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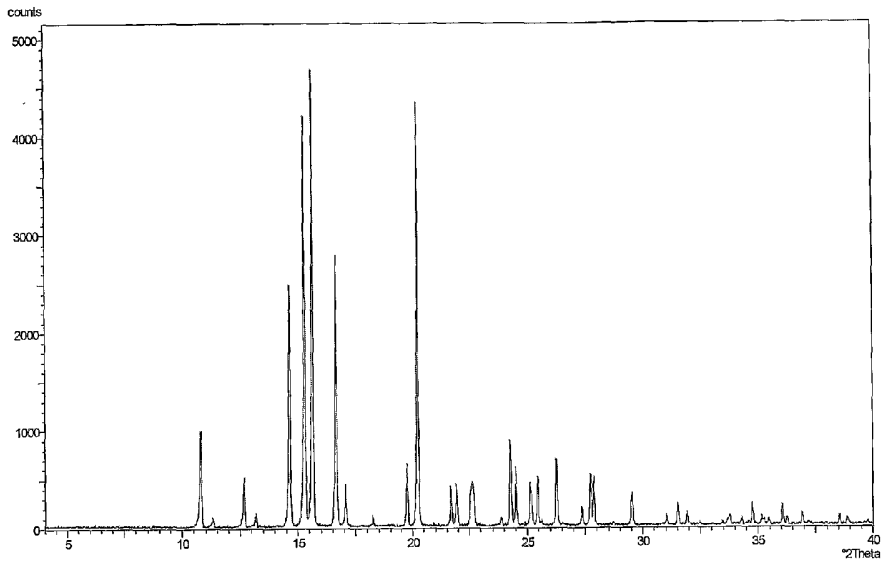
(54) **Title:** PREPARATION OF CRYSTALLINE ROTIGOTINE BASE

FIG. 1.




(57) **Abstract:** The present invention relates to processes of preparing rotigotine form its heminaphthalene -1,5- disulfonate salt as a free base in solid cyrstalline form.

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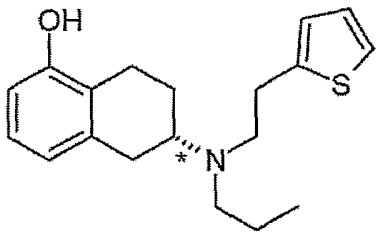
# PREPARATION OF CRYSTALLINE ROTIGOTINE BASE

## FIELD OF INVENTION

**[0001]** The present invention relates to new processes for preparing rotigotine as a free base in solid crystalline form.

## BACKGROUND

**[0002]** Aminotetralins constitute an important class of biologically active compounds. For example, the aminotetralin drug rotigotine ((S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol) is a non-ergot (or non-ergotamine) dopamine D2 agonist and is used for the treatment of Parkinson's disease and restless legs syndrome.




Rotigotine

**[0003]** Rotigotine has been reported in at least two forms. U.S. Patent No. 6,884,434 describes the HCl salt and the free base ("rotigotine base"). This patent also describes a pharmaceutical formulation of rotigotine in the form of a transdermal therapeutic system (transdermal patch) comprising an adhesive matrix layer containing rotigotine in an amount effective for the treatment of the symptoms of Parkinson's disease.

**[0004]** A crystal structure of what appears to be rotigotine base is disclosed in the Cambridge Structural Database under reference code RALMOG (deposited by M. Nieger, K.H. Dotz, Department of Inorganic Chemistry, University of Bonn, Germany, *Private Communication*, 2001, CCDC 163602).

## SUMMARY

**[0005]** In accordance with one aspect, the present invention provides new processes of preparing solid crystalline rotigotine base (rotigotine base) having superior chemical and enantiomeric purity. The processes include neutralizing rotigotine heminaphthalene-1,5-disulfonate to give rotigotine base and crystallizing rotigotine base from a solvent, selected from the group consisting of an alcohol, ketone, alkane, chlorinated alkane, ether, and combinations of any two or more thereof. The rotigotine naphthalene-1,5-disulfonate can be neutralized by contacting it with at least one suitable base such as an alkali metal hydroxide and/or a carbonate. For example, suitable bases include NaOH, KOH, sodium carbonate, and potassium carbonate.

**[0006]** A wide variety of solvents may be used in the crystallization step. Thus, suitable alcohols for use in the methods herein include methanol, ethanol, and isopropanol. Suitable ketones for use in the methods herein include acetone, methyl ethyl ketone, cyclohexanone and 3-pentanone. Chlorinated alkanes suitable for use in the methods described herein include dichloromethane and chloroform. Suitable ethers for use in inventive methods include diethyl ether and diisopropyl ether. Alternatively, a combination solvents may be used such as a ketone and an alkane. Exemplary combinations include acetone with heptane and acetone with cyclohexane.

## BRIEF DESCRIPTION OF THE DRAWINGS

**[0007]** FIG. 1 is an X-ray powder diffraction (XRPD) pattern of crystalline rotigotine base.

**[0008]** FIG. 2 is an infrared (IR) spectrum of a polymorph of crystalline rotigotine base.

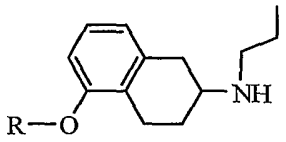
**[0009]** FIG. 3. is a differential scanning calorimetry (DSC) thermogram of a polymorph of crystalline rotigotine base.

**[0010]** FIG. 4. is a thermogravimetric (TG) thermogram of crystalline rotigotine base.

## DETAILED DESCRIPTION

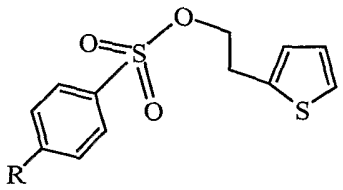
**[0011]** Processes for the preparation of N,N-disubstituted aminotetralins, specifically, for the preparation of enantiomerically enriched or enantiomerically pure rotigotine base are provided herein. In one aspect, the processes include the step of:

a) reacting an enantiomerically enriched or enantiomerically pure compound of Formula (I),



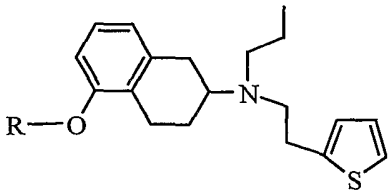
(I)

with 2-(2-thienyl)ethanol arylsulfonate of Formula (II),



(II)

to provide a compound of Formula (IV),



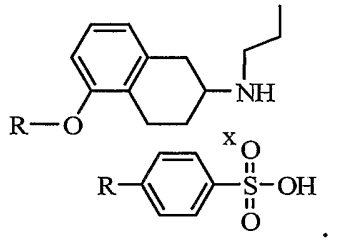
(IV)

wherein each R is independently selected from hydrogen or a methyl group.

**[0012]** The reaction may be performed without added base because Formula (I) serves as both the reactant and the base at the same time. In some embodiments, the compound of Formula (II) can be 2-(2-thienyl)ethanol benzenesulfonate or 2-(2-thienyl)ethanol toluenesulfonate. The reaction is typically carried out in an organic solvent, heated to a temperature of from about 60 °C to about 120 °C, and preferably from about 80 °C to about 110 °C. Suitable solvents that may be heated to such temperatures include but are not limited to isopropyl acetate, isobutyl acetate, isoamyl acetate, toluene and xylene. Preferably,

isobutyl acetate or isoamyl acetate are used. In some embodiments, the amount of the compound of Formula (II) is present at about 1 to about a 2.5-fold molar excess, preferably from about a 1.2 to about a 2.0-fold molar excess with respect to the amount the compound of Formula (I).

**[0013]** Advantageously, unreacted starting aminotetralin precipitates from the reaction mixture as the salt of Formula (III):

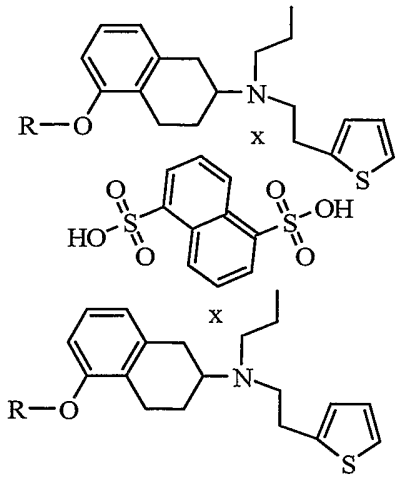


(III)

Thus, the present processes may further comprise the following step: b) filtering the reaction mixture to isolate the precipitate comprising the salt having Formula (III). The filtrate will therefore comprise the product, the compound of Formula (IV).

**[0014]** The present processes may further comprise the following step: c) contacting the salt having Formula (III) with a suitable base to convert it to the compound of Formula (II). Suitable bases are well known in the art and include, e.g., alkali metal hydroxides, carbonates, and the like. For example, 10% aqueous NaOH may be used to neutralize the salt and allow the compound of Formula (II) to be extracted into an organic solvent such as dichloromethane or the like.

**[0015]** The present processes may further comprise the following step: d) treating the filtrate containing the compound of Formula (IV) with 1,5-naphthalenedisulfonic acid or its hydrates, to give the enantiomerically enriched or enantiomerically pure salt having Formula (V),



(V)

wherein R is as defined above. The salt having Formula (V) is a useful intermediate in the synthesis allowing ready purification of the N,N-disubstituted aminotetralin by crystallization, and avoiding the use of chromatography. Treatment of the filtrate is optionally conducted with the addition of an organic solvent, such as acetone, methanol, isopropanol, or the like. Optionally, the salt having Formula (V) is recrystallized.

**[0016]** The processes for preparing N,N-disubstituted aminotetralins as the free base may further include the following step: e) contacting the salt of Formula (V) with a suitable base to provide the enantiomerically enriched or enantiomerically pure compound of Formula (IV). Suitable bases for salt neutralization are well known in the art and include for example, alkali metal hydroxides and carbonates. When R is H, rotigotine base is produced.

**[0017]** By the use of the term enantiomerically enriched it is meant that the enantiomeric excess (ee) is greater than 80%. In some embodiments greater than 90% or greater than 95%.

**[0018]** By use of the term enantiomerically pure it is meant that the enantiomeric excess (ee) is greater than 98%, ideally greater than 99% and ideally enantiomerically pure means greater than 99.5%.

**[0019]** Rotigotine base produced by the processes disclosed herein may be crystallized from a variety of solvent or solvent combinations including alcohols, ketones, alkanes, chlorinated alkanes, ethers, and combinations of any two or more thereof. Suitable solvents

include methanol, ethanol, isopropanol, acetone, methyl ethyl ketone, cyclohexanone, 3-pentanone, dichloromethane, chloroform, diethyl ether and diisopropyl ether. Suitable combinations of solvents that may be used to crystallize rotigotine base include ketones and alkanes, such as acetone with heptane or acetone with cyclohexane.

**[0020]** Crystalline rotigotine base was characterized by XRPD, IR, DSC and TG analysis. XRPD was carried out as described in Example 4 and provided the diffractogram shown in FIG. 1. Characteristic diffraction peaks were observed at °2θ: 10.8, 14.7, 15.3, 15.6, 16.7, 20.3 and 11.3, 12.7, 13.2 17.1, 18.2, and 19.7.

**[0021]** FIG. 2 shows a typical IR spectrum of rotigotine base. In the IR spectrum characteristic bands are observed as shown in Table 1.

Table 1

| **wave number / $cm^{-1}$** |
|---|
| 2970 ± 4 |
| 2933 ± 4 |
| 1585 ± 4 |
| 1466 ± 4 |
| 1347 ± 4 |
| 1281 ± 4 |
| 1204 ± 4 |
| 1081 ± 4 |
| 1011 ± 4 |
| 776 ± 4 |
| 701 ± 4 |

**[0022]** A typical DSC thermogram of rotigotine base is shown in FIG. 3. The observed melting point is 76 °C ± 2 °C.

**[0023]** A typical TG thermogram of rotigotine base is shown in FIG. 4. Decomposition of rotigotine base was noted in the temperature range from 145 to 270 °C, with mass loss of 99.92%

**[0024]** All publications, patent applications, issued patents, and other documents referred to in this specification are herein incorporated by reference as if each individual publication, patent application, issued patent, or other document was specifically and

individually indicated to be incorporated by reference in its entirety. Definitions that are contained in text incorporated by reference are excluded to the extent that they contradict definitions in this disclosure.

**[0025]** The present invention, thus generally described, will be understood more readily by reference to the following examples, which are provided by way of illustration and are not intended to be limiting of the present invention.

## EXAMPLES

### Example 1: Preparation of (S)-6-(Propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate

**[0026]** (-)-5-Hydroxy-N-(n-propyl)-2-aminotetralin (3.02 g, 14.7 mmol) and 2-(2-thienyl)ethanol toluenesulfonate (8.30 g, 29.4 mmol) were suspended in isobutylacetate (30 mL) under an inert atmosphere. The reaction mixture was heated at 110 °C for 10 hours and then filtered while hot to give 2.62 g (6.96 mmol) of (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin toluenesulfonate and filtrate. The filtrate was evaporated to dryness, dissolved in a mixture of acetone-isopropanol, and 1.91 g (5.30 mmol) of 1,5-naphthalenedisulfonic acid was added. The resulting mixture was stirred at room temperature. The product was filtered, washed with 2-PrOH (30 mL) and dried under reduced pressure to yield 2.92 g (6.36 mmol) of (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate.

### Example 2: Preparation of (S)-6-(Propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol

**[0027]** (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate (1.4 g, prepared according to the procedure above) was suspended in mixture of 40 ml of dichloromethane and 40 ml of water. The suspension was stirred and cooled down at 0-5 °C. An aqueous solution of 10% NaOH was added dropwise until a pH value of 12 was obtained. The resulting mixture was stirred for additional 30 minutes at 0-10 °C. The layers were separated and the organic layer was washed with 50 ml of water and dried over anhydrous $MgSO_4$. Dichloromethane was removed under reduced

pressure to yield 0.8 g of an oil, rotigotine base. If the oil is left overnight in an open vessel, preferably under refigertaion, then crystalline material is produced.

**Example 3: Crystallization of (S)-6-(Propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol**

**[0028]** Crystalline rotigotine base was prepared by crystallization of (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol from single solvents, including dichloromethane, diisopropyl ether and ethanol. Crystalline rotigotine base was also prepared by crystallization from solvent/antisolvent mixtures, including acetone/cyclohexane and acetone/heptane.

**[0029]** Example 3A: 20 mg of rotigotine prepared according to Example 2 was dissolved in 1 ml of dichloromethane. Prepared solution was filtered and left at room temperature in $N_2$ atmosphere to evaporate and crystallize. Crystals of rotigotine base were obtained.

**[0030]** Example 3B: 20 mg of rotigotine according to Example 2 was dissolved in 1 ml of diisopropyl ether. The resulting solution was filtered and left at room temperature under nitrogen atmosphere to evaporate and crystallize. Crystals of rotigotine base were obtained.

**[0031]** Example 3C: 20 mg of rotigotine according to Example 2 was dissolved in 1 ml of ethanol. The resulting solution was filtered and left at room temperature under nitrogen atmosphere to evaporate and crystallize. Crystals of rotigotine base were obtained.

**[0032]** Example 3D: 100 mg of rotigotine according to Example 2 was dissolved in 0.7 ml of acetone. 3.0 ml of cyclohexane was added to the solution. The resulting solution was filtered and left at room temperature in $N_2$ atmosphere to evaporate and crystallize. Crystals of rotigotine base were obtained.

**[0033]** Example 3E: 150 mg of rotigotine according to Example 2 was dissolved in 2.0 ml of acetone. 5.0 ml of heptane was added to the solution. The resulting solution was stirred at room conditions in opened flask. Crystals of rotigotine base were obtained.

**Example 4: X-ray Powder Diffraction**

**[0034]** X-ray powder diffraction analysis of rotigotine base was performed according to the experimental parameters detailed in Table 2 on Philips X'Pert PRO diffractometer using CuKα1 radiation.

Table 2:

X-ray powder diffraction experimental conditions

| | |
|---|---|
| **Sample holder preparation** | Samples after being powdered in a mortar and pestle are applied directly on silicon PW1817/32 "zero background" holder |
| **Instrument** | Philips X'Pert PRO |
| **Goniometer** | PW3050/60 |
| **Generator** | PW3040; 45 kV, 40 mA |
| **X-Ray tube** | PW3373/00; Cu anode LFF |
| **Focus** | Linear |
| **Sample stage** | PW3072/60 or PW3064 |
| **Scan angle range (2Θ)** | 4 – 40° |
| **Scan mode** | Continuous absolute scan |
| **Step size (2Θ)** | 0.016° |
| **Time per step** | 100 seconds |
| **X-ray radiation** | λ(CuKα1) = 1.540598 Å |
| **Primary soller slit** | 0.04 rad |
| **PDS** | Fixed, divergence ½° |
| **Primary mask** | 10 mm |
| **Secondary soller slit** | 0.04 rad |
| **Anti-Scatter Slit** | Fixed, divergence ½° |
| **Monochromator** | Inc. Beam α1 Cu/Co for reflection mode |
| **Detector** | X'Celerator (2.022° 2Θ) |
| **Control program** | X'Pert Data Collector |
| **Temperature** | 293±2K |

**Example 5: Infrared Analysis**

**[0035]** The IR spectrum of rotigotine base as shown in FIG. 2 was obtained between 4000 $cm^{-1}$ and 370 $cm^{-1}$, with resolution of 4 $cm^{-1}$, using a KBr pellet with a Spectrum GX manufactured by Perkin-Elmer.

**Example 6: DSC Analysis**

**[0036]** The DSC thermogram of rotigotine base is shown in FIG. 3, and was measured on a Q 1000 MDSC TA instrument under a dynamic flow of nitrogen (50 ml/min) and a heating rate of 10 C/min. A standard closed aluminum pan was used.

**Example 7: Thermogravimetric Analysis**

**[0037]** Thermogravimetric analysis was performed on a TGA 2950 TA Instrument, under dynamic flow of nitrogen (60 ml/min) and a heating rate of 10 °C/min. The resulting thermogram is shown in FIG. 4.

**[0038]** As will be understood by one skilled in the art, for any and all purposes, particularly in terms of providing a written description, all ranges disclosed herein also encompass any and all possible subranges and combinations of subranges thereof. Any listed range can be easily recognized as sufficiently describing and enabling the same range being broken down into at least equal halves, thirds, quarters, fifths, tenths, etc. As a non-limiting example, each range discussed herein can be readily broken down into a lower third, middle third and upper third, etc. As will also be understood by one skilled in the art all language such as "up to," "at least," "greater than," "less than," and the like include the number recited and refer to ranges which can be subsequently broken down into subranges as discussed above. Finally, as will be understood by one skilled in the art, a range includes each individual member. Thus, for example, a group having 1-3 atoms refers to groups having 1, 2, or 3 atoms. Similarly, a group having 1-5 atoms refers to groups having 1, 2, 3, 4, or 5 atoms, and so forth.

**[0039]** While certain embodiments have been illustrated and described, it should be understood that changes and modifications can be made therein in accordance with ordinary skill in the art without departing from the invention in its broader aspects as defined in the following claims.

## CLAIMS

WHAT IS CLAIMED IS:

1. A process comprising neutralizing rotigotine heminaphthalene-1,5-disulfonate to give rotigotine base and crystallizing rotigotine base from a solvent selected from the group consisting of an alcohol, ketone, alkane, chlorinated alkane, ether, and combinations of any two or more thereof.

2. The process of claim 1 wherein the alcohol is methanol or ethanol.

3. The process of claim 1 wherein the ketone is selected from the group consisting of acetone and methyl ethyl ketone.

4. The process of claim 1 wherein the chlorinated alkane is selected from the group consisting of dichloromethane and chloroform.

5. The process of claim 1 wherein the ether is selected from the group consisting of diethyl ether and diisopropyl ether.

6. The process of claim 1 wherein the solvent is a combination of a ketone and an alkane.

7. The process of claim 6 wherein the combination of solvents is acetone and heptane or acetone and cyclohexane.

8. The process of claim 1 wherein the rotigotine naphthalene-1,5-disulfonate is neutralized by contacting it with at least one suitable base selected from the group consisting of an alkali metal hydroxide and a carbonate to produce rotigotine free base.

9. The process of claim 8 wherein the suitable base is NaOH or KOH.

10. The process of claim 8 wherein the suitable base is sodium carbonate or potassium carbonate.

FIG. 1.

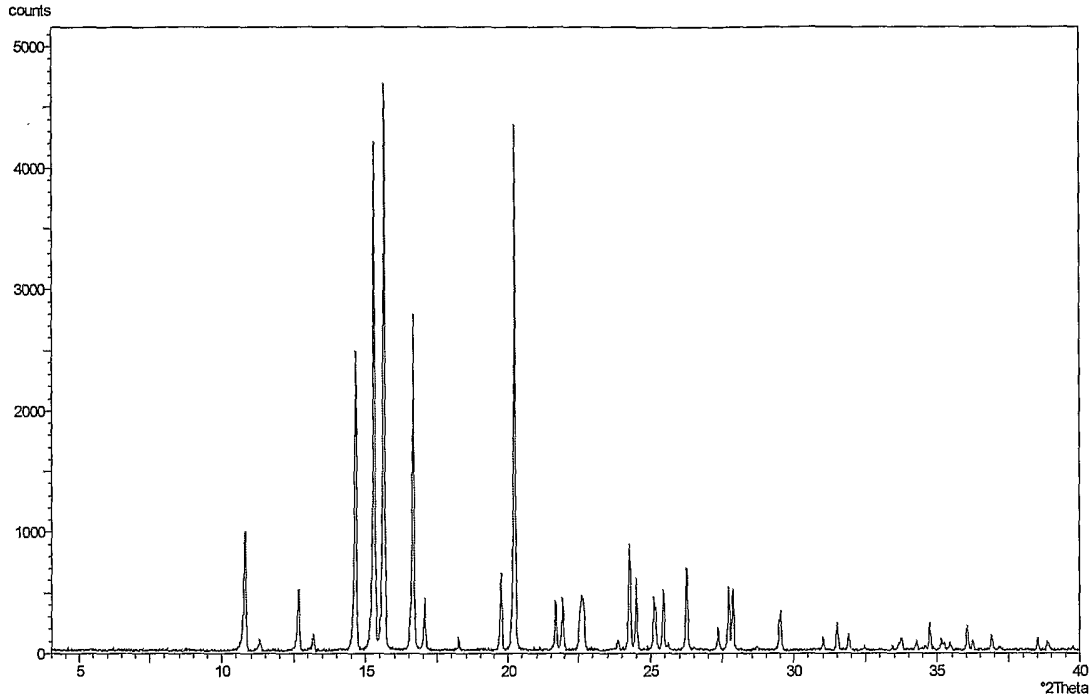

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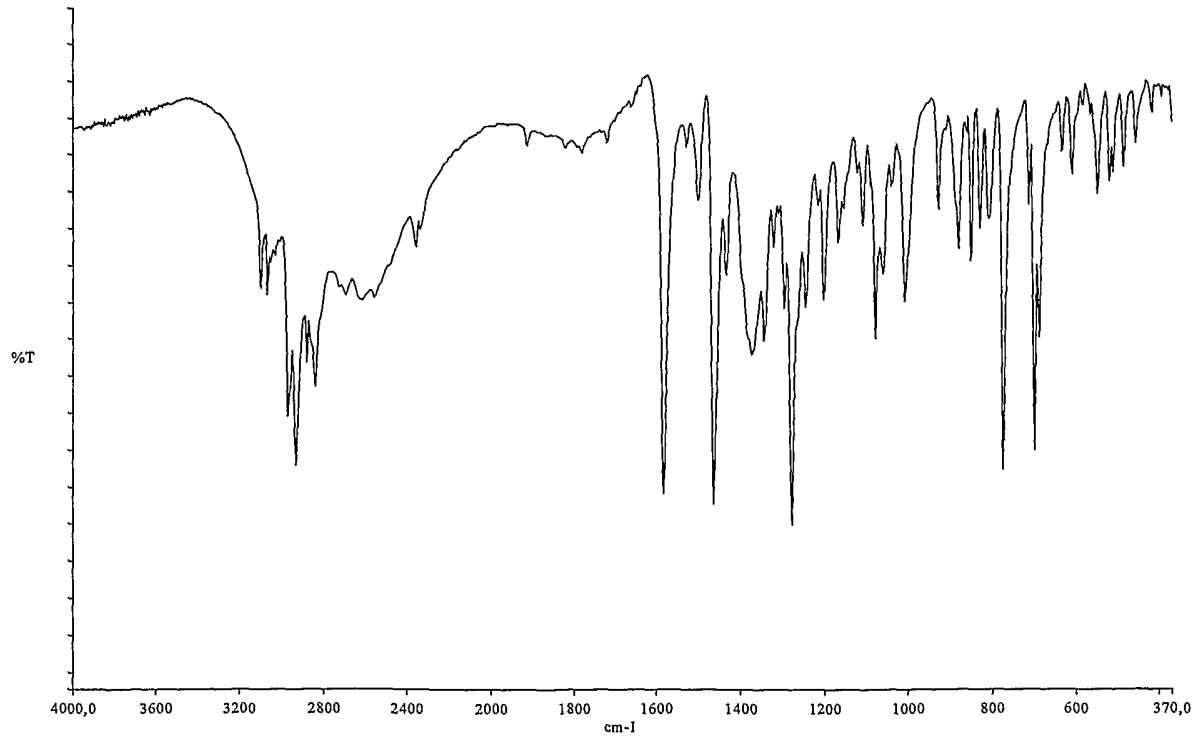
FIG. 2.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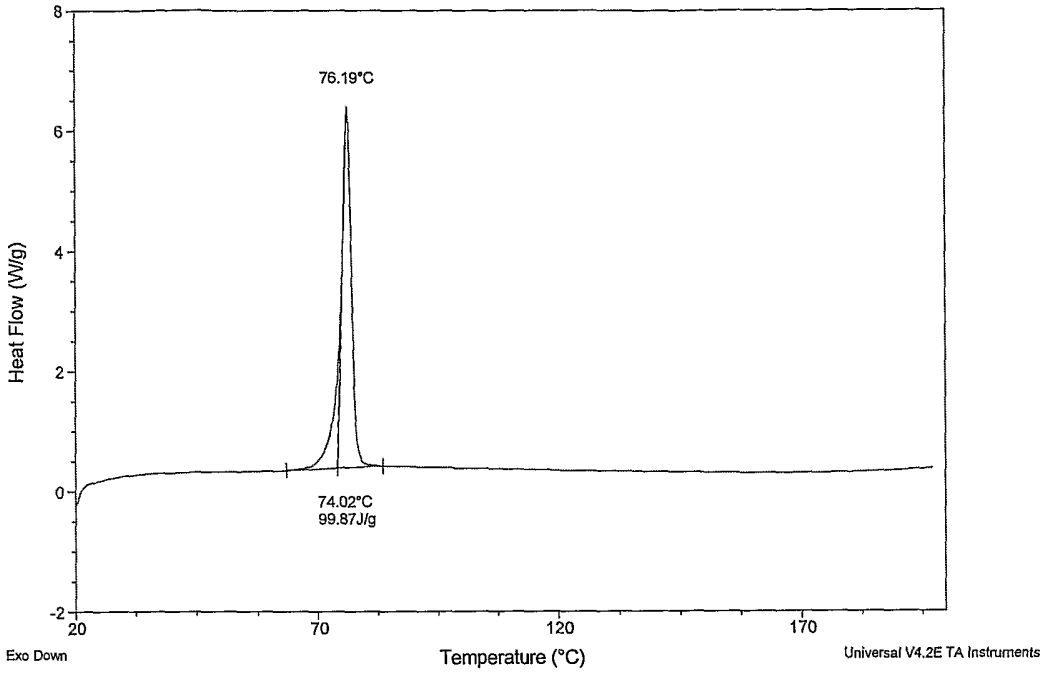
1400
1200
1000
800
600
370,0
cm-1

FIG. 3.


76.19°C
74.02°C
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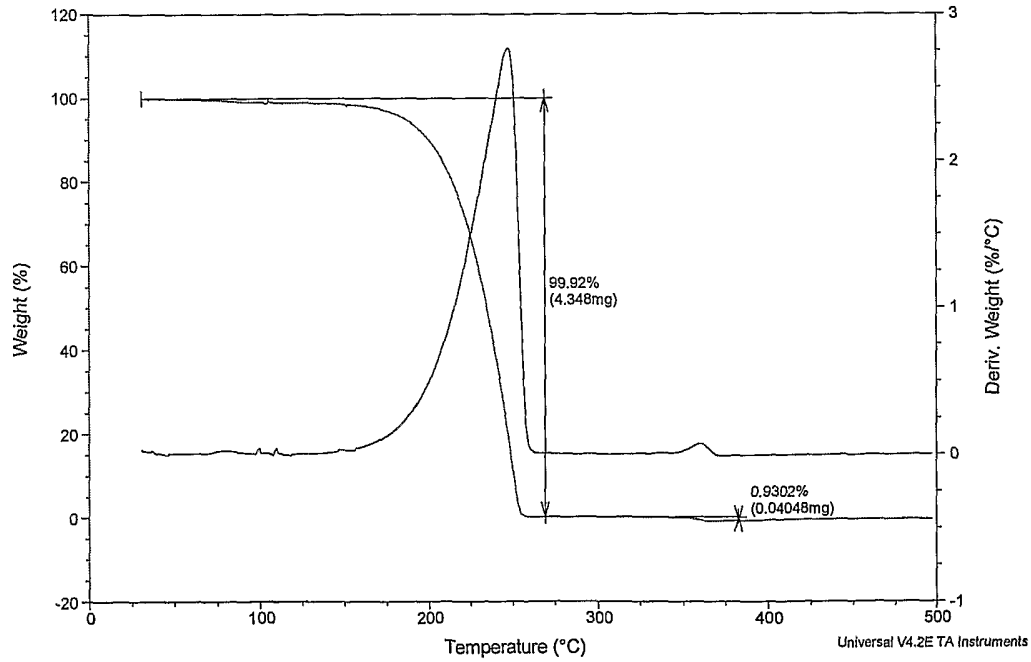
Heat Flow (W/g)
Temperature (°C)
Exo Down
Universal V4.2E TA Instruments

FIG. 4.


99.92%
(4.348mg)
0.9302%
(0.04048mg)
Weight (%)
Deriv. Weight (%/°C)
Temperature (°C)
Universal V4.2E TA Instruments

# INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003729

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D333/20 A61P25/16 A61K31/381

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61P A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

| Category* | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No. |
|---|---|---|
| X | US 4 564 628 A (HORN ALAN S [NL])<br>14 January 1986 (1986-01-14)<br>cited in the application<br>example 2<br>----- | 1-10 |
| X | TIMMERMAN W ET AL: "Microdialysis and striatal dopamine release: stereoselective actions of the enantiomers of N-0437"<br>EUROPEAN JOURNAL OF PHARMACOLOGY, ELSEVIER BV, NL,<br>vol. 162, no. 1,<br>1 January 1989 (1989-01-01), pages 143-150, XP002325505<br>ISSN: 0014-2999<br>paragraph [2.1.]<br>-----<br>-/-- | 1-10 |

[X] Further documents are listed in the continuation of Box C. [X] See patent family annex.

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