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Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, Delaware 19850-5437 (US).

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(74) Agent: **ASTRAZENECA INTELLECTUAL PROPERTY**; AstraZeneca AB, SE-151 85 Södertälje (SE).

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(71) Applicant (*for all designated States except US*): **ASTRAZENECA AB** [SE/SE]; SE-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BLACK, Simon Nicholas** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **COSGROVE, Stephen David** [GB/GB]; AstraZeneca R&D Charnwood, Bakewell Road, Loughborough Leicestershire LE11 5RH (GB). **McCORMICK, Marc** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **OSBORN, Jim** [US/US]; AstraZeneca R&D Wilmington, 1800 Concord Pike, P.O. Box 15437, Wilmington, Delaware 19850-5437 (US). **REID, Julie** [GB/GB]; AstraZeneca, Charter Way, Macclesfield Cheshire SK10 2NA (GB). **WU, Dedong** [US/US]; AstraZeneca R&D

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(54) Title: CRYSTALLINE FORM OF 4-AMINO-8-(2-FLUORO-6-METHOXY-PHENYL)-N-PROPYLCINNOLINE-3-CARBOXAMIDE HYDROGEN SULPHATE, FOR TREATMENT OF ANXIETY DISORDERS

(57) Abstract: 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate, polymorphs thereof, pharmaceutical compositions contain them, methods of making them are described. They are useful in treating anxiety disorders.



Crystalline form of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate, for treatment of anxiety disorders.

FIELD OF THE INVENTION

The present invention relates to a new salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide and polymorphs thereof. The invention also concerns
5 pharmaceutical compositions which include the salt, as well as processes for the manufacture of the salt.

BACKGROUND OF THE INVENTION

10 In the formulation of drug compositions, it is desirable for the drug substance to be in a form in which it can be conveniently handled and processed. This is of importance, not only from the point of view of obtaining a commercially-viable manufacturing process, but also from the point of view of subsequent manufacture of pharmaceutical formulations comprising the active compound. Further, in the manufacture of drug compositions, it is
15 desirable that a reliable, reproducible and constant plasma concentration profile of drug is provided following administration to a patient.

Chemical stability, solid state stability, and "shelf life" of the active ingredients are also desirable factors. The drug substance, and compositions containing it, should preferably
20 be capable of being effectively stored over appreciable periods of time, without exhibiting a significant change in the active component's physico-chemical characteristics (e.g. its chemical composition, density, hygroscopicity and solubility).

Moreover, it is also desirable to be able to provide drug in a form which is as chemically
25 pure as possible.

The skilled person will appreciate that, typically, if a drug can be readily obtained in a stable form, such as a stable crystalline form, advantages may be provided, in terms of ease of handling, ease of preparation of suitable pharmaceutical formulations, and a more
30 reliable solubility profile.

U.S. Pat. No. 7,465,795 describes a method of preparing 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide, which modulates GABAA receptor activity.

However, there is still a need for a salt and/or polymorphs thereof, which has one or more improved physical properties such as stability, solubility, processability, and bioavailability.

BRIEF DESCRIPTION OF DRAWINGS

FIG. 1 shows an X-ray powder diffractogram for the form A of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

FIG. 2 shows an X-ray powder diffractogram for the form N of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

FIG. 3 shows an X-ray powder diffractogram for the form B of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

FIG. 4 shows an X-ray powder diffractogram for the amorphous form of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

FIG. 5 shows the DSC trace of the amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

FIG. 6 shows the dynamic vapor absorption/desorption isotherm for amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment, the present invention provides a salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide.

In another embodiment, the present invention relates to a salt of the compound 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide, which is a sulphate of said compound.

5 In a further embodiment, the present invention provides 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

In an even further embodiment, the present invention provides a 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate, which is
10 substantially crystalline.

Another embodiment of the invention relates to a hydrogen sulphate salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide having an X-ray powder diffraction pattern with specific peaks at 2Θ values at about 9.37, about 14.57, about
15 22.08, about 27.61 and about 28.13 °, and/or essentially as defined in Table 1 and/or essentially as defined in Figure 1.

Another embodiment of the invention relates to a hydrogen sulphate salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide having an X-ray powder
20 diffraction pattern with specific peaks at 2Θ values at about 14.22, about 21.07, about 23.47 and about 26.02 °, and/or essentially as defined in Table 2 and/or essentially as defined in Figure 2.

A further embodiment of the invention relates to a hydrogen sulphate salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide having an X-ray powder
25 diffraction pattern with specific peaks at 2Θ values at about 7.12, about 8.20, about 16.36 and about 22.89 °, and/or essentially as defined in Table 3 and/or essentially as defined in Figure 3.

A further embodiment of the invention relates to an amorphous hydrogen sulphate salt of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide.

5 The X-ray powder diffraction patterns for typical samples of the salts of the present invention are shown in the Figures hereinafter. It will be understood that the X-ray powder diffraction patterns may vary slightly from one machine to another or from one sample to another, and so the 2Θ values quoted are not to be construed as absolute.

10 According to a further aspect of the invention there is provided a salt of the invention in substantially crystalline form.

Although we have found that it is possible to produce salts of the invention in forms which are greater than 80% crystalline, by "substantially crystalline" we include greater than 20%, preferably greater than 30%, and more preferably greater than 40% (e.g. greater
15 than any of 50, 60, 70, 80 or 90%) crystalline.

According to a further aspect of the invention there is also provided a salt of the invention in partially crystalline form. By "partially crystalline" we include 5% or between 5% and 20% crystalline.

20

The degree (%) of crystallinity may be determined by the skilled person using X-ray powder diffraction (XRPD). Other techniques, such as solid state NMR, FT-IR, Raman spectroscopy, differential scanning calorimetry (DSC) and microcalorimetry, may also be used.

25 The term "stability" as defined herein includes chemical stability and solid state stability.

By "chemical stability", we include that it may be possible to store salts of the invention in an isolated form, or in the form of a formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form,

such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of chemical degradation or decomposition.

By "solid state stability", we include that it may be possible to store salts of the invention in an isolated solid form, or in the form of a solid formulation in which it is provided in admixture with pharmaceutically acceptable carriers, diluents or adjuvants (e.g. in an oral dosage form, such as a tablet, capsule etc.), under normal storage conditions, with an insignificant degree of solid state transformation (e.g. crystallisation, recrystallisation, solid state phase transition, hydration, dehydration, solvation or desolvation).

Examples of "normal storage conditions" include temperatures of between minus 80 and plus 50°C (preferably between 0 and 40°C and more preferably room temperatures, such as 15 to 30°C), pressures of between 0.1 and 2 bars (preferably at atmospheric pressure), relative humidities of between 5 and 95% (preferably 10 to 60%), and/or exposure to 460 lux of UV/visible light, for prolonged periods (i.e. greater than or equal to six months).

Under such conditions, salts of the invention may be found to be less than 15%, more preferably less than 10%, and especially less than 5%, chemically degraded/decomposed, or solid state transformed, as appropriate. The skilled person will appreciate that the above-mentioned upper and lower limits for temperature, pressure and relative humidity represent extremes of normal storage conditions, and that certain combinations of these extremes will not be experienced during normal storage (e.g. a temperature of 50°C and a pressure of 0.1 bar).

A further aspect of the present invention comprises processes for the preparation of the salts. The precise conditions under which the salts are formed may be empirically determined. The salts may be obtained by crystallisation under controlled conditions.

One embodiment of the invention relates to a process for the preparation of a salt according to the present invention, which process comprises addition of the appropriate acid to a

solution or slurry of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide in suitable solvent or liquid.

In one embodiment of the inventive process the appropriate acid is added to 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide dissolved in a solvent selected from the group: DMSO, DMF, acetates, lower alkyl alcohols, aliphatic and aromatic hydrocarbons, dialkyl ethers, dialkyl ketones, acetonitrile, chlorinated alkanes, aqueous solvents, or mixtures thereof.

