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(81) **Designated States** *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

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(54) **Title**: A CARBON DIOXIDE ADDUCT OF PALBOCICLIB

(57) **Abstract**: The present invention provides a carbon dioxide adduct of palbociclib designated as crystalline Form VA. It also relates to the preparation of a carbon dioxide adduct of palbociclib, its pharmaceutical composition, and its use for the treatment of cyclin- dependent kinase (cdk) associated diseases.

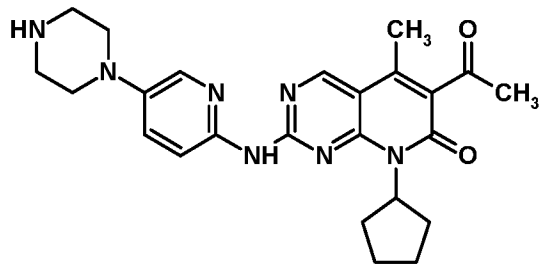
A CARBON DIOXIDE ADDUCT OF PALBOCICLIB

Field of the Invention

The present invention provides a carbon dioxide adduct of palbociclib designated as crystalline Form VA. It also relates to the preparation of a carbon dioxide adduct of palbociclib, its pharmaceutical composition, and its use for the treatment of cyclin-dependent kinase (cdk) associated diseases.

Background of the Invention

Palbociclib of Formula I is chemically described as 6-acetyl-8-cyclopentyl-5-methyl-2-[[5-(1-piperazinyl)-2-pyridinyl]amino]pyrido[2,3-*d*]pyrimidin-7(8*H*)-one.



Formula I

U.S. Patent No. 6,936,612 provides a process for the preparation of palbociclib hydrochloride.

U.S. Patent No. 7,781,583 provides a process for the preparation of palbociclib isoethionate.

U.S. Patent No. 7,863,278 provides polymorphs of various salts of palbociclib.

PCT Publication No. WO 2014/128588 provides crystalline Forms A and B of palbociclib.

Summary of the Invention

The present invention provides a carbon dioxide adduct of palbociclib designated as crystalline Form VA. It also relates to the preparation of a carbon dioxide adduct of palbociclib, its pharmaceutical composition, and its use for the treatment of cyclin-dependent kinase (cdk) associated diseases.

Brief Description of the Drawings

Figure 1 depicts an X-Ray Powder Diffraction (XRPD) pattern of a carbon dioxide adduct of palbociclib.

Figure 2 depicts a Differential Scanning Calorimetry (DSC) thermogram of a carbon dioxide adduct of palbociclib.

Figure 3 depicts an Infra-red (IR) spectrum of a carbon dioxide adduct of palbociclib.

Figure 4 depicts a Thermogravimetric analysis (TGA) thermogram of a carbon dioxide adduct of palbociclib.

Figure 5 depicts a Scanning electron microscopy (SEM) image of a carbon dioxide adduct of palbociclib.

Detailed Description of the Invention

The term "about," as used herein, refers to any value which lies within the range defined by a number up to ±10% of the value.

The term "ambient temperature," as used herein, refers to a temperature in the range of 25°C to 35°C.

The term "contacting," as used herein, refers to dissolving, slurrying, stirring, suspending, or combinations thereof.

The term "cyclin-dependent kinase (cdk) associated diseases," as used herein, refers to the diseases mediated by cdk, which include, but are not limited to, the cancers of the breast, ovary, cervix, prostate, testis, esophagus, and stomach.

The term "adduct," as used herein, refers to a product of a direct combination of two or more separate molecular entities, in such a way that there is no loss of atoms.

A first aspect of the present invention provides a carbon dioxide adduct of palbociclib designated as crystalline Form VA, characterized by an XRPD pattern having peaks at d-spacing of about 11.3, 6.8, 5.3, 4.2, and 3.7 Å, and further characterized by additional peaks at d-spacings of about 15.5, 10.0, 4.4, 4.1, and 3.3 Å.

Table 1 provides the d-spacing values (Å), the corresponding 2θ values, and the relative intensity of a carbon dioxide adduct of palbociclib.

Table 1

d-spacing (Å)	Position (±0.2° 2θ)	Relative Intensity (%)
15.5	5.7	42.4
11.3	7.8	100.0
10.7	8.3	24.2
10.0	8.8	54.6
7.8	11.4	20.0
7.2	12.4	4.0
6.8	13.0	59.9
6.0	14.7	3.9
5.5	16.1	23.4
5.3	16.6	95.1
5.2	17.1	9.2
5.0	17.6	10.1
4.8	18.3	25.8
4.5	19.5	36.8
4.4	20.0	41.9
4.3	20.7	34.2
4.2	21.1	62.9
4.1	21.4	49.1
4.1	21.6	34.4
4.0	22.2	17.8
3.7	24.0	73.2
3.6	24.9	14.3
3.3	26.7	52.4
3.3	27.4	15.9
3.2	27.8	12.1
3.1	29.1	10.7
3.0	30.2	8.9
2.8	31.5	12.2
2.8	32.5	9.9
2.6	34.5	10.2
2.5	35.5	7.4
2.4	37.3	10.0
2.3	38.7	9.8

A carbon dioxide adduct of palbociclib is characterized by a DSC thermogram having endothermic peaks at about 146.0°C and 267.0°C, and an exothermic peak at about 221.5°C.

