissolved in 3.5 mL MeOH and was added dropwise 32 % $HCl_{(aq)}$ at -5~5°C, until the pH of C2 mixture reached between 1-2. The reaction mixture was stirred at -5~5°C until the deprotection was completed, then it was quenched with saturated $NaHCO_{3(aq)}$ and extracted with CH_2Cl_2. The organic layer was concentrated and purified by recrystallization (CH_2Cl_2/Hexane) at about -18~10°C, about 760 mmHg, for over an hour to yielded cabazitaxel as white solid (yield: 65 %; 280 mg, LC purity: 98 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 7.6 Hz, 2H), 7.60 (t, J = 7.4 Hz, 1H), 7.48 (t, J = 8.0 Hz, 2H), 7.42-7.36 (m, 4H), 7.36-7.29 (m, 1H), 6.20 (t, J = 8.6 Hz, 1H), 5.63 (d, J = 7.2 Hz, 1H), 5.43 (d, J = 9.6 Hz, 1H), 5.26 (d, J = 8.8 Hz, 1H), 4.97 (d, J = 8.0 Hz, 1H), 4.79 (s, 1H), 4.62 (s, 1H), 4.23 (dd, J = 8.2, 50.0 Hz, 2H), 3.90-3.77 (m, 2H), 3.50-3.40 (m, 4H), 3.30 (s, 3H), 2.75-2.64 (m, 1H), 2.36 (s, 3H), 2.32-2.18 (m, 2H), 1.88 (s, 3H), 1.84-1.74 (m, 2H), 1.71 (s, 3H), 1.67 (s, 1H), 1.36 (s, 9H), 1.23-1.17 (m, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 204.9, 172.6, 170.3, 166.8, 155.3, 138.7, 138.3, 135.4, 133.6, 130.1, 129.1, 128.7, 128.6, 127.9, 126.7, 84.0, 82.5, 81.6, 80.7, 80.1, 78.6, 76.4, 74.5, 73.7, 72.4, 57.2, 57.0, 56.8, 47.3, 43.2, 35.2, 32.0, 28.1, 26.7, 22.6, 20.6, 14.5, 10.3.

Example 18. Synthesis of Amorphous Cabazitaxel

The cabazitaxel solid (in a crystalline form) of Example 17 was dissolved in dichloromethane (0.6 mL), ethanol (2.0 mL), methanol (0.6 mL), or acetone (0.8 mL), followed by concentration to dryness under reduced pressure (< 100 mm Hg) at 40°C for about 5-10 minutes. The solid obtained was an amorphous form of cabazitaxel, characterized by the analysis in Example 19.

Example 19. Characterization of Amorphous Cabazitaxel

The amorphous cabazitaxel of Example 18 (prepared by dissolving in ethanol) is identified by the following analyses.

Differential scanning calorimetry (DSC) spectrum

FIG.. 1 shows a thermogram of differential scanning calorimetry (DSC) spectrum of the amorphous cabazitaxel. The DSC was run at a heating rate of 10°C/min. There was one endothermal band in the spectrum. The onset temperature was at 143.62°C and the endothermal maximum of melting is at 145.06°C.

Powder X-ray diffraction analysis

Powder X-ray diffraction (PXRD) analysis of the amorphous cabazitaxel was performed using a SHIMADZU XRD-6000 diffractometer. There was no sharp angel 2 θ peak. The PXRD pattern is shown in FIG. 2, where the X-axis is 2-Thera (2 θ) and the Y-axis is relative intensity (I/I_0).

IR Spectrum

The IR spectrum of the amorphous cabazitaxel was recorded using a Perkin Elmer Spectrum 100. The IR spectrum was shown with absorption bands ν_{max} at about 709, 1102, 1171, 1245, 1496, 1723, 2980 and 3442 (cm^{-1}) (FIG. 3) The peaks show the special functional groups of cabazitaxel.

While the present invention has been described with reference to the specific embodiments thereof, it should be understood by those skilled in the art that various changes may be made and equivalents may be substituted without departing from the scope of the invention.

What is Claimed is:

1. An amorphous form of cabazitaxel characterized by DSC as in FIG. 1 and/or X-ray powder diffraction pattern as in FIG. 2.

2. The amorphous form of cabazitaxel of Claim 1, characterized by X-ray powder diffraction pattern as in FIG. 2.

3. The amorphous form of cabazitaxel of Claim 1, characterized by DSC as in FIG. 1.

4. A pharmaceutical formulation comprising the amorphous form of cabazitaxel of Claim 1, and a pharmaceutically acceptable carrier.

5. A process of preparing the amorphous form of cabazitaxel of Claim 1, comprising:

dissolving a solid form of cabazitaxel in an organic solvent or an organic solvent mixture, and

removing the organic solvent or organic solvent mixture to form the amorphous form of cabazitaxel.

6. The process of Claim 5, wherein the solid form is a crystalline form.

7. The process of Claim 5, wherein said organic solvent is C_{1-4} halogenated hydrocarbon, C_{1-4} alcohols, C_{3-5} ketone, C_{1-4} nitrile, C_{2-8} ether, or C_{3-7} ester.

8. The process of Claim 7, wherein said organic solvent is dichloromethane, ethanol, methanol,

or acetone.

9. The process of Claim 5, wherein the organic solvent or the organic solvent mixture is removed by evaporation, vacuum condensation, spray drying, or filtration and drying.

10. The process of Claim 5, wherein the organic solvent or solvent mixture is removed at 25 - 60°C and under a pressure less than about 700 mm Hg.

11. The process of Claim 5, wherein the organic solvent or solvent mixture is removed within 3-30 minutes.

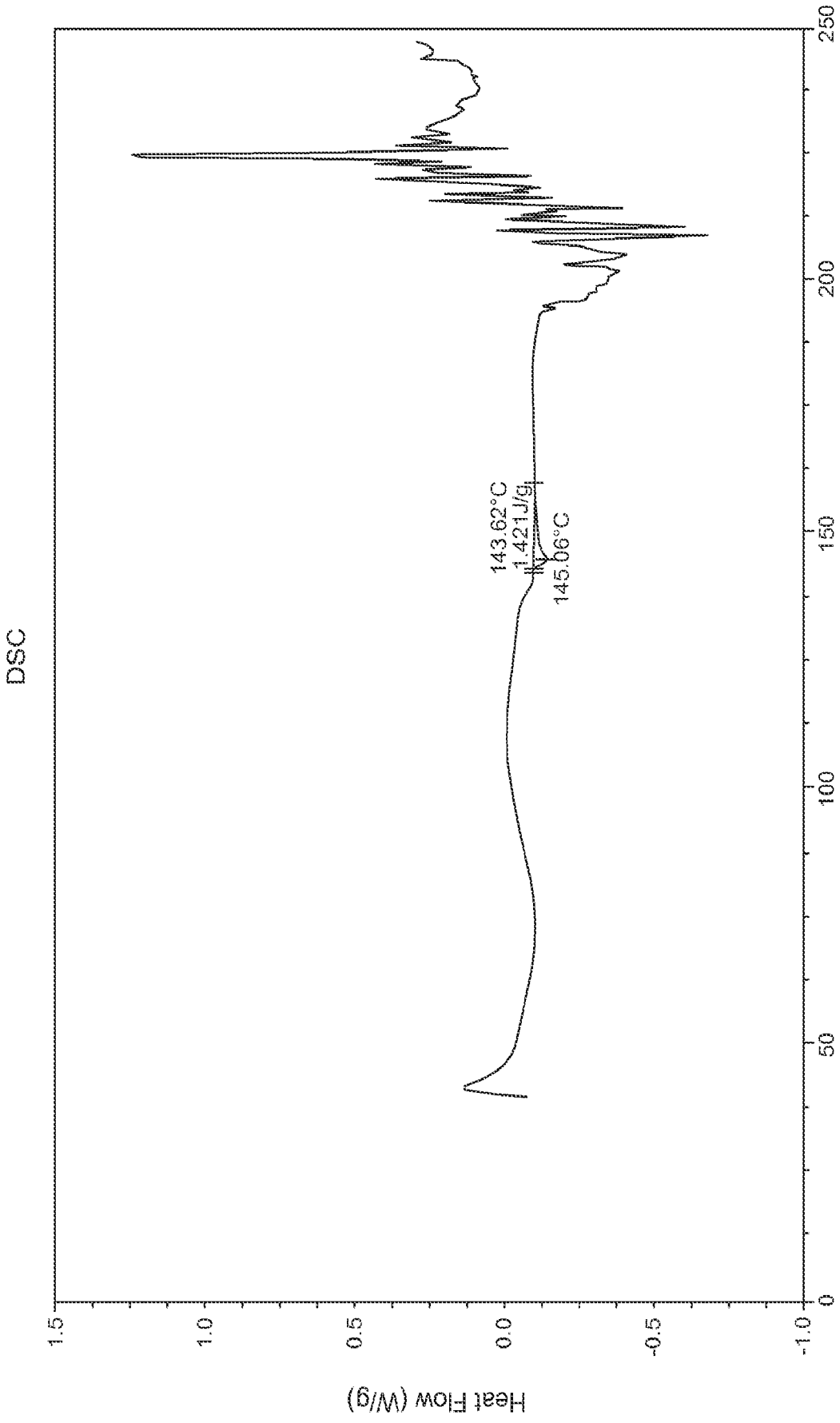

DSC
Heat Flow (W/g)
1.5
1.0
0.5
0.0
-0.5
-1.0
0
50
100
150
200
250
Temperature (°C)
143.62°C
1.421J/g
145.06°C

FIG. 1

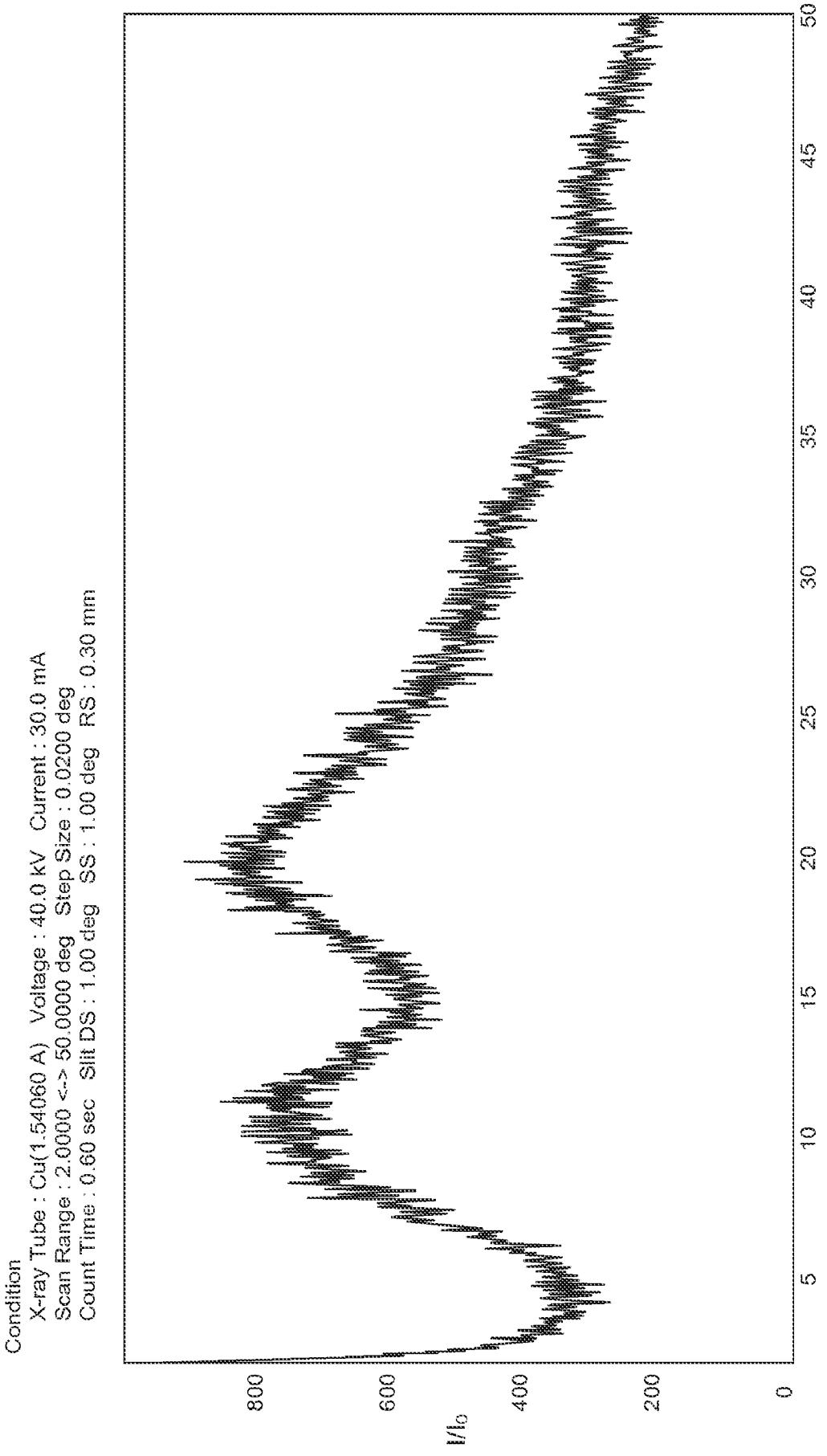

Condition
X-ray Tube : Cu(1.54060 A) Voltage : 40.0 kV Current : 30.0 mA
Scan Range : 2.0000 <-> 50.0000 deg Step Size : 0.0200 deg
Count Time : 0.60 sec Slit DS : 1.00 deg SS : 1.00 deg RS : 0.30 mm
I/I0
800
600
400
200
0
5
10
15
20
25
30
35
40
45
50
2-Theta

