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(54) Titre : COMPOSE CRISTALLIN NOVATEUR
(54) Title: NOVEL CRYSTALLINE COMPOUND

(57) Abrégé/Abstract:
This invention relates to a novel crystalline form of 6[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, and suitable processes for the preparation thereof. The compound 6-[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is a selective androgen receptor modulator (SARM).

Abstract

This invention relates to a novel crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, and suitable processes for the preparation thereof. The compound 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is a selective androgen receptor modulator (SARM).

Novel Crystalline Compound

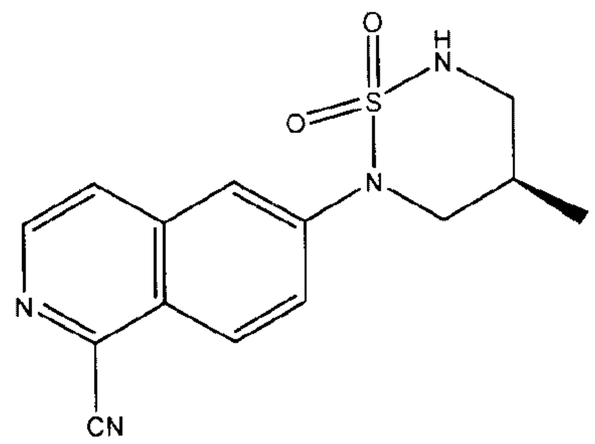
Field of the Invention

The present invention relates to a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, compositions thereof and to processes for the preparation thereof.

Background

The androgen receptor ("AR") is a ligand-activated transcriptional regulatory protein that mediates induction of male sexual development and function through its activity with endogenous androgens. Androgenic steroids play an important role in many physiologic processes, including the development and maintenance of male sexual characteristics such as muscle and bone mass, prostate growth, spermatogenesis, and the male hair pattern. The endogenous steroidal androgens include testosterone and dihydrotestosterone ("DHT"). Steroidal ligands which bind the AR and act as androgens (e.g. testosterone enanthate) or as antiandrogens (e.g. cyproterone acetate) have been known for many years and are used clinically.

6-[(4*R*)-4-Methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Formula I), in its free base form, has the chemical formula $C_{14}H_{14}N_4SO_2$ and the following structural formula:



Formula I

Synthesis of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is disclosed in co-pending international patent application, PCT/IB2013/060381,

filed 25th November 2013, and published as WO 2014/087298 on 12th June 2014, assigned to the assignee of the present invention. 6-[(4*R*)-4-Methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is known to be active as a selective androgen receptor modulator (SARM) and, as such, may therefore be useful for treating and/or preventing a variety of hormone-related conditions, for example, conditions associated with androgen decline, such as, *inter alia*, anaemia; anorexia; arthritis; bone disease; musculoskeletal impairment; cachexia; frailty; age-related functional decline in the elderly; growth hormone deficiency; hematopoietic disorders; hormone replacement; loss of muscle strength and/or function; muscular dystrophies; muscle loss following surgery; muscular atrophy; neurodegenerative disease; neuromuscular disease; obesity; osteoporosis; and, muscle wasting.

Identification of new solid forms of a known active ingredient may provide a means of optimising either the physicochemical, stability, manufacturability and/or bioperformance characteristics of the active ingredient without modifying its chemical structure. Based on a chemical structure, one cannot predict with any degree of certainty whether a compound will crystallise, under what conditions it will crystallise, or the solid state structure of any of those crystalline forms. The specific solid form chosen for drug development may have dramatic influence on the properties of the drug product. The selection of a suitable solid form may be partially dictated by yield, rate and quantity of the crystalline structure. In addition, hygroscopicity, stability, solubility and the process profile of the solid form such as compressibility, powder flow and density may be important considerations.

As such, there is a need to identify solid forms of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile that may exhibit acceptable physicochemical, stability, manufacturability and/or bioperformance properties.

Summary of the Invention

This invention relates to a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile.

In another aspect, this invention relates to a pharmaceutical composition comprising a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile and a pharmaceutical carrier or excipient.

In a further aspect, this invention relates to a process for preparing a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile.

In particular, the crystalline form of the present invention has been shown to have suitable physicochemical, stability, manufacturability and/or bioperformance properties which render it useful for further development.

Brief Description of the Drawings

Figure 1 is a characteristic PXRD pattern of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1)). (Vertical axis – intensity (counts); horizontal axis:2-theta (degrees)).

Figure 2 is a characteristic Raman spectrum of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1)). (Vertical axis intensity (counts), horizontal axis: Raman shift (cm^{-1})).

Figure 3 is a characteristic solid state NMR spectrum of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1)). (Horizontal axis peak shift (ppm)).

Figure 4 is a characteristic DSC diffractogram of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1)). (Vertical axis heat flow (W/g), horizontal axis temperature (°C)).

Detailed Description of the Invention

This invention relates to a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile.

According to the present invention, 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is in its free base form.

In another embodiment, the present invention relates to a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile which is Form (1).

There are a number of analytical methods one of ordinary skill in the art can use to analyze solid forms, in particular crystalline solid forms. The term "analyze" as used herein shall be taken to mean to obtain information about the solid state structure of solid forms. For example, X-ray powder diffraction is one such suitable technique for differentiating amorphous solid forms from crystalline solid forms and for characterizing and identifying

crystalline solid forms since different crystalline forms exhibit different X-ray powder patterns. A discussion of the theory of X-ray powder diffraction patterns can be found in Clearfield, Reibenspies and Bhuvanesh (Editors), Principles and Applications of Powder Diffraction: Edition 1, Wiley, John & Sons, Incorporated (2008).

Due to differences in instruments, samples and sample preparation, minor variation in peak values in spectroscopic techniques can occur. In an X-ray powder diffraction pattern typical precision of a 2-theta x-axis value of an x-ray powder pattern is of the order of plus or minus 0.2º 2-theta. As such, a peak value reported to be at 9.2° 2-theta could occur at anywhere between 9.0° 2-theta and 9.4° 2-theta when measured on most x-ray diffractometers under most conditions. In a FT-Raman spectra typical precision of a Raman shift is of the order of plus or minus 2cm^{-1}. In a solid state NMR the typical precision of a ^{13}C peak shift is of the order of plus or minus 0.2ppm.

In a further preferred embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2.

In a yet further preferred embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, and 15.2 and one or more additional characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) selected from the group consisting of 17.1, 17.3, and 18.5.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2 and 17.1.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2 and 17.3.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-

ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2 and 18.5.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2, 17.1 and 17.3.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2 17.1, and 18.5.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2 17.3, and 18.5.

In a still further preferred embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2, 17.1, 17.3, and 18.5.

In an even further preferred embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) as depicted in Table 1.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708, 1555 and 2230.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) as depicted in Table 2.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a solid

state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3, 136.6 and 143.2.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) as depicted in Table 3.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9 and exhibits a FT-Raman spectra having one or more characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) selected from the group consisting of 708, 1555 and 2230.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9 and exhibits a FT-Raman spectra having a characteristic peak expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2 and exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708, 1555 and 2230.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9 and exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2 and exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2 and exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230 and exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230 and exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708, 1555 and 2230 and exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9, a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230 and exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-

ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9, a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230 and exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2, a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708, 1555 and 2230 and exhibits a solid state NMR spectra having characteristic peaks expressed in ppm (±0.2ppm) at 15.3 and 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8 and 10.9 and exhibits either a FT-Raman spectra having one or more characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) selected from the group consisting of 708, 1555 and 2230; and / or a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230 and exhibits either an X-ray powder diffraction pattern having one or more characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) selected from the group consisting of 7.8, 10.9, 15.2, 17.1, 17.3, and 18.5; and / or a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6 and exhibits either an X-ray powder diffraction pattern having one or more characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) selected from the group consisting of 7.8, 10.9, 15.2, 17.1, 17.3, and 18.5; and / or exhibits a FT-Raman spectra having one or more characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) selected from the group consisting of 708, 1555 and 2230.

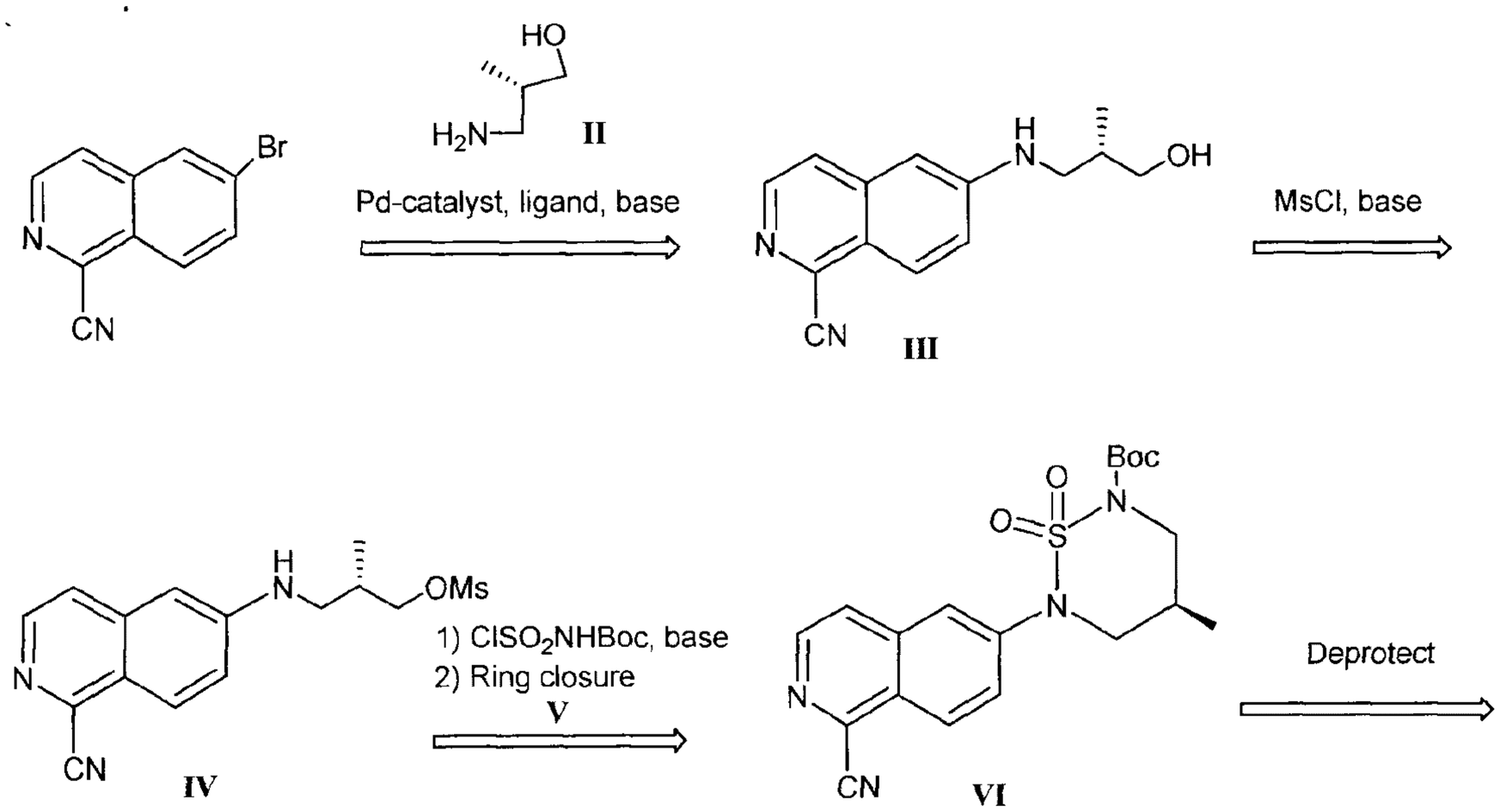
In an embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile is anhydrous.

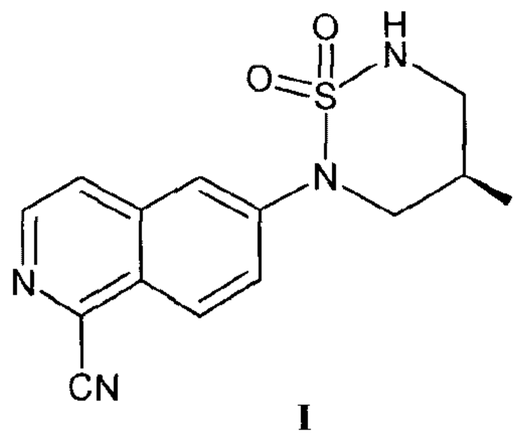
In another embodiment of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) is anhydrous.

As used herein the term "anhydrous" shall be taken to mean that the crystalline form contains less than about 5% w/w, more preferably less than about 1% w/w and even more preferably less than about 0.5% w/w of the solvent of crystallisation or water. In another embodiment the term "anhydrous" shall be taken to mean that the crystalline form contains less than about 1% w/w of the solvent of crystallisation or water.

The crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, including crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1), can be prepared from commercially available starting materials, compounds known in the literature, or readily prepared intermediates by employing the general reaction schemes provided herein in conjunction with standard synthetic methods and procedures known to those skilled in the art. Standard synthetic methods and procedures for the preparation of organic molecules and functional group transformations and manipulations can be readily obtained from the relevant scientific literature or from standard text books in the field. It will be appreciated that where typical or preferred process conditions are stated (i.e. reaction temperatures, times mole rations or reactants, solvents, pressures etc.), one of ordinary skill may substitute these with alternative process conditions unless otherwise stated. Optimum reaction conditions can vary with the particular reactants or solvent used. Those skilled in the art will recognize that the nature and order of the synthetic steps presented can be varied for the purpose of optimizing the formation of the compounds described herein.

The general reaction schemes provided herein illustrate the preparation of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Formula I).





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The starting material bromide is coupled with an aminoalcohol II under coupling conditions such as Pd-catalyzed coupling conditions. The hydroxyl group of compound III is activated as a leaving group by mesylate formation among other methods in the presence of a base to generate compound IV. The treatment of compound IV with the reagent V produces Boc-protected intermediates VI. Boc-group de-protection followed by alkylation or acylating of intermediate NH compounds culminates the synthesis forming the compound of Formula I.

A crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, including Form (1), can then be prepared by crystallization of the compound of Formula I from a solvent, preferably a solvent comprising acetone or, in an alternative embodiment, from a solvent comprising acetone and water. In one embodiment the solvent is acetone. In another embodiment the solvent is acetone and water. The crystalline form so prepared can be further dried, preferably under vacuum, to form the anhydrous form.

Accordingly, this invention also relates to a process for preparing a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, which process comprises the step of crystallization of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile from a solvent, wherein the solvent preferably comprises acetone. In an alternative embodiment, the solvent comprises acetone and water.

Accordingly, this invention also relates to a process for preparing crystalline 6-[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1), which process comprises the step of crystallization of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile from a solvent, wherein the solvent preferably comprises acetone. In an alternative embodiment, the solvent comprises acetone and water.

The present invention also relates to a pharmaceutical composition comprising a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile and a pharmaceutically acceptable carrier or excipient, and to methods for preparing such pharmaceutical compositions.

In another embodiment, the present invention also relates to a pharmaceutical composition comprising crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) and a pharmaceutically acceptable carrier or excipient, and to methods for preparing such pharmaceutical compositions.

As used herein the term "excipient" is taken to mean any ingredient in the pharmaceutical composition other than the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile. The choice of excipient may depend on factors such as the particular mode of administration, the effect of the excipient on solubility and stability, and the nature of the dosage form, which factors are well known to the person skilled in the art. The term "excipient" encompasses diluent, carrier or adjuvant.

Pharmaceutical compositions suitable for the delivery of a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile and methods for their preparation can be readily determined by one skilled in the art. Such compositions and methods for preparation may be found, for example, in Remington's Pharmaceutical Sciences, 19th Edition (Mack Publishing Company, 1995).

Pharmaceutical compositions of the present invention may be those suitable for oral administration. Oral administration may involve swallowing, so that the active ingredient

enters the gastrointestinal tract, or alternatively, oral administration may involve buccal or sublingual administration by which the active ingredient enters the blood stream directly from the mouth. Formulations suitable for oral administration may include solid formulations such as tablets, capsules containing particulates, liquids, or powders, lozenges (including liquid filled), chews, multi- and nano-particulates, gels, solid solution, liposomes, films, ovules, sprays and liquid formulations.

Tablet formulations suitable for oral administration usually comprise from about 0.1% w/w to about 80% w/w of the active ingredient, more typically from 5% w/w to about 60% w/w of the dosage form. For some tablet formulations, a lower amount of active ingredient may be appropriate, for example from about 0.1% w/w to about 20% w/w of the active ingredient. One of ordinary skill will appreciate how to determine the level of active ingredient suitable for inclusion in a tablet for oral administration.

In addition to the active ingredient, tablets suitable for oral administration may also comprise one or more of the following excipients. Tablets generally contain a disintegrant. Examples of disintegrants include sodium starch glycolate, sodium carboxymethyl cellulose, calcium carboxymethyl cellulose, croscarmellose sodium, crospovidone, polyvinylpyrrolidone, methyl cellulose, microcrystalline cellulose, lower alkyl-substituted hydroxypropyl cellulose, starch, pregelatinized starch and sodium alginate. Generally, a disintegrant comprises from about 1% w/w to about 25% w/w. In one embodiment of the present invention, the disintegrant may comprise from about 5% w/w to about 20% w/w of the dosage form. Binders are generally used to impart cohesive qualities to a tablet formulation. Examples of binders include microcrystalline cellulose, gelatin, sugars, polyethylene glycol, natural and synthetic gums, polyvinylpyrrolidone, pregelatinized starch, hydroxypropyl cellulose and hydroxypropyl methylcellulose. Tablets may also contain diluents, such as lactose (monohydrate, spray-dried monohydrate, anhydrous and the like), mannitol, xylitol, dextrose, sucrose, sorbitol, microcrystalline cellulose, starch and dibasic calcium phosphate dihydrate. Tablets may also optionally comprise surface active agents, such as sodium lauryl sulfate and polysorbate 80, and glidants such as silicon dioxide and talc. When present, surface active agents may comprise from about 0.2% w/w to about 5% w/w of the tablet, and glidants may comprise from about 0.2% w/w to about 1% w/w of the tablet. Tablets also generally contain lubricants such as magnesium stearate, calcium stearate, zinc stearate, sodium stearyl fumarate, and mixtures of magnesium stearate with sodium lauryl sulfate. Lubricants generally comprise from about 0.25% w/w to about 10% w/w. In one embodiment of the present invention, lubricants may comprise from about 0.5%

w/w to about 3% w/w of the tablet. Other possible ingredients include anti-oxidants, colorants, flavoring agents, preservatives and taste-masking agents.

For example, a tablet formulation may comprise up to about 80% w/w of a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, from about 0% w/w to about 90% w/w binder, from about 0% w/w to about 95% w/w diluent, from about 1% w/w to about 25% w/w disintegrant, and from about 0.25% w/w to about 10% w/w lubricant.

Tablet blends may be compressed directly or by roller to form tablets. Tablet blends, or portions of blends, may alternatively be wet-, dry-, or melt-granulated, melt congealed, or extruded before tableting. The final formulation may comprise one or more layers, and may be coated or uncoated; it may even be encapsulated. Formulations of tablets are discussed in Pharmaceutical Dosage Forms: Tablets, Vol. 1, by H. Lieberman and L. Lachman (Marcel Dekker, New York, 1980).

When preparing pharmaceutical compositions of the present invention, it may be desirable to adjust the particle volume mean diameter and/or the particle size distribution of the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile to potentially further optimise possible physicochemical properties or other possible properties such as stability manufacturability and/or bioperformance. For example, in some cases there may be a desire to reduce the particle size to try and increase the rate of dissolution. Particle size reduction may also sometimes be used to for content uniformity for formulations which have very low loading of active ingredients. In some embodiments of the present invention, the crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile may have a volume mean diameter of no more than 50µm and a particle size distribution such that 95% of the sample volume particles have a diameter of no more than 130µm, as measured by laser diffraction, with dry dispersion, using standard techniques.

Formulations suitable for oral administration may also include fast-dissolving or fast-disintegrating dose forms such as those described in Expert Opinion in Therapeutic Patents, 11(6), 981-986 by Lang and Chen (2001).

Solid formulations for oral administration may be formulated to be immediate and/or modified release. Modified release may include delayed, sustained, pulsed, controlled, targeted and programmed release. Examples of modified release formulations that may be useful for the purposes of the invention are described in US Patent No. 6,106,864. Details of other possible release technologies such as high energy dispersions and osmotic and

coated particles are to be found in Pharmaceutical Technology On-line, 25(2), 1-14, by Verma *et al.* (2001). The use of chewing gum to achieve controlled release is described in WO-A-00/35298.

Other pharmaceutical compositions of the present invention suitable for oral administration may include consumable oral films. These are typically pliable water-soluble or water-swellable thin film dosage forms which may be rapidly dissolving or mucoadhesive and typically comprise a film-forming polymer, a binder, a solvent, a humectant, a plasticizer, a stabilizer or emulsifier, a viscosity-modifying agent and a solvent. Some components of the formulation may perform more than one function. Film-forming polymer may be selected from natural polysaccharides, proteins, or synthetic hydrocolloids and when included in a composition is typically present in the range of about 0.01% w/w to about 99% w/w, more typically in the range of about 30% w/w to about 80% w/w. Other possible ingredients include anti-oxidants, colorants, flavorings and flavor enhancers, preservatives, salivary stimulating agents, cooling agents, co-solvents (including oils), emollients, bulking agents, anti-foaming agents, surfactants and taste-masking agents. Films are typically prepared by evaporative drying of thin aqueous films coated onto a peelable backing support or paper. This may be done in a drying oven or tunnel, typically a combined coater dryer, or by freeze-drying or vacuuming.

Other suitable pharmaceutical compositions of the present invention may also include liquid formulations. Liquid formulations may include suspensions, solutions, syrups and elixirs. Such formulations may be employed as fillers in soft or hard capsules and typically comprise a carrier, for example, water, ethanol, polyethylene glycol, propylene glycol, methylcellulose, or a suitable oil, and one or more emulsifying agents and/or suspending agents. Liquid formulations may also be prepared by the reconstitution of a solid, for example, from a sachet.

Pharmaceutical compositions of the present invention may also be adapted for administration of the active directly into the blood stream, into muscle, or into an internal organ. Such parenteral administration may include intravenous, intraarterial, intraperitoneal, intrathecal, intraventricular, intraurethral, intrasternal, intracranial, intramuscular and subcutaneous administration. Devices for parenteral administration include needle (including microneedle) injectors, needle-free injectors and infusion techniques. Suitable pharmaceutical compositions may also include those for topical administration to the skin or mucosa, that is, dermally or transdermally.

Yet another pharmaceutical composition may be those adapted for intranasal administration or for inhalation, typically in the form of a dry powder (either alone, as a

mixture, for example, in a dry blend with lactose, or as a mixed component particle, for example, mixed with phospholipids, such as phosphatidylcholine) from a dry powder inhaler, as an aerosol spray from a pressurized container, pump, spray, atomizer (preferably an atomizer using electrohydrodynamics to produce a fine mist), or nebulizer, with or without the use of a suitable propellant, such as 1,1,1,2-tetrafluoroethane or 1,1,1,2,3,3,3-heptafluoropropane, or as nasal drops. For intranasal use, the powder may comprise a bioadhesive agent, for example, chitosan or cyclodextrin. The pressurized container, pump, spray, atomizer, or nebulizer may contain a solution or suspension of the active ingredient, which solution or suspension may also comprise for example, ethanol, aqueous ethanol, or a suitable alternative agent for dispersing, solubilizing, or extending release of the compound, a propellant as solvent and an optional surfactant, such as sorbitan trioleate, oleic acid, or an oligolactic acid. Prior to use in a dry powder or suspension formulation, the drug product may be micronized to a size suitable for delivery by inhalation (typically less than 5μm). This may be achieved by any appropriate comminuting method, such as spiral jet milling, fluid bed jet milling, supercritical fluid processing to form nanoparticles, high pressure homogenization, or spray drying. Capsules (made, for example, from gelatin or hydroxypropylmethylcellulose), blisters and cartridges for use in an inhaler or insufflator may be formulated to contain a powder mix of the compound, a suitable powder base such as lactose or starch and a performance modifier such as l-leucine, mannitol, or magnesium stearate. The lactose may be anhydrous or in the form of the monohydrate, preferably the latter. Other suitable excipients include dextran, glucose, maltose, sorbitol, xylitol, fructose, sucrose and trehalose. Formulations for intranasal administration may be formulated to be immediate and/or modified release using, for example, PGLA. Modified release may include delayed, sustained, pulsed, controlled, targeted and programmed release.

Pharmaceutical compositions of the present invention may also include those formulated to be administered directly to the eye or ear, typically in the form of drops of a micronized suspension or solution in isotonic, pH-adjusted, sterile saline.

Pharmaceutical compositions of the present invention may optionally comprise flavors. Flavors, such as menthol and levomenthol, or sweeteners, such as saccharin or saccharin sodium, may be added.

Pharmaceutical compositions of the present invention may optionally also comprise soluble macromolecular entities, such as cyclodextrin and suitable derivatives thereof or polyethylene glycol-containing polymers, in order to potentially improve the solubility, dissolution rate, taste, bioavailability and/or stability of the active ingredient when using any of the aforementioned modes of administration. Drug-cyclodextrin complexes, for example,

are generally considered useful for most dosage forms and administration routes. Both inclusion and non-inclusion complexes may be used. As an alternative to direct complexation with the drug, the cyclodextrin may be used as an auxiliary additive, i.e., as a carrier, diluent, or solubilizer. Most commonly used for these purposes are alpha-, beta- and gamma-cyclodextrins, examples of which may be found in international patent publications WO-A-91/11172, WO-A-94/02518 and WO-A-98/55148.

In one embodiment, pharmaceutical compositions of the present invention are those which are suitable for oral administration. In another embodiment, pharmaceutical compositions of the present invention are in the form of a tablet or capsule.

All publications (including accession numbers, websites and the like), patents, and patent applications cited herein are referenced in their entirety for all purposes to the same extent as if individually denoted.

Examples

The following non limiting Examples further illustrate the present invention.

Unless otherwise stated, all starting materials and reagents are commercially available.

Powder X-ray diffraction

Powder X-ray diffraction analysis was conducted using a Bruker AXS D8 ADVANCE diffractometer equipped with a Cu radiation source (K-α average). The system is equipped with a Gobel Mirror and 2.5 axial Soller slits on the primary side. The secondary side utilizes 2.5 axial Soller slits and motorized slits. Diffracted radiation was detected by a Lynx Eye XE detector. The X-ray tube voltage and amperage were set to 40 kV and 40 mA respectively. Data was collected in the Theta-2-Theta configuration with a Cu K-alpha (average) wavelength source scanning from 3.0 to 40.0 degrees 2-Theta using a step size of 0.03 degrees and a step time of 1.0 seconds, at ambient temperature. Samples were prepared by placing them in a silicon low background holder and rotated during collection. Data were collected using Bruker DIFFRAC Plus software (Version 2.0) and analysis was performed by EVA diffract plus software (Version 3.1).

PXRD data file was not processed prior to peak searching. Using the peak search algorithm in the EVA diffract plus software (Version 3.1), peaks were selected with a threshold value of 1 and a width value of 0.3 were used to make preliminary peak

assignments. The output of automated assignments was visually checked to ensure validity and adjustments manually made if necessary, in accordance with the routine practice of one of ordinary skill. Peaks with relative intensity of ≥ 10% were generally chosen. The peaks which were not resolved or were consistent with noise were also discarded. A typical error associated with the peak position from PXRD is +/- 0.2° 2-theta.

As used herein the terms "PXRD" and "x-ray powder diffraction pattern" are considered interchangeable and synonymous with the term "powder X-ray diffraction pattern".

Fourier Transform Raman (FT-Raman)

FT-Raman spectra analysis was conducted using a Nicolet NXR FT-Raman accessory attached to the FT-IR bench. The spectrometer was equipped with a 1064 nm Nd:YVO_4 laser and a liquid nitrogen cooled Germanium detector. Prior to data acquisition, instrument performance and calibration verifications were conducted using polystyrene. Samples were analyzed in glass NMR tubes that were spun during spectral collection. The spectra were collected using 0.5 W of laser power and 512 co-added scans. The collection range was 3700-50 cm^{-1}. The API spectra were recorded using 2 cm^{-1} resolution, and Happ-Genzel apodization was utilized for all of the spectra. A typical error associated with the FT-Raman peak shift is ±2cm^{-1}. It is expected that, due to the similarity of FT-Raman and dispersive Raman spectra techniques, peak positions reported herein obtained using FT-Raman spectroscopy would be likely to be consistent with those which would be observed using dispersive Raman spectroscopy assuming appropriate instrument calibration.

Solid State NMR

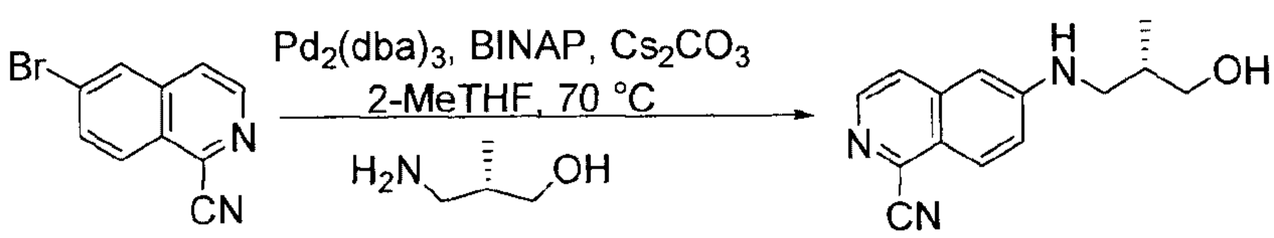
Solid State NMR (ssNMR) spectra analysis was conducted at 25°C on a Varian 4 mm CPMAS probe positioned into a Varian VNMR 400 MHz (1H frequency) NMR spectrometer. The sample was packed into a rotor and the rotor was oriented at the magic angle and spun at 8.0 kHz. The carbon ssNMR spectrum was collected using a proton decoupled cross-polarization magic angle spinning (CPMAS) experiment with TOSS (Total suppression of spinning sidebands) spinning sideband suppression. The cross-polarization contact time was set to 3 ms and the recycle delay to 30 seconds. The carbon spectrum was referenced using an external standard of crystalline adamantane, setting its downfield resonance to 38.5 ppm (as determined from neat TMS).

The ssNMR data file was processed prior to peak searching. Automatic peak picking was performed using Bruker-BioSpin TopSpin software (Version 3.1). Generally, a threshold value of 5% relative intensity was used for peak selection. A typical error associated with the ^{13}C chemical shift (ppm) x-axis value for ssNMR is ±0.2 ppm.

DSC

DSC measurements were performed with a Discovery DSC (TA instruments) equipped with a refrigerated cooling accessory. Approximately 2-5 mg of solid sample was weighed into a standard /Tzero aluminum pan and non-hermetically sealed. The sample was placed in a cell with continuous dry nitrogen purge (50 mL/min) and heated from 25 °C to 250 °C at 10 °C/min heating rate. The cell constant was determined using indium and tin as standards. The experimental data were analyzed using commercially available software (TA Universal Analysis 2000/Trios software, TA Instruments).

Example 1

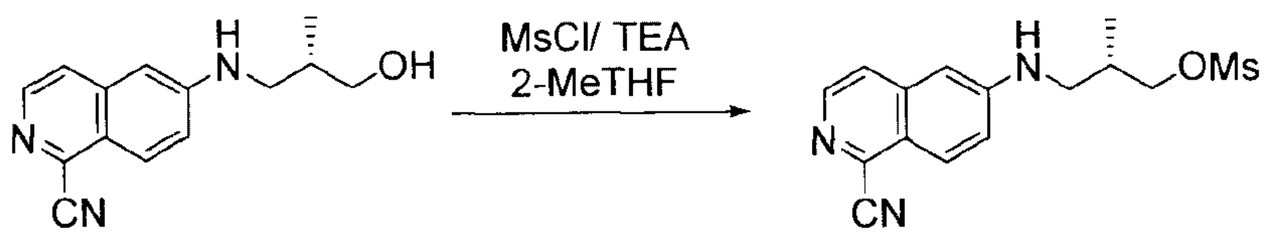


Procedure:

Into a 2L 3-neck round bottom flask equipped with a mechanical stirrer, reflux condenser and thermocouple with heating mantle was placed 2-methyltetrahydrofuran (2-MeTHF) (10 mL/g; 8.15 moles; 817 mL; 702 g) followed by racemic-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl (BINAP) (0.04 equiv (molar); 14.0 mmol; 8.74 g) and bis(dibenzylideneacetone)palladium ($Pd_2(dba)_3$) (0.04 equiv (molar); 14.0 mmol; 8.07 g). The mixture was degassed by pulling vacuum and refilling with nitrogen three times then heated to 75 °C for 15 minutes and cooled to ambient temperature. In a separate flask, (S)-3-amino-2-methylpropan-1-ol (1.60 equiv; 561 mmol; 50.0 g, prepared using literature methods, for example as disclosed in EP-

A-0,089,139 published on 21st September 1983) was dissolved in 2-methyltetrahydrofuran (5 mL/g; 4.08 moles; 409 mL; 351 g) and degassed by pulling vacuum and refilling with nitrogen three times. Into the pot containing the catalyst was added 6-(bromoisoquinoline-1-carbonitrile) (1.00 equiv; 351 mmol; 81.75 g) and cesium carbonate (1.6 equiv (molar); 561 mmol; 185 g) in single portions followed by the solution of the aminoalcohol via addition funnel. The reaction mixture was again degassed by pulling vacuum and refilling with nitrogen three times. The reaction was heated to 70 °C for 3 hours. The reaction was cooled to ambient temperature and filtered through a pad of Celite. The contents of the flask were rinsed out with three 100 mL portions of 2-methyltetrahydrofuran. The filtrate was transferred into a 2L round bottom flask equipped with a thermocouple and mechanical stirrer under nitrogen. Silica Gel (Silicylate SiliaMet® Thiol) (0.4 g/g-pure-LR; 544 mmol; 32.7 g) was charged and the flask was stirred at 40 °C overnight. The following morning, the reaction was cooled to < 30 °C and filtered again through Celite. The pad was washed with 100mL of 2-methyltetrahydrofuran (or until no yellow color persisted in the filtrate). The filtrate was placed into a 3L round bottom flask equipped with a magnetic stir bar, distillation head (with condenser and receiving flask), and thermocouple. The mixture was heated to 60 °C and placed under vacuum (~450-500 mbar) to distil out 1.3 L total of 2-methyltetrahydrofuran. 500 mL of toluene was added to precipitate the desired product. The heating mantle was removed and the reaction was allowed to reach ambient temperature. The mixture was stirred for 1 hour at ambient temperature and then the solids were collected by vacuum filtration on a sintered glass funnel. The cake was dried overnight on the funnel under vacuum. The following morning, the solids were transferred into an amber bottle and weighed (71.9 g; 298 mmol). The product was used in the next step without further purification.

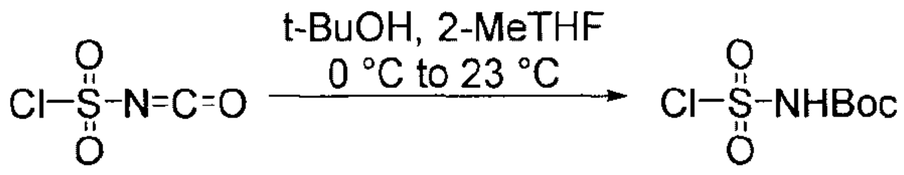
Example 2



Procedure:

In a 1L reactor equipped with a temperature probe and overhead stirring was added the product of Example 1 (20.0 g; 1.00 equiv; 82.9 mmol) and 2-methyltetrahydrofuran (2-MeTHF) (30 mL/g-pure-LR; 5.98 moles; 600 mL; 515 g). The reaction mixture was gently warmed to 40°C to achieve partial solubility. The reaction was cooled to 0°C. Once the reaction reached 0°C methanesulfonyl chloride (MsCl) (1.4 equiv (molar); 116 mmol; 8.98 mL; 13.3 g) was added in a single portion followed immediately by triethylamine (TEA) (1.4 equiv (molar); 116 mmol; 16.2 mL; 11.7 g) dropwise via syringe over a period of 15 minutes. The reaction mixture was further stirred for 30 min at 0°C and then warmed to 23°C for 60 minutes. The product (26.47 g; 1.00 equiv; 82.88 mmol; 26.47 g; 100% assumed yield) was then used without purification for the sulfonylation reaction.

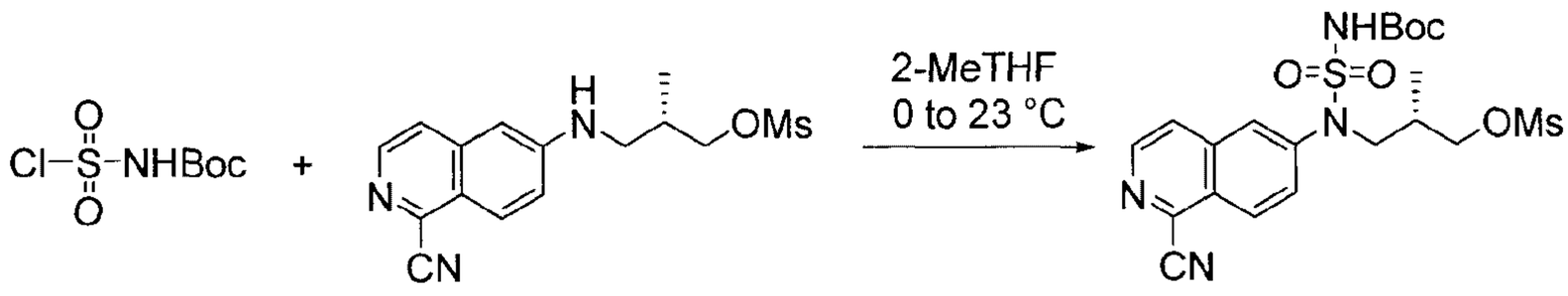
Example 3



Procedure:

To a solution of t-butyl alcohol (t-BuOH) (1 equiv (molar); 116 mmol; 11.0 mL; 8.60 g) in 2-methyltetrahydrofuran (2-MeTHF) (1 M; 1.16 moles; 116 mL; 99.6 g) at 0°C was added chlorosulfonyl isocyanate (116 mmol; 1.00 equiv; 10.1 mL; 16.4 g) dropwise. The homogeneous solution was stirred for 30 minutes at ambient temperature and then used directly in the sulfonylation reaction.

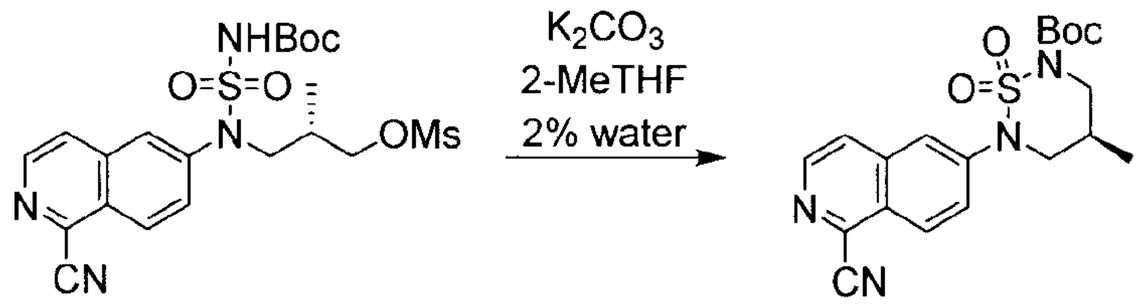
Example 4



Sulfonylation Reaction Procedure:

A previously prepared solution of the product of Example 3 (1.4 equiv (molar); 116 mmol; 116 g) in 2-methyltetrahydrofuran was added to a suspension of the product of Example 2 (1.00 equiv; 82.89 mmol; 26.5 g) at 0°C. The mixture was warmed to ambient temperature over 30 minutes. HPLC analysis revealed the reaction was complete. The reaction was quenched with a 10% sodium carbonate solution (2 equiv (molar); 165 mmol; 101 mL; 117 g) and water (to dissolve salts) (5 L/kg; 7.35 moles; 132 mL; 132 g). The top organic layer was removed and passed through a plug of Carbon (Darco™ G60) (0.5 g/g) on a filter. A significant improvement in color (dark orange to yellow) was observed. The solution was concentrated to 10 total volumes and used in the next step without purification.

Example 5

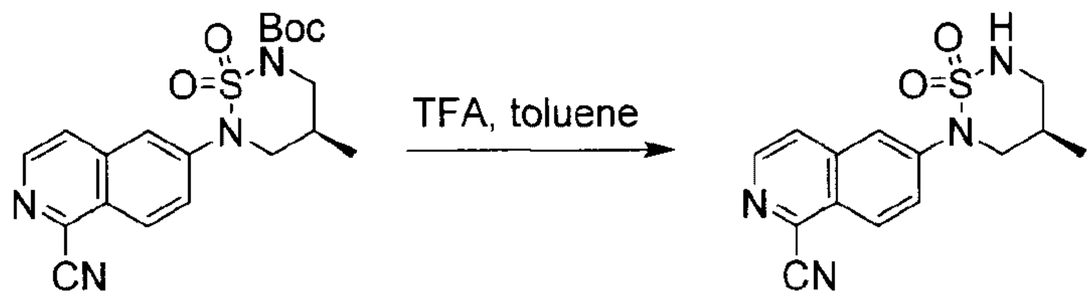


Procedure:

A solution of the product of Example 4 (1.00equiv; 82.9 mmol; 41.3 g) in 2-methyltetrahydrofuran (2-MeTHF) (10mL/g; 4.12 moles; 413 mL; 355 g) was placed into a 1 L reactor equipped with an overhead stirrer and temperature probe. Next, potassium carbonate (K_2CO_3) (325 mesh) (6 equiv (molar); 497 mmol; 69.4 g) and water (0.0 L/100-g-bulk-LR; 459 mmol; 8.26 mL; 8.26 g) were added and the mixture heated to 40°C (jacket temperature) and stirred overnight. The reaction was cooled to ambient temperature and water (4L/kg-pure-LR; 9.17 moles; 165 mL; 165 g]) was added. The biphasic reaction was stirred for 1 hour at 23 °C. The aqueous layer was extracted and removed. The organic layer was passed through a plug of Carbon (Darco™ G60) (0.5 g/g-pure-LR; 20.7g) in a disposable filter. The 2-methyltetrahydrofuran solution was switched to a 10 volume solution of toluene via a constant strip-and-replace distillation to no more than 1% 2-

methyltetrahydrofuran. The toluene solution of the reaction product (1.00 equiv; 82.9 mmol; 33.4 g; 100% assumed yield) was used as-is in the next step without further purification.

Example 6



Procedure:

To a 1L reactor under nitrogen and equipped with overhead stirring and a temperature probe was added the product of Example 5 (1.00 equiv; 78.7 mmol; 33.4 g) as a solution in toluene (10 mL/g-pure-LR; 3.00 moles; 317 mL; 276 g). Next, trifluoroacetic acid (TFA) (10 equiv (molar); 787 mmol; 59.5 mL; 89.8 g) was added to the reaction over a period of 1hour keeping the internal temperature below 30°C. The dark red mixture was stirred for 1 hour. The reaction was quenched at 23 °C by the addition of sodium carbonate (5 equiv (molar); 394 mmol; 240 mL; 278 g). The reaction was quenched slowly, over a period of 1 hour to form the TFA salt of the product. Once the charge was complete, the mixture was cooled to 0°C, held for 1hour and filtered. The next morning, the solid product (6-[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile in its free base form) was weighed (0.89 equiv; 70.0 mmol; 21.2 g; 89.0% yield) and used in the next step without further purification.

Example 7

Crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1)) was prepared as follows.

In a 1 L 3-neck round bottom flask was added 6-[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (1.00 equiv; 70.0 mmol; 21.2 g) a magnetic stir bar and acetone (40mL/g; 11.5 moles; 847 mL; 669 g). The mixture was heated to reflux (approximately 57°C) and stirred for 1 hour. The mixture was concentrated by atmospheric distillation (heating mantle set at 65°C) and 40mL of acetone was collected into a graduated cylinder. Next, water (25 mL/g; 29.4 moles; 530 mL; 530 g) was charged

over a period of one hour. The mixture was stirred at ambient temperature for 60min before being cooled to 0°C at 1°C /min for 1 hour. The solids were collected by filtration in a disposable funnel. Crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1), 0.88 equiv; 61.9 mmol; 18.7 g; 88.3% yield) was dried under vacuum overnight at 40 °C. Typical purity after crystallization is 98%.

Example 8

The powder X-ray diffraction pattern of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile was collected using a Bruker AXS D8 ADVANCE diffractometer equipped with a Cu radiation source and then processed as set out above. The results are shown in Figure 1 and are summarised in Table 1 below.

Table 1 – PXRD Peak list for crystalline 6-[(4R)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1))

Angle degrees 2-Theta (± 0.2° 2-theta)	Intensity %*
7.8	54
10.9	69
15.2	22
15.6	17
16.8	30
17.1	92
17.3	100
18.5	82
20.1	65
21.8	23
22.8	40
23.0	76
23.4	26

24.3	44
27.7	17
28.1	24
29.0	23
29.6	15
30.0	10
31.4	13
39.5	10

*Relative intensities may vary depending on sample orientation, crystal size and / or morphology.

Example 9

The Raman spectra of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1)) was collected using a Nicolet NXR FT-Raman accessory attached to the FT-IR bench, equipped with a 1064 nm Nd:YVO_4 laser and a liquid nitrogen cooled Germanium detector in accordance with the experimental details and data processing details set out above. The results are shown in Figure 2 and are summarised in Table 2 below.

Table 2 – Raman spectra peak list for crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1))

Position (cm^{-1})	**Intensity (W = weak, M = medium, S = strong)**
207	M
667	W
708	S
795	M
1496	W
1555	M
1575	W

1624	W
2230	S
3067	M
3077	W
3095	W
3116	W
3265	W

Example 10

The solid state NMR (ssNMR) spectra of crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1)) was collected at 25 °C using a Varian 4 mm CPMAS probe positioned into a Varian VNMR 400 MHz (1H frequency) NMR spectrometer in accordance with the experimental details and data processing details set out above. The results are shown in Figure 3 and are summarised in Table 3 below.

Table 3 – Solid state NMR (ssNMR) peak list for crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base (Form (1))

^{13}C Chemical Shifts [ppm]
15.3
32.3
49.6
59.1
116.4
118.0
124.7
124.9
126.5

128.1
128.6
134.4
136.6
143.2
144.4

Example 11 – Immediate Release Tablet

An immediate release tablet formulation comprising crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1)) may be prepared as shown. Tablets may be prepared using three different strengths of active ingredient (A).

	Tablet 1 (1mgA Dose)		Tablet 2 (5mgA Dose)		Tablet 3 (25mgA Dose)	
Ingredient	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet	%w/w
Active (SARM)[1]	1	1%	5	5%	25	5%
Microcrystalline cellulose, NF[2]	63.3	63%	60.7	61%	303.5	61%
Lactose monohydrate, NF[3]	31.7	32%	30.3	30%	151.5	30%
Sodium starch glycolate, NF[4]	3	3%	3	3%	15	3%
Magnesium stearate, NF[5]	1	1%	1	1%	5	1%
Total	100	100%	100	100%	500	100%

[1] Assumes 100% purity and no salt form. When a potency adjustment is required the amounts of microcrystalline cellulose and lactose monohydrate may be adjusted

[2] Avicel PH102, FMC Corporation

[3] Fast Flo™, Foremost Farms

[4] Explotab™, Penwest Pharmaceuticals

[5] Vegetable derived; Malinkrodt™

The tablet formulation may be prepared using direct compression or wet or dry granulation processes. Alternatively, the formulation may be used for filling hard-shell capsules or other dosage forms.

In this case, direct compression may be used to manufacture the tablet and a standard blend-mill-blend process may be used to prepare the blend. For example, first, all of the ingredients except magnesium stearate would be added to a bin. The material would then be mixed until well blended. The material would then be passed through a mill. The material would then be mixed again until well blended. The magnesium stearate would then

be added to the mixture and mixed again. Finally, the resulting mixture would then be compressed into a tablet.

Example 12 – Immediate Release Tablet Formulation

An immediate release tablet formulation comprising crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1)) may be prepared as shown. Tablets may be prepared using three different strengths of active ingredient (A).

	Tablet 1 (1mgA Dose)		Tablet 2 (5mgA Dose)		Tablet 3 (25mgA Dose)	
Ingredient	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet	%w/w
Active (SARM)[1]	1	1%	5	5%	25	5%
Microcrystalline cellulose, NF[2]	47.5	48%	45.5	46%	227.5	46%
Lactose monohydrate, NF[3]	47.5	48%	45.5	46%	227.5	46%
Sodium starch glycolate, NF[4]	3	3%	3	3%	15	3%
Magnesium stearate, NF[5]	1	1%	1	1%	5	1%
Total	100	100%	100	100%	500	100%

[1] Assumes 100% purity and no salt form. When a potency adjustment is required the amounts of microcrystalline cellulose and lactose monohydrate may be adjusted

[2] Avicel PH102, FMC Corporation

[3] Fast Flo, Foremost Farms

[4] Explotab, Penwest Pharmaceuticals

[5] Vegetable derived; Malinkrodt

Tablets containing the ingredients shown may can be prepared by the direct compression method described in Example 11. Alternatively, the formulation may be used for filling hard-shell capsules or tableted using a wet or dry granulation process.

Example 13 – Immediate Release Tablet Formulation

An immediate release tablet formulation comprising crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1) may be prepared as

shown. Tablets may be prepared using three different strengths of active ingredient (A).

	Tablet 1 (1mgA Dose)		Tablet 2 (5mgA Dose)		Tablet 3 (25mgA Dose)	
Ingredient	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet	%w/w
Active (SARM)[1]	1	1%	5	5%	25	5%
Microcrystalline cellulose, NF[2]	63.3	63%	60.7	61%	303.5	61%
Calcium phosphate, dibasic anhydrous[3]	31.7	32%	30.3	30%	151.5	30%
Sodium starch glycolate, NF[4]	3	3%	3	3%	15	3%
Magnesium stearate, NF[5]	1	1%	1	1%	5	1%
Total	100	100%	100	100%	500	100%

[1] Assumes 100% purity and no salt form. When a potency adjustment is required the amounts of microcrystalline cellulose and lactose monohydrate may be adjusted

[2] Avicel PH102, FMC Corporation

[3] A-tab, Rhodia Incorporated

[4] Explotab, Penwest Pharmaceuticals

[5] Vegetable derived; Malinkrodt

Tablets containing the ingredients shown may be prepared by the direct compression method described in Example 11. Alternatively, the formulation may be used for filling hard-shell capsules or tableted using a wet or dry granulation process.

Example 14 – Immediate Release Tablet Formulation

An immediate release tablet formulation comprising crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile (Form (1)) may be prepared as shown. Tablets may be prepared using three different strengths of active ingredient (A).

	Tablet 1 (1mgA Dose)		Tablet 2 (5mgA Dose)		Tablet 3 (25mgA Dose)	
Ingredient	mg/tablet	%w/w	mg/tablet	%w/w	mg/tablet	%w/w
Active (SARM)[1]	1	1%	5	5%	25	5%
Microcrystalline cellulose, NF[2]	47.5	48%	45.5	46%	227.5	46%
Calcium phosphate, dibasic anhydrous[3]	47.5	48%	45.5	46%	227.5	46%
Sodium starch glycolate, NF[4]	3	3%	3	3%	15	3%
Magnesium stearate, NF[5]	1	1%	1	1%	5	1%
Total	100	100%	100	100%	500	100%

[1] Assumes 100% purity and no salt form. When a potency adjustment is required the amounts of microcrystalline cellulose and lactose monohydrate may be adjusted

[2] Avicel PH102, FMC Corporation

[3] A-tab, Rhodia Incorporated

[4] Explotab, Penwest Pharmaceuticals

[5] Vegetable derived; Malinkrodt

Tablets containing the ingredients shown may be prepared by the direct compression method described in Example 11. Alternatively, the formulation may be used for filling hard-shell capsules or tableted using a wet or dry granulation process.

The characterization data disclosed herein confirms the crystalline nature of the 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile free base Form (1) material and, as such, that it may therefore be a useful form for pharmaceutical development. For example, crystalline materials are generally considered to be an advantageous form for drug substance manufacturing because, for example, they are more easily purified, can be prepared with higher yields, have improved filtration and drying characteristics and improved flow and handling characteristics. Crystalline 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile Form (1) also demonstrates physicochemical properties which render it useful for drug product manufacturing such as its thermal stability and non-hygroscopic nature demonstrated by the high DSC melting point and DSC profile.

CLAIMS:

1. A crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile.

2. A crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile, which exhibits an X-ray powder diffraction pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9 and 15.2.

3. A crystalline form according to claim 2, wherein the X-ray powder diffraction pattern further has one or more additional peaks expressed in degrees 2-theta (± 0.2° 2-theta) selected from the group consisting of 17.1, 17.3, and 18.5.

4. A crystalline form according to claim 2, which exhibits an PXRD pattern having characteristic peaks expressed in degrees 2-theta (± 0.2° 2-theta) at 7.8, 10.9, 15.2, 17.1, 17.3, and 18.5.

5. A crystalline form according to any one of claims 1 to 4, which exhibits a FT-Raman spectra having one or more characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) selected from the group consisting of 708, 1555 and 2230.

6. A crystalline form according to claim 5, which exhibits a FT-Raman spectra having characteristic peaks expressed in cm^{-1} ($\pm 2cm^{-1}$) at 708 and 2230.

7. A crystalline form according to any one of claims 1 to 6, which exhibits a solid state NMR spectra having a characteristic peak expressed in ppm (±0.2ppm) at 136.6.

8. A crystalline form according to any one of claims 1 to 7, which crystalline form is anhydrous.

9. A pharmaceutical composition comprising a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile as defined in any one of claims 1 to 8, and a pharmaceutically acceptable carrier or excipient.

10. A pharmaceutical composition according to claim 9, which is an oral dosage form.

11. A pharmaceutical composition according to claim 10, wherein the composition is a tablet or capsule.

12. A process for preparing a crystalline form of 6-[(4*R*)-4-methyl-1,1-dioxido-1,2,6-thiadiazinan-2-yl]isoquinoline-1-carbonitrile as defined in any one of claims 1 to 8, which comprises the step of crystallising the crystalline form from a solvent, wherein the solvent comprises acetone.

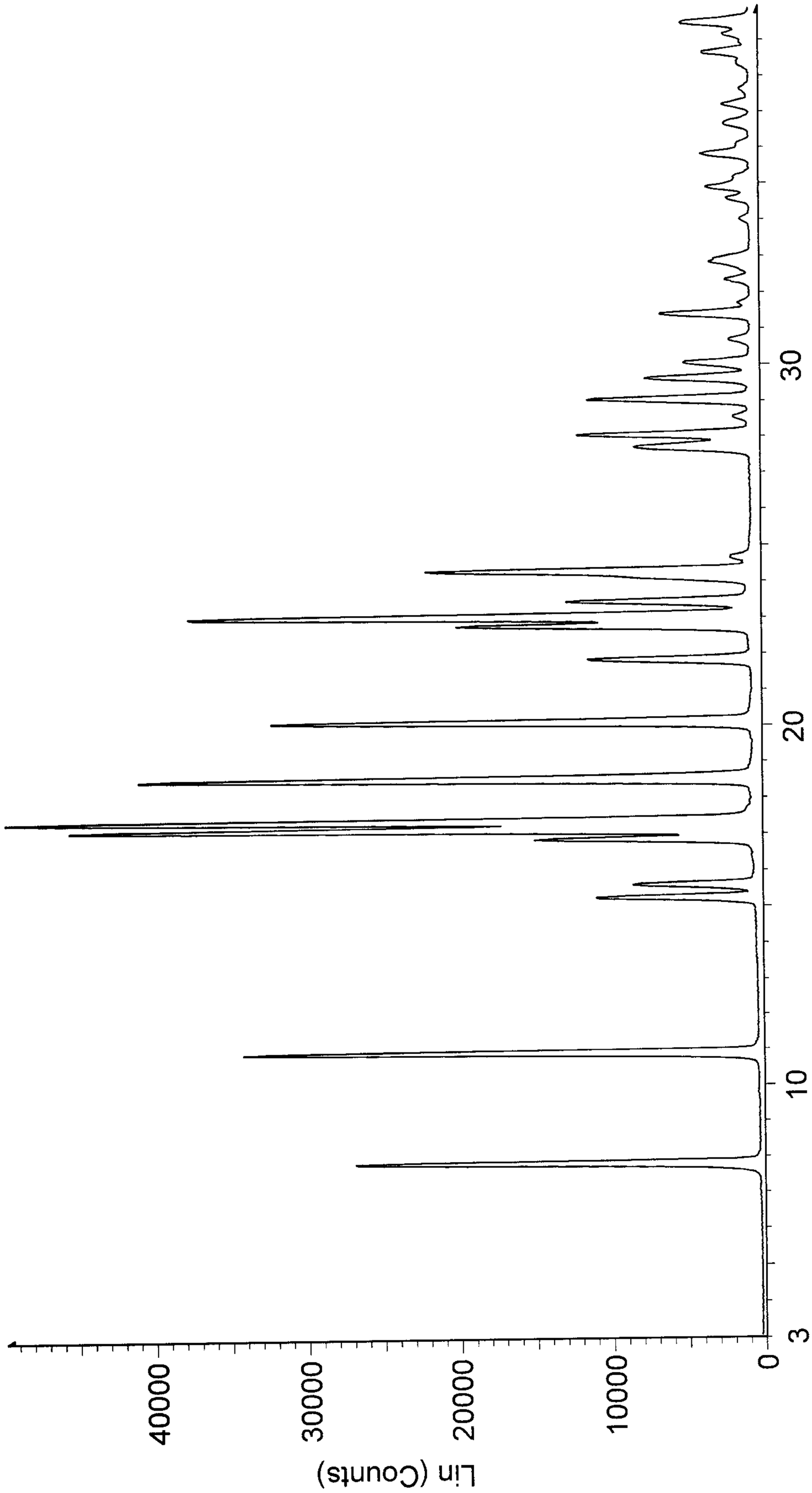
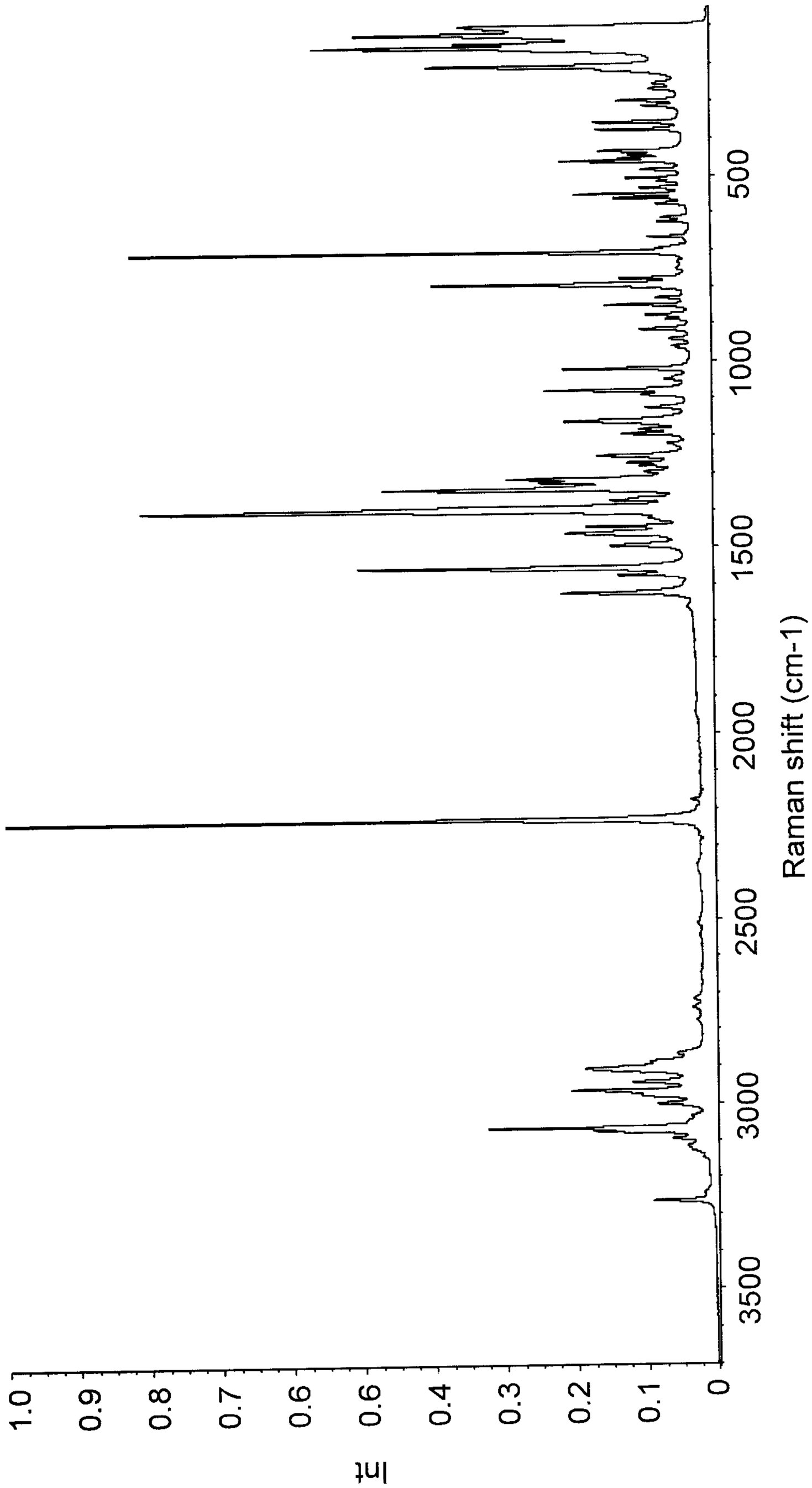


FIG. 1

FIG. 2


500
1000
1500
2000
2500
3000
3500
Raman shift (cm-1)
Int
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0.9
0.8
0.7
0.6
0.6
0.4
0.3
0.2
0.1
0

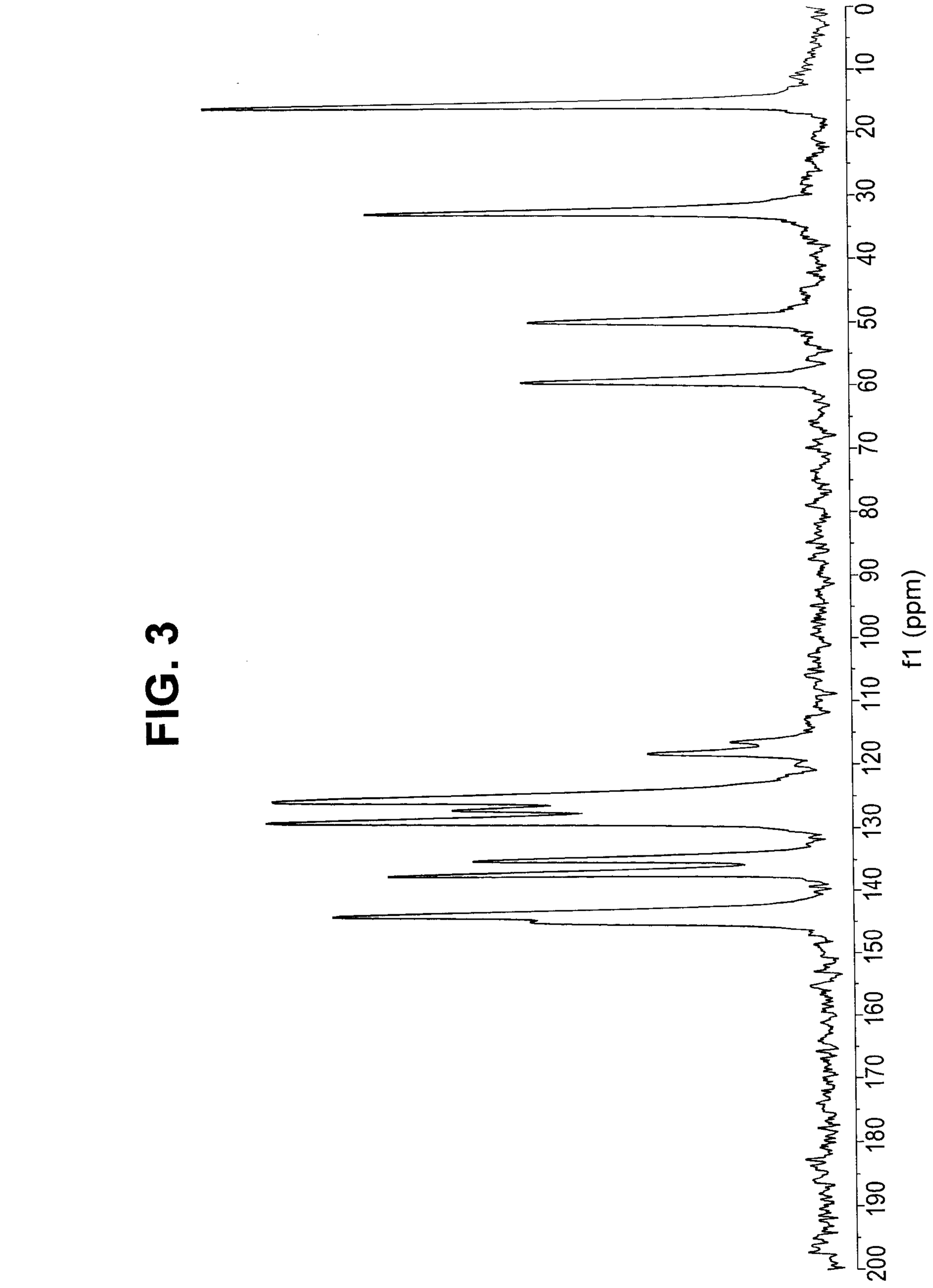
0
10
20
30
40
50
60
70
80
90
100
110
120
130
140
150
160
170
180
190
200
f1 (ppm)

FIG. 3

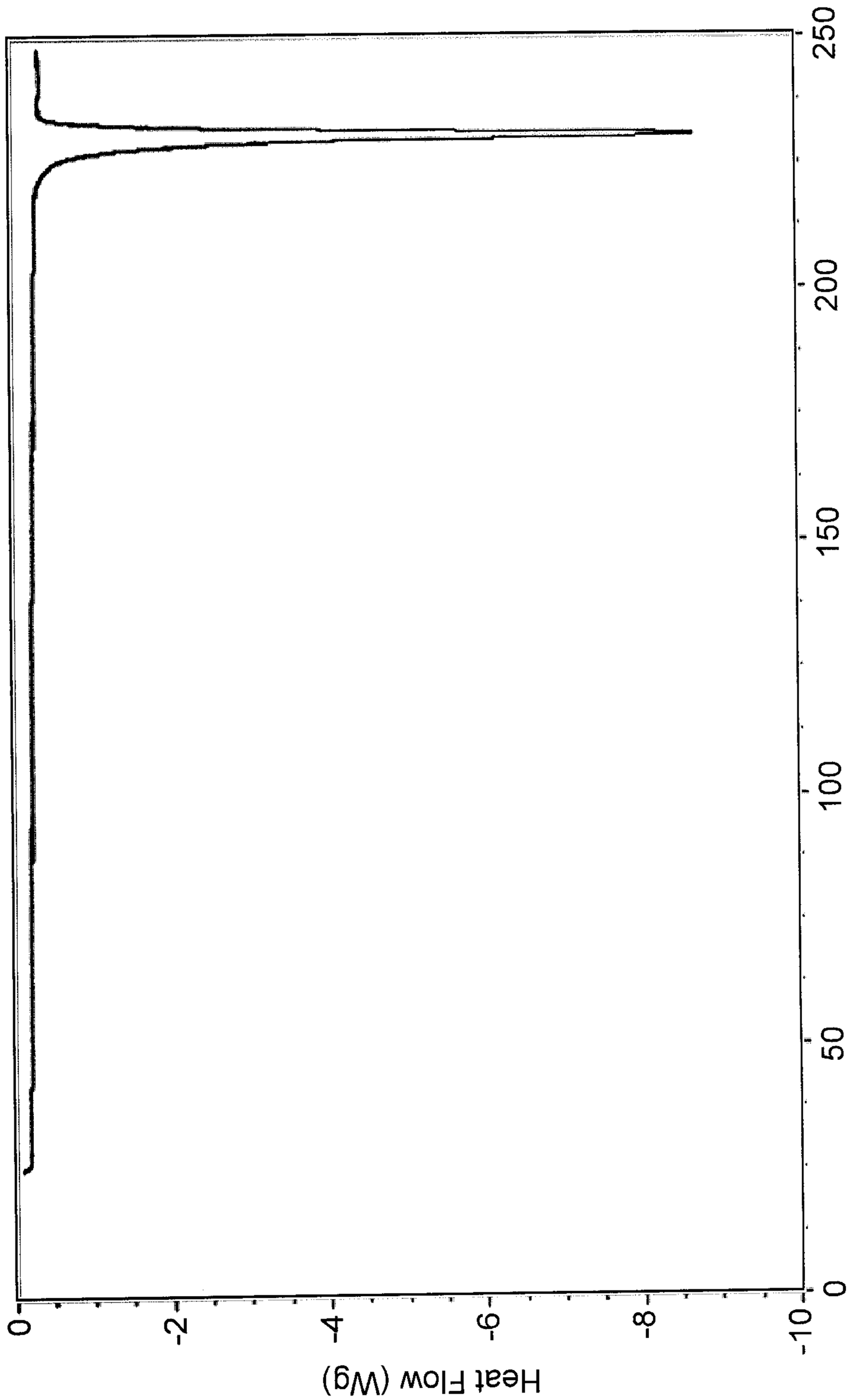

FIG. 4