(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 June 2017 (29.06.2017)

WIPO | PCT

(10) International Publication Number
WO 2017/108781 A1

(51) International Patent Classification:
C07D 401/14 (2006.01) *A61P 35/00* (2006.01)
A61K 31/506 (2006.01)

(21) International Application Number:
PCT/EP2016/081908

(22) International Filing Date:
20 December 2016 (20.12.2016)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
15202053.3 22 December 2015 (22.12.2015) EP

(71) Applicant: **RATIOPHARM GMBH** [—/DE]; Graf-Arco-Straße 3, 89079 Ulm (DE).

(72) Inventors: **ALBRECHT, Wolfgang**; Alfred-Mendler-Weg 25/1, 89075 Ulm (DE). **RABE, Sebastian**; König-Wilhelm-Str.17, 89073 Ulm (DE).

(74) Agent: **TER MEER STEINMEISTER & PARTNER PATENTANWÄLTE MBB**; Aechter, Bernd, Nymphenburger Straße 4, 80335 München (DE).

(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, DJ, 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, KH, KN, KP, KR, KW, 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.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

— *with international search report (Art. 21(3))*

WO 2017/108781 A1

(54) Title: ABEMACICLIB FORM IV

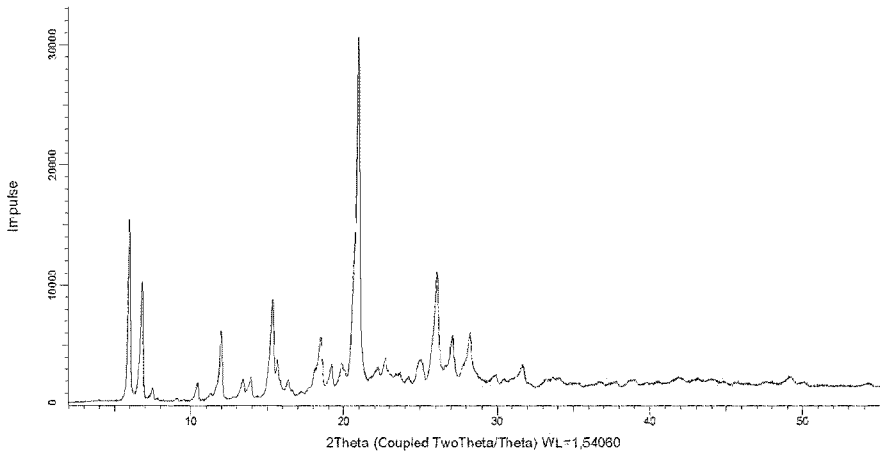


Figure 1: X-ray powder diffractogram of Abemaciclib Form IV

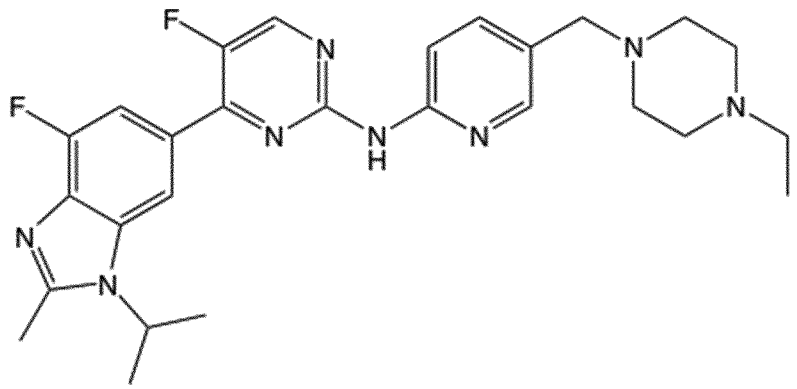
(57) Abstract: The present invention relates to a crystalline form of abemaciclib, a method of preparing the same, as well as a pharmaceutical composition comprising the same.

Abemaciclib Form IV

The present invention relates to a crystalline form of abemaciclib, a method of preparing the same, as well as a pharmaceutical composition comprising the same.

The IUPAC name of abemaciclib is N-{5-[(4-ethyl-1-piperazinyl)methyl]-2-pyridinyl}-5-fluoro-4-(4-fluoro-1-isopropyl-2-methyl-1H-benzimidazol-6-yl)-2-pyrimidinamine. Further abemaciclib can be referred to as [5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-yl]-[5-fluoro-4-(7-fluoro-3-isopropyl-2-methyl-3H-benzoimidazol-5-yl)-pyrimidin-2-yl]-amine.

Abemaciclib is represented by the following chemical structure according to Formula (I):



Formula (I)

Abemaciclib (also known as bemaciclib, LY-2835219) is an orally available selective inhibitor of the cycline dependent kinases 4 and 6 (CDK4/6). CDKs are a family of protein kinases which aroused curiosity due their role in regulating the cell cycle. It was found that they play a crucial role in many human cancers, where they are overactive or CDK-inhibiting proteins are not functional. Hence, it is rational to inhibit CDK function in order to prevent unregulated proliferation of cancer cells.

The active pharmaceutical ingredient is developed for the treatment of breast cancer and the non-small-cell lung carcinoma (NSCLC).

The active pharmaceutical ingredient abemaciclib in form of the free base is known from WO 2010/075074 A1. Further, said document discloses that the described compounds may be in form of an addition salt, wherein the hydrochloride and the mesylate are reported to be preferred.

Example 1 of WO 2010/075074 A1 describes the final coupling of 5-[(4-ethylpiperazin-1-yl)methyl]pyridin-2-amine and 6-(2-chloro-5-fluoro-4-pyrimidinyl)-4-fluoro-2-methyl-1-(1-methylethyl)-1H-benzimidazole (CAS-no. 1231930-42-9) in a twenty-gram scale. The product abemaciclib in form of the free base was purified by silica gel chromatography using dichloromethane/methanol (98/2) followed by dichloromethane/2M NH_3 in methanol (98/2) as eluents. The resulting product appears to be obtained in an amorphous state.

Further, two examples of said patent application relate to the preparation of abemaciclib in two different polymorphic forms, namely in crystalline forms I and III.

In Example 31 crystalline Form I was obtained by mixing amorphous abemaciclib with acetone and isolating the precipitate by vacuum filtration and subsequent drying.

In Example 32 crystalline Form III was obtained by mixing amorphous abemaciclib with acetone and heating the slurry. The product was isolated by vacuum filtration and subsequent drying.

With regard to these forms corresponding X-ray powder diffractograms were disclosed in Tables 1 and 2 of WO 2010/075074, respectively.

Abemaciclib Form I is described to be a yellow solid. However, abemaciclib Form I is reported to have an disadvantageous high hygroscopicity, especially at higher humidity and/or temperatures, which is undesirable in the production of a pharmaceutical formulation. Further, said Form I is also reported to have unfavourable electrostatic properties which significantly hamper the processability to a dosage form.

Abemaciclib Form III is decribed to be a yellow solid. However, the solubility of abemaciclib Form III seems to be improvable. In addtion, abemaciclib Form III is reported to show a disadvantageous hygroscopicity, in particular at higher humiditiy and/or temperatures. As mentioned above, the properties of form III result in difficulties during the production of oral dosage forms.

Consequently, there is still a need for a crystalline form of abemaciclib having superior properties. Hence, it was an object of the present invention to overcome the drawbacks of the above-mentioned prior art.

In particular, it was an object of the present invention to provide a form of abemaciclib which on the one hand shows advantageous properties when being processed into oral dosage forms and on the other hand shows advantageous solubility in water. In addition, it was an object to provide a form of abemaciclib which is rather stable and/or little hygroscopic under humid conditions. More specifically, it was an object of the present invention to provide a form of abemaciclib having an advantageously reduced hygroscopicity while the solubilty of the known forms is at least maintained.

Additionally, abemaciclib should be provided in a form being little electrostatic.

Finally, abemaciclib should be provided in stable from, wherein the form should show a stability being not inferior compared to the stability of forms I and III.

According to the present invention, the above objectives are unexpectedly achieved by a specific crystalline form of abemaciclib.

Thus, a subject of the invention is a crystalline form of abemaciclib having an X-ray powder diffraction peak at 6.8 degrees 2θ (± 0.2 degrees 2θ). This form of abemaciclib is hereinafter referred to as polymorphic Form IV of abemaciclib. Abemaciclib Form IV is present in the form of the free base and can preferably also refer to solvates and hydrates thereof.

A crystal form may be referred to herein as being characterized by data selected from two or more different data groupings, for example by a powder XRD pattern, having a group of specific peaks or by a powder XRD pattern as shown in a figure depicting a diffractogram, or by "a combination thereof" (or "combinations thereof" or "any combination thereof"). These expressions, e.g. "any combination thereof", contemplate that the skilled person may characterize a crystal form using any combination of the recited characteristic analytical data. For example, the skilled person may characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement this characterization with one or more additional feature(s) observed in the powder X-ray diffractogram, e.g., an additional peak, a characteristic peak shape, a peak intensity or even the absence of a peak at some position in the powder XRD pattern. Alternatively, the skilled person may in some instances characterize a crystal form using a group of three, four or five characteristic powder XRD peaks and supplement that characterization with one or more additional feature(s) observed by using another analytical method, for example using one or more characteristic peaks in a solid state IR

spectrum, solid state NMR or characteristics of the DSC thermogram of the crystal form that is being characterized.

Unless otherwise indicated, XRPD peaks are recorded using copper $K\alpha_1/K\alpha_2$ radiation with a wavelength of 1.5406 Å (weighted mean of Cu $K\alpha_1$ and Cu $K\alpha_2$). Further, unless indicated otherwise, XRPD peaks are reported as degrees 2θ values with a standard error of ± 0.2 degrees 2θ.

A crystal form may be referred to herein as being characterized by graphical data "as depicted in" a particular figure. Such data include for example powder X-ray diffractograms. The skilled person will understand that such graphical representation of data may be subject to small variations, e.g. in peak relative intensities and peak positions, due to factors such as variations in instrument response and variations in sample concentration and purity, which are well-known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the figures herein with graphical data generated for an unknown crystal form and confirm as to whether the two sets of graphical data characterize the same crystal form or two different crystal forms.

In a preferred embodiment abemaciclib Form IV can preferably have one or more further X-ray powder diffraction peaks at 15.3, 27.1 and/or 28.2 degrees 2θ (± 0.2 degrees 2θ).

In a preferred embodiment abemaciclib Form IV can preferably have one or more further XRPD diffraction peak(s) at 6.0, 12.0, 18.5, 21.0 and/or 26.1 degrees 2θ (± 0.2 degrees 2θ).

In an alternatively further preferred embodiment of the present invention abemaciclib Form IV can be characterized by XRPD diffraction peak(s) at degrees 2θ ± 0.2 degrees 2θ (intensity %): 6.0 (52), 6.8 (32), 7.5 (3), 10.4 (5), 12.0 (19), 13.4 (5), 13.9 (6), 15.3 (29), 15.6 (10), 16.3 (5), 18.2 (7), 18.5 (16), 19.2 (8), 19.9 (7), 21.0 (100), 22.2 (5), 22.7 (8), 25.0 (7), 26.1 (32), 27.1 (14), 28.2 (14) and 31.7 (6).

An XRPD diffraction pattern of the crystalline form of abemaciclib according to the present invention, abemaciclib Form IV, is shown in Figure 1.

In a preferred embodiment the abemaciclib Form IV can preferably have an endotherm with an onset temperature of 123°C (±5°) and a peak temperature of

133°C (±1°). The temperatures are measured by differential scanning calorimetry, wherein the measurement is carried out at Mettler Toledo DSC 822 E at a temperature range of 30°C to 350°C, a heating rate of 10°C/min and using software: STARe Version.8.10.