The carbon dioxide adduct of palbociclib has 0.5 moles of carbon dioxide per mole of palbociclib.

The carbon dioxide adduct of palbociclib has a water content of about 0.5%.

The carbon dioxide adduct of palbociclib has weight loss of about 4.5% to about 5% as determined through thermogravimetric analysis (TGA).

The carbon dioxide adduct of palbociclib has weight loss of about 5% on drying (LOD). LOD was carried out under vacuum (5 mm of mercury) at a temperature of about 120°C for about 3 hours.

The carbon dioxide adduct of palbociclib shows a loss of carbon dioxide as determined through TGA MS technique.

The carbon dioxide adduct of palbociclib has a specific surface area (SSA) of greater than 2 m^2/g. In an embodiment of the present invention, the carbon dioxide adduct of palbociclib has a specific surface area (SSA) of about 3 m^2/g to about 10 m^2/g.

The carbon dioxide adduct of palbociclib has a particle size distribution (PSD) having at least one of:

a) a D10 value of about 1 μm to about 5 μm;

b) a D50 value of about 5 μm to about 20 μm;

c) a D90 value of about 15 μm to about 50 μm.

The carbon dioxide adduct of palbociclib has a volume mean diameter (D[4,3]) of about 5 μm to about 50 μm.

The carbon dioxide adduct of palbociclib has improved filterability, electrostatic nature, flowability, and stability.

The carbon dioxide adduct of palbociclib is characterized an XRPD pattern substantially as depicted in Figure 1, a DSC thermogram substantially as depicted in Figure 2, an Infra-red (IR) spectrum as depicted in Figure 3, a TGA thermogram as depicted in Figure 4, or an SEM image as depicted in Figure 5.

A second aspect of the present invention provides a process for the preparation of a carbon dioxide adduct of palbociclib, comprising:

a) contacting palbociclib hydrochloride with a mixture of water and methanol or a mixture of water or acetone; and

b) adding an inorganic base to the reaction mixture of step a) to obtain the carbon dioxide adduct of palbociclib.

Palbociclib hydrochloride used for the preparation of a carbon dioxide adduct of palbociclib may be prepared by any method provided in the art, for example, the methods

as disclosed in U.S. Patent Nos. 7,863,278, 6,936,612, or 7,781,583, or by the method as described herein.

Examples of inorganic bases include sodium bicarbonate, potassium bicarbonate, and calcium bicarbonate.

The preparation of the carbon dioxide adduct of palbociclib is carried out at about 20°C to about 55°C for a period of about 30 minutes to about 5 hours, for example, for about one hour to about 4 hours.

A carbon dioxide adduct of palbociclib may be isolated by filtration, decantation, extraction, distillation, evaporation, chromatography, precipitation, concentration, crystallization, centrifugation, or recrystallization, and dried under reduced pressure, by air drying, or vacuum tray drying.

A third aspect of the present invention provides a pharmaceutical composition comprising a carbon dioxide adduct of palbociclib and one or more pharmaceutically acceptable carriers, diluents, or excipients.

A fourth aspect of the present invention provides a method for treating cyclin-dependent kinase associated diseases comprising administering to a patient in need thereof a therapeutically effective amount of a pharmaceutical composition comprising a carbon dioxide adduct of palbociclib.

While the present invention has been described in terms of its specific aspects and embodiments, certain modifications and equivalents will be apparent to those skilled in the art, and are intended to be included within the scope of the present invention.

Methods

XRPD of the samples was determined using a PANalytical® instrument; Model X'pert PRO; Detector: X'celerator®.

NMR of the samples was determined using a Bruker® instrument, Model Avance III 400, using a 5 mm PABBO probe. ^{1}H frequency: 400 MHz; ^{13}C Frequency: 100 MHZ.

IR of the samples was recorded using a PerkinElmer® instrument, potassium bromide pellet method.

DSC of the samples was recorded using a Mettler-Toledo® 821e instrument.

TGA was recorded using a TA Instruments® Q500.

SEM analysis was carried out using a JEOL JSM-6010LV. The samples were coated by a platinum sputter coater (JEOL, JFC 1600, auto fine coater).

Particle size distribution was measured using a Malvern® Mastersizer® 2000 instrument.

Specific surface area was determined using a Micromeritics® Gemini™ VII 2390 (Software: Gemini™ VII, version 1.03).

Water content was determined using a Metrohm® KF Tiltrotor: Model: 795 KFT Titrino®.

Loss on drying (LOD) was determined using a Yamato Scientific vacuum drying oven, Model: ADP200.

The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Example 1: Preparation of palbociclib hydrochloride

Concentrated hydrochloric acid (77.5 g) was added to a solution of *tert*-butyl 4-(6-{[6-(1-butoxyethenyl)-8-cyclopentyl-5-methyl-7-oxo-7,8-dihydropyrido[2,3-*d*]pyrimidin-2-yl]amino}pyridin-3-yl)piperazine-1-carboxylate (90 g) (obtained as per procedure disclosed in U.S. Patent No. 7,781,583) in a mixture of methanol (1350 mL) and water (180 mL) at 60°C to 65°C to obtain a reaction mixture. The reaction mixture was heated at 60°C to 65°C for 4 hours and then lowered to ambient temperature. Sodium hydroxide solution (20%, 20 mL) was added to the reaction mixture at 35°C to 40°C to adjust the pH to 10.5 to 11 and to obtain a solid. The solid was stirred at 25°C to 30°C for one hour. The solid was filtered, then washed with water (180 mL), and then washed with methanol (180 mL) to obtain a wet compound. The obtained wet compound was charged in methanol (600 mL) to obtain a solution. The temperature of the solution was raised to 60°C to 65°C, and then concentrated hydrochloric acid (27 g) was added to the solution to obtain a reaction mixture. The reaction mixture was stirred for 2 hours at 60°C to 65°C, and then cooled to 10°C to 15°C in one hour to obtain a slurry. The slurry was stirred for 2 hours at 60°C to 65°C to obtain a yellow solid. The yellow solid obtained was filtered, and then washed with methanol (1 x 60 mL) to obtain the title compound.

Yield: 66.8 g

Example 2: Preparation of a carbon dioxide adduct of palbociclib

Palbociclib hydrochloride (100 g, as obtained in Example 1) was dissolved in a mixture of water (1500 mL) and methanol (2000 mL) at 25°C to 30°C to obtain a reaction mixture. Eno antichromos carbon (20 g) and sodium metabisulphite (2 g) were added to the reaction mixture, and then the mixture was stirred for 30 minutes. The reaction mixture was filtered through a Hyflo®, and then washed with water (500 mL) to obtain a filtrate. The filtrate was passed through 0.45 micron filter. The filtrate obtained was heated at 40°C to 50°C. The filtrate was treated with aqueous sodium bicarbonate (5%) over a period of 90 minutes at 40°C to 50°C to adjust the pH to 7.0 to 7.2. The reaction mixture was stirred at 40°C to 50°C for 2 hours to 3 hours. The reaction mixture was filtered, and then washed with water (2×200 mL), methanol (1×200 mL), and acetone (1×200 mL) to obtain a solid. The solid obtained was dried at 50°C to 60°C for 12 hours to obtain the title compound.

Yield: 75 g

CHN Data: C: 62.06 H: 5.81 N: 20.7

^{1}H NMR (TFA d_6, 400 MHz): δ 9.24 (2H, s), 8.24-8.27 (1H, d), 8.16 (1H, s), 7.91-7.93 (1H, d), 5.92-5.97 (1H, m), 3.79-3.81 (8H), 2.77 (3H, s), 2.58 (3H, s), 2.33-2.34 (2H, m), 2.08 (4H), 1.79 (2H).

^{13}C NMR (TFA d_6, 100 MHz): δ 208.5, 156.8, 154.2, 152.6, 143.6, 141.5, 136.1, 132.9, 125.1, 123.4, 112.3, 56.9, 45.3, 44.3, 30.3, 27.9, 25.1, 12.9.

We claim:

1. A carbon dioxide adduct of palbociclib, characterized by an X-ray powder diffraction (XRPD) pattern having peaks at d-spacing of about 11.3, 6.8, 5.3, 4.2, and 3.7 Å.
2. The carbon dioxide adduct of claim 1, characterized by an XRPD pattern having additional peaks at d-spacings of about 15.5, 10.0, 4.4, 4.1, and 3.3 Å.
3. The carbon dioxide adduct of claim 1, characterized by a differential scanning calorimetry (DSC) thermogram having endothermic peaks at about 146.0°C and 267.0°C, and an exothermic peak at about 221.5°C.
4. The carbon dioxide adduct of claim 1, characterized by an XRPD pattern substantially as depicted in Figure 1.
5. The carbon dioxide adduct of claim 1, characterized by a DSC thermogram substantially as depicted in Figure 2.
6. The carbon dioxide adduct of claim 1, characterized by an IR spectrum substantially as depicted in Figure 3.
7. The carbon dioxide adduct of claim 1, characterized by a scanning electron microscopy (SEM) image substantially as depicted in Figure 5.
8. A carbon dioxide adduct of palbociclib having 0.5 moles of carbon dioxide per mole of palbociclib.
9. A carbon dioxide adduct of palbociclib having a water content of about 0.5%.
10. A carbon dioxide adduct of palbociclib having weight loss of about 4.5% to about 5% as determined through thermogravimetric analysis (TGA).
11. The carbon dioxide adduct of claim 10 is characterized by a TGA thermogram as depicted in Figure 4.
12. A carbon dioxide adduct of palbociclib having weight loss of about 5% on drying (LOD).
13. A carbon dioxide adduct of palbociclib having a specific surface area (SSA) of greater than 2 m^2/g.
14. The carbon dioxide adduct of claim 13 having a specific surface area of about 3 m^2/g to about 10 m^2/g.

15. A carbon dioxide adduct of palbociclib having a particle size distribution (PSD) having at least one of:

    a) a D10 value of about 1 μm to about 5 μm;

    b) a D50 value of about 5 μm to about 20 μm;

    c) a D90 value of about 15 μm to about 50 μm.

16. The carbon dioxide adduct of claim 15 having a volume mean diameter (D[4,3]) of about 5 μm to about 50 μm.

17. A process for the preparation of a carbon dioxide adduct of palbociclib comprising

    a) contacting palbociclib hydrochloride with a mixture of water and methanol or a mixture of water or acetone; and

    b) adding an inorganic base to the reaction mixture of step a) to obtain the carbon dioxide adduct of palbociclib.

18. The process of claim 17, wherein the inorganic base is selected from the group consisting of sodium bicarbonate, potassium bicarbonate, and calcium bicarbonate.

19. A pharmaceutical composition comprising a carbon dioxide adduct of palbociclib, and one or more pharmaceutically acceptable carriers, diluents, or excipients.

20. A method for treating cyclin dependent kinase associated diseases comprising administering to a patient a therapeutically effective amount of a composition comprising the carbon dioxide adduct of palbociclib according to any one of claims 1-16.

Figure 1

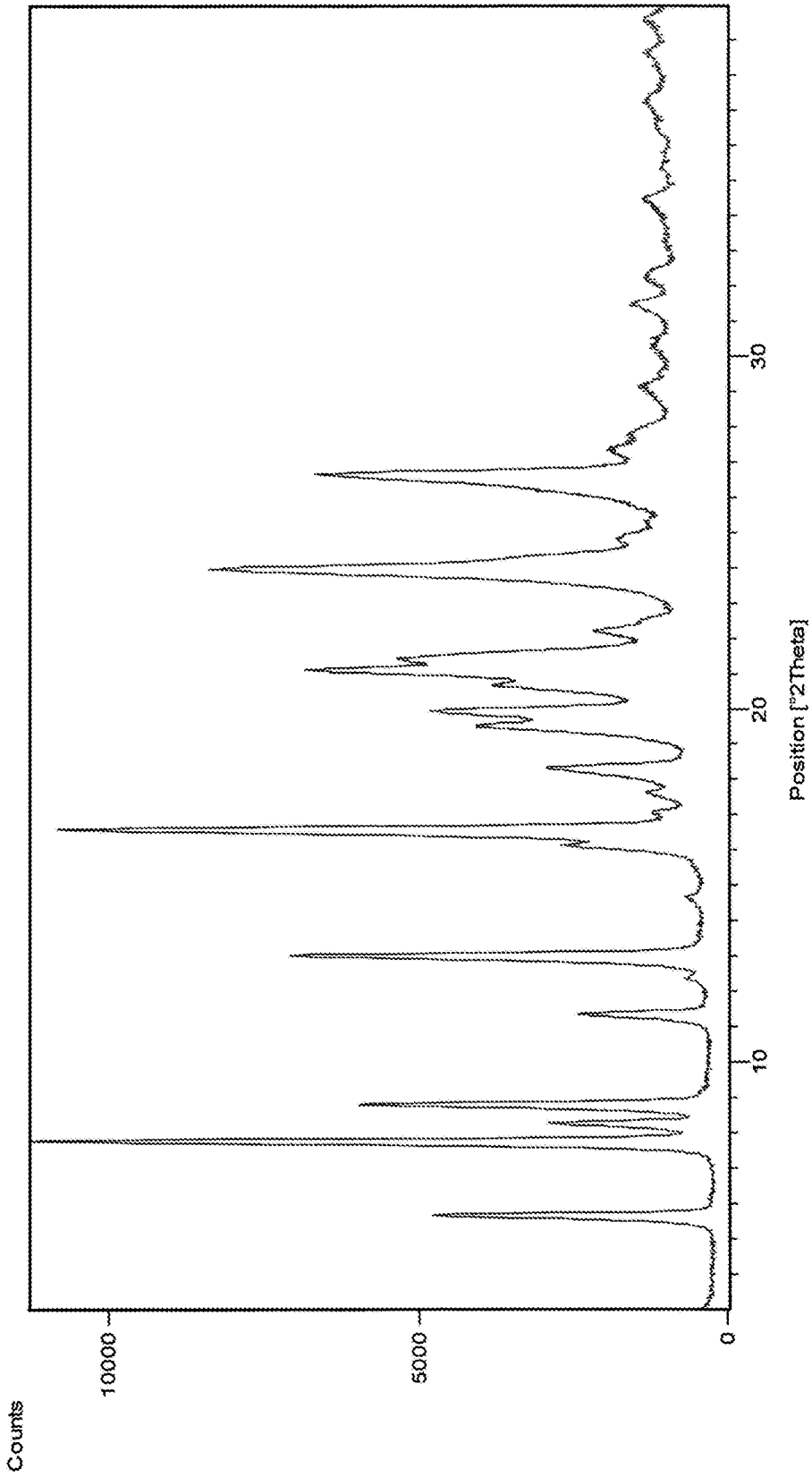


Figure 2

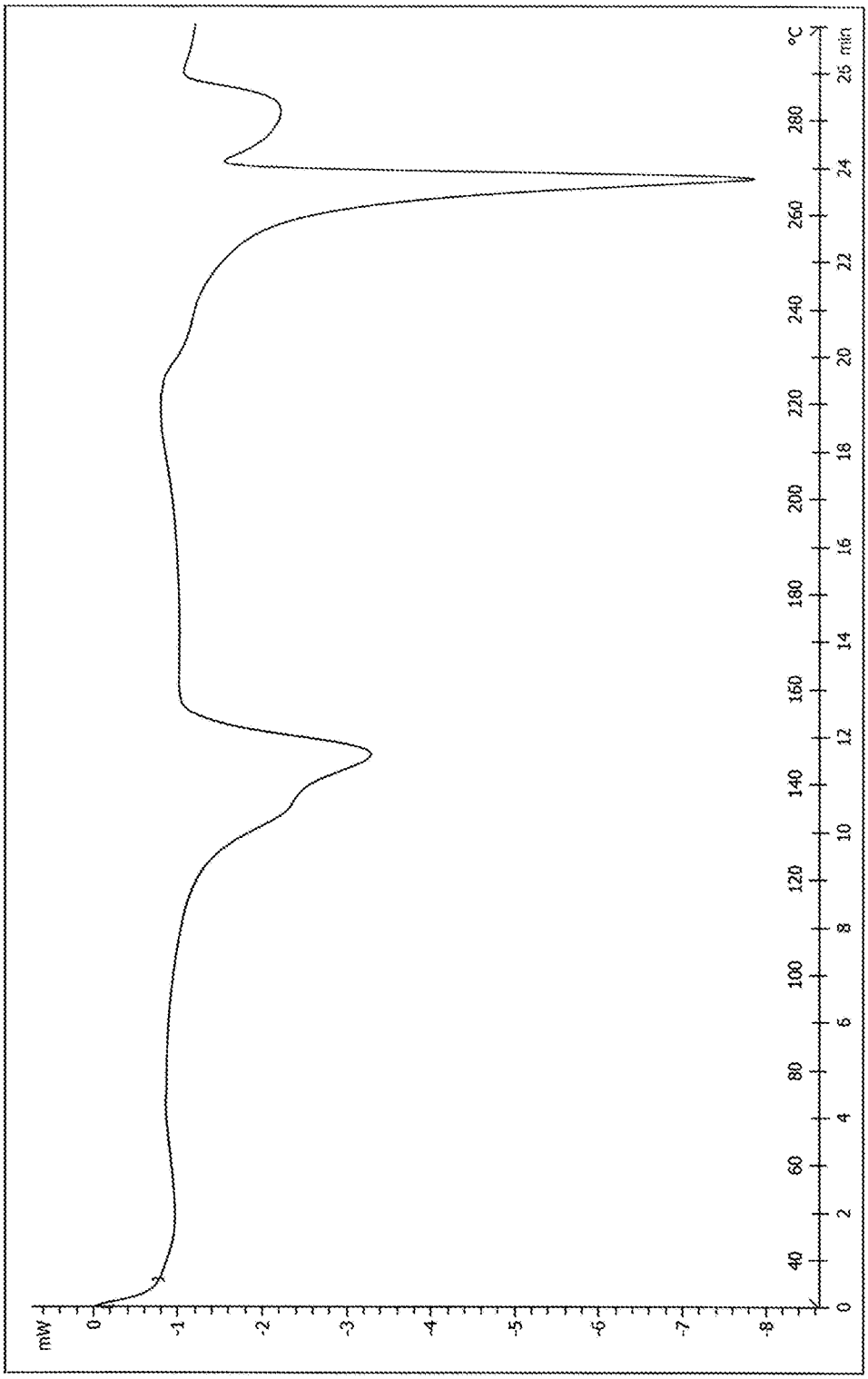

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Figure 3

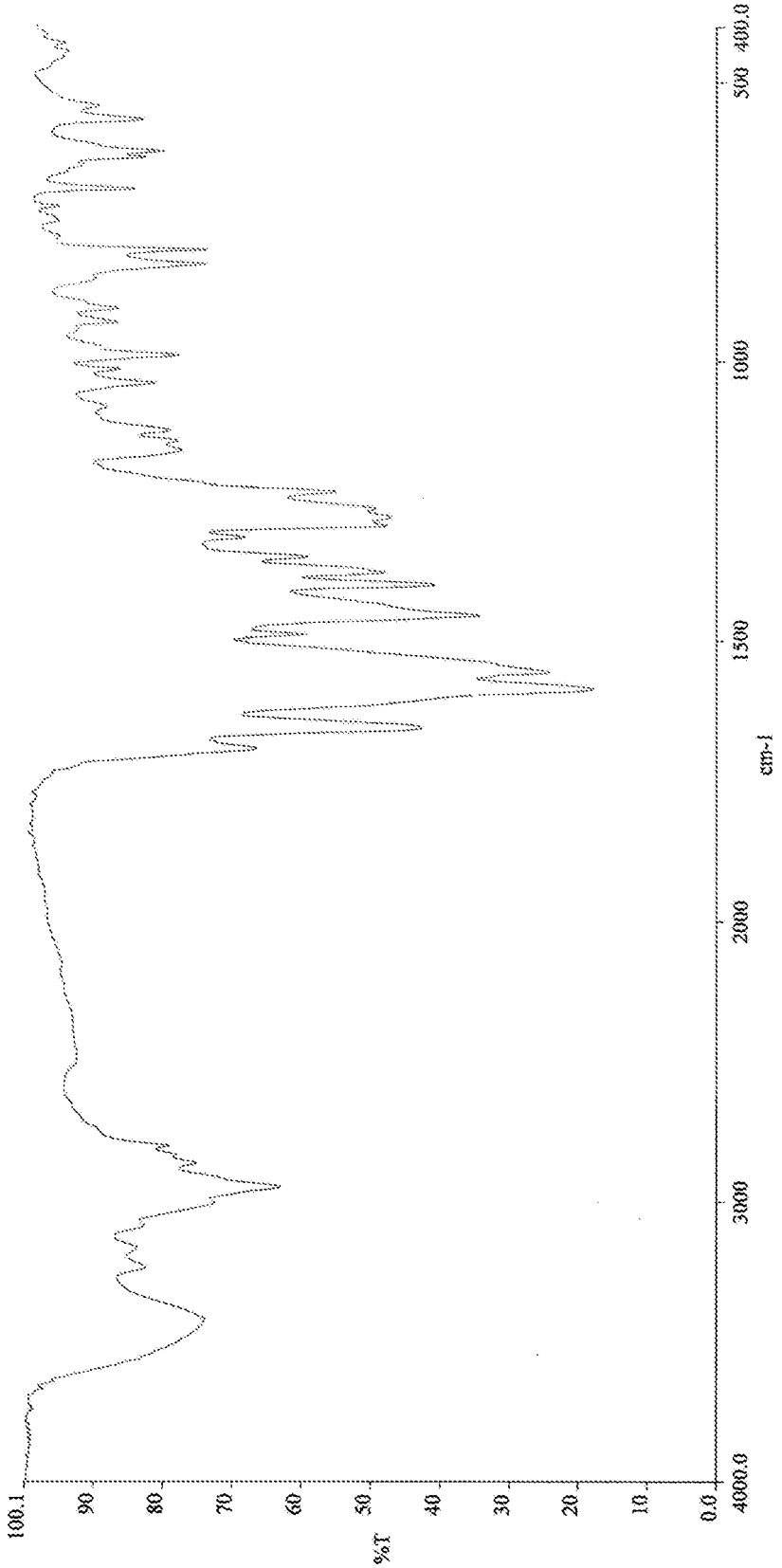

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Figure 4

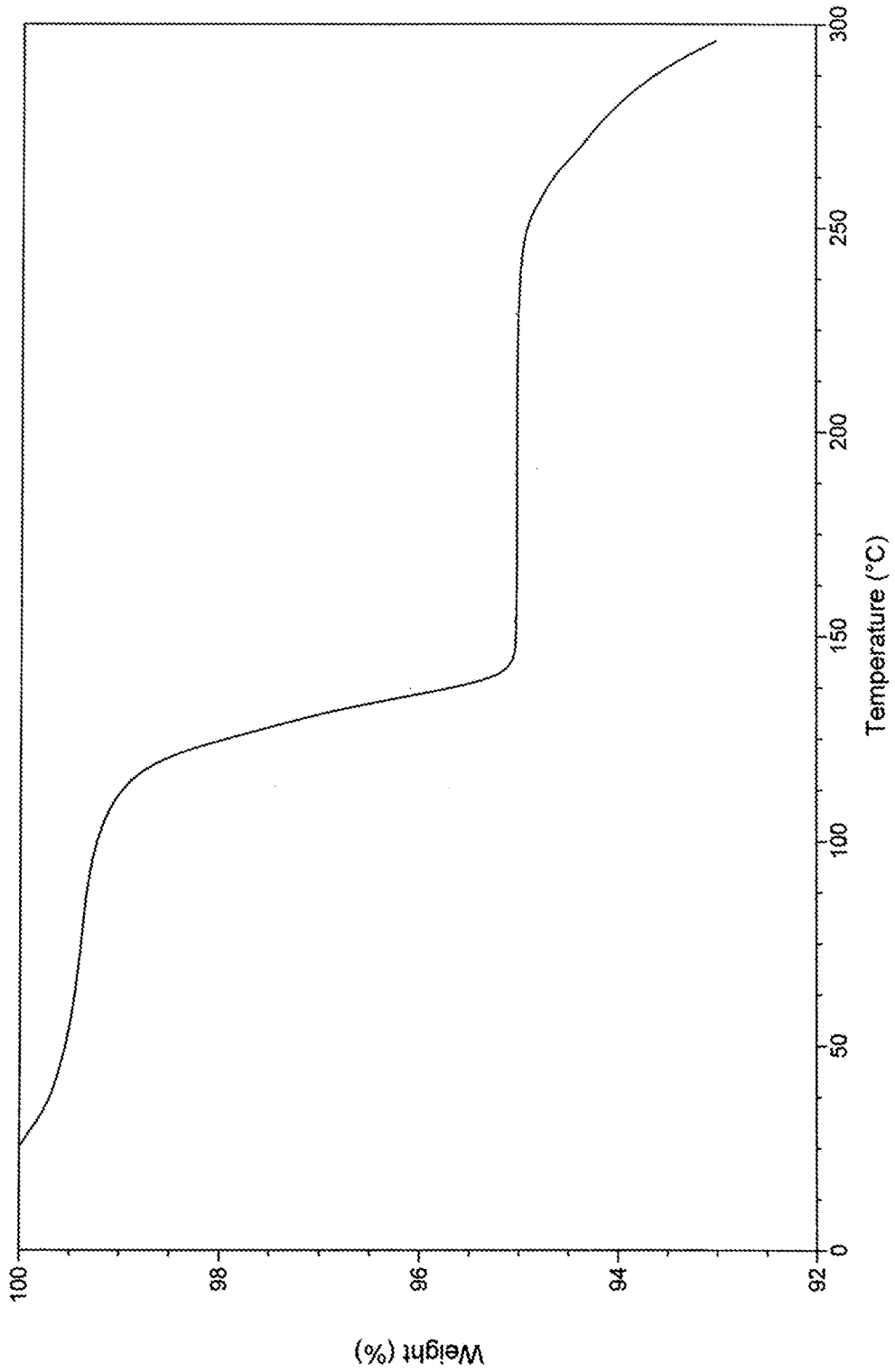
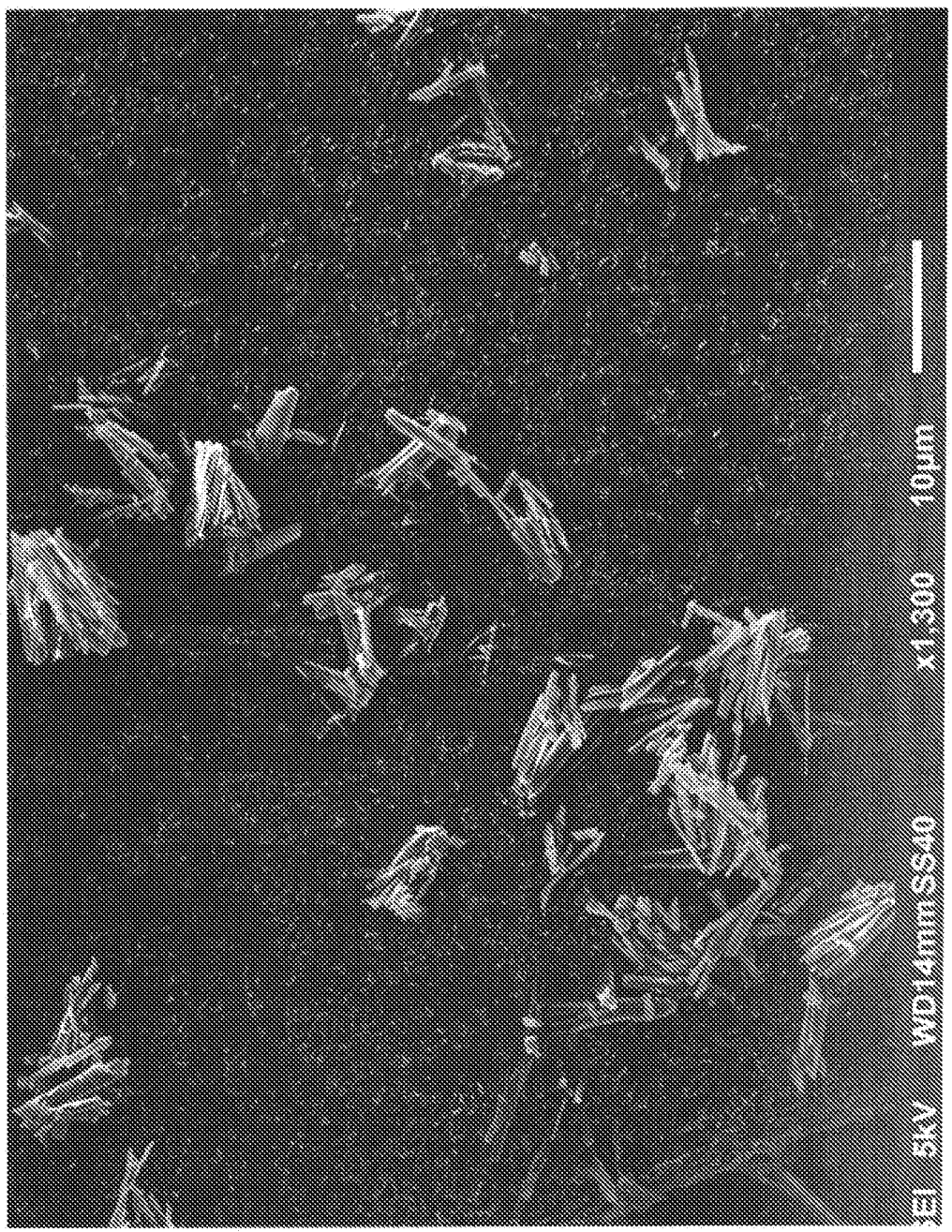