FIG. 2

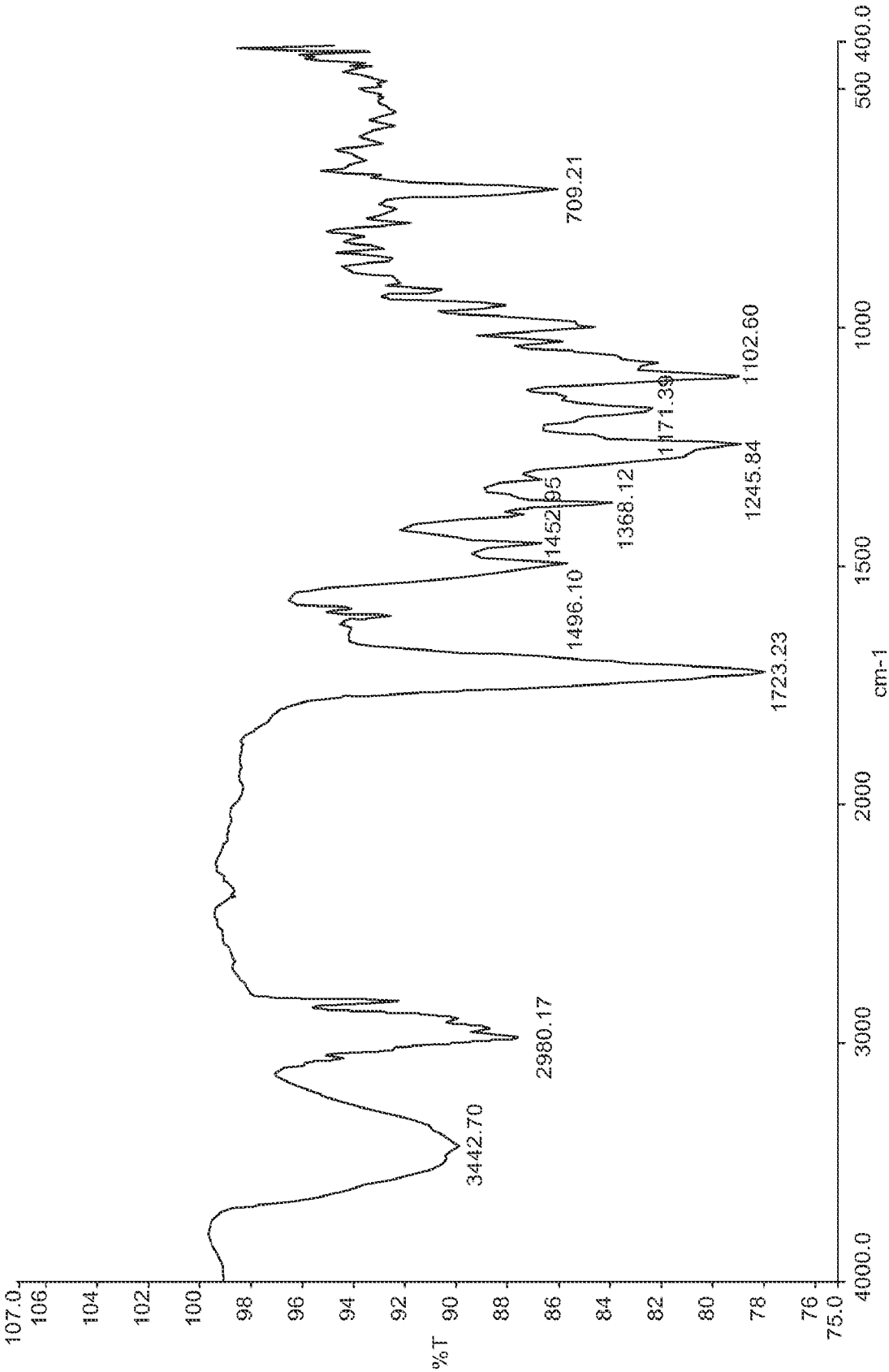

107.0
106
104
102
100
98
96
94
92
90
88
86
84
82
80
78
76
75.0
%T
4000.0
3000
2000
1500
1000
500 400.0
cm-1
3442.70
2980.17
1723.23
1496.10
1452.65
1368.12
1245.84
1171.39
1102.60
709.21

FIG. 3

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2013/052366

A. CLASSIFICATION OF SUBJECT MATTER

C07D 305/14(2006.01)i, A61K 31/337(2006.01)i, A61P 35/00(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D 305/14; A61K 31/337; A61K 31/164; A61K 31/56; A61P 35/00

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
Korean utility models and applications for utility models
Japanese utility models and applications for utility models

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
eKOMPASS(KIPO internal) & Keywords: cabazitaxel*, amorphous*

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
PX	US 2013-0109870 A1 (SASWATA LAHIRI et al.) 02 May 2013 See whole document	1-11
A	WO 2011-051894 A1 (AVENTIS PHARMA S.A.) 05 May 2011 See whole document	1-11
A	US 2012-0149925 A1 (KUNG LIANG-RERN et al.) 14 June 2012 See whole document	1-11
A	US 2012-0065255 A1 (PALEPU NAGESH) 15 March 2012 See whole document	1-11

☐ Further documents are listed in the continuation of Box C.

☒ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents,such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 November 2013 (27.11.2013)	**28 November 2013 (28.11.2013)**

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.
PCT/US2013/052366

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