

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
22 May 2009 (22.05.2009)

PCT

(10) International Publication Number
WO 2009/063171 A1

(51) International Patent Classification:

C07D 333/20 (2006.01) **A61P 25/16** (2006.01)
A61K 31/381 (2006.01)

(21) International Application Number:

PCT/GB2008/003741

(22) International Filing Date:

6 November 2008 (06.11.2008)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

60/988,587 16 November 2007 (16.11.2007) US

(71) Applicant (for all designated States except US): **PLIVA HRVATSKA d.o.o.** [HR/HR]; Ulica grada Vukovara 49, 10000 Zagreb (HR).

(71) Applicant (for LR only): **BUCKS, Teresa, Anne** [GB/GB]; Boulton Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **AVDAGIC, Amir** [HR/HR]; Gustava Krkleca 24, 10000 Zagreb (HR). **MUNDORFER, Tina** [HR/HR]; Rendiceva 32, 10000 Zagreb (HR). **MARKOVIC, Marina** [HR/HR]; Mrnjaki 2a, 10000 Zagreb (HR). **SILJKOVIC, Zvonimir** [HR/HR]; Stanciceva 11, 10000 Zagreb (HR).

(74) Agents: **BUCKS, Teresa, Anne et al.**; Boulton Wade Tennant, Verulam Gardens, 70 Gray's Inn Road, