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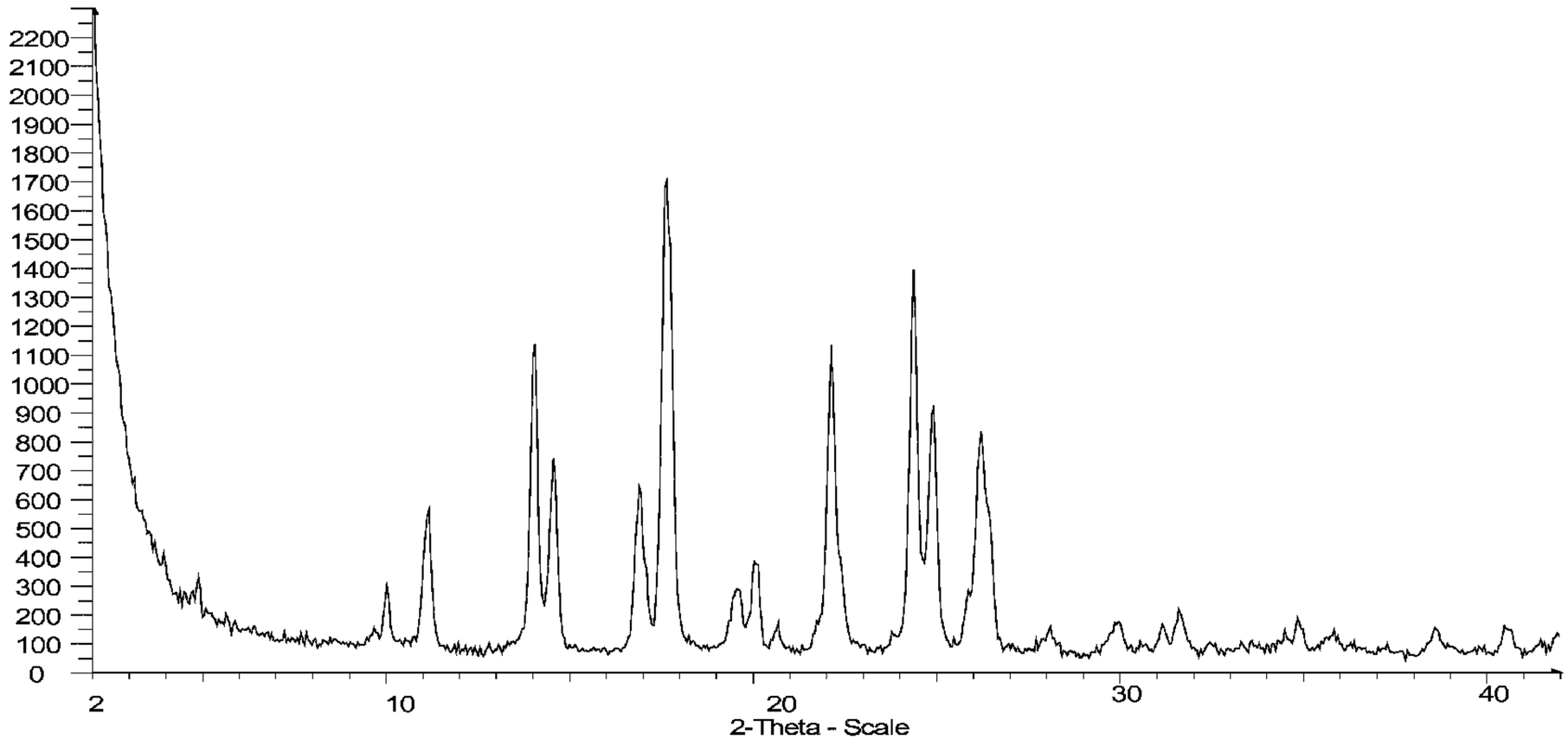
Figure 1

XRPD diffractogram of Compound (I) Form I



(57) Abrégé/Abstract:
The invention relates to polymorphic forms of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]py yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile and their use as therapeutic agents for the treatment of respiratory diseases.

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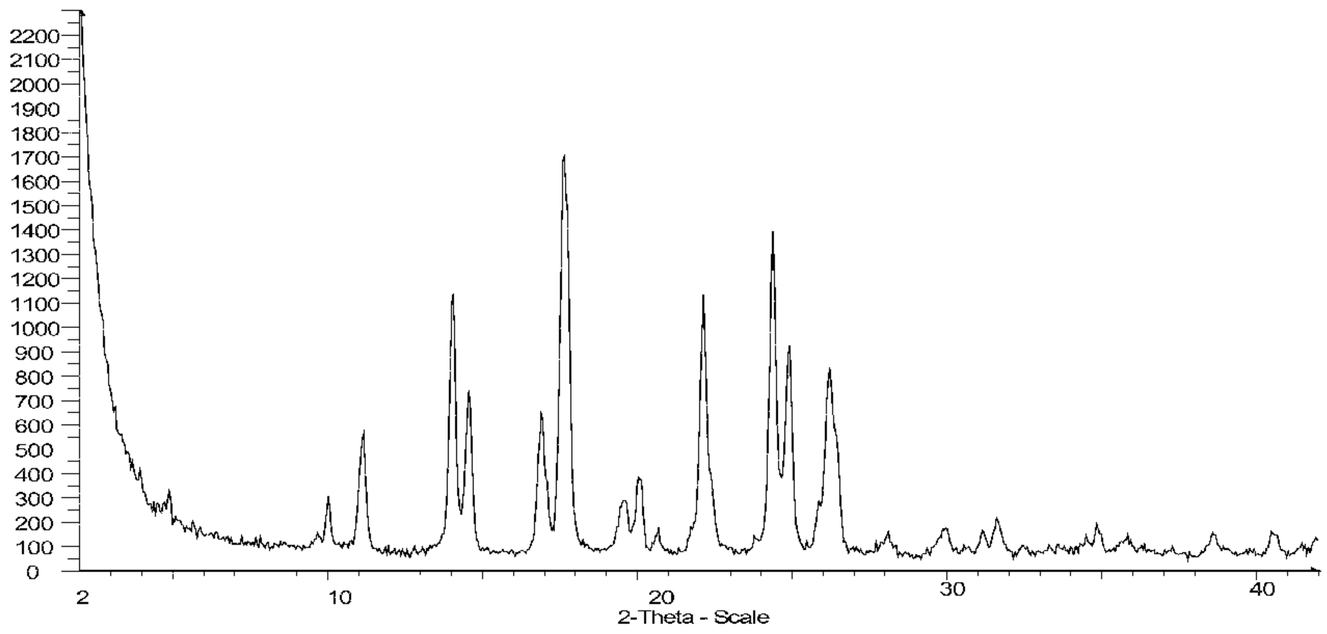
Figure 1

XRPD diffractogram of Compound (I) Form I



(57) **Abstract**: The invention relates to polymorphic forms of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]py yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile and their use as therapeutic agents for the treatment of respiratory diseases.

WO 2016/124464 A1

Novel Polymorphs

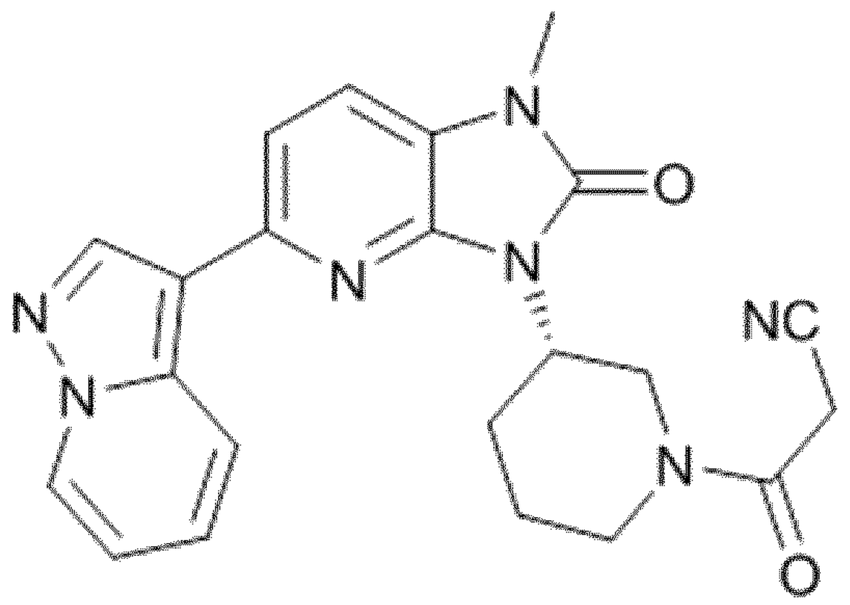
The present invention relates to new polymorphic forms of pharmaceutical compounds, pharmaceutical compositions containing them and their use as therapeutic agents.

WO2011/051452 discloses compounds which are useful as Janus kinase inhibitors, in particular JAK3 inhibitors. The compounds disclosed therein have utility in the treatment of various diseases, including respiratory indications such as asthma and COPD.

Drugs for the treatment of respiratory diseases are frequently administered via dry powder inhalation devices. Formulating respiratory drugs as dry powders with inhalation excipients such as lactose is complicated and unpredictable. There is a continuing need for stable dry powder formulations which exhibit desirable bioavailability and physical properties. Bioavailability and physical characteristics are important for efficient handling and processing of the drug substance, to ensure that an effective dose is delivered to the correct part of the lung, and that the drug is effective in treating respiratory diseases. Factors such as crystallinity, stability, density, flow characteristics and electrostatic charge all have a complicated influence on the handling and delivery of the drug substance.

Different formulation techniques are known in the art and can be applied to drug compounds in an attempt to produce inhalation powders having the desired physiochemical properties.

It has now been found that a drug substance disclosed in WO2011/051452, namely the compound (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile having the structure shown below and known herein as compound (I) can be prepared in different polymorphic forms. Surprisingly one form exists as a polymorph with particularly advantageous stability properties. Compound (I) as prepared following the process in WO2011/051452 is known as Form I herein.



Compound (I)

Therefore, in one embodiment the invention comprises a novel polymorphic form of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile (Compound(I)).

In one embodiment the invention provides a polymorph of the Compound (I) selected from the polymorphs described below as Form II or Form III.

In one embodiment the invention comprises a polymorph of Compound (I) characterised in that it provides an X-ray powder diffraction pattern which shows the following diffraction angles (2Theta) using copper Kα radiation:

at approximately 14.04°

at approximately 16.89°

at approximately 17.64°

at approximately 22.14°

at approximately 24.39°

at approximately 24.93°

at approximately 26.23°

The invention further comprises a polymorph of Compound (I) characterised in that it provides an X-ray powder diffraction pattern which shows the following diffraction angles (2Theta) using copper Kα radiation:

at 14.04°, at 16.89°, at 17.64°, at 22.14°, at 24.39°, at 24.93° and at 26.23°

This polymorph is known as Form I herein.

The Form I polymorph is further characterised as having a XPRD diffractogram substantially as shown in Figure 1. In one embodiment the Form I polymorph is characterised as having a XPRD diffractogram as shown in Figure 1. The Form I polymorph is further characterised as having a DSC endotherm onset of 142°C, an exotherm onset of 155°C and an endotherm onset of 235°C.

In one embodiment the invention comprises a polymorph of Compound (I) characterised in that it provides an X-ray powder diffraction pattern which shows the following diffraction angles (2Theta) using copper Kα radiation:

at approximately 8.25°

at approximately 13.25°

at approximately 15.40°

at approximately 17.65°

at approximately 25.39°

The invention further comprises a polymorph of Compound (I) characterised in that it provides an X-ray powder diffraction pattern which shows the following diffraction angles (2Theta) using copper Kα radiation:

at 8.25°, at 13.25°, at 15.40°, at 17.65° and at 25.39°

This polymorphic form is known as Form II herein.

The Form II polymorph is further characterised as having a XPRD diffractogram substantially as shown in Figure 2. In one embodiment the Form II polymorph is characterised as having a XPRD diffractogram as shown in Figure 2. The Form II polymorph is further characterised as having a DSC endotherm onset of 239°C.

The Form II polymorph exhibits greater thermodynamic stability when compared to the other polymorphic forms or the solvates and hydrates disclosed herein at temperatures up to 50°C. It is therefore more suitable as a pharmaceutical product than the other forms or the solvates and hydrates disclosed herein.

In a further embodiment the invention provides a Form III polymorph of compound (I) having the following diffraction angles (2Theta) using copper Kα radiation:

at approximately 11.40°

at approximately 13.60°

at approximately 15.60°

at approximately 22.80°

at approximately 26.69°

The invention further comprises a Form III polymorph of compound (I) having the following diffraction angles (2Theta) using copper Kα radiation:

at 11.40°, at 13.60°, at 15.60°, at 22.80° and at 26.69°

This polymorph is known as Form III herein.