Figure 5



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB 15/59952

A. CLASSIFICATION OF SUBJECT MATTER
IPC(8) - A61K 31/497, A61P 35/00, C07D 471/04 (2016.01)
CPC - C07D 471/04
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)
IPC(8): A61K 31/497, A61 P35/00, C07D 471/04 (2016.01)
CPC: C07D 471/04

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
USPC: 514/252.16, 544/279

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
PatBase; Keyword limited: palbociclib solid form/crystalline/polymorph/carbon dioxide adduct; palbociclib hydrochloride/ isethionate/carbamate/carbamic acid; palbociclib X-ray powder diffraction/XRPD/PXRD; palbociclib thermogravimetric analysis/TGA/differential scanning calorimetry/DSC; PD0332991; pyrido[2,3-d]pyrimidin-7-one

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2008/0021037 A1 (BEYLIN et al.) 24 January 2008 (24.01.2008), entire document, especially: para [0014]; para [0015]-[0018]; Figures 1-3; para [0066]-[0067]; para [0084].	1-20
A	WO 2014/128588 A1 (PFIZER INC.) 28 August 2014 (28.08.2014), entire document, especially: Table 1, 3; Figure 1, 3; pg 4, ln 11-15; pg 11, ln 33 to pg 12, ln 4; pg 13, ln 17-20; pg 16, ln 4-18.	1-20
A	WO 2006/003479 A2 (EGIS GYOGYSZERGYAR RT.) 12 January 2006 (12.01.2006), entire document, especially: abstract; pg 8, Table; pg 11, para 2, DTG; pg 22, Example 2.	1-20
X,E	WO 2016/024249 A1 (SUN PHARMACEUTICAL INDUSTRIES LTD) 18 February 2016 (18.02.2016), entire document, especially:	1-20

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

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"A" document defining the general state of the art which is not considered to be of particular relevance
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"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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"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
28 March 2016	25 APR 2016
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer: Lee W. Young PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774