In a preferred embodiment abemaciclib Form IV can preferably have two further endotherm with an onset temperature of 174°C (± 2°) and 181°C (± 2°) as well as peak temperatures of 176°C (±1°) and 182°C (±1°), respectively. The measurements are carried out as described above.

In a further preferred embodiment the abemaciclib Form IV can preferably have an exotherm with an onset temperature of 137°C (±5°) and a peak temperature of 140°C (±2°). The measurements are carried out as described above.

A DSC thermogram of the crystalline form of abemaciclib according to the present invention, abemaciclib Form IV, is shown in Figure 2.

The abemaciclib of the present invention shows an advantageous solubility in water, for example compared to abemaciclib Form III. In addition, the present abemaciclib shows an advantageous hygroscopicity, for example compared to abemaciclib Form I.

A further subject of the present invention is a process for preparing the crystalline form of the abemaciclib according to the present invention, comprising the steps of

(a) providing abemaciclib
(b) suspending abemaciclib in a suitable organic solvent, in particular acetonitrile
(c) isolating the crystalline from of abemaciclib

In step (a) abemaciclib, preferably abemaciclib in form of its free base, for example amorphous abemaciclib, abemaciclib Form I and/or abemaciclib Form III as described in WO 2010/075074 A1, is provided. Abemaciclib in form of its free base can preferably also refer to solvates and hydrates thereof.

In step (b) the abemaciclib from step (a) is suspended in an organic solvent. Preferably, solvents having similar properties as acetonitrile are used. In particular acetonitrile is used. It is preferred that step (b) is carried out at a temperature of from 20°C to the boiling point of acetonitrile. The boiling point of acetonitrile is

82°C at a pressure of 1013 mbar. However, due to the contained amount of abemaciclib and the resulting boiling point elevation, the boiling point of the acetonitrile in the suspension might be slightly higher than 82°C. It is more preferred that step (b) is carried out at a temperature of from 60°C to the boiling point of acetonitrile. Particularly preferred step (b) can be carried out at the boiling point of acetonitrile in the suspension, i.e. under reflux conditions.

It is preferred that step (b) is carried out under mechanical movement, such as stirring.

In a preferred embodiment step (b) includes keeping the suspension at a temperature between 20°C and the boiling point of acetonitrile, preferably at the boiling point of acetonitrile, and stirring for 0.5 to 6 hours, preferably 0.75 to 4 hours, more preferably 1 to 2.5 hours.

In case the suspension is raised to a temperature above 20°C the suspension can preferably be cooled again to 20°C, preferably under stirring.

Step (c) of isolating the crystalline form of the abemaciclib of the present invention can preferably comprise filtering the solution of step (b), for example through a folded filter to obtain the resulting solid.

The resulting solid can preferably be triturated and subsequently preferably dried. Drying can preferably be carried out under reduced pressure of from 5 to 200 mbar, in particular 10 to 150 mbar. Drying can be preferably carried out at a temperature of 20°C to 80°C, more preferably 30°C to 70°C. Drying can for example be carried out in a compartment dryer. Drying can preferably last 2 to 8 hours. The resulting product is crystalline abemaciclib Form IV.

As can be seen from the above, abemaciclib Form IV is easily available by a process without the use of complex, time and cost-intensive process steps.

The present invention furthermore relates to pharmaceutical compositions comprising the crystalline form of abemaciclib according to the present invention, wherein the pharmaceutical compositons additionally contain at least one pharmaceutically acceptable excipient.

Pharmaceutically acceptable excipient(s) can for example be fillers, binders, glidants, disintegrants, lubricants, flow regulating agents and release agents.

Suitable excipients are for example disclosed in "Lexikon der Hilfsstoffe für Pharmazie, Kosmetik und angrenzende Gebiete", published by H.P. Fielder, 4th Edition, and "Handbook of Pharmaceutical Excipients", 3rd Edition, published by A.H. Kibbe, American Pharmaceutical Association, Washington, USA, and Pharmaceutical Press, London.

The term filler generally means substances which serve to form the body of the tablet in the case of tablets with small amounts of active agent (e.g. less than 60% by weight). This means that fillers "dilute" the active agent(s) in order to produce an adequate tablet compression mixture. The normal purpose of fillers therefore is to obtain a suitable tablet size. Examples of preferred fillers are lactose, lactose derivatives, starch, starch derivatives, treated starch, chitin, cellulose and derivatives thereof, calcium phosphate, calcium hydrogen phosphate, sucrose, calcium carbonate, magnesium carbonate, magnesium oxide, maltodextrin, calcium sulphate, dextrates, dextrin and/or dextrose and hydrogenated vegetable oil. Fillers can be present in an amount of 0 to 80% by weight, preferably in an amount of 10 to 60% by weight based on the total weight of the composition.

A binder is generally a substance which is capable of increasing the strength of the resulting dosage form, especially the resulting tablets. Suitable binders are for example polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, methylcellulose, hydroxyethyl cellulose, sugars, dextran or corn starch. Binders can be present in an amount of 0 to 30% by weight, preferably in an amount of 2 to 15% by weight based on the total weight of the composition.

Glidants can be used to improve the flowability. Suitable glidants are for example alkaline earth metal salts of fatty acids, like stearic acid. The glidant can be present for example in an amount of 0 to 2% by weight, preferably in an amount of 0.5 to 1.5% by weight based on the total weight of the composition.

Disintegrants are compounds which enhance the ability of the dosage form, preferably the ability of the tablet, to break into smaller fragments when in contact with a liquid, preferably water. Suitable disintegrants are for example croscarmellose sodium, sodium carboxymethyl starch, cross-linked polyvinylpyrrolidone (crospovidone), sodium carboxymethylglycolate and sodium bicarbonate. The disintegrant can be present in an amount of 0 to 20% by weight, preferably in an amount of 1 to 15% by weight based on the total weight of the composition.

A suitable flow regulating agent is for example colloidal silica. The flow regulating agent can be present in an amount of 0 to 8% by weight, preferably in an amount of 0.1 to 3% by weight based on the total weight of the composition.

A suitable release agent is for example talcum. The release agent can be present in an amount of 0 to 5% by weight, preferably in an amount of 0.5 to 3% by weight based on the total weight of the composition.

The parmaceutical composition can preferably be further processed into an oral doasage form, such as a capsule or tablet.

The oral dosage form, preferably a tablet or a capsule, more preferably a tablet, can preferably be coated, preferably film coated.

In the present invention the following three types of film coatings are possible:

- film coatings without affecting the release of the active ingredient,
- gastric juice-resistant film coatings,
- retard film coatings.

Generally, film coatings can be prepared by using film-forming agents, such as waxes, cellulose derivatives, poly(meth)acrylate, polyvinylpyrrolidone, polyvinyl acetate phthalate, and/or shellac or natural rubbers, such as carrageenan.

It is preferred that the present tablet is coated with a gastric juice-resistant film coating. Alternatively, a capsule comprising a gastric juice-resistant film coating can be used.

The gastric juice-resistant film coating preferably is a film coating being stable in the pH range of about 0.7 to 3.0, which is supposed to be the pH value of human gastric juice found in the stomach. However, in an environment with a pH value of 5 to 9, which is supposed to be present in the (small) intestine of the human body, the gastric juice-resistant film coating preferably dissolves and the drug can be released.

The gastric juice-resistant film coating (often also referred to as enteric coating) can comprise film-forming agents, for example fats, fatty acids, waxes, alginates, shellac, polyvinyl acetate phthalate, cellulose derivatives such as carboxy methyl ethyl cellulose, cellulose acetate succinate, cellulose acetate phthalate,

hydroxypropyl methyl cellulose phthalate, hydroxypropyl methyl cellulose acetate succinate, cellulose acetate trimellitate, and meth(acrylic)acid copolymers, such as methyl acrylate-methacrylic acid copolymers, methyl methacrylate-methacrylic acid copolymers, and Eudragits (for example Eudragit® L30D, Eudragit® L, Eudragit® S).

The coating is preferably free of active ingredient. It is further preferred that the thickness of the coating is 10 µm to 2 mm, preferably from 50 to 500 µm.

The preferred coating may comprise a film-forming agent and one or more of the following: lubricant, surfactant, glidant, pigment and water.

The preferred coating according to an embodiment of the present invention can comprise, along with the film-forming agent, e.g. stearic acid as lubricant for plasticizing and dissolving the polymer, sodium lauryl sulfate as a surfactant for wetting and dispersing, talc as glidant, iron oxide yellow and/or titanium oxide as pigment(s) and optionally purified water.

The present pharmaceutical composition and/or the oral dosage form of the present invention can be prepared by the methods well-known to a person skilled in the art, such as dry and wet granulation and direct compression.

In a preferred embodiment, the pharmaceutical composition and/or the oral dosage form can be administered one to three times a day, preferably once or twice a day, more preferably once a day.

In a preferred embodiment the pharmaceutical composition and/or the oral dosage form can be administered every 12 hours, wherein the administration can be carried out continuously, i.e. contrary to other similar active pharmaceutical ingredients, such as palbociclib and ribociclib, there is no need for a discontinuation of the administration after 3 weeks.

The present invention further relates to the crystalline form of abemaciclib according to the present invention for use in the treatment of cancer, preferably for use in the treatment of breast cancer.

The term "cancer" includes both solid tumors and hematological malignancies. Cancers include, but are not limited to, breast cancer, ovarian cancer, cervical cancer, endometrial cancer, prostate cancer, testicular cancer, pancreatic cancer,

esophageal cancer, head and neck cancer, gastric cancer, bladder cancer, lung cancer (e.g. adenocarcinoma, NSCLC and SCLC), bone cancer (e.g. osteosarcoma), colon cancer, rectal cancer, thyroid cancer, brain and central nervous system cancers, glioblastoma, neuroblastoma, neuroendocrine cancer, rhabdoid cancer, keratoacanthoma, epidermoid carcinoma, seminoma, melanoma, sarcoma (e.g. liposarcoma), bladder cancer, liver cancer (e.g. hepatocellular carcinoma), kidney cancer (e.g. renal cell carcinoma), myeloid disorders (e.g. AML, CML, myelodysplastic syndrome and promyelocytic leukemia) and lymphoid disorders (e.g. leukemia, multiple myeloma, mantle cell lymphoma, ALL, CLL, B-cell lymphoma, T-cell lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma).

Further, the present invention is directed to a method of treating and/or preventing cancer, preferably treating and/or preventing breast cancer, comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline from of abemaciclib according to the present invention or the pharmaceutical composition according to the present invention.

Experimental Part

Analytical Methods

HPLC/UV

Instrument:	Agilent 1100
Injection volume:	3 µl
Solvent A:	acetonitrile
Solvent B:	water + 0.1% formic acid + 0.05% heptafluorobutyric acid
Flow:	1.0 ml/min
Temperature:	40°C
Column:	Agilent Eclipse XDB-C18, 150 * 4.6 mm, 5 µm

time [min]	solvent B [%]
0.00	85
5.00	50
12.00	50
12.50	85
15.00	85

LCMS

Instrument:	Agilent 1260 Infinity
Injection volume:	2 µl
Solvent A:	acetonitrile
Solvent B:	water + 0.2% formic acid + 0.1% heptafluorobutyric acid
Flow:	1 ml/min
Temperature:	40°C
Column:	Phenomenex Kinetex 2.6 µm C18 100A 150 * 4.6mm 2.6 µm
Mass instrument:	Agilent 6110 Quadrupol LC/MS

time [min]	solvent B [%]
0.00	75
8.00	25
9.00	15
10.00	15
10.10	75
15.00	75

Mass spectrometry

Instrument:	Waters TQD (QBB985)
Software:	Masslynx 4.1
Detection mode:	electrospray / positive ions (ESP+)
Capillary voltage	2.13 KV
Source temperature:	100°C
Desolvation temperature:	450°C
Cone voltage:	41 V
Desolvation gas N_2:	450 L/h
Cone gas: N_2:	0 L/h
Scan [m/z]	50 – 1000

Nuclear magnetic resonance (NMR) spectroscopy

NMR-measurements were performed with Varian Mercury 400 Plus NMR Spectrometer, Oxford AS, 400 MHz.

Differential Scanning Calorimetry (DSC)

Instrument:	Mettler Toledo DSC 822E coupled with a Mettler Toledo Gas-Flow-Controller TS0800GC1 (Mettler-Toledo GmbH, Gießen, Germany)
Aluminium crucible:	40 µL

Lid:	Perforated
Temperature range:	30°C to 350°C
Heating rate:	10°C/ min
Nitrogen flush:	50 mL / min
Software:	STARe Version. 8.10
Interpretation:	Endothermic modus

X-Ray Powder Diffraction (XRPD)

The sample was analyzed on a D8 Advance X-ray powder diffractometer (Bruker-AXS, Karlsruhe, Germany). The sample holder was rotated in a plane parallel to its surface at 20 rpm during the measurement. Further conditions for the measurements are summarized in the table below. The raw data were analyzed with the program EVA (Bruker-AXS, Germany). The samples were layered onto a silicon specimen holder.

	standard measurement
Radiation	Cu K_α (λ=1.5406Å)
Source	38 kV / 40 mA
Detector	Vantec
detector slit	Variable
divergence slit	v6
antiscattering slit	v6
2θ range / °	$2 \leq 2\theta \leq 55$
step size / °	0.017

Dynanic Vapor sorption Analysis (DVS)

The hygroscopicity was determined by dynamic vapor sorption (DVS) analysis. Approximately 200 mg of each solid state were weighed on a sample plate and subjected to the apparatus. The humidity inside was varied in a range of 0 to 95% RH and the mass change (dm [%]) of the samples measured continuously.

Vapour sorption experiments were performed in the instrument SPSx-1µ (Projekt Messtechnik, Ulm, Germany) at a temperature of 25°C, using the humidity cycles specified below:

Cycle No.	rel. humidity (% RH) start value	rel. humidity (% RH) end value	Number of Steps	Time (h)	Comments
1	40	0	4		
2	5	65	6		
3	75	75	1	24 h	To investigate the absorption of water at the upper humidity level during stress conditions
4	85	95	1		
5	90	0	9		
6	5	35	3		

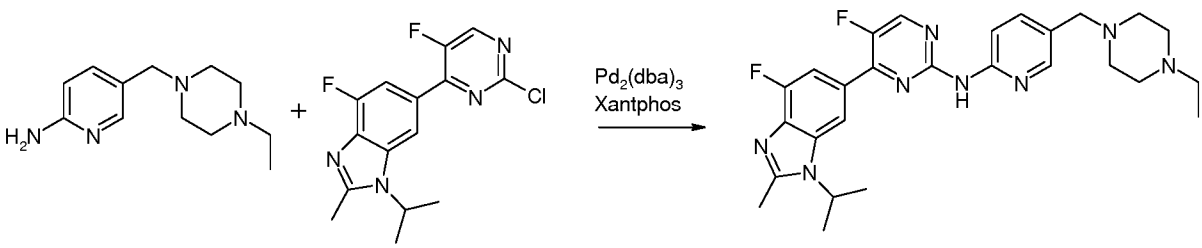
Solubility determination

280 mg (exactly weighed) test substance was weighed into a glass vial, followed by addition of 2.5 mL solvent (water, 0.01M HCl, 20 mM NaOAc/HOAc pH 4.5, 50 mM KH_2PO_4 pH 6.8, FASSIf). A stirring bar was added, the vial was fixed in a block heater at 37°C and the suspension was stirred with approximately 250 rpm. After 15 min and 1 hour samples were withdrawn, filtered through a 0.2 µm disposable filter, diluted with solvent and quantified by UHPLC/UV.

EXAMPLES

Starting Material:

Preparation of abemaciclib (Form I)



In analogy to Example 33 of WO 2010/075074, nitrogen was bubbled for 5 min through a mixture of 6-(2-chloro-5-fluoro-pyrimidin-4-yl)-4-fluoro-1-isopropyl-2-methyl-1H-benz-imidazole (5 g; 15.5 mmol), 5-(4-ethyl-piperazin-1-ylmethyl)-pyridin-2-ylamine (3.48 g; 15.8 mmol), K_2CO_3 (4.71 g; 34.1 mmol) and Xantphos (179 mg; 0.3 mmol) in t-amylalcohol (25 mL). Tris(dibenzylidene-

acetone)dipalladium(0) (142 mg; 0.2 mmol) was added and the slurry heated to 100°C. The slurry was stirred for 19 h when HPLC indicated complete conversion of pyrimidyl benzimidazol. The mixture was allowed to cool to room temperature and diluted with dichloromethane. The slurry was filtered over a Whatman glass fiber filter and the obtained filtrate extracted with aqueous HCl (4N; 2 x 25 mL). The collected aqueous extracts were stirred with charcoal (250 mg), filtered (Whatman) and basified with aqueous NaOH (17%; 30 mL). The resulting mixture was extracted with DCM (2 x 20), dried over Na_2SO_4, filtered, stirred over Quadrasil (800 mg), filtered and concentrated under reduced pressure. The remaining crude yellow solid was slurried in acetone, filtered, washed with acetone and dried under reduced pressure to isolate a fine yellowish powder.

Yield: 4.5 g (57.3%)
Chemical purity: 99.4% (peak area at λ=320 nm).

Example 1: Preparation of Abemaciclib Form IV

Abemaciclib Form I (5 g; 9.8 mmol) was suspended in acetonitrile (50 mL) and stirred under reflux conditions for 2 hours and subsequently for one hour at 20°C. The slurry was filtered off and dried under reduced pressure for 2 hours.

Yield: 4.5 g (90%)
Chemical purity: 99.5% (peak area at λ=320 nm)
^{1}H-NMR (400 MHz, $CDCl_3$) [δ ppm]:1.09 (t, J=7.23 Hz, 3 H) 1.72 (d, J=7.04 Hz, 6 H) 2.17 - 2.66 (m, 10 H) 2.70 (s, 3 H) 3.51 (s, 2 H) 4.74 (quin, J=6.94 Hz, 1 H) 7.69 (dd, J=8.41, 2.15 Hz, 1 H) 7.80 (d, J=11.73 Hz, 1 H) 8.20 (d, J=0.78 Hz, 1 H) 8.29 (d, J=1.96 Hz, 1 H) 8.40 (d, J=8.60 Hz, 1 H) 8.47 (d, J=3.91 Hz, 1 H) 8.57 (s, 1 H)

The mass spectrum was recorded by means of LC-MS:
Abemaciclib (m/z = 507.2 ($[M+H]^+$, mode: electrospray ionization, positive mode).

XRPD [2θ (intensity %)]: 6.0 (52), 6.8 (32), 7.5 (3), 10.4 (5), 12.0 (19), 13.4 (5), 13.9 (6), 15.3 (29), 15.6 (10), 16.3 (5), 18.2 (7), 18.5 (16), 19.2 (8), 19.9 (7), 21.0 (100), 22.2 (5), 22.7 (8), 25.0 (7), 26.1 (32), 27.1 (14), 28.2 (14), and 31.7 (6).

DSC: endotherms (onset T):123°C, 174°C, 181°C

Comparison with prior art:

Hygroscopicity

The hygroscopicity of three different polymorphic forms of abemaciclib were determined by dynamic vapor sorption (DVS) analysis. The results are shown in the following Table 1:

	Relative weight change (dm) [%]						
RH [%]	40	-> 0	-> 75	-> 95	-> 40	-> 0	-> 35
Abemaciclib Form I Ref	0	-0.3	1.4	8.5	0.1	-0.3	0
Abemaciclib Form III Ref	0	-0.1	0.6	6.0	0.1	-0.1	0
Abemaciclib Form IV Invention	0	-2.3	0.7	1.1	0	-2.3	-0.2

Table 1: Water adsorption of the different polymorphs of abemaciclib at distinct humidity

It turned out that abemaciclib forms I and III show a considerable hygroscopicity with a mass increase of 6 and 8.5% w/w respectively, representing approximately 2 equivalents of water. Abemaciclib Form IV already contained of 2.3% w/w water under ambient conditions, increasing to a maximum of 3.4% w/w at 95% RH, which represents 1 equivalent of water. Water absorption and desorption is reversible and also the crystalline form remained unchanged for all polymorphs after completion of the experiment.

Solubility:

The solubility properties of the three different polymorphic forms of abemaciclib were studied in four different aqueous buffers with distinct pH values.

Solubilities of prior art abemaciclib Form I and abemaciclib Form III as well as abemaciclib Form IV according to the present invention at 37°C are shown in the following Table 2:

		Solubility [mg/ml]		
	time	Form I Ref	Form III Ref	Form IV Invention
0.01 N HCl pH ~2.2	15 min	-	8.23	21.40
20 mM Na-acetate pH 4.5	15 min	-	33.53	46.22
50 mM KH_2PO_4 pH 6.8	15 min	21.65	2.38	21.32
FaSSiF (SIF-powder)	15 min	24.15	9.66	20.51

Table 2: Solubility studies

As can be seen from Table 2, abemaciclib Form IV shows a signifcantly higher solubility than abemaciclib Form III in all investigated solvents. Further, abemaciclib Form IV shows substantially the same solubility as abemaciclib Form I in 50 mM KH_2PO_4 having a pH corresponding to the one in the small intestine and in FaSSiF simulating the intestine under sober conditions.

Stability:

In a stability test, the chemical and physical stability of ABM base, Form III and Form IV was compared. Different batches were used and stored at 25°C/60% RH; 30°C/65% RH and 40°C/75% RH over a period of 8 weeks in open and closed vials. The stability was checked after 4 and 8 weeks. Physical stability was determined by XRD analysis. Further, the results of HPLC/UV analysis, expressed as [area-%] are given in the following Table 3:

	25°C/ 60%RH	30°C/65%RH	40°C/75%RH
solid state / time	Form IV	Form IV	Form IV
initial XRD	Congruent	Congruent	Congruent
initial HPLC	99.3%	99.3%	99.3%
after 4 weeks in closed vial	unchanged	unchanged	Unchanged
	98.9%	98.9%	98.8%
after 4 weeks in open vial	unchanged	unchanged	Unchanged
	98.9%	98.8%	98.8%
after 8 weeks in closed vial	unchanged	unchanged	Unchanged
	98.9%	98.8%	98.9%
after 8 weeks in open vial	unchanged	unchanged	Unchanged
	98.8%	98.9%	98.9%

Table 3: Results of the stability test (abemaciclib base Form IV; 25°C/60% RH, 30°C/65% RH and 40°C/75% RH, open and closed containers)

In this test both polymorphs of abemaciclib proved to be chemically and physically stable at each condition over the whole observation period.

Conclusion:

A novel polymorph of abemaciclib, namely abemaciclib Form IV, has been provided. Abemaciclib Form IV exhibits an advantageous stability. Further, abemaciclib Form IV shows a significantly reduced hygroscopicity compared to the known polymorphs I. Further the solubilty of Form IV is superior compared to known polymorphic Form III. Consequently, Form IV is little hygroscopic on the one hand and well soluble on the other hand.

Claims

1. Crystalline form of abemaciclib having an X-ray powder diffraction peak at 6.8 degrees 2θ (± 0.2 degrees 2θ).

2. Abemaciclib according to claim 1 having one or more further X-ray powder diffraction peak(s) at 15.3, 27.1 and/or 28.2 degrees 2θ (± 0.2 degrees 2θ).

3. Abemaciclib according to claim 1 or 2, having one or more further characteristic X-ray powder diffraction peaks at 6.0, 12.0, 18.5, 21.0 and/or 26.1 degrees 2θ (± 0.2 degrees 2θ).

4. Abemaciclib according to any one of claims 1 to 3 having an endotherm with an onset temperature of 123°C (± 5°C) and a peak temperature of 133°C (± 1°C), measured by differential scanning calorimetry.

5. Method for preparing a crystalline form of abemaciclib according to any one of claims 1 to 4 comprising the steps of

(a) providing abemaciclib
(b) suspending abemaciclib in a organic solvent, preferably acetonitrile
(c) isolating the crystalline form of abemaciclib.

6. Method according to claim 5, wherein step (b), suspending abemaciclib in acetonitrile, is carried at a temperature of from 20°C to the boiling point of the acetonitrile.

7. Pharmaceutical composition comprising a crystalline form of abemaciclib according to any one of claims 1 to 4 and further at least one pharmaceutically acceptable excipient.

8. Crystalline form of abemaciclib according to any one of claims 1 to 4 for use in the treatment of cancer, preferably for the use in the treatment of breast cancer.

9. Method for treating and/or preventing cancer, preferably for treating or preventing breast cancer, comprising administering to a subject in need thereof a therapeutically effective amount of the crystalline form of abemaciclib according to any one of claims 1 to 4.

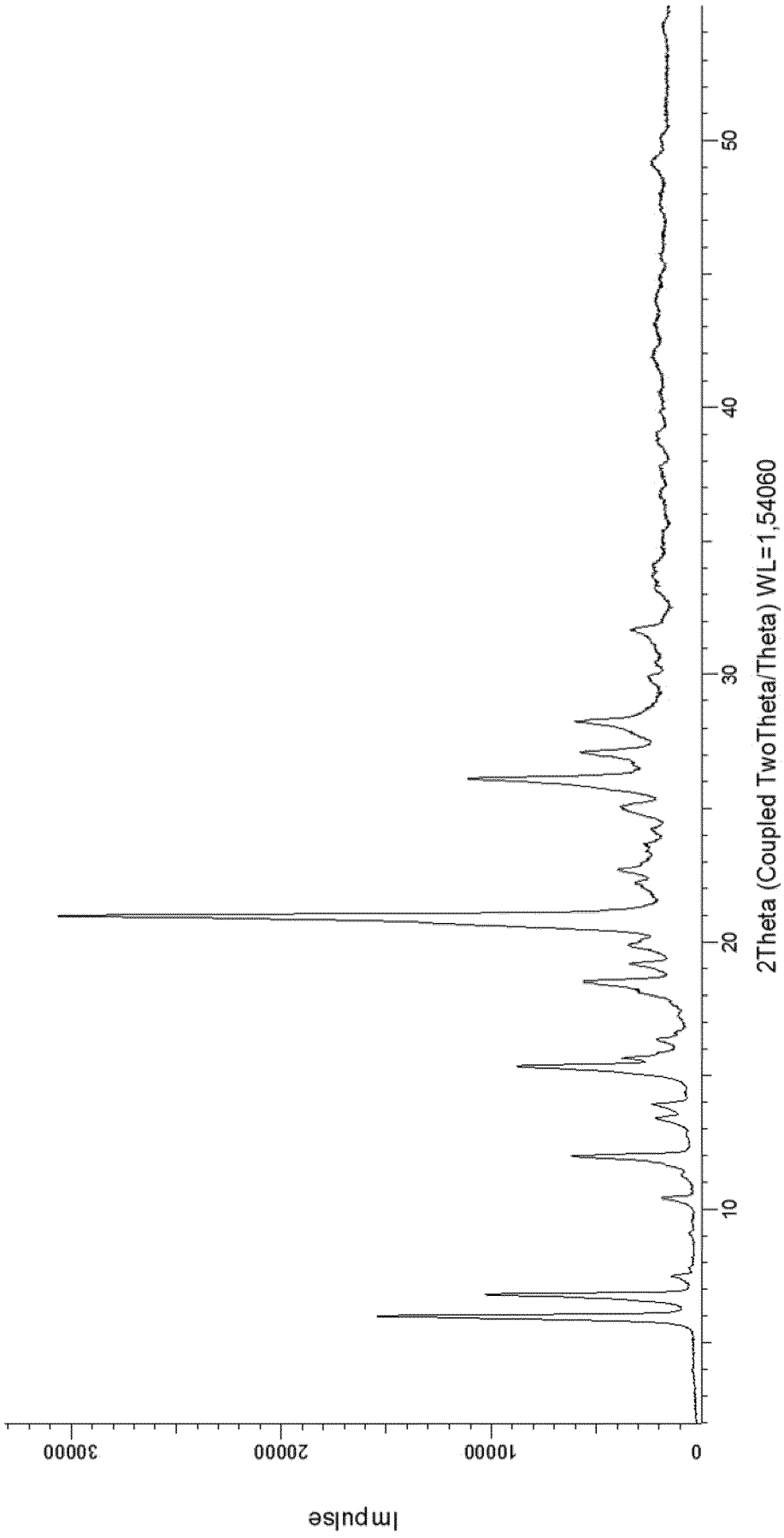


Figure 1: X-ray powder diffractogram of Abemaciclib Form IV

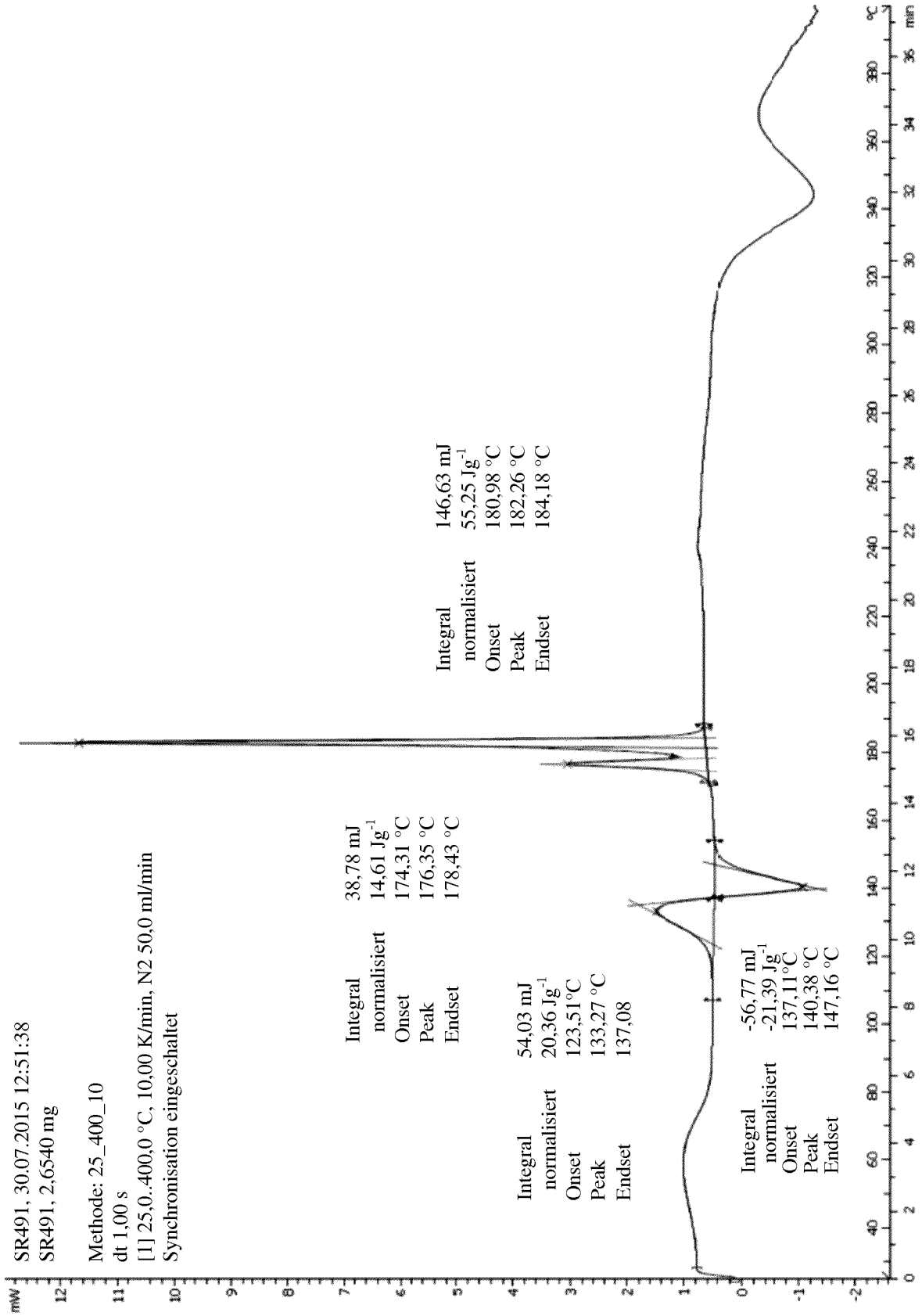


Figure 2: DSC thermogram of abemaciclib Form IV

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2016/081908

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D401/14 A61K31/506 A61P35/00
ADD.

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

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2010/075074 A1 (LILLY CO ELI [US]; COATES DAVID ANDREW [US]; DE DIOS MAGANA ALFONSO [U) 1 July 2010 (2010-07-01) cited in the application examples 1,31,32; tables 1,2 -----	1-9
A	MICHAEL O. FREDERICK ET AL: "A synthesis of abemaciclib utilizing a Leuckart-Wallach reaction", TETRAHEDRON LETTERS, vol. 56, no. 7, 1 February 2015 (2015-02-01), pages 949-951, XP055255707, GB ISSN: 0040-4039, DOI: 10.1016/j.tetlet.2014.12.082 Note 16. -----	1-9

☐ 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

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"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

"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
14 February 2017	22/02/2017

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Seelmann, Ingo

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2016/081908

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2010075074 A1	01-07-2010	AR 074575 A1	26-01-2011
		AU 2009330365 A1	01-07-2010
		BR PI0924183 A2	05-07-2016
		CA 2747055 A1	01-07-2010
		CN 102264725 A	30-11-2011
		CO 6382125 A2	15-02-2012
		CR 20110343 A	14-09-2011
		DK 2379528 T3	14-10-2013
		DO P2011000204 A	30-09-2011
		EA 201170872 A1	30-12-2011
		EC SP11011157 A	29-07-2011
		EP 2379528 A1	26-10-2011
		ES 2435798 T3	23-12-2013
		GT 201100181 A	08-04-2014
		HK 1159630 A1	14-03-2014
		HN 2011001701 A	22-07-2013
		HR P20131051 T1	06-12-2013
		IL 213350 A	31-08-2014
		JO 2885 B	15-03-2015
		JP 5417453 B2	12-02-2014
		JP 2012513396 A	14-06-2012
		KR 20110091551 A	11-08-2011
		MA 32903 B1	01-12-2011
		MY 150547 A	30-01-2014
		NZ 593114 A	30-11-2012
		PA 8852901 A1	27-07-2010
		PE 01072012 A1	20-02-2012
		PT 2379528 E	25-11-2013
		RS 53061 B	30-04-2014
		SG 172331 A1	28-07-2011
		SI 2379528 T1	29-11-2013
		TN 2011000293 A1	17-12-2012
		TW 201031653 A	01-09-2010
		UA 104603 C2	25-02-2014
		US 2010160340 A1	24-06-2010
		WO 2010075074 A1	01-07-2010
		ZA 201104505 B	28-11-2012