In a further embodiment of the inventive process the solvent is selected from the group: DMSO, DMF, C₁₋₆-alkyl acetates, linear or branched C₁₋₆-alkyl alcohols, C₆₋₁₂-aliphatic hydrocarbons, C₆₋₁₀-aromatic hydrocarbons, di-C₁₋₆-alkyl ethers, di-C₁₋₆-alkyl ketones, chlorinated methanes or ethanes, acetonitrile, water, or mixtures thereof.

In a yet further embodiment of the inventive process the solvent is selected from the group: DMSO, DMF, ethyl acetate, *iso*-propyl acetate, methanol, ethanol, *iso*-propanol, *n*-heptane, diethyl ether, acetone, dichloromethane, water, or mixtures thereof.

In a further embodiment of the inventive process the solvent is selected from the group: water, DMSO, DMF, ethyl acetate, methyl *iso*-butyl ketone, and *iso*-propyl acetate.

In another embodiment of the inventive process the appropriate acid is added to 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide slurried in a liquid selected from the group: DMSO, DMF, acetates, lower alkyl alcohols, aliphatic and aromatic hydrocarbons, dialkyl ethers, dialkyl ketones, acetonitrile, chlorinated alkanes, aqueous liquids, or mixtures thereof.

In a further embodiment of the inventive process the liquid is selected from the group: DMSO, DMF, C₁₋₆alkyl acetates, linear or branched C₁₋₆ alkyl alcohols, C₆₋₁₂ aliphatic hydrocarbons, C₆₋₁₀aromatic hydrocarbons, di-C₁₋₆ alkyl ethers, di-C₁₋₆ alkyl ketones, chlorinated methanes or ethanes, acetonitrile, water, or mixtures thereof.

In a yet further embodiment of the inventive process the liquid is selected from the group: DMSO, DMF, ethyl acetate, *iso*-propyl acetate, methanol, ethanol, 1-propanol, *iso*-propanol, *n*-heptane, diethyl ether, acetone, dichloromethane, water, or mixtures thereof.

5

In a further embodiment of the inventive process the liquid is 1-propanol, isopropyl acetate, DMSO, water or a mixture thereof.

10

Crystallisation temperatures and crystallisation times depend upon the salt that is to be crystallised, the concentration of that salt in solution, and the solvent system which is used.

15

Crystallisation may also be initiated and/or effected by way of standard techniques, for example with or without seeding with crystals of the appropriate crystalline salt of the invention.

20

In one embodiment, certain polymorph of the present invention shows an improved solid state stability under normal storage conditions. Particularly, form A of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate may show an improved solid state stability.

25

One embodiment of the invention relates to a pharmaceutical formulation including a salt according to the present invention in admixture with a pharmaceutically acceptable adjuvant, diluent or carrier.

Another embodiment of the invention relates to a salt according to the present invention for use as a medicament.

30

A yet further embodiment of the invention relates to the use of a salt according to the present invention in the manufacture of a medicament for the therapy of pain.

One embodiment of the invention relates to the use of a salt according to any the present invention in the manufacture of a medicament for the treatment of anxiety disorders.

- 5 Another embodiment of the invention relates to the use of a salt according to the present invention in the manufacture of a medicament for the treatment of dementia, Alzheimer's disease, cognition deficiency, cognition deficiency associated with schizophrenia.

- A further embodiment of the invention relates to a method for the therapy of anxiety disorders in a warm-blooded animal, comprising the step of administering to the animal in need of such therapy a therapeutically effective amount of a salt according to the present invention.

- A yet further embodiment of the invention relates to a method for the treatment of anxiety disorders, whereby a pharmaceutically and pharmacologically effective amount of a salt according to the present invention is administered to a subject in need of such treatment.

- One embodiment of the invention relates to a method for the treatment of pain, whereby a pharmaceutically and pharmacologically effective amount of a salt according to the present invention is administered to a subject in need of such treatment.

- The quantity of the compound to be administered will vary for the patient being treated and will vary from about 100 ng/kg of body weight to 100 mg/kg of body weight per day and preferably will be from 10 pg/kg to 10 mg/kg per day. For instance, dosages can be readily ascertained by those skilled in the art from this disclosure and the knowledge in the art. Thus, the skilled artisan can readily determine the amount of compound and optional additives, vehicles, and/or carrier in compositions and to be administered in methods of the invention.

In some embodiments, the salts and polymorphs thereof described herein are central nervous system depressants and may be used as tranquilizers or ataractic agents for the relief of anxiety and tension states, for example, in mice, cats, rats, dogs and other mammalian species such as humans, in the same manner as chlordiazepoxide. For this purpose salts may be administered orally or parenterally in a conventional dosage form such as tablet, pill, capsule, injectable or the like. The dosage in mg/kg of body weight of salts of the present invention in mammals will vary according to the size of the animal and particularly with respect to the brain/body weight ratio. In general, a higher mg/kg dosage for a small animal such as a dog will have the same effect as a lower mg/kg dosage in an adult human. A minimum effective dosage for the salts will be at least about 0.1 mg/kg of body weight per day for mammals with a maximum dosage for a small mammal such as a dog, of about 100 mg/kg per day. For humans, a dosage of about 0.1 to 12 mg/kg per day will be effective, for example, about 5 to 600 mg/day for an average man. The dosage can be given once daily or in divided doses, for example, 2 to 4 doses daily, and such dosage will depend on the duration and maximum level of activity of the salt. The dose may be conventionally formulated in an oral or parenteral dosage form by compounding about 5 to 250 mg per unit of dosage of conventional vehicle, excipient, binder, preservative, stabilizer, flavor or the like as called for by accepted pharmaceutical practice, for example, as described in U.S. Pat. No. 3,755,340. The salts of this invention may be used in pharmaceutical compositions comprising a salt described herein or can be contained in the same formulation with or co-administered with one or more known drugs.

Some example tests that can be conducted to demonstrate the anxiolytic activity of the present compounds include binding tests of GABAA receptors. In some embodiments, the binding test was directed to a subtype of GABAA receptors, such as GABAA1 receptors (i.e., those containing the α_1 subunit), GABAA2 receptors (i.e., those containing the α_2 subunit), GABAA3 receptors (i.e., those containing the α_3 subunit) and GABAA5 receptors (i.e., those containing the α_5 subunit).

Presently available GABAA modulator anxiolytics work via interactions at the classical benzodiazepine binding site. To a large degree these anxiolytics lack GABAA receptor subtype-selectivity. The subtype-selective GABAA receptor modulators may offer more advantages. For example, a growing body of work suggests that desirable anxiolytic activity is driven primarily by interactions with GABAA receptors containing the α_2 subunit. Sedation, a side-effect common to all marketed benzodiazepines, is believed to be mediated by interactions at GABAARs containing the α_1 subunit. To develop anxiolytics with minimal liabilities due to interactions with other subunits, an electrophysiological assay was developed to screen modulatory effects of various compounds on different GABA subunit combinations heterologously expressed in *Xenopus* oocytes.

GABAA receptors are heterologously expressed in *Xenopus* oocytes by injecting cRNA corresponding to human α_1 , α_2 , α_3 , α_5 , β_2 , β_3 and γ_2 subunits of the GABAA receptor genes. The specific subunit combinations (subtypes) are as follows: $\alpha_1\beta_2\gamma_2$, $\alpha_2\beta_3\gamma_2$, $\alpha_3\beta_3\gamma_2$, and $\alpha_5\beta_3\gamma_2$. The EC₁₀ of GABA is approximated for each cell. Stability of GABA-mediated (EC₁₀) current is established. Modulatory effect of test compound is determined and compared across subtypes. The assay developed has reproducibility which allows discrimination of modulatory activity down to minimal effect of about 25% potentiation (prior to normalization to standard) for all four subtypes. Thus, the assay can characterize modulatory effects and determine subtype selectivity of test compounds on major subtypes of GABAA receptors. In some embodiments, a salt can selectively bind to one subtype of GABAA receptor (by showing about 25% or more of binding comparing to another subtype of GABAA receptor).

Anxiolytic activity is indicated in the GABAA binding test by a displacement of the flunitrazepam such as is exhibited by benzodiazepines or by enhancement of the binding such as is shown by cartazolate and tracazolate.

In some embodiments, the salts of the invention can bind to GABAA receptors. In some embodiments, the salts of the invention can bind to GABAA receptors by displacement of

benzodiazepines. Accordingly, the salts of the invention can be used to modulate activities of GABAA receptors. In some embodiments, the salts of the invention can selectively bind to a subtype of GABAA receptors, such as such as GABAA1 receptors (i.e., those containing the α_1 subunit), GABAA2 receptors (i.e., those containing the α_2 subunit), GABAA3 receptors (i.e., those containing the α_3 subunit) or GABAA5 receptors (i.e., those containing the α_5 subunit). In some embodiments, the salts of the invention can selectively bind to a subtype of GABAA receptors by displacement of benzodiazepines. Accordingly, the salts of the invention can be used to selectively modulate activities of a subtype of GABAA receptors, such as GABAA1 receptors, GABAA2 receptors, GABAA3 receptors or GABAA5 receptors.

In some embodiments, certain salts of the invention are GABAA1 receptor antagonists and GABAA2 receptor agonists.

Because the salts of the invention can be used to modulate activities of GABAA receptors, or to selectively modulate activities of a subtype of GABAA receptors, the salts of the invention are envisioned to be useful for treating or preventing diseases mediated by GABAA receptors or a subtype of GABAA receptors. Such disease, include, but is not limited to, stroke, head trauma, epilepsy, pain, migraine, mood disorders, anxiety, post traumatic stress disorder, obsessive compulsive disorders, schizophrenia, seizures, convulsions, tinnitus, neurodegenerative disorders including Alzheimer's disease, amyotrophic lateral sclerosis, Huntington's Chorea, Parkinson's disease, depression, bipolar disorders, mania, trigeminal and other neuralgia, neuropathic pain, hypertension, cerebral ischemia, cardiac arrhythmia, myotonia, substance abuse, myoclonus, essential tremor, dyskinesia and other movement disorders, neonatal cerebral hemorrhage, spasticity, cognitive disorder, and sleeping disorder.

The efficacy of the salts of the invention may be further demonstrated by carrying out the assays disclosed in the literature, such as U.S. Patent No. 7,465,795, which is

incorporated by reference herein for its disclosures on the methods of measuring GABAA bindings at col. 199-204, and its biological results for the corresponding free base.

XRPD Analysis

5

X-ray powder diffraction analysis (XRPD) is performed using variable slits on samples prepared according to standard methods, for example those described in Giacovazzo, C. *et al* (1995), *Fundamentals of Crystallography*, Oxford University Press; Jenkins, R. and Snyder, R. L. (1996), *Introduction to X-Ray Powder Diffractometry*, John Wiley & Sons, New York; Bunn, C. W. (1948), *Chemical Crystallography*, Clarendon Press, London; or Klug, H. P. & Alexander, L. E. (1974), *X-ray Diffraction Procedures*, John Wiley and Sons, New York. X-ray analyses are performed using Bruker D5000 diffractometer. The testing sample is mounted on to a zero background silicon wafer. The radiation is Cu K_α with a wavelength of 1.54Å. The scan start angle is 2°2θ and the scan finish angle is 40°2θ with increments at 0.03°2θ. The scan time is 30 minutes.

15

It will be appreciated by the skilled person that crystalline forms of compounds of the invention may be prepared by analogy with processes described herein and/or in accordance with the Examples below, and may show essentially the same XRPD diffraction patterns as those disclosed herein. By “essentially the same” XRPD diffraction patterns, we include those instances when it is clear from the relevant patterns (allowing for experimental error) that essentially the same crystalline form has been formed. When provided, XRPD 2θ values may vary in the range ±0.1°. It will be appreciated by the skilled person that XRPD intensities may vary when measured for essentially the same crystalline form for a variety of reasons including, for example, preferred orientation.

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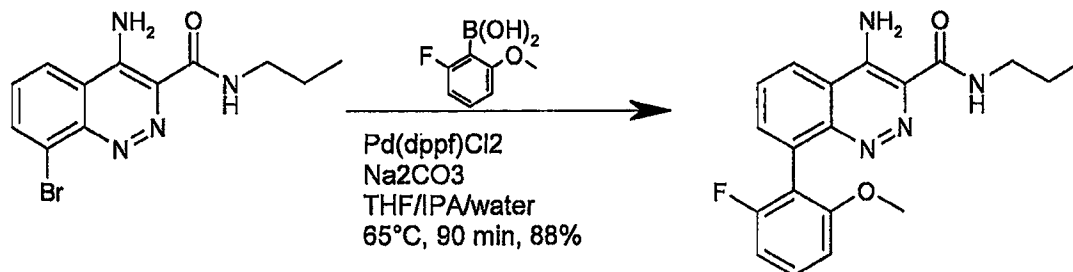
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The invention will now be illustrated by the following non-limiting Example.

EXAMPLES

30

Example 1: Synthesis of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide



5

A 2 L, 3-necked flask equipped with a reflux condenser, mechanical stirrer, and 250 mL addition funnel was charged with 4-amino-8-bromo-N-propyl-cinnoline-3-carboxamide (36.80 g, 119.09 mmol), 2-fluoro-6-methoxy-phenylboronic acid (60.70g, 357.06 mmol), and Pd(dppf)Cl₂·CH₂Cl₂ (7.40 g, 9.06 mmol) under Argon at ambient temperature. A gentle vacuum was applied and the apparatus was back-filled with Argon two times.

10

Tetrahydrofuran (515 mL, anhydrous) and isopropanol (147 mL, anhydrous) were added and the resulting red suspension was stirred at room temperature for 15 minutes. A solution of sodium carbonate (57.0 g, 537.7 mmol) in water (220 mL) was added rapidly through the addition funnel and the resulting mixture immediately placed into a pre-heated 80°C oil bath.

15

After 90 minutes at reflux (observed internal temperature 65°C), the reaction mixture was cooled to room temperature and filtered through a bed of Celite supported on a sintered glass funnel topped with Norite decolorizing carbon (30 g). The residual salts and filter-cake were washed with 4:1 (v/v) THF: isopropanol until no additional material could be detected in the eluent by TLC (silica gel, 1:1 (v/v) hexanes: ethyl acetate, UV detection, R_f = 0.25). The dark red solution was concentrated to a small volume under reduced pressure and then diluted with ethyl acetate (250 mL). The organic phase was separated and the aqueous phase extracted with ethyl acetate (2 x 250 mL). The combined organic layers were washed with brine, dried over sodium sulfate, filtered and then concentrated under reduced pressure.

20

The residues were passed through a small pad of silica gel on a sintered glass funnel washing with ethyl acetate until no more material was detected in the eluent. The solution was evaporated to afford the crude product as a foamy red-brown solid. This material was purified by flash chromatography

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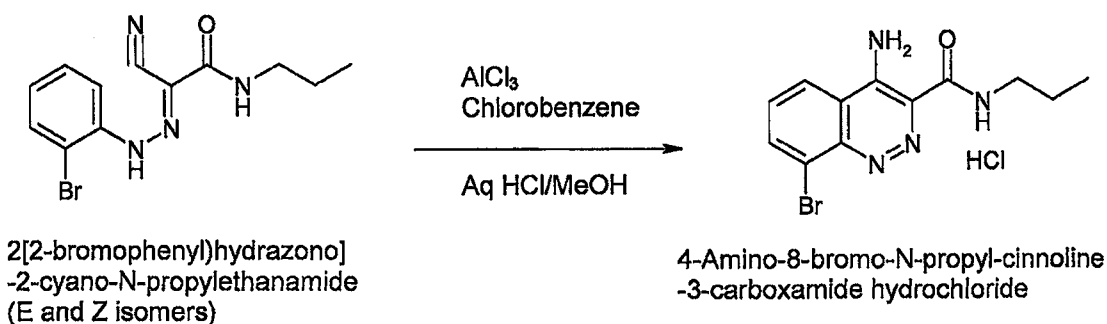
on silica gel using a gradient of 40 to 50% ethyl acetate in hexanes. Product containing fractions were combined and evaporated. The residue was precipitated from dichloromethane by addition of hexanes at room temperature. Recrystallization of this material from hot 1:1 (v/v) ethanol: water afforded the title compound as off-white white crystals (32.78 g, 78% yield). Additional title compound (4.30 g, 10% yield) was isolated by processing the residues from the crystallization liquors through an acid-base extractive workup.

^1H NMR (500.3 MHz, CDCl_3) δ 8.54 (br, 1H), 7.90 (dd, $J = 8$, 1Hz, 1H), 7.75-7.67 (m, 2H), 7.37-7.31 (m, 1H), 6.86-6.80 (m, 2H), 3.69 (s, 3H), 3.44 (qd, $J = 7$, 1Hz, 2H), 1.64 (apparent sextet, $J = 7$ Hz, 2H), 0.99 (t, $J = 7$ Hz, 3H). The 4-Amino protons were not observable in the reported proton NMR spectra recorded at 30°C due to severe broadening into the baseline. These protons can be clearly observed by recording the spectrum at -20°C. HRMS ($\text{C}_{19}\text{H}_{19}\text{FN}_4\text{O}_2$) Cal'd = 355.1570, Observed = 355.1531. HPLC 1.68 min.

Example 2: 4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide

4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide may be prepared according to the method described in the U.S. Patent No. 4,886,800 example 35a.

Example 3: 4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide hydrochloride

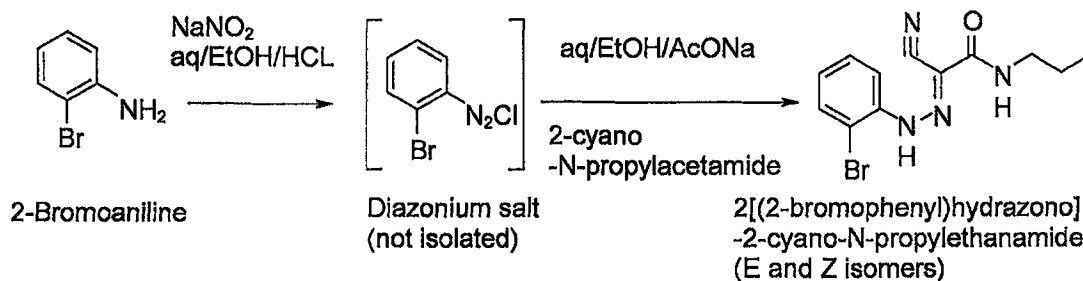


A 1 litre jacketed vessel equipped with an overhead stirrer was charged with 2[(2-bromophenyl)hydrazono]-2-cyano-N-propylethanamide (140g, 0.453 mol) and

chlorobenzene (840 ml, 6 rel vols) and the mixture was stirred for at least 15 minutes before charging aluminium trichloride (181.14g, 1.358 mol). The reaction mixture was heated to 100°C, causing it to quickly turn dark green / black, and was held at 100°C for at least five hours. A 3 litre jacketed vessel was charged with 2M aqueous hydrogen chloride solution
 5 (700 ml, 5 rel vols) and methanol (980 ml, 7 rel vols) which were heated to 55°C. The reaction mixture was cooled to 55°C and added to the methanol and aqueous hydrochloric acid mixture, at such a rate that the temperature of the exothermic addition was maintained between 50 and 60°C, followed by two line washes of methanol (140ml, 1 rel vol). Stirring was stopped and the mixture separated into two phases. The lower organic phase was
 10 separated off and methanol (280 ml, 2 rel vols) was added to the remaining aqueous phase, which was then cooled to 40°C. 4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide hydrogen chloride form 1 seed (0.35g, 0.0025 rel weight) was charged and the mixture was held at 40°C for 30 minutes then cooled to 0°C over at least 4 hours and held at 0°C for at least another 2 hours. If the seed dissolved on addition at 40°C the mixture was cooled to
 15 35°C before charging further 4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide hydrogen chloride form 1 seed (0.35g, 0.0025 rel weight). Water (560ml, 4 rel vols) was added over at least 30 minutes and the mixture was then held at 0°C for at least another 30 minutes before isolating the product by filtration. The filter cake was washed twice with a mixture of 2M aqueous hydrogen chloride (70 ml, 0.5 rel vols), water (140 ml, 1 rel vol) and methanol (70
 20 ml, 0.5 rel vols) and dried under vacuum at 40°C to yield 4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide hydrochloride (144.33g).

Example 4: Preparation of a mixture of E and Z isomers of 2[(2-bromophenyl)hydrazono]-2-cyano-N-propylethanamide

25



2-bromoaniline (150g, 0.872 mol) and ethanol (75 ml, 0.5 rel vol) were charged to a 1 litre jacketed vessel, maintaining the temperature above 20°C to avoid crystallisation of the 2-bromoaniline). 36% aqueous hydrochloric acid (187.2ml, 2.5 mol) was charged, at such a rate as to maintain the temperature below 30°C, followed by a line wash of water (37.5 ml, 0.25 rel vol). Fine white solid precipitated during the addition. The mixture was then cooled to between -5°C and 5°C before charging a solution of sodium nitrite (60.16g, 1 mol equivalent) in water (225 ml, 1.5 rel vol) at such a rate that the temperature was maintained between 0 and 2.5°C followed by water (75 ml, 0.5 rel vol) as a line wash. During addition the solid dissolved to form an orange solution.

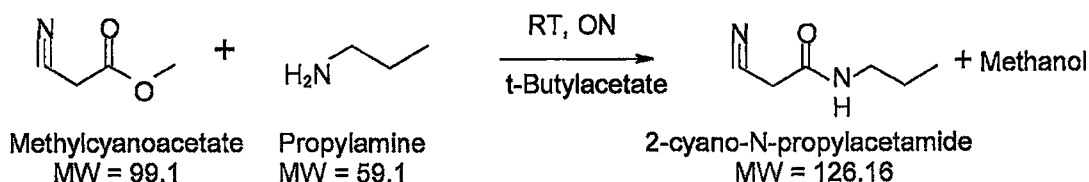
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A 3-litre jacketed vessel was charged with sodium acetate (143.1g, 2 mol eq), 2-cyano-N-propylacetamide (121g, 1.1 mol eq), ethanol (750 ml, 5 rel vol) and water (300ml, 2 rel vol) and the mixture was heated to 50°C to form a clear colourless solution.

The diazonium solution was added to the 3 litre vessel via a peristaltic pump over at least 30 minutes, maintaining the batch temperature between 45 and 52°C, followed by a line wash of ethanol (75 ml, 0.5 rel vol). Solid crystallised out early in the addition. The mixture was held at 50°C for 30 minutes before charging 2[(2-bromophenyl)hydrazono]-2-cyano-N-propylethanamide seed (0.75g, 0.5% rel weight) and heating to reflux (77°C) for at least 1 hour, during which time 2[(2-bromophenyl)hydrazono]-2-cyano-N-propylethanamide will convert from form 1 to form 2. The mixture was cooled to 20°C over at least 1 hour and held at 20°C for at least 1 hour before isolating the solid by filtration. The filter cake was washed twice with a mixture of water (150 ml, 1 rel vol) and ethanol (150ml, 1 rel vol) then dried at 40°C under vacuum to yield 2[(2-bromophenyl)hydrazono]-2-cyano-N-propylethanamide (226.6g)

25

Example 5: Preparation of 2-cyano-N-propylacetamide



A 2 litre jacketed vessel fitted with a temperature probe and a retreat curve agitator was inerted with nitrogen and charged with n-propylamine (196.86g, 274.25 ml, 3.33 moles) and t-butylacetate (540 ml, 1.8 rel vol). The mixture was cooled to 15°C. Methylcyanoacetate (300g, 267.62ml, 302.76 mol) was charged via a dropping funnel over at least 30 minutes, maintaining the batch temperature between 20 and 25°C, followed by t-butylacetate (60 ml) as a line wash. The reaction mixture was stirred at 20°C for between 10 and 17 hours until the level of methylcyanoacetate remaining was below 0.5 mol%.

The vessel was set for vacuum distillation with a vacuum of 160 mbar and the mixture was heated to between 46 and 61°C until 3.43 relative volumes of distillate had been collected. t-Butylacetate (549 ml, 1.83 rel vol) was then charged and the mixture was cooled to between 22 and 20°C before charging 2-cyano-N-propylacetamide seed (3g, 1% rel weight). The batch was cooled to 15°C over at least 1 hour and held at 15°C for at least 30 minutes before charging heptane (900 ml, 3 rel vol) over at least 3 hours, cooling further to 5°C over at least 4 hours and holding at 5°C for at least 30 minutes. The solid was isolated by filtration, washed with premixed heptane (199.8 ml, 0.666 rel vol) and t-butylacetate (100.2 ml, 0.334 rel vol) then heptane (300 ml, 1 rel vol) and dried under vacuum at ambient temperature to yield 2-cyano-N-propylacetamide (354.7g).

Example 6: Preparation of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate

4-Amino-8-bromo-N-propyl-cinnoline-3-carboxamide hydrochloride (175.0 g) is charged to a vessel. 2-fluoro-6-methoxy-phenylboronic acid (120.5 g, 1.40 mol eq) is charged to the vessel. (1,1'-bis(ditertbutylphosphine)ferrocene)palladium(II) chloride (8.25 g, 0.025 mol eq) is charged to the vessel. The content of the vessel is heated to 70°C with agitation.

Triethylamine (247.0 mL, 3.5 mol eq) is charged to the vessel while maintaining the temperature at 65 to 75°C followed by addition of water (262.5 mL, 1.5 rel vol). The mixture was allowed to react for at least 6 hours at 70°C. The contents of the vessel are cooled to 50°C and the aqueous layer is separated and removed. The organic layer is washed with 10% w/v aqueous citric acid solution (525 mL, 3.0 rel vol) and 10% w/v aqueous sodium chloride solution (437.5 mL, 2.5 rel vol). The residual water in the organic layer is distilled off. Dimethyl sulfoxide (87mL) is added to the organic layer (approximately 1825ml anisole solution) to which is then added a solution of sulfuric acid (1.0 mol eq) in Dimethyl sulfoxide (87mL) in a controlled manner at 70°C together with crude 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate seed. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate crystals form in the vessel, they are filtered, washed with additional Anisole and n-heptane and dried under vacuum at 40°C to give a dried weight of 182.02g.

EXAMPLE 7: Recrystalization of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate to prepare Form A

39.95 g of crude 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate made according to Example 6 and 15% v/v water 85% v/v 1-propanol (380 ml, 9.5ml) are added to a vessel and the content of the vessel is heated up to 80°C to dissolve crude 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate. The solution is cooled down to 62°C. To the solution, pure seed crystal of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate is added. The mixture is then cooled down to 25°C over a 2-hour period. To the mixture, isopropyl acetate (400 ml) was added over a 2-hour period. The mixture is further cooled down to 0°C for over 24 hours and the solid formed in the mixture is isolated by filtration and washed by 1:1 isopropyl acetate: 15% aqueous 1-propanol (80 ml). The solid is dried in a vacuum oven at 40°C and 700 mbar to yield 33 g of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

The crystals of Example 7 are analyzed by XRPD and the results are tabulated below (Table 1) and are shown in Figure 1. Further water analysis is performed according to USP 921 on this material to show that Form A is anhydrous.

5

Table 1: Form A main peaks

Peak	2θ	Intensity
1	9.37	1456
2	14.57	850
3	18.61	366
4	22.08	1151
5	23.36	515
6	27.61	699
7	28.13	660
8	29.98	368

Example 8: Preparation of Form N

- 10 6 g of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate crystals made in Example 7 and 100 mL water are mixed and stirred at 18°C for 4 days. The resulting crystals are separated and air dried. This form is named Form N.

- 15 The crystals of Example 8 are analyzed by XRPD and the results are tabulated below (Table 2) and are shown in Figure 2. Further analysis is conducted on this sample to show that Form N is a sesquihydrate of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

Table 2 (Form N)

Peak	2θ	Intensity
------	----	-----------

1	10.92	83
2	14.22	237
3	15.66	161
4	19.36	122
5	21.07	217
6	23.47	287
7	26.02	452
8	27.48	174

Example 9: Preparation of Form B

6 g of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen
sulphate crystals made in Example 7 and 100 mL water are mixed and stirred at 8°C for
14 days at 250 rpm followed by two additional days of stirring at 5°C. The resulting
crystals are separated and air dried. This form is named Form B.

The crystals of Example 9 are analyzed by XRPD and the results are tabulated below
(Table 3) and are shown in Figure 3. Further analysis is conducted on this sample to
show that Form B is a heptahydrate of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-
propylcinnoline-3-carboxamide hydrogen sulphate.

Table 3: Form B main peaks

Peak	2 θ	Intensity
1	7.12	736
2	8.20	1483
3	9.43	239
4	16.36	634
5	19.35	186
6	22.89	275
7	27.70	195

8	28.44	222
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Example 10: Preparation of Amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate

A water solution of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate is prepared, filtered through a 0.2- μ m filter, and frozen in liquid nitrogen. The frozen sample is lyophilized using an FTS system Flexi-Dry to result in an amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate. The lyophilization temperature is not controlled.

Alternately, the amorphous form may be obtained by drying 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate Form N at 40°C, under 500mBar vacuum for 5 days. A weight loss of 48% occurs and the sample changes colour from off white to distinctly yellow.

The amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate is analyzed by XRPD and the results are shown in Figure 4. XRPD pattern exhibits a broad halo indicative of amorphous material. Cyclic DSC of the sample (as shown in FIG. 5) shows a step transition at 52 °C (inflection) followed by a recrystallization exotherm at 207 °C and a broad endotherm at 249 °C, presumably a melt. DVS analysis of the sample (as shown in FIG. 6) shows 19% weight gain between 5 – 85% relative humidity indicating hygroscopicity.

Milling the amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate in the presence of a solvent may result in Form A. An acetone slurry of the amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate may also convert the amorphous form into Form A. When the amorphous 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-

propylcinnoline-3-carboxamide hydrogen sulphate is dissolved and reprecipitated from an ethanol water mixture, Form A is generally formed. When the amorphous sample is exposed to ethanol vapor, the amorphous sample is also converted to Form A.

5 Abbreviations

br = broad (in relation to NMR)

d = doublet (in relation to NMR)

DCM = dichloromethane

DMSO = dimethylsulfoxide

10 dd = doublet of doublets (in relation to NMR)

Et = ethyl

h = hour(s)

HCl = hydrochloric acid

m = multiplet (in relation to NMR)

15 Me = methyl

min. = minute(s)

MS = mass spectroscopy

Pd/C = palladium on carbon

q = quartet (in relation to NMR)

20 rt = room temperature

s = singlet (in relation to NMR)

t = triplet (in relation to NMR)

UV = ultraviolet

25 Prefixes *n*-, *s*-, *i*-, *t*- and *tert*- have their usual meanings: normal, secondary, *iso*, and tertiary.

CLAIMS:

1. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate.

5

2. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate which is substantially crystalline.

3. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen

10

sulphate having an X-ray powder diffraction pattern, when measured using radiation with a wavelength of $1.54\text{\AA}$, with specific peaks at 2Θ -values at about 9.4, about 14.6, about 22.1, about 27.6 and about 28.1°.

4. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen

15

sulphate as claimed in claim 3 having an X-ray powder diffraction pattern, when measured using radiation with a wavelength of $1.54\text{\AA}$, with specific peaks at 2Θ values at about 9.4, about 14.6, about 18.6, about 22.1, about 23.4, about 27.6, about 28.1 and about 30.0°.

5. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen

20

sulphate as claimed in claim 3 having an X-ray powder diffraction pattern essentially as defined in Figure 1.

6. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen

25

sulphate as claimed in claim 2 having an X-ray powder diffraction pattern essentially as defined in Figure 2.

7. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen

sulphate as claimed in claim 2 having an X-ray powder diffraction pattern essentially as defined in Figure 3.

30

8. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate which is substantially amorphous.

5 9. A pharmaceutical composition comprising 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate as claimed in any one of claims 1 to 8 in admixture with a pharmaceutically acceptable diluent or carrier.

10. 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate according to any one of claims 1-8 for use as a medicament.

10

11. The use of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate according to any one of claims 1-8 in the manufacture of a medicament for the treatment of anxiety disorders.

15

12. A method for the therapy of anxiety disorders in a warm-blooded animal, comprising the step of administering to said animal in need of such therapy a therapeutically effective amount of 4-Amino-8-(2-fluoro-6-methoxy-phenyl)-N-propylcinnoline-3-carboxamide hydrogen sulphate according to any one of claims 1-8.

20

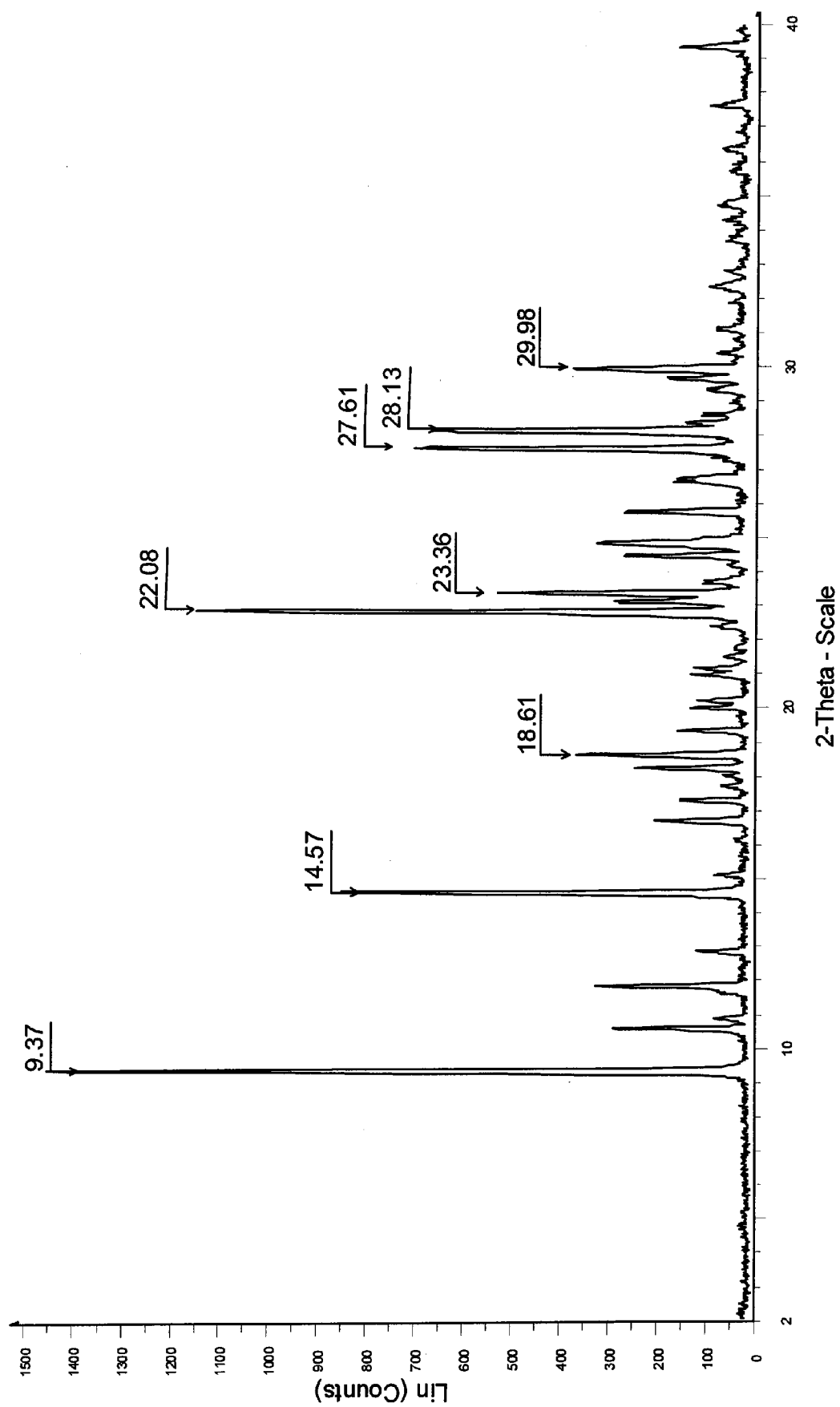


FIG. 1

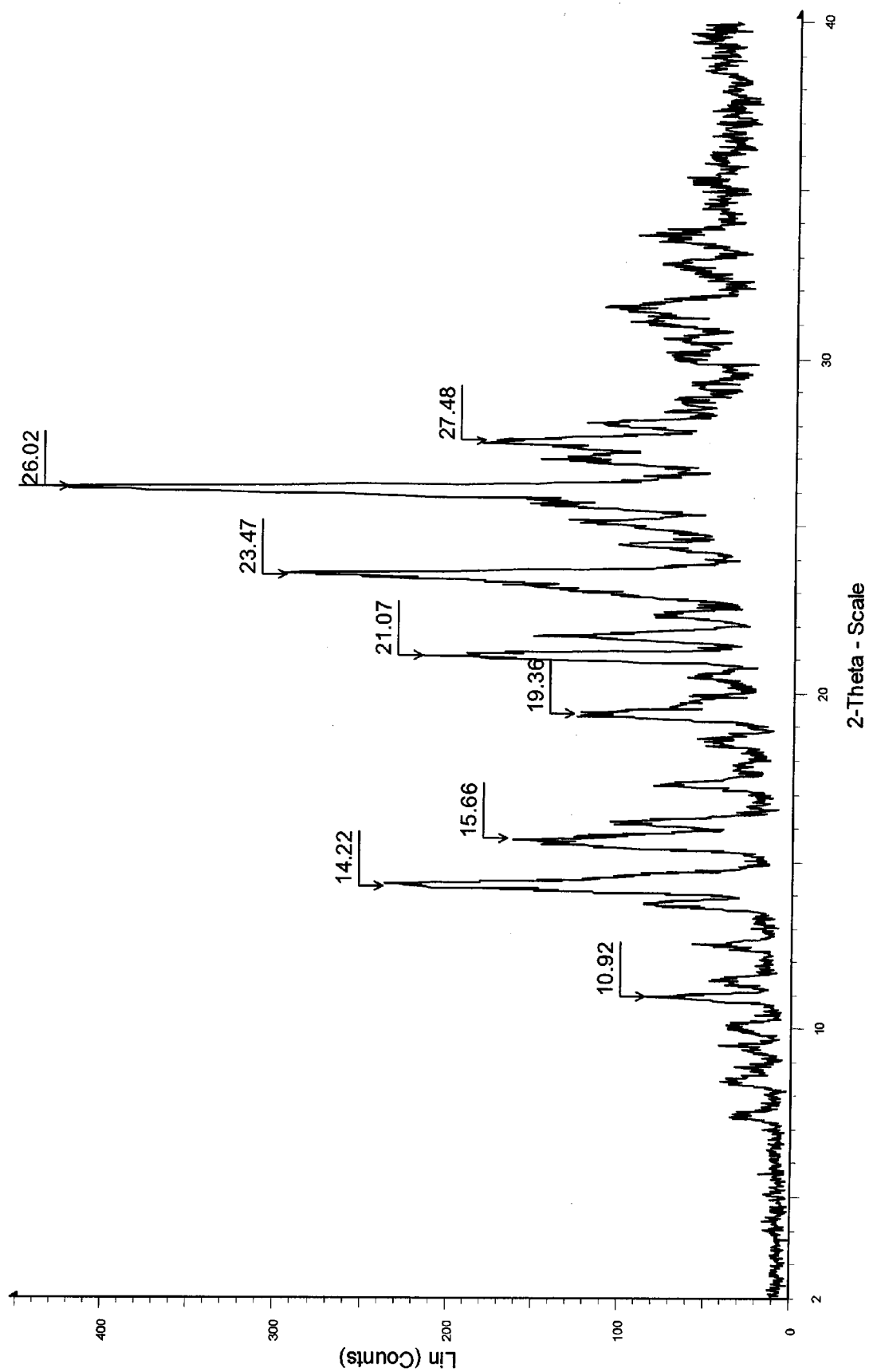


FIG. 2

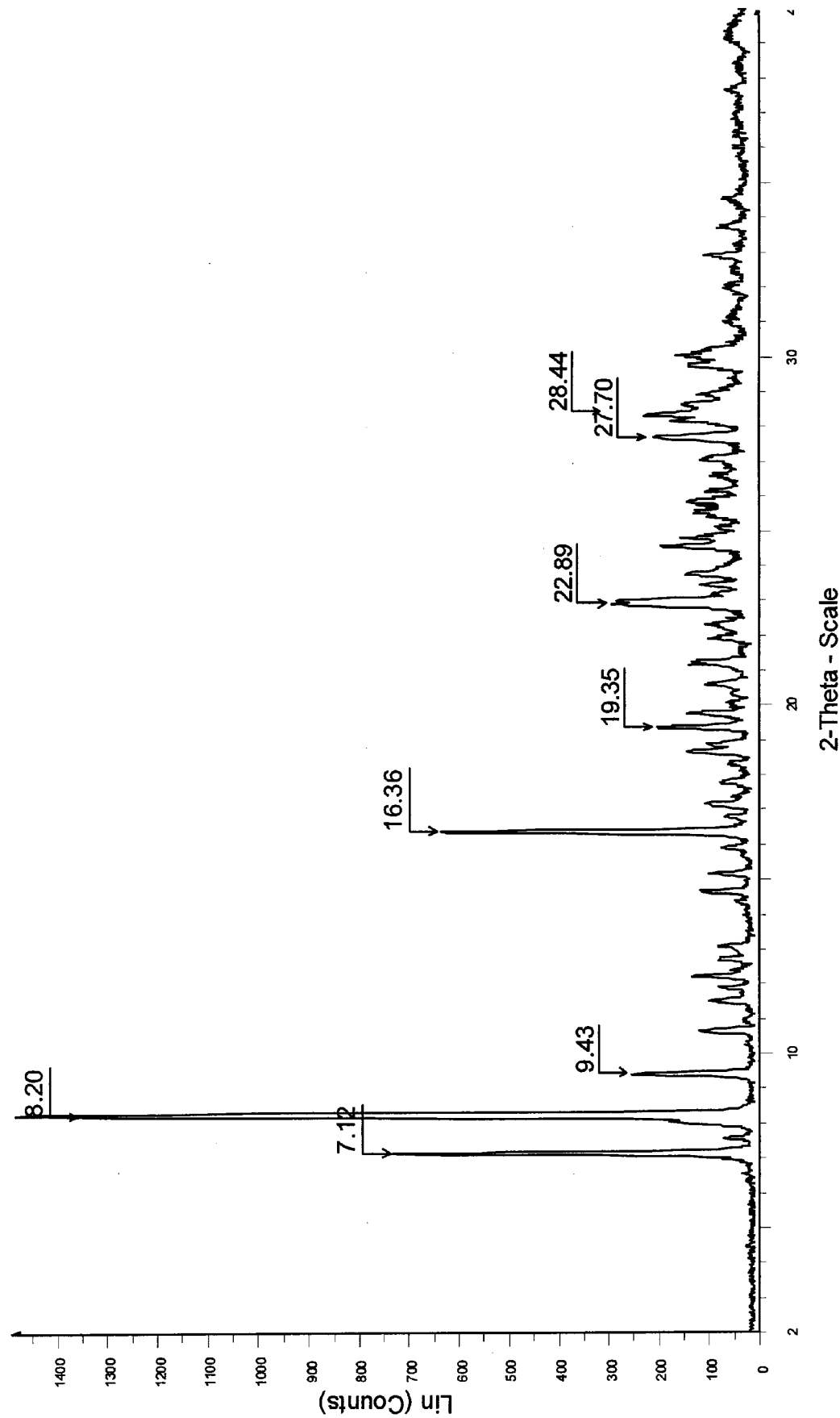
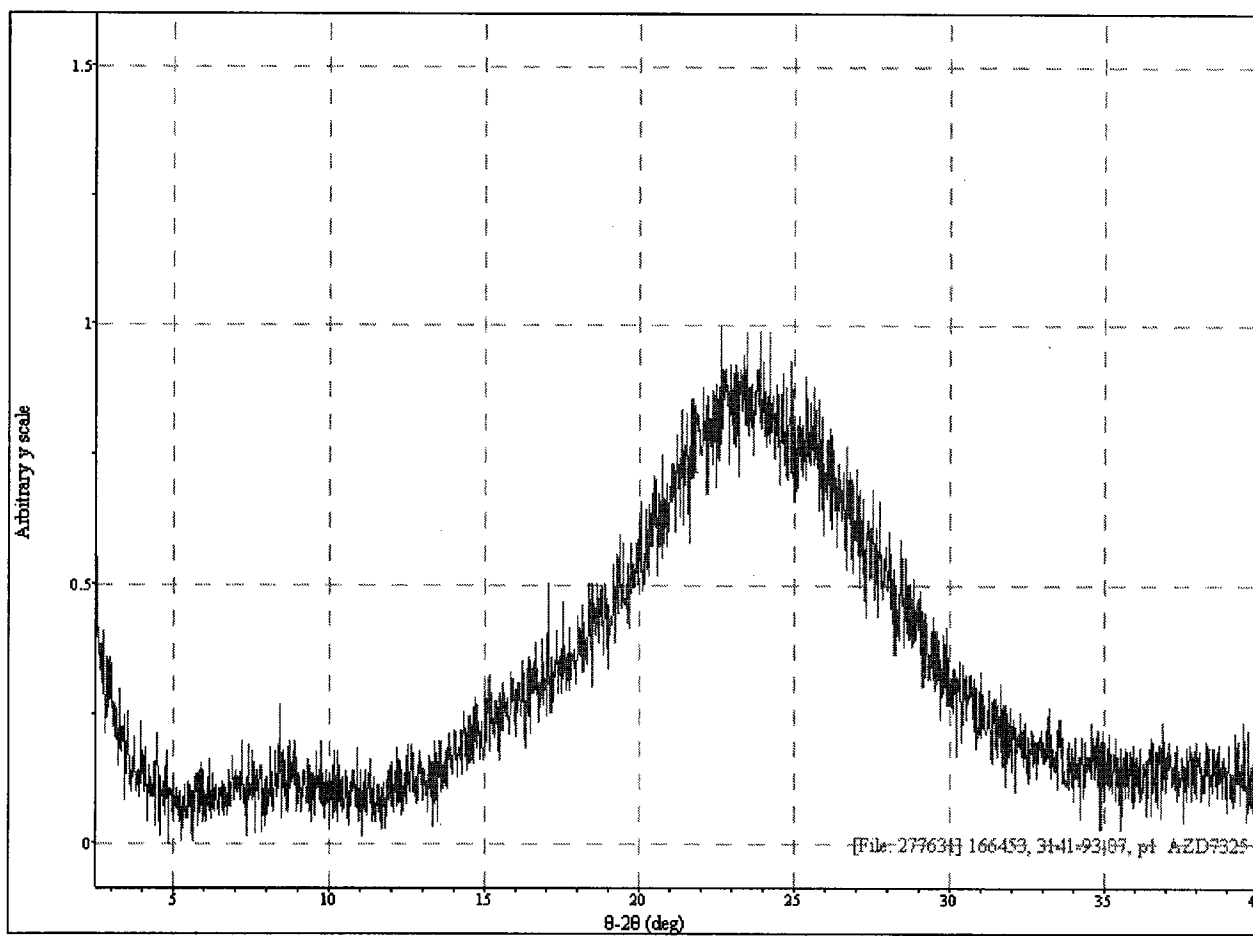


FIG. 3

**FIG. 4**

DSC

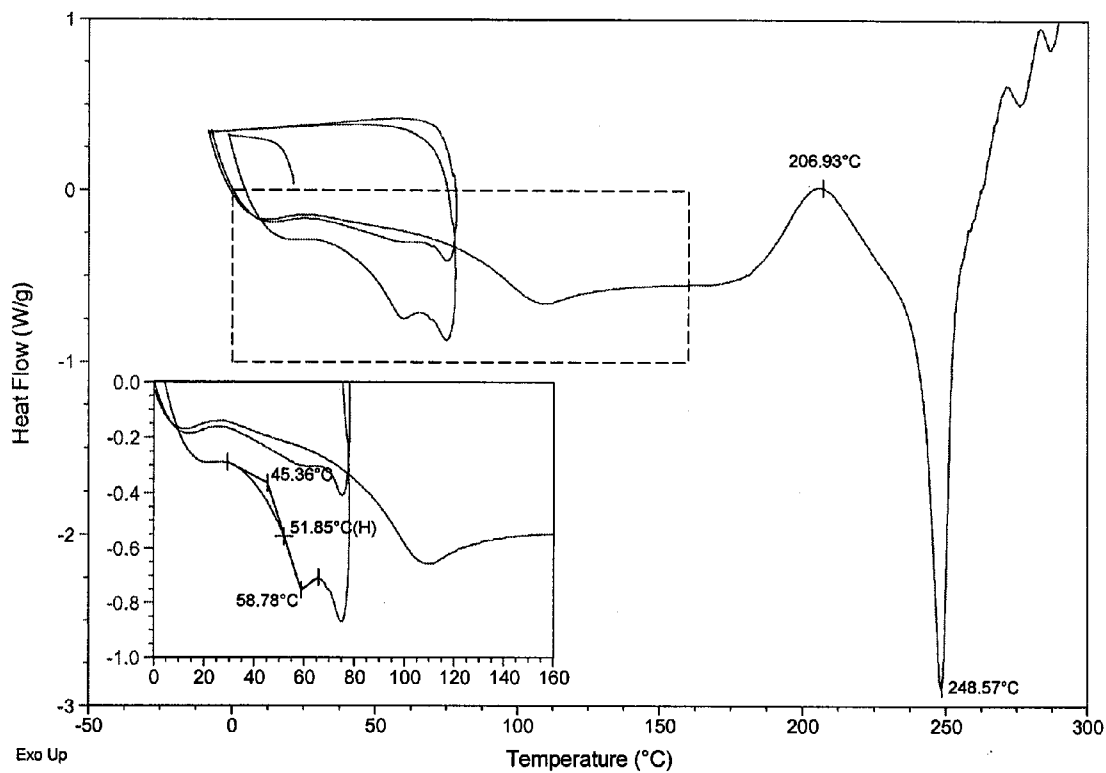


FIG. 5

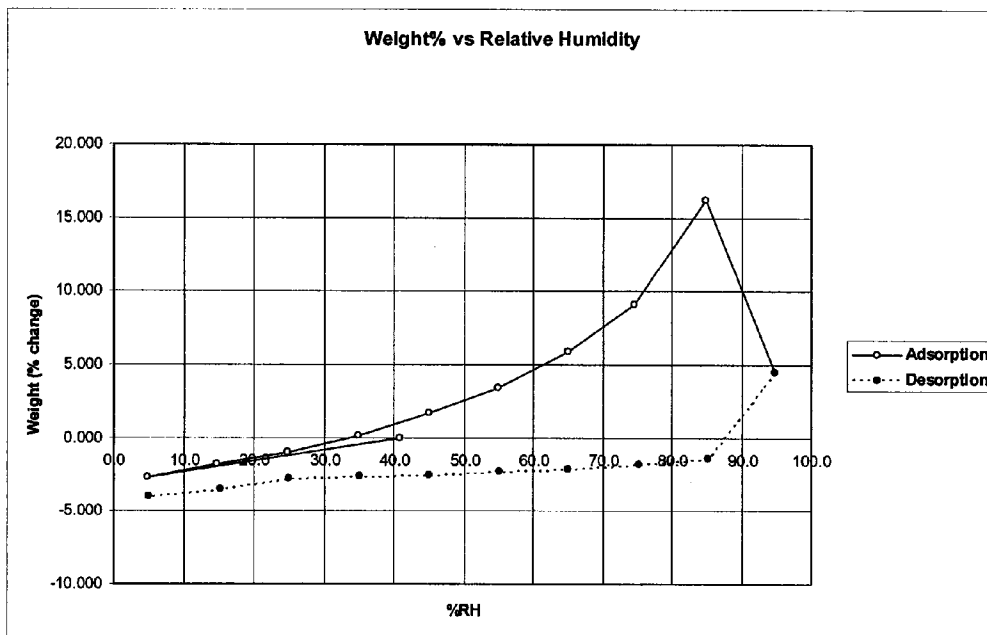


FIG.6

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050425

A. CLASSIFICATION OF SUBJECT MATTER

IPC: see extra sheet

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC:A61K, A61P

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

SE, DK, FI, NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, PAJ, WPI data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008155573 A1 (ASTRAZENECA AB ET AL), 24 December 2008 (2008-12-24); abstract; page 71; claims 1, 23; example 64	1-12
X	WO 2007073283 A1 (ASTRAZENECA AB ET AL), 28 June 2007 (2007-06-28); abstract; page 173	1-12
A	EP 0328282 A2 (ICI AMERICA INC), 16 August 1989 (1989-08-16); abstract; claims	1-12
A	EP 0205272 A2 (ICI AMERICA INC), 17 December 1986 (1986-12-17); abstract; page 2	1-12

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

☒ See patent family annex.

* Special categories of cited documents:

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“&” document member of the same patent family

Date of the actual completion of the international search

20-07-2010

Date of mailing of the international search report

21-07-2010

Name and mailing address of the ISA/SE

Patent- och registreringsverket

Box 5055

S-102 42 STOCKHOLM

Facsimile No. + 46 8 666 02 86

Authorized officer

Lena Rimsten

Telephone No. + 46 8 782 25 00

INTERNATIONAL SEARCH REPORT

International application No.
PCT/SE2010/050425

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:

Claim 12 relates to a method for treatment of the human or animal body by surgery or by therapy, as well as diagnostic methods, see PCT rule 39.1(iv). Nevertheless, a search has been made for this claim. The search has been directed to the technical content of the claim.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Continuation of: second sheet

International Patent Classification (IPC)

A61K 31/502 (2006.01)

A61P 25/22 (2006.01)

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Paper copies can be ordered at a cost of 50 SEK per copy from PRV InterPat (telephone number 08-782 28 85).

Cited literature, if any, will be enclosed in paper form.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No.

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INTERNATIONAL SEARCH REPORT

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International application No.

PCT/SE2010/050425

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