The Form III polymorph is further characterised as having a XPRD diffractogram substantially as shown in Figure 3. In one embodiment the Form III polymorph is further characterised as having a XPRD diffractogram as shown in Figure 3. The Form III polymorph is further characterised as having a DSC endotherm onset of 235°C.

Compound (I) can also form solvates and hydrates, and these provide a further embodiment of the invention. These solvates and hydrates are unstable under certain conditions and generally revert to one of the polymorphic forms as defined above.

In a further embodiment the invention provides a hydrate of Compound (I), in particular the dihydrate of Compound (I).

In a further embodiment the invention provides a solvate of Compound (I), in particular a solvate selected from the dichloromethane, trichloromethane or 1,4-dioxane solvate of Compound (I).

The amorphous form of Compound (I) provides a further embodiment of the invention.

The Form II polymorph of Compound (I) exhibits surprisingly advantageous thermodynamic stability when compared to the Form 1 and Form III polymorphs in competitive slurrying experiments. The Form II polymorph of Compound (I) is therefore advantageous when formulated as dry powder compositions for inhalation, in particular for the treatment of respiratory indications.

In one embodiment the invention relates to a polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile (Compound (I)) as a therapeutic agent, in particular the Form II polymorph. The polymorphs of the invention may be used to treat the diseases disclosed in WO2011/051452, in particular respiratory diseases. Particular diseases that may be treated with the polymorphs of the invention include asthma, COPD, pulmonary arterial hypertension (PAH), idiopathic pulmonary fibrosis (IPF) and lung cancer. In one embodiment the invention relates to the Form II polymorph of Compound (I) as a therapeutic agent. In one embodiment the invention relates to the use of Form II of Compound (I) for the treatment of respiratory diseases.

In one embodiment the invention relates to the Form II polymorph of Compound (I) for use in the treatment or prophylaxis of asthma or COPD, in particular severe asthma.

In a further embodiment the invention relates to a method of treatment of a respiratory disease which comprises administering to a patient in need thereof the Form II polymorph of Compound (I), optionally in the presence of a pharmaceutical carrier or excipient.

In a further embodiment the invention relates to the use of the Form II polymorph of Compound (I), in the manufacture of a medicament for treating respiratory diseases such as asthma or COPD, in particular severe asthma.

The polymorphs of the invention can be administered with one or more additional therapeutic agents, either simultaneously of sequentially. For respiratory indications the polymorphs of the invention can be administered in combination with a therapeutic agent selected from inhaled corticosteroid, ß-agonists, long-acting muscarinic agonists, PDE4 inhibitors, or a biological agent such as an agent active at the IL-13, IL-5, IL-4/13, IL-17, IL-25 or IL-33 receptors. In particular the polymorphs of the invention can be administered with one or more compounds selected from salbutamol, glycopyrrolate, pirfenidone, nintedanib, beclomethasone, fluticasone, budesonide, mometasone, tiotropium, formoterol, indacaterol, vilanterol, umeclidinium and roflumilast.

In one embodiment the invention provides the Form II polymorph of Compound (I) in combination with one or more additional therapeutic agents. In one embodiment the invention provides the Form II polymorph of Compound (I) in combination with one or more compounds selected from salbutamol, glycopyrrolate, pirfenidone, nintedanib, beclomethasone, fluticasone, budesonide, mometasone, tiotropium, formoterol, indacaterol, vilanterol, umeclidinium and roflumilast.

The polymorphs of the invention are administered as pharmaceutical compositions, typically with a pharmaceutically acceptable carrier or excipient. Suitable compositions can be in the form of tablets, capsules, liquid suspensions, topical compositions, transdermal compositions or inhalable compositions. Solid dosage forms in which the crystalline polymorph is maintained are desirable,

and provide a further embodiment of the invention. In one embodiment the invention provides an inhalable composition comprising the Form (II) polymorph of Compound (I).

For the treatment of respiratory diseases inhalable compositions which can be delivered via a dry powder inhaler (DPI) form a further embodiment of the invention. Compositions in the form of a suspension for delivery via a pressurised metered dose inhaler (pMDI) form a further aspect of the invention.

In one embodiment the invention relates to a pharmaceutical composition comprising the Form II polymorph of Compound (I) with one or more pharmaceutically acceptable excipients.

For administration by inhalation using a dry powder inhaler, the polymorphs of the invention can be administered as dry powder formulations with one or more carrier substances. Suitable inhalation carriers are known in the art and in one embodiment include crystalline sugars such as monosaccharides or disaccharides. In one preferred embodiment the carrier is lactose.

Dry powder formulations of the invention may also have additional excipients such as force control agents. A force control agent is an additive which reduces the cohesion between the fine particles within the powder formulation. This promotes de-agglomeration when the powder is dispensed from the inhaler. Suitable force control agents are known in the art. In one embodiment the force control agent is a metal stearate such as magnesium stearate.

The dry powder formulations of the invention are typically formulated to have a particle size for inhalation. In one embodiment the polymorphs of the invention are formulated to have an average particle size of less than about 10µm, in one embodiment less than about 5µm and in a further preferred embodiment in the range of about 1µm to about 5µm.

In one embodiment the Form II polymorph is administered as a dry powder formulation with lactose, optionally magnesium stearate the formulation having an average particle size in the range of about 1µm to about 5µm.

The dry powder formulations of the invention can be administered using various dry powder inhalers such as GyroHaler® or a lever operated inhaler such as that disclosed in WO2009/092770. In a further embodiment the invention provides a kit comprising an inhaler in combination with a polymorph of Compound (I) and one or more pharmaceutically acceptable excipients. In a further embodiment the invention provides a kit comprising a dry powder inhaler in combination with the Form II polymorph of Compound (I) and one or more pharmaceutically acceptable excipients. In a further embodiment the invention provides a kit comprising a GyroHaler® dry powder inhaler in combination with the Form II polymorph of Compound (I) and one or more pharmaceutically acceptable excipients. In a still further embodiment the invention provides a kit comprising a lever operated dry powder inhaler disclosed in WO 2009/092770 in combination with the Form II polymorph of Compound (I) and one or more pharmaceutically acceptable excipients.

In a further embodiment the invention provides a process for the preparation of the Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile which comprises suspending the compound as an alternative form in a suitable solvent, optionally heating and then isolating the resulting product. In

one embodiment the invention provides a process for the preparation of the Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile which comprises suspending the Form I in aqueous THF and heating the resulting slurry between ambient temperature and about 50°C. In one embodiment the aqueous THF contains water, for example about 5% water. The polymorph is typically isolated by filtration followed by drying.

The hydrates, solvates and amorphous form of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile can be prepared using the techniques exemplified herein.

The following examples illustrate the invention.

Examples

The following examples illustrate the invention.

1. General Instruments and Methodology Details

1.1 X-Ray Powder Diffraction (XRPD)

X-Ray Powder Diffraction patterns were collected on a Bruker D8 diffractometer using CuKa radiation (40 kV, 40 mA), θ-2-θ goniometer, and divergence of V4 and receiving slits, a Ge monochromator and a Lynxeye detector. The instrument is performance checked using a certified Corundum standard (NIST 1976). The software used for data collection was Diffrac *Plus* XRD Commander v2.6.1 and the data were analysed and presented using Diffrac *Plus* EVA v13.0.0.2 or v15.0.0.0.

Samples were run under ambient conditions as flat plate specimens using powder as received. The sample was gently packed into a cavity cut into polished, zero-background (510) silicon wafer. The sample was rotated in its own plane during analysis. The details of the data collection are:

- Angular range: 2 to 42 °2θ
- Step size: 0.05 °2 θ
- Collection time: 0.5 s/step

1.2. Nuclear Magnetic Resonance (NMR)

NMR spectra were collected on a Bruker 400MHz instrument equipped with an auto-sampler and controlled by a DRX400 console. Automated experiments were acquired using ICONNMR v4.0.7 running with Topspin v1.3 using the standard Bruker loaded experiments. For non-routine spectroscopy, data were acquired through the use of Topspin alone.

Samples were prepared in DMSO-*d6*, unless otherwise stated. Off-line analysis was carried out using Topspin v1.3 or ACD SpecManager v12.5 or ACD Labs 2012 release (build 61851).

1.3 Differential Scanning Calorimetry (DSC)

DSC data were collected on a Mettler DSC 823E equipped with a 34 position auto-sampler. The instrument was calibrated for energy and temperature using certified indium. Typically 0.5-3 mg of each sample, in a pin-holed aluminium pan, was heated at 10 °C/min from 25 °C to 300 °C. A nitrogen purge at 50 ml/min was maintained over the sample.

The instrument control and data analysis software was STARe v9.20.

2. Preparation of polymorphic forms of Compound (I)

2.1. Form I

The compound (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I was prepared according to the procedures outlined in WO2011/051452.

Form I had DSC endotherm onsets of 142°C and 235°C and an exotherm onset of 155°C.

The product was identified as Form I and had an XRPD diffractogram as shown in Figure 1 with peak data shown in the table below.

Angle (°2θ)	Intensity	Rel. Intensity (%)
3.90	410	24.1
4.35	280	16.5
4.85	328	19.3
9.99	295	17.3
11.14	561	33.0
14.04	1136	66.7
14.54	737	43.3
16.89	640	37.6
17.64	1702	100.0
19.54	286	16.8
20.04	380	22.3
20.69	169	9.9
22.14	1133	66.6
24.39	1396	82.0
24.93	923	54.2
25.88	281	16.5
26.23	832	48.9
29.98	171	10.0
31.63	215	12.6
34.88	186	10.9

2.2. Form II

(S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I (500 mg) was suspended in THF + 5% water (5.0 ml). The resulting slurry was shaken for 24 h, cycling between ambient temperature and 50°C at 8 h intervals. The solid present was isolated by filtration and air dried to give 315 mg of an off white solid.

Form II had an endotherm onset of 239°C.

Form II had an XRPD diffractogram as shown in Figure 2 with peak data shown in the table below.

Angle (°2θ)	Intensity	Rel. Intensity (%)
8.25	5933	100.0
10.80	1472	24.8
12.60	761	12.8
13.25	2310	38.9
15.40	3572	60.2
17.65	2549	43.0
18.35	420	7.1
18.80	1325	22.3
20.15	1081	18.2
20.70	1393	23.5
20.90	687	11.6
22.55	938	15.8
24.29	1301	21.9
24.74	480	8.1
25.39	2776	46.8
25.99	627	10.6
26.24	585	9.9
26.74	1481	25.0
27.34	451	7.6
32.99	542	9.1

2.3. Form III

(S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I (250 mg) was placed in an oven at a temperature of 206°C for 30 minutes. Material was then cooled to room temperature to give 250 mg of an off white solid.

Form III had an endotherm onset of 235°C.

Form III had an XRPD diffractogram as shown in Figure 3 with peak data shown in the table below.

Angle (°2θ)	Intensity	Rel. Intensity (%)
6.75	458	9.8
8.70	710	15.1
11.40	2594	55.3
13.60	3965	84.5
14.85	498	10.6
15.25	324	6.9
15.60	1893	40.3
16.20	904	19.3
17.15	665	14.2
17.40	632	13.5
19.30	1056	22.5
20.45	1001	21.3
22.00	1463	31.2
22.80	4692	100.0
25.44	275	5.9
25.94	650	13.9
26.14	614	13.1
26.69	1871	39.9
29.64	273	5.8
31.74	263	5.6

3. Preparation of the hydrate, solvates and amorphous forms of Compound (I)

3.1 1,2 Dimethoxyethane Solvate

S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I (500 mg) was suspended in 1,2-dimethoxyethane (5.0 ml). The resulting slurry was shaken for 24 h, cycling between ambient temperature and 50 °C at 8 h intervals. The solid present was isolated by filtration and air dried to give 425 mg of an off white solid

The solvate had endotherm onsets of 143°C and 235°C and an exotherm onset of 151°C.

3.2 Hydrate

Amorphous (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile was prepared by rapid concentration of a solution of the compound (1.2g) in trichloromethane under vacuum at 50°C. A portion of the resulting glassy solid (270mg) was suspended in water (2ml), briefly sonicated and then shaken overnight at ambient temperature. The resulting solid was isolated by filtration and air dried to give 182 mg of an off-white solid.

The hydrate had endotherm onsets of 48°C and 236°C and an exotherm onset of 146°C.

3.2 $CHCl_3$ Solvate

A saturated solution was prepared by slurrying ca. 500mg of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I in trichloromethane (2 ml) at ambient temperature for 30 minutes. After passing through a 1 μm glass filter, the filtrate was cooled to 5°C for three days. After this time a solid had evolved. This was isolated by filtration and air dried to give 130mg of an off-white solid.

The solvate had endotherm onsets of 141°C and 238°C and an exotherm onset of 168°C.

3.3 Dichloromethane Solvate

Amorphous (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile was prepared by rapid concentration of a solution of the compound (1.2g) in DCM under vacuum at 50°C. A portion of the resulting glassy solid (400 mg) was suspended in DCM (5 ml), and stirred at ambient temperature for four hours. The resulting solid was isolated by filtration and air dried to give 242 mg of an off-white solid.

The solvate had endotherm onsets of 135°C and 238°C and an exotherm onset of 175°C.

3.4 1,4-Dioxane Solvate

A saturated solution was prepared by slurrying ca. 500mg of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile Form I in 1,4-dioxane (5 ml) at ambient temperature overnight. After passing through a 1 μm glass filter, the filtrate was allowed to evaporate overnight. The suspended solid present was isolated by filtration and air dried to give 52 mg of an off-white solid.

The solvate had endotherm onsets of 121°C and 235°C and an exotherm onset of 133°C.

4. NMR Data for the polymorphs

1H NMR data demonstrated that the chemical structures of the Form I, II and III polymorphs were identical. See Figures 4 and 5.

5. Competitive slurrying experiments

Procedure

10 mg (+/- 1mg) each of the Form I, Form II, Form III, 1,2-dimethoxtethane solvate and the hydrate of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile was added to each of twelve vials. To each vial was added 500 µl of the solvent system shown in the table below. The solvent systems used had been pre-saturated with (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile by shaking a slurry of Form I at the relevant temperature for 16 hours and then passing through a 1 µm glass filter.

The resulting slurries were agitated at the temperature shown for a period of one week. The solids present were then isolated by filtration, air dried and characterised by XRPD.

Results

Vial Number	Solvent	Temperature (°C)	XRPD characterisation
1	water	5	Form II / Hydrate*
2	water	25	Form II / Form III / Hydrate
3	water	50	Form II
4	MEK	5	Form II
5	MEK	25	Form II
6	MEK	50	Form II
7	EtOAc	5	Form II / 1,2-dimethoxyethane solvate
8	EtOAc	25	Form II / 1,2-dimethoxyethane solvate
9	EtOAc	50	Form II
10	IPA	5	Form II
11	IPA	25	Form II / 1,2-dimethoxyethane solvate
12	IPA	50	Form II

*poor recovery hampered interpretation

Of the three anhydrous forms, Form II is the most thermodynamically stable at all three temperatures evaluated. No Form I or Form III material was visible in any of the isolated solids, except one of the experiments in water. This is likely to be attributable to the poor solubility of the compound in water, slowing the rate of conversion.

The same result was observed for Hydrate I, with complete conversion to Form II observed in water at 50 °C, but not at 25°C or 5°C. No Hydrate was observed in any solvent system other than pure water, showing the hydrate to be less stable than the anhydrous Form II in organic solvents.

The results from the MEK experiments show that Form II can be reliably isolated even at sub-ambient temperatures.

AMENDED CLAIMS
received by the International Bureau on 21 July 2016 (21.07.2016)

1. A Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile with the following diffraction angles (2Theta) based on cupric Kα1:

   at approximately 8.25°

   at approximately 13.25°

   at approximately 15.40°

   at approximately 17.65°

   at approximately 25.39°

2. A polymorph according to claim 1 further characterised as having a XPRD diffractogram as shown in Figure 2.

3. A polymorph according to claim 1 or 2 further characterised as having a DSC endotherm onset of 239°C.

4. A polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile according to any one of claims 1 to 3 for use as a therapeutic agent.

5. The use of a polymorph according to any one of claims 1 to 3 for the treatment or prophylaxis of a respiratory disorder.

6. The use according to claim 5 where the respiratory disorder is asthma or COPD.

7. The use according to claim 5 where the respiratory disorder is severe asthma.

8. A method of treatment of a respiratory disease which comprised administering to a patient in need thereof a polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile as defined in any one of claims 1 to 3.

9. A process for the preparation of Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile which comprises suspending the compound as Form I in aqueous THF and heating the resulting slurry between ambient temperature and about 50°C.

AMENDED SHEET (ARTICLE 19)

9. A Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile according to any one of claims 2 to 4 for use as a therapeutic agent.

10. The use of a polymorph according to any one of claims 2 to 4 for the treatment or prophylaxis of a respiratory disorder.

11. The use according to claim 10 where the respiratory disorder is asthma or COPD.

12. The use according to claim 10 where the respiratory disorder is severe asthma.

13. A method of treatment of a respiratory disease which comprised administering to a patient in need thereof a polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile as defined in any one of claims 1 to 7.

14. A method of treatment of a respiratory disease which comprised administering to a patient in need thereof a Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile as defined in any one of claims 2 to 4.

15. A process for the preparation of Form II polymorph of (S)-3-(3-(1-methyl-2-oxo-5-(pyrazolo[1,5-a]pyridine-3-yl)-1H-imidazo[4,5-b]pyridine-3(2H)-yl)piperidin-1-yl)-3-oxopropanenitrile which comprises suspending the compound as Form I in aqueous THF and heating the resulting slurry between ambient temperature and about 50°C.

