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[Continued on next page]

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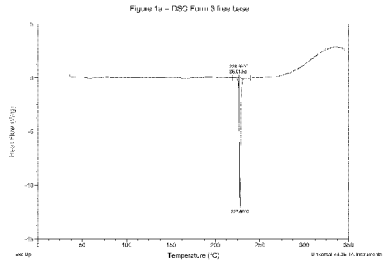
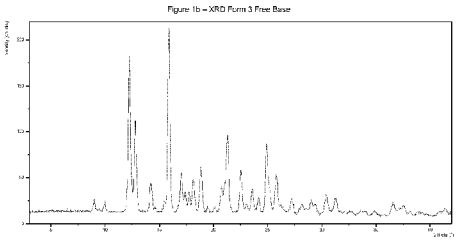
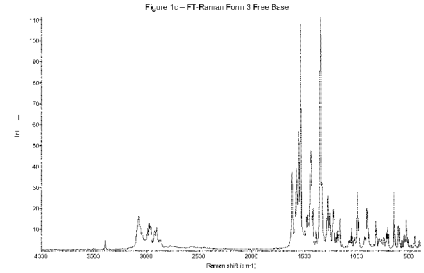
(54) Title: CRYSTAL FORM OF N-{3-[5-(2-AMINO-4-PYRIMIDINYL)-2-(1,1-DIMETHYLETHYL)-1,3-THIAZOL-4yl}-2-FLUOROPHENYL}-2,6-DIFLUOROBENZENESULFONAMIDE







(57) Abstract: The invention relates to a novel anhydrous crystalline form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and pharmaceutical compositions containing the same.

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CRYSTAL FORM OF *N*-{3-[5-(2-AMINO-4-PYRIMIDINYL)-2-(1,1-DIMETHYLETHYL)-1,3-THIAZOL-4-yl]-2-FLUOROPHENYL}-2,6-DIFLUOROBENZENESULFONAMIDE

BACKGROUND OF THE INVENTION

The present invention relates to a crystalline form of the kinase inhibiting compound *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, pharmaceutical formulations comprising the crystalline forms, their use in therapy and processes for preparing the same.

The compound *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and a genus of compounds encompassing that compound have been found to be active inhibitors of particular kinases, particularly the B-Raf kinase. Such usefulness is disclosed in, for instance, international patent publication WO2009/137391. The WO'391 publication specifically discloses a number of crystal forms of the *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide compound and the mesylate salt thereof.

It is desired to provide an additional crystal form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide having properties suitable for use in pharmaceutical formulations.

BRIEF SUMMARY OF THE INVENTION

As a first aspect, the present invention provides a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (referred to hereinafter as "form 3 free base") characterized by substantially the same differential scanning calorimetry (DSC) thermogram as **Figure 1a**, wherein the DSC thermogram is obtained at a scan rate of 15°C per minute using a sample size of between 1 and 2 mg according to the procedures described herein.

As a second aspect, the present invention provides a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by substantially the

same X-ray powder diffraction (XRD) pattern as **Figure 1b**, wherein the XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation.

As a third aspect, the present invention provides a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by an XRD pattern expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, wherein the XRD pattern comprises 2 theta angles at four or more positions selected from the group consisting of 12.2±0.1, 12.8±0.1, 15.9±0.1, 17.0±0.1, 18.9±0.1, 21.3±0.1, 22.5±0.1, 24.9±0.1, and 25.8±0.1 degrees.

As a forth aspect, the present invention provides a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by an XRD pattern expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, wherein the XRD pattern comprises 2 theta angles 12.2±0.1, 12.8±0.1, 15.9±0.1, 21.3±0.1, and 24.9±0.1 degrees.

The invented crystalline form is characterized by substantially the same Raman spectrum as **Figure 1c**, wherein the Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1} resolution. This FT-Raman spectrum is not used herein to distinguish the invented form from alternative crystal forms of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. Indeed, the FT-Raman spectrum of the invented crystal form has substantial overlap with one or more of the comparitive free base crystal forms described herein.

As another aspect, the present invention provides a pharmaceutical composition comprising a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according to the present invention. The pharmaceutical composition may further comprise one or more pharmaceutically acceptable carriers or diluents.

In another aspect of the present invention, there is provided a method of treating a susceptible neoplasm in a mammal in need thereof, comprising administering to the mammal a therapeutically effective amount of the crystalline *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according described by Figures 1a-1d and the embodiments above, taken either independently or collectively. Susceptible neoplasms include e.g., Barret's adenocarcinoma; billiary tract carcinomas; breast cancer; cervical cancer; cholangiocarcinoma; central nervous system tumors including primary CNS tumors such as glioblastomas, astrocytomas (e.g., glioblastoma multiforme) and ependymomas, and secondary CNS tumors (i.e., metastases to the central nervous system of tumors originating outside of the central nervous system); colorectal cancer including large intestinal colon carcinoma; gastric cancer; carcinoma of the head and neck including squamous cell carcinoma of the head and neck; hematologic cancers including leukemias and lymphomas such as acute lymphoblastic leukemia, acute myelogenous leukemia (AML), myelodysplastic syndromes, chronic myelogenous leukemia, Hodgkin's lymphoma, non-Hodgkin's lymphoma, megakaryoblastic leukemia, multiple myeloma and erythroleukemia; hepatocellular carcinoma; lung cancer including small cell lung cancer and non-small cell lung cancer; ovarian cancer; endometrial cancer; pancreatic cancer; pituitary adenoma; prostate cancer; renal cancer; sarcoma; skin cancers including melanomas; and thyroid cancers.

In another aspect of the present invention, there is provided a method of treating breast cancer, cholangiocarcinoma, colorectal cancer, melanoma, non-small cell lung cancer, ovarian cancer, or thyroid cancer, in a mammal, particularly a human, in need thereof, comprising administering to the mammal (e.g. human) a therapeutically effective amount of the crystalline *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according described by Figures 1a-1d and the embodiments above, taken either independently or collectively.

The crystalline form(s) of the instant invention are contrasted with the crystal forms of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide previously disclosed in WO2009/137391.

For instance, example 58a in the WO2009/137391 publication describes the synthesis of a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (hereinafter referred to as "form 1 free base") having a crystal form characterized by the spectra and characteristics summarized in Table 1 below.

Example 58b and 58c in the WO2009/137391 publication describe the synthesis of a crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide (hereinafter referred to as "form 2 free base") having a crystal form characterized by the spectra and characteristics summarized in Table 1 below.

Examples 58d and 58e in the WO2009/137391 publication describe the synthesis of an anhydrous crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide methanesulfonate (hereinafter referred to as "form 1 mesylate salt") having a crystal form characterized by the spectra and characteristics summarized in Table 1 below.

Table 1

	Form 1 free base	Form 2 free base	Form 1 mesylate salt
DSC†	**Figure 2a**	**Figure 3a**	**Figure 4a**
XRD Pattern*	**Figure 2b**	**Figure 3b**	**Figure 4b**
XRD – Predominate 2theta angles*	9.5±0.1, 10.1±0.1, 12.7±0.1, 16.1±0.1, 19.0±0.1 degrees	7.9±0.1, 13.6±0.1, 14.6±0.1, 15.8±0.1, 20.3±0.1, 21.9±0.1 degrees***	6.3±0.1, 10.6±0.1, 15.2±0.1, 16.5±0.1, 18.8±0.1, 20.8±0.1, 22.2±0.1 degrees.
FT-Raman Spectrum**	**Figure 2c**	**Figure 3c**	**Figure 4c**

† Differential scanning calorimetry (DSC) was carried out on a TA Q1000 TA calorimeter. Scan rate of 15°C per minute. Sample size of between 1 and 2mg.

* XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation

** Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1} resolution

***Though not necessarily the most predominate 2theta angles, these are the predominate 2theta angles that show distinction from the form 1 mesylate salt.

BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWINGS

Figure 1a. The differential scanning calorimetry (DSC) thermogram of the crystal form according to the present invention. The thermogram is obtained at a scan rate of 15°C per minute using a sample size of between 0.4 and 2 mg according to the procedures described herein.

Figure 1b. The XRD pattern according to the present invention. The XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, according to the procedures described herein.

Figure 1c. The Raman spectrum according to the present invention. The Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1} resolution with an InGaAs or liquid nitrogen cooled Ge detector according to the procedures described herein.

Figure 2a. The differential scanning calorimetry (DSC) and thermal gravimetric (TGA) thermograms of form 1 of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The thermogram is obtained at a scan rate of 15°C per minute using a sample size of between 0.4 and 2 mg according to the procedures described herein.

Figure 2b. The XRD pattern of form 1 of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, according to the procedures described herein.

Figure 2c. The Raman spectrum according to the present invention. The Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1}

resolution with an InGaAs or liquid nitrogen cooled Ge detector according to the procedures described herein.

Figure 3a. The differential scanning calorimetry (DSC) and thermal gravimetric (TGA) thermograms of form 2 of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The thermogram is obtained at a scan rate of 15°C per minute using a sample size of between 0.4 and 2 mg according to the procedures described herein.

Figure 3b. The XRD pattern of form 2 of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, according to the procedures described herein.

Figure 3c. The Raman spectrum according to the present invention. The Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1} resolution with an InGaAs or liquid nitrogen cooled Ge detector according to the procedures described herein.

Figure 4a. The differential scanning calorimetry (DSC) and thermal gravimetric (TGA) thermograms of form 1 of the mesylate salt of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The thermogram is obtained at a scan rate of 15°C per minute using a sample size of between 0.4 and 2 mg according to the procedures described herein.

Figure 4b. The XRD pattern of form 1 of the mesylate salt of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, according to the procedures described herein.

Figure 4c. The Raman spectrum according to the present invention. The Raman spectrum is obtained using a FT-Raman spectrometer at 4 cm^{-1} resolution with an InGaAs or liquid nitrogen cooled Ge detector according to the procedures described herein.

DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a novel crystalline form of *N*-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide exhibiting one or more advantageous pharmaceutical properties or other advantages over various hydrated and other crystal forms of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and the mesylate salt thereof.

The various forms of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide may be characterized and differentiated using a number of conventional analytical techniques, including but not limited to X-ray powder diffraction (XRD) patterns, infrared (IR) spectra, Raman spectra, differential scanning calorimetry (DSC), thermogravimetric analysis (TGA) and solid state NMR.

"Form 3" or "Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide " as used herein refers to any of:

1) an anhydrous crystalline form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide having substantially the same differential scanning calorimetry (DSC) thermogram as shown in **Figure 1a,** obtained at a scan rate of 15°C per minute, using a sample size of between 0.4 and 2 mg according to the procedures described herein; or 2) an anhydrous crystalline form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide having substantially the same XRD pattern as shown in **Figure 1b** when measured with a properly aligned diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation.

The differential scanning calorimetry (DSC) thermogram of the anhydrous crystalline form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according to the present invention (i.e., Form 3) can be determined using conventional equipment and techniques known to those skilled in the art of analytical chemistry and physical characterization. The differential scanning calorimetry (DSC) thermogram of **Figure 1a** was obtained with a differential scanning calorimeter, scan rate of 15°C per minute, and sample size of between 0.4 and 2mg.

The X-ray powder diffraction pattern of Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide can be determined using conventional techniques and equipment known to those skilled in the art of analytical chemistry and physical characterization. The diffraction pattern of **Figure 1b** was obtained with a diffractometer using copper Kα X-radiation.

A powder sample of Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide was used to produce the XRD pattern of **Figure 1b**. 2 Theta angles in degrees (x-axis) is plotted against peak intensity in terms of the count rate per seconds (y-axis). The XRD pattern for each anhydrous crystalline form and hydrated N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide is unique to the particular form; exhibiting a unique set of diffraction peaks which can be expressed in 2 theta angles (°), d-spacings (Å) and/or relative peak intensities.

2 Theta diffraction angles and corresponding d-spacing values account for positions of various peaks in the XRD pattern. D-spacing values are calculated with observed 2 theta angles and copper Kα1 wavelength using the Bragg equation. Slight variations in observed 2 theta angles and d-spacings are expected based on the specific diffractometer employed and the analyst's sample preparation technique. More variation is expected for the relative peak intensities. Identification of the exact crystal form of a compound should be based primarily on observed 2 theta angles or d-spacings with lesser importance place on relative peak intensities. To identify Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-

difluorobenzenesulfonamide , the certain characteristic 2 theta angle peaks occur at 12.2±0.1, 12.8±0.1, 15.9±0.1, 21.3±0.1, and 24.9±0.1 degrees.

Although one skilled in the art can identify Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide from these characteristic 2 theta angle peaks, in some circumstances it may be desirable to rely upon additional 2 theta angles or d-spacings for the identification of Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . In one embodiment at least five, particularly seven and more particularly all, of the following 2 theta angles are employed to identify Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide : 12.2±0.1, 12.8±0.1, 15.9±0.1, 17.0±0.1, 18.9±0.1, 21.3±0.1, 22.5±0.1, 24.9±0.1, and 25.8±0.1 degrees.

Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide typically exhibits 2 theta angle peaks in addition to the foregoing peaks. For example, Form 3 may exhibit 2 theta angle peaks at essentially the following positions: 9.0±0.1, 10.0±0.1, 12.2±0.1, 12.8±0.1, 14.1±0.1, 15.9±0.1, 17.0±0.1, 17.4±0.1, 17.7±0.1, 18.1±0.1, 18.9±0.1, 20.1±0.1, 20.7±0.1, 21.3±0.1, 22.5±0.1, 23.6±0.1, 24.2±0.1, 24.9±0.1, 25.8±0.1, 27.2±0.1, 28.1±0.1, 29.0±0.1, 30.4±0.1, 31.2±0.1, 33.8±0.1, 34.8±0.1, 36.6±0.1, 37.6±0.1, 41.4±0.1.

Some margin of error is present in each of the 2 theta angle assignments and d-spacings reported above. The error in determining d-spacings decreases with increasing diffraction scan angle or decreasing d-spacing. The margin of error in the foregoing 2 theta angles is approximately ±0.1 degrees for each of the foregoing peak assignments.

Since some margin of error is possible in the assignment of 2 theta angles and d-spacings, the preferred method of comparing XRD patterns in order to identify a the particular form of a sample of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide is to overlay the XRD pattern of the unknown sample over the XRD pattern of a known form.

Although 2 theta angles or d-spacings are the primary method of identifying a particular crystalline form, it may be desirable to also compare relative peak intensities. As noted above, relative peak intensities may vary depending upon the specific diffractometer employed and the analyst's sample preparation technique. The peak intensities are reported as intensities relative to the peak intensity of the strongest peak. The intensity units on the XRD are counts/sec. The absolute counts = counts/time x count time = counts/sec x 10 sec.

Considering 2 theta angles, Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide exhibits the following XRD pattern characteristics:

Peak #	2 theta angle (°) [1]
1	9.0
2	10.0
3	12.2
4	12.8
5	14.1
6	15.9
7	17.0
8	17.4
9	17.7
10	18.1
11	18.9
12	20.1
13	20.7
14	21.3
15	22.5
16	23.6
17	24.2
18	24.9
19	25.8
20	27.2
21	28.1
22	29.0
23	30.4
24	31.2
25	33.8
26	34.8
27	36.6
28	37.6
29	41.4

[1] Margin of error = approx. ±0.1 degrees.

Raman spectroscopy is another useful analytical technique for identifying the physical characteristics of a sample of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and distinguishing Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide. The Raman spectrum of the anhydrous crystalline form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according to the present invention (i.e., Form 3) can be determined using conventional equipment and techniques known to those skilled in the art of analytical chemistry and physical characterization. The Raman spectrum of **Figure 1c** was obtained using FT-Raman spectrometer. Samples were prepared by placing the solid sample as received into a glass NMR tube. The sample was rotated during the measurement. In **Figure 1c**, Raman shift in cm^{-1} (x-axis) is plotted against Raman intensity (y-axis).

The choice of detector is not believed to be critical to obtaining a spectrum suitable for comparison with that provided at **Figure 1c**. As is known to those skilled in the art, a different detector will likely affect the intensity of the peaks. However, peak positions should remain relatively the same. For a definitive comparison, when determining whether the Raman spectrum of an unknown form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide is Form 3, preferably the spectrum will be obtained using an InGaAs or liquid nitrogen cooled Ge detector.

Slight variations in observed peaks are expected based on the specific spectrometer employed, the resolution of the data and the analyst's sample preparation technique. Some margin of error is present in each of the peak assignments reported above. The margin of error in the foregoing peak assignments is approximately ± 1 cm^{-1}.

Since some margin of error is possible in the peak assignments, the preferred method of determining whether an unknown form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide is Form 3 is to overlay the Raman spectrum of the sample over the Raman spectrum provided in **Figure 1c**.

Any of the foregoing analytical techniques can be used alone or in combination to identify a particular form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . In addition, other methods of physical characterization can also be employed to identify and characterize Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . Examples of suitable techniques which are known to those skilled in the art to be useful for the physical characterization or identification of a crystalline form or solvate include but are not limited to XRPD, solid state NMR, DSC, and thermogravimetric analysis. These techniques may be employed alone or in combination with other techniques to characterize a sample of an unknown form.

The present invention includes Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide both in substantially pure form and in admixture with other forms of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, including admixtures of salts, particularly the mesylate salt thereof.

In another aspect, the present invention provides pharmaceutical compositions comprising Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide . Such pharmaceutical compositions may further comprise one or more other forms of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and/or one or more pharmaceutically acceptable carriers or diluents. Examples of suitable pharmaceutical compositions and methods for their preparation are described in PCT Publication No. WO2009/137391, the subject matter of which is incorporated herein by reference in their entirety. Conveniently, suitable pharmaceutical compositions can be prepared using conventional techniques, and when employed, carriers and diluents. Pharmaceutical compositions for oral administration, such as tablet (and caplet) and capsule formulations, are preferred.

Form 3 N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide and pharmaceutical formulations thereof for use in the instant invention may be used in combination

with other therapeutic agents as described in PCT publication No. WO2009/137391.

The following examples are intended for illustration only and are not intended to limit the scope of the invention in any way.

Example 1: Preparation of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide, Form 3

19.8mg of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide Form 1 was obtained using techniques analogous to those disclosed in example 58a of WO2009/137391 and was combined with 500µL of dichloromethane in a 2mL vial at room temperature. A solid sample was obtained by evaporative crystallization. The solids were analyzed by Raman, PXRD, and DSC which indicated the unique crystal form of N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide described herein as Form 3.

CLAIMS

1. Anhydrous crystalline N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by substantially the same differential scanning calorimetry (DSC) thermogram as **Figure 1a**, wherein said differential scanning calorimetry (DSC) thermogram is obtained at a scan rate of 15°C per minute, using a sample size of between 1 and 2 mg.

2. Anhydrous crystalline N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by substantially the same X-ray powder diffraction (XRD) pattern as **Figure 1b**, wherein said XRD pattern is expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation.

3. Anhydrous crystalline N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide characterized by an XRD pattern expressed in terms of 2 theta angles and obtained with a diffractometer equipped with a diffracted beam graphite monochromator using copper Kα X-radiation, wherein said XRD pattern comprises 2 theta angles at 12.2$\pm$0.1, 12.8$\pm$0.1, 15.9$\pm$0.1, 21.3$\pm$0.1, and 24.9$\pm$0.1 degrees.

4. A pharmaceutical composition comprising the anhydrous crystalline N-{3-[5-(2-Amino-4-pyrimidinyl)-2-(1,1-dimethylethyl)-1,3-thiazol-4-yl]-2-fluorophenyl}-2,6-difluorobenzenesulfonamide according to any of claims 1-3.

5. The pharmaceutical composition according to claim 4 further comprising one or more pharmaceutically acceptable carriers or diluents.

Figure 1a – DSC Form 3 free base

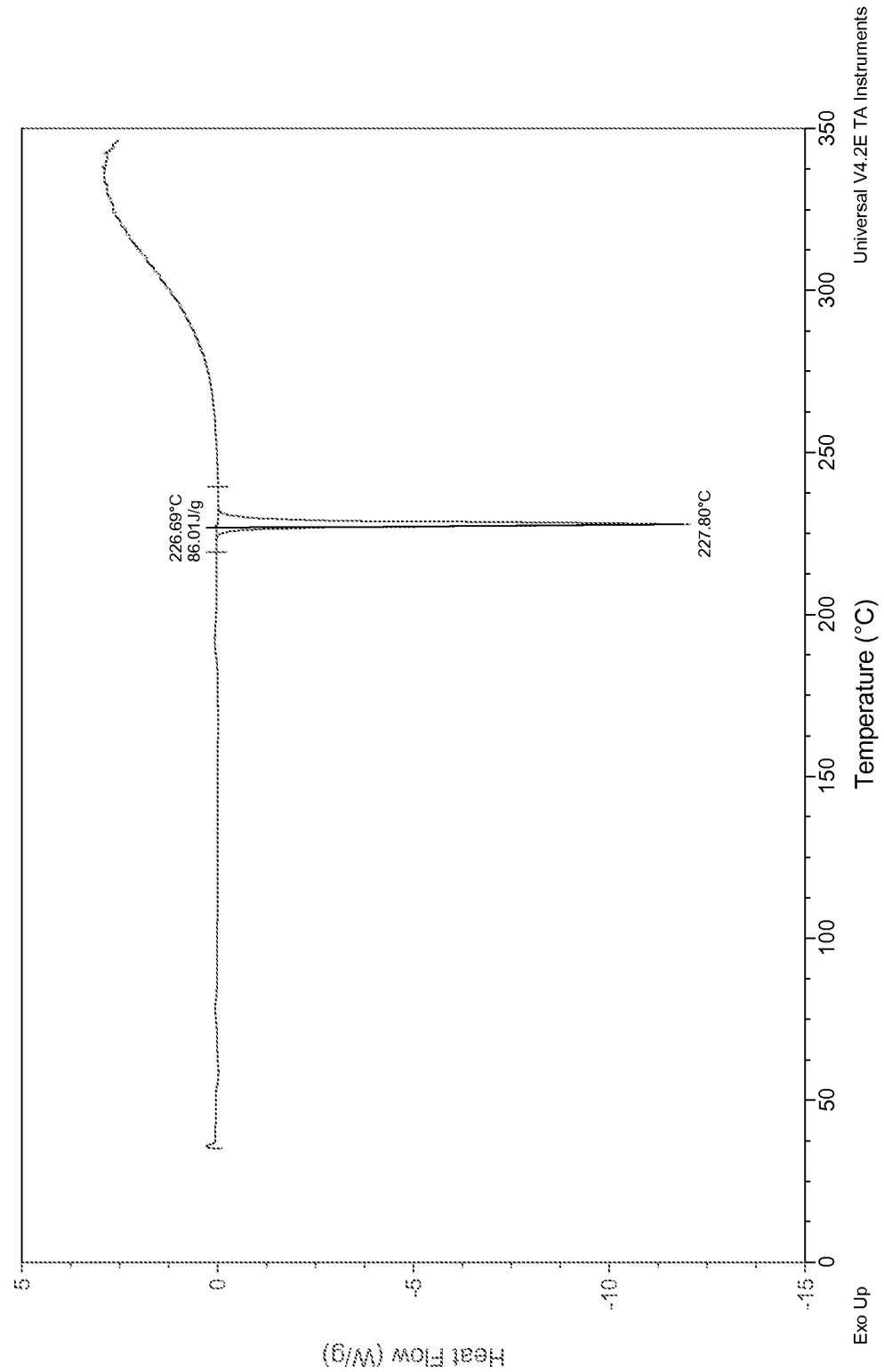


Figure 1b – XRD Form 3 Free Base

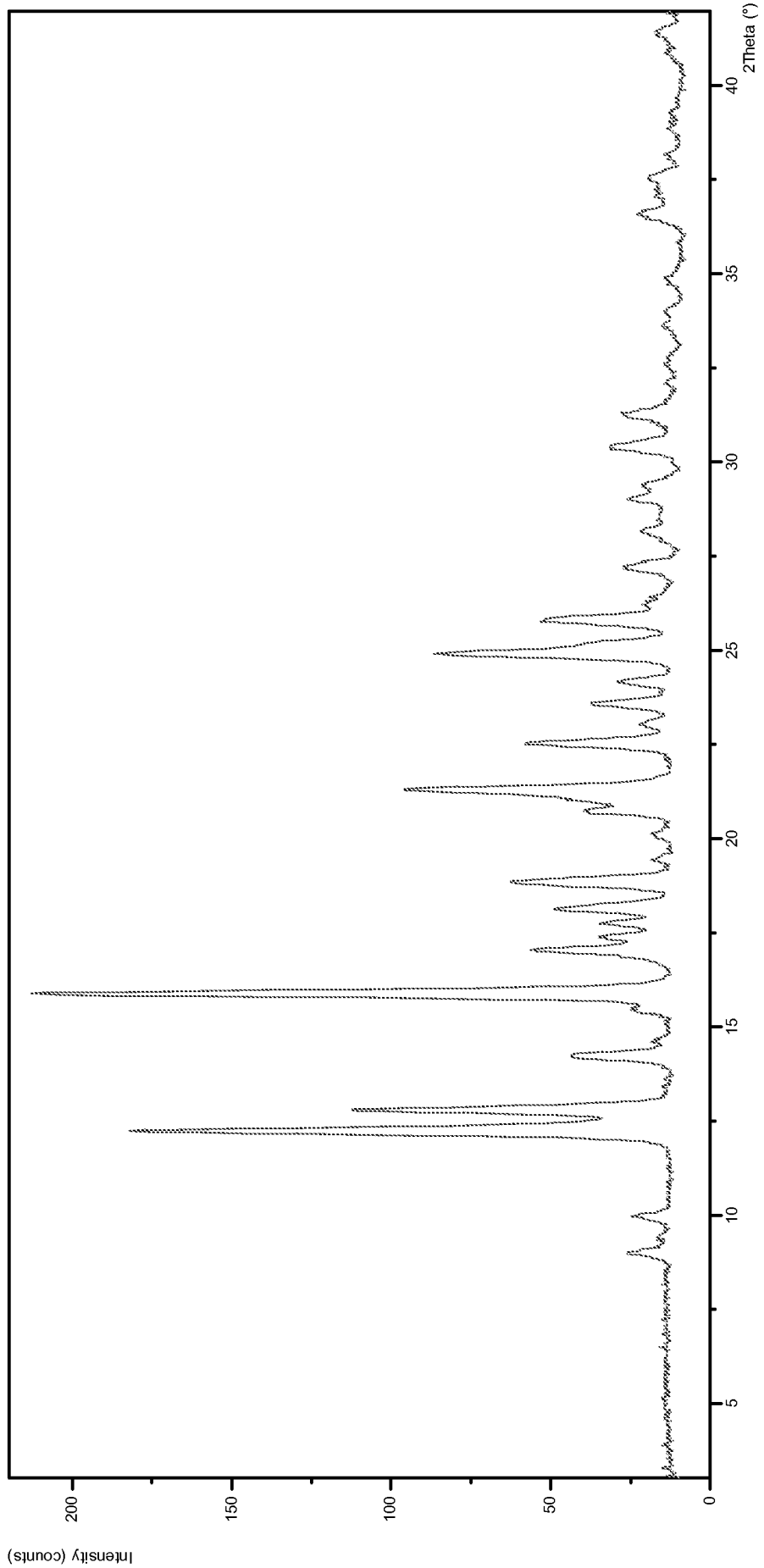
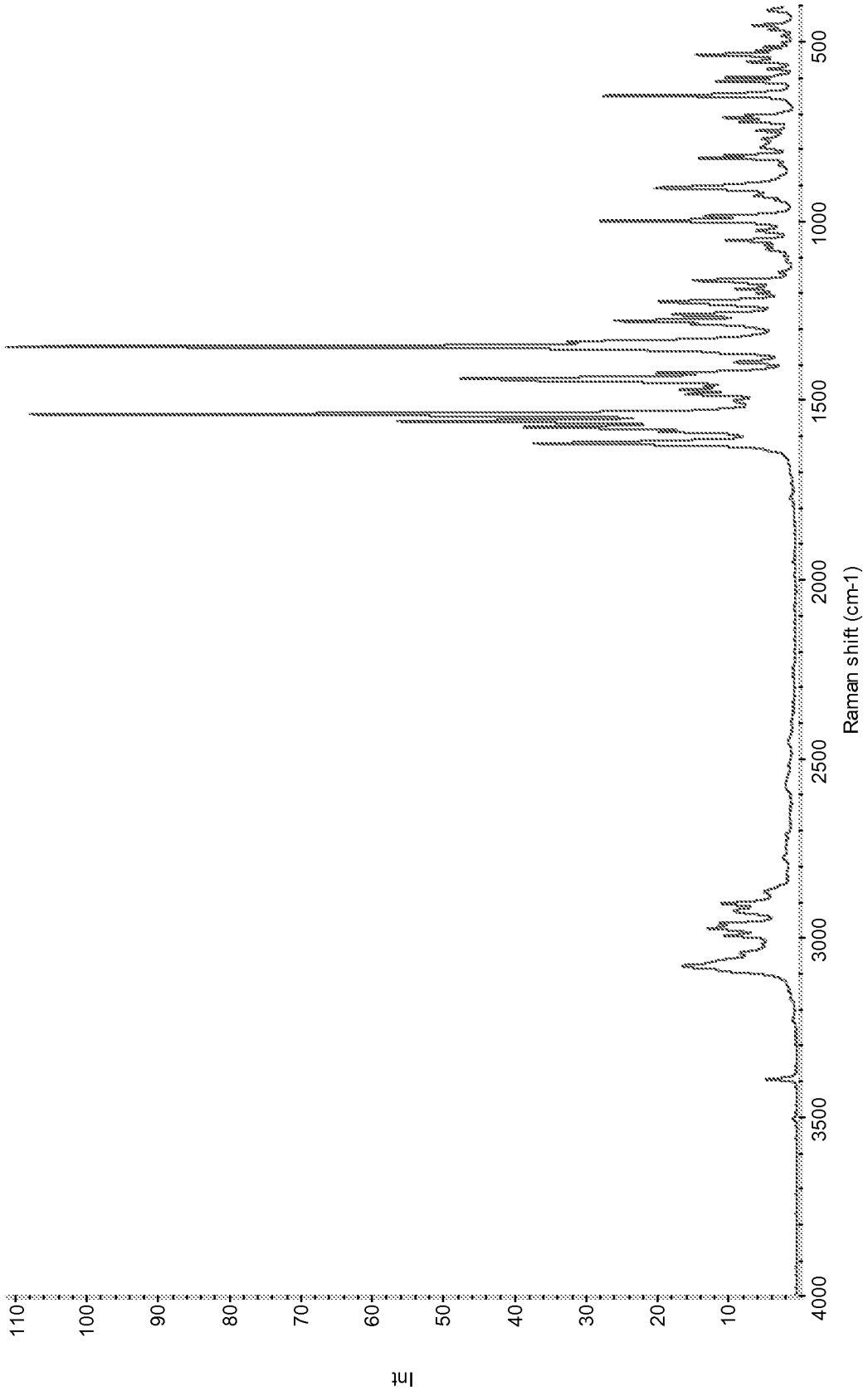


Figure 1c – FT-Raman Form 3 Free Base



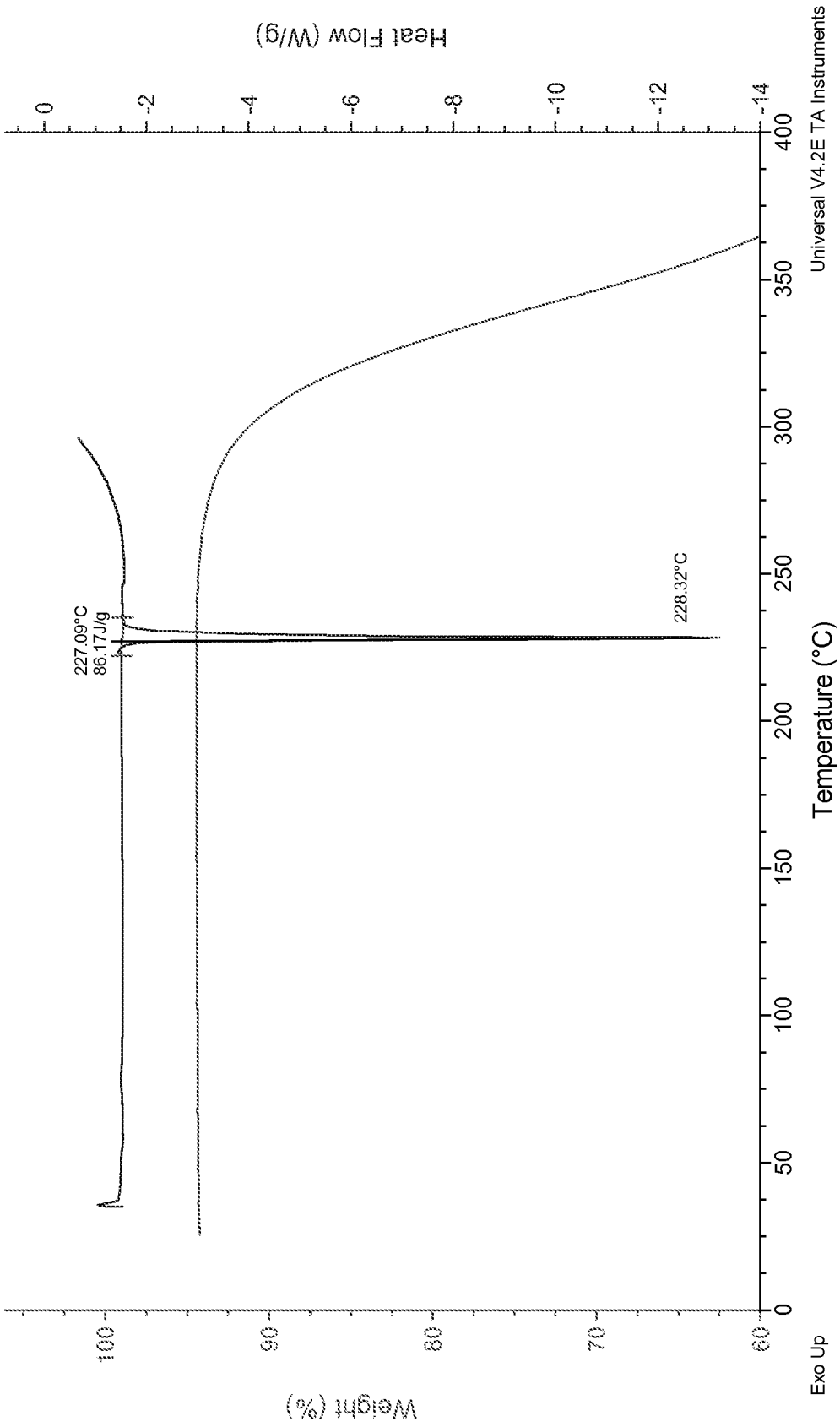


Figure 2a – DSC/TGA Form 1 Free Base

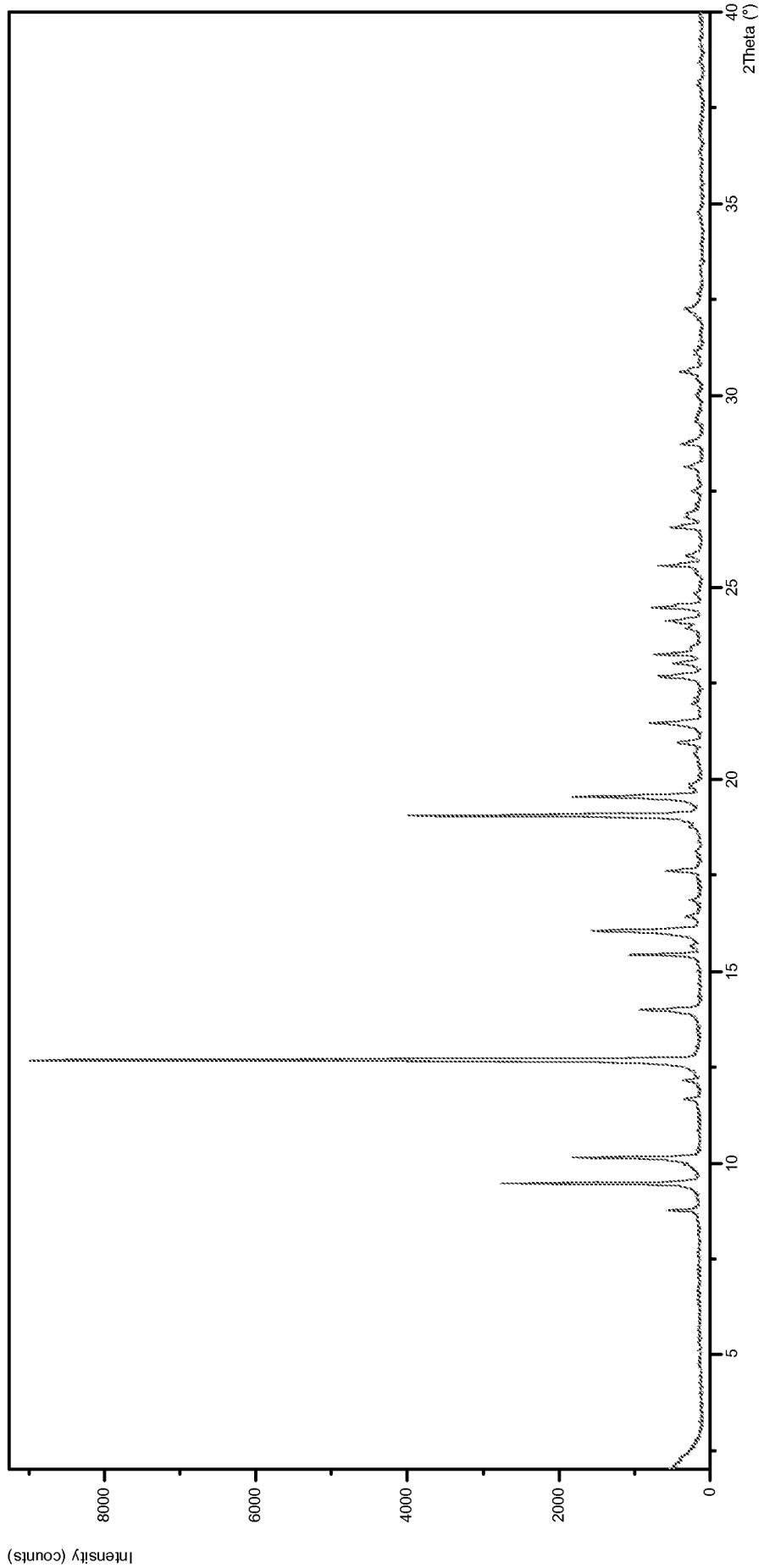
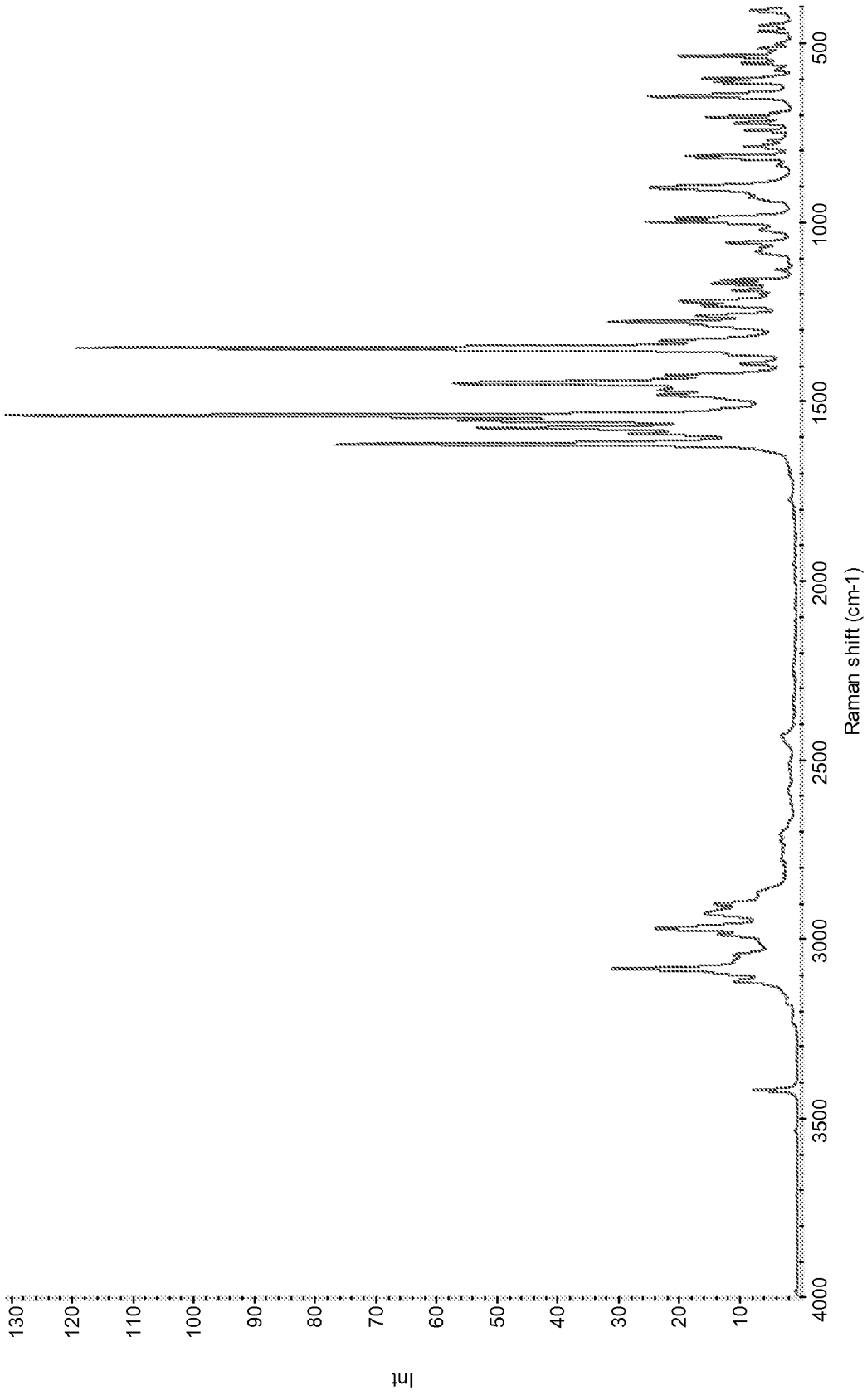


Figure 2b – XRD Form 1 Free Base

Figure 2c – FT-Raman Form 1 Free Base



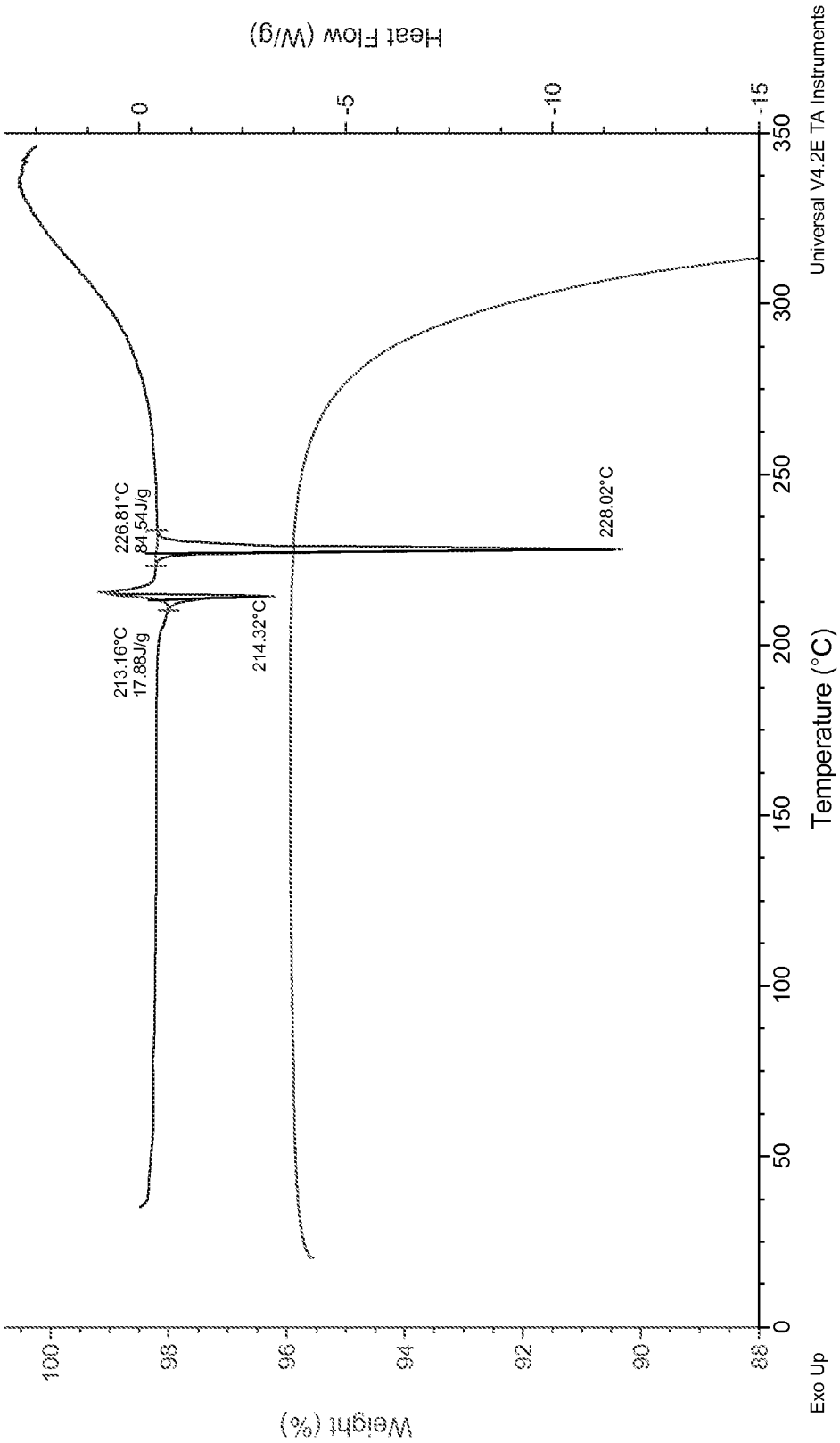


Figure 3a – DSC/TGA Form 2 Free Base

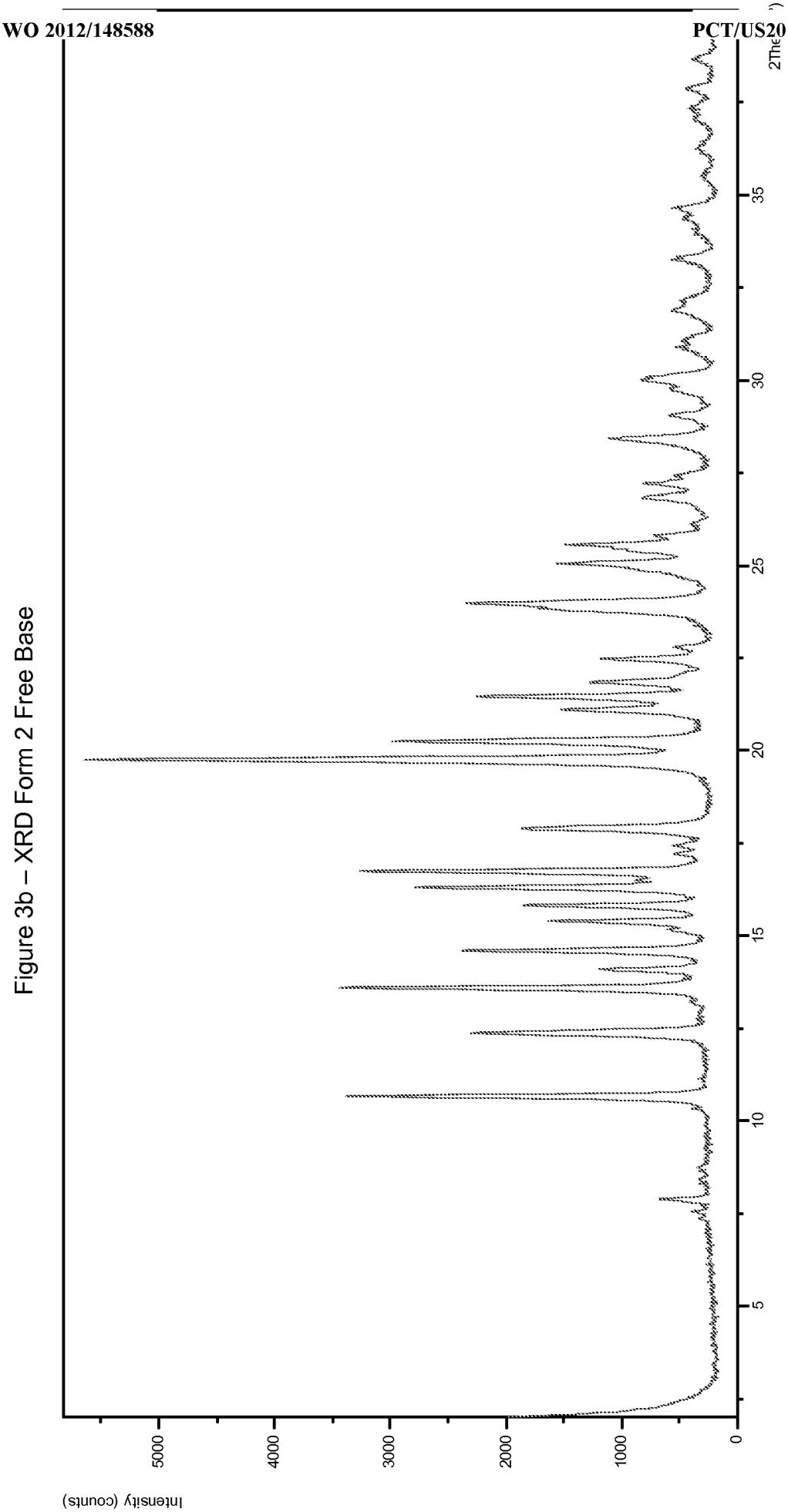
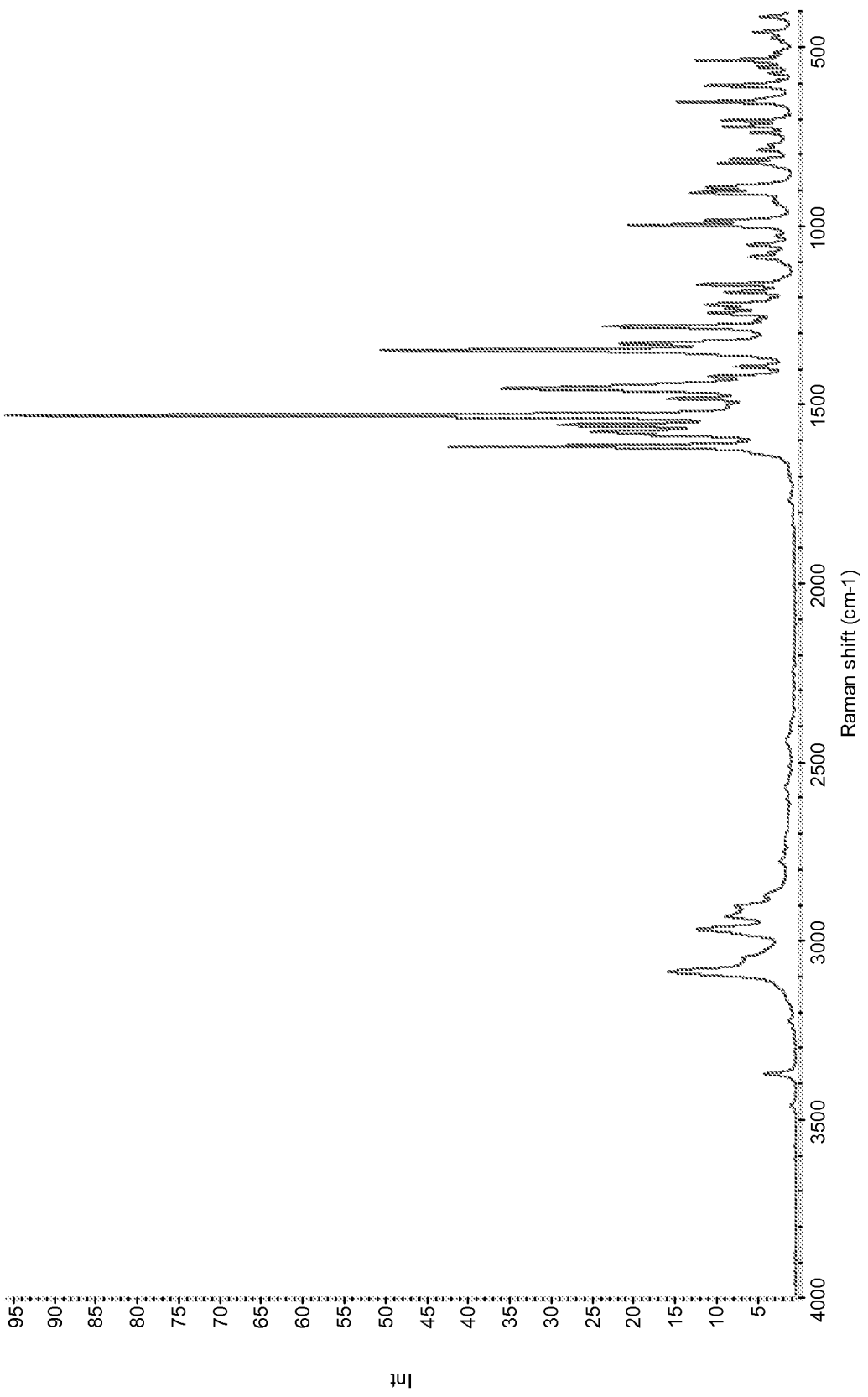


Figure 3b – XRD Form 2 Free Base

Figure 3c – FT-Raman Form 2 Free Base



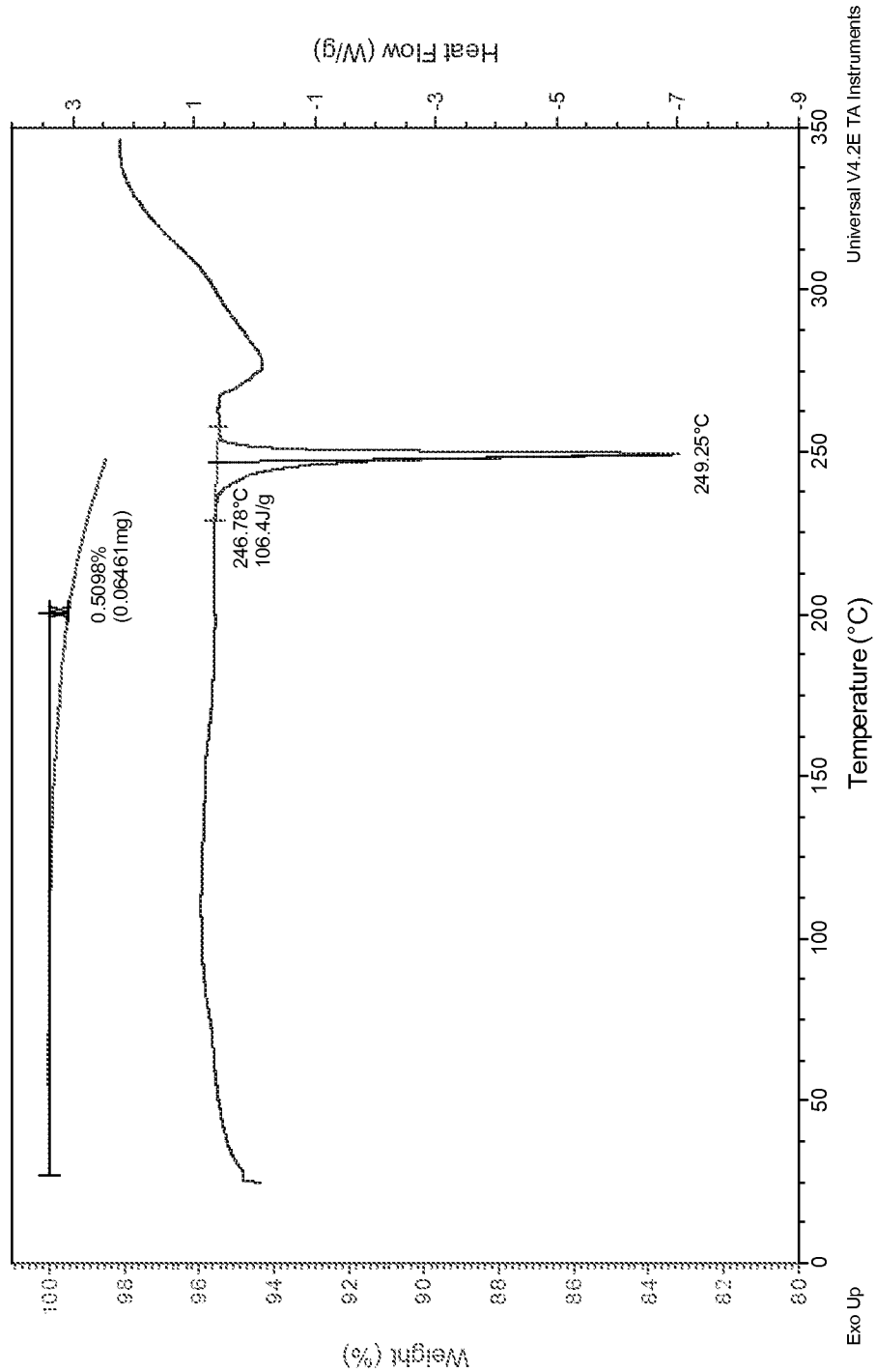


Figure 4a – DSC/TGA Form 1 Salt

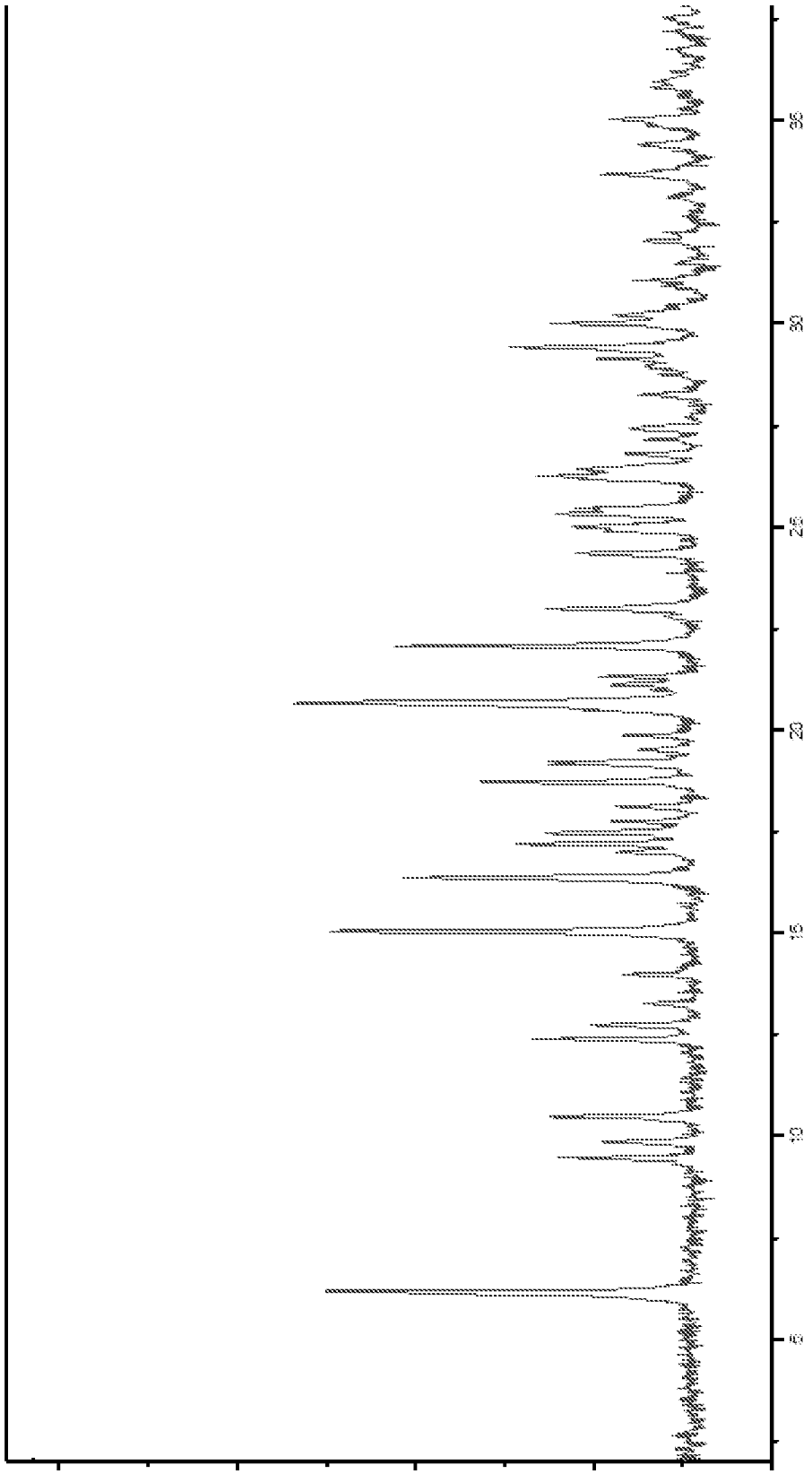


Figure 4b – XRD Form 1 Salt

Figure 4c – FT-Raman Form 1 Salt