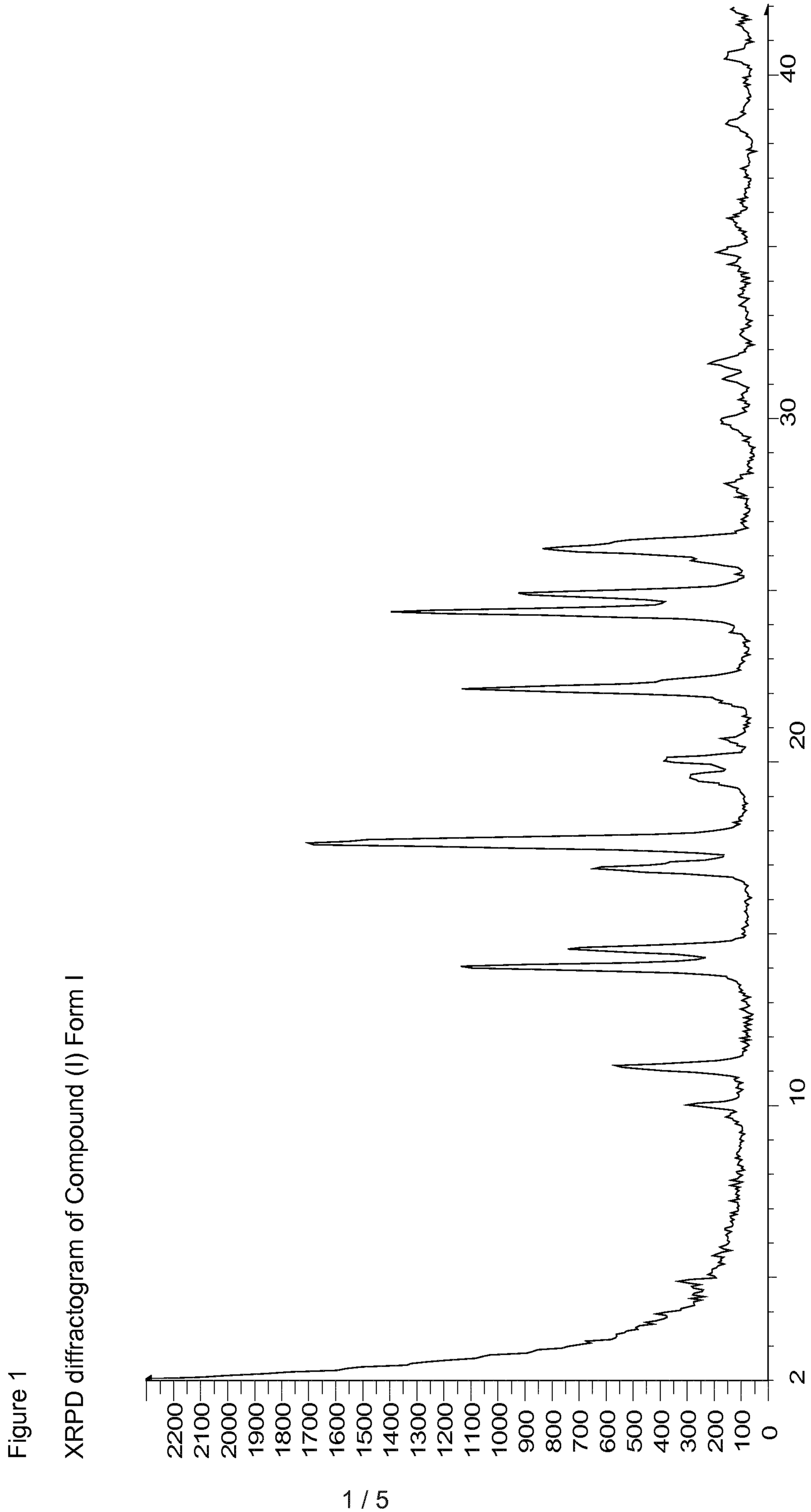

XRPD diffractogram of Compound (I) Form I
2-Theta - Scale
0
100
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
1500
1600
1700
1800
1900
2000
2100
2200
2
10
20
30
40

Figure 1

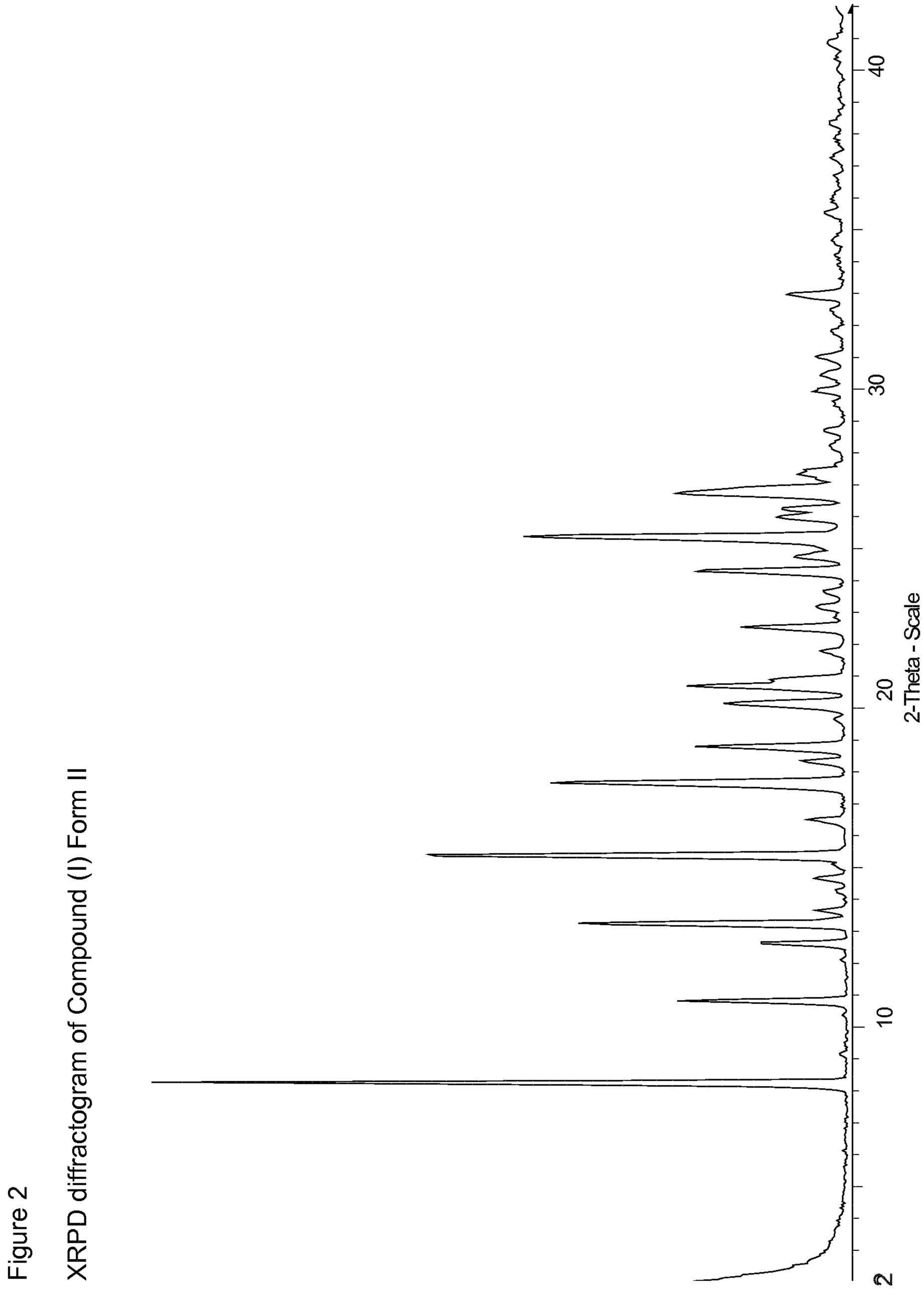


Figure 2

XRPD diffractogram of Compound (I) Form II

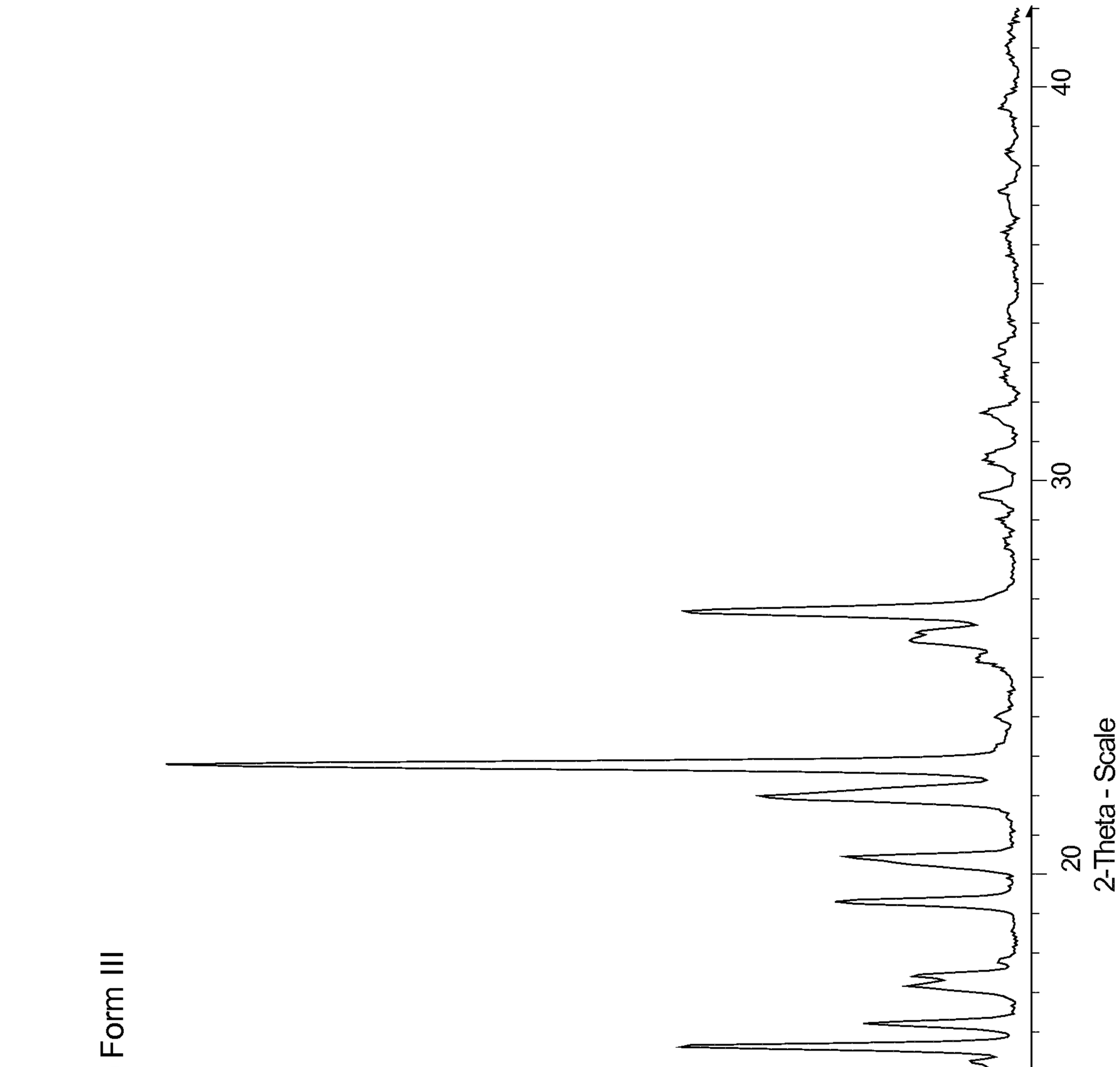


Figure 3

XRPD diffractogram of Compound (I) Form III

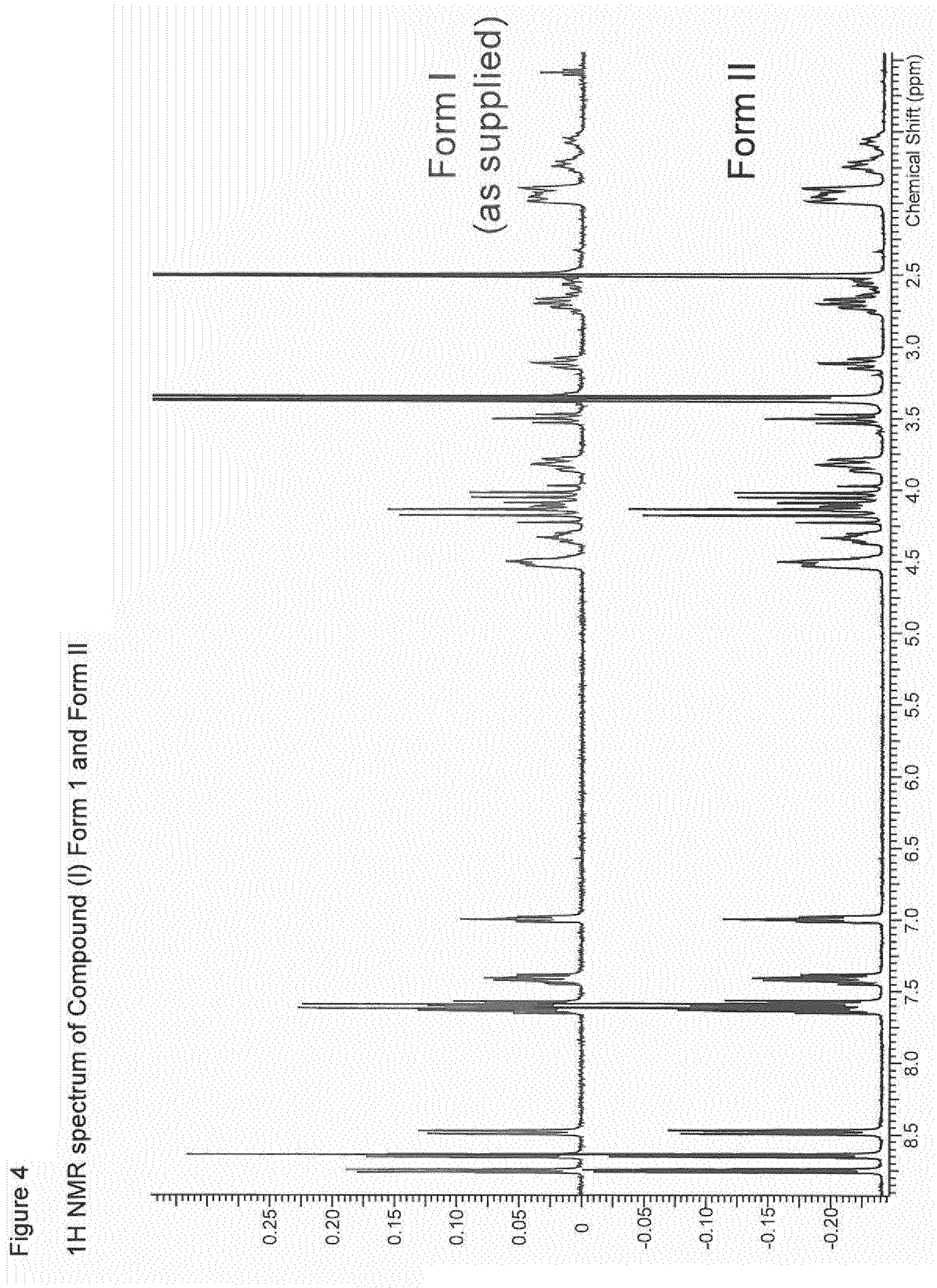


Figure 4

1H NMR spectrum of Compound (I) Form 1 and Form II

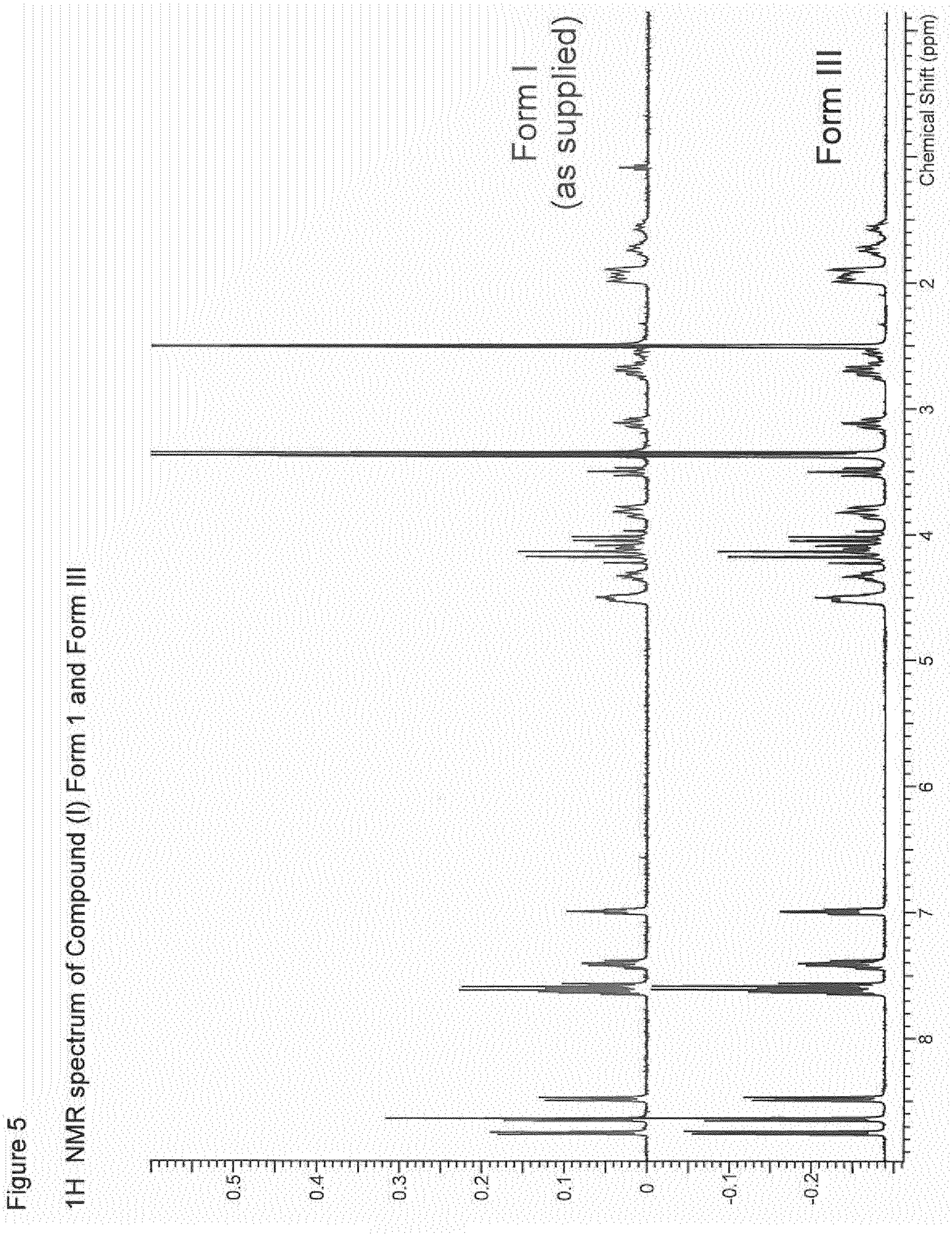

Form I
(as supplied)
Form III
Chemical Shift (ppm)
1H NMR spectrum of Compound (I) Form 1 and Form III
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
2
3
4
5
6
7
8

Figure 5

Figure 1

XRPD diffractogram of Compound (I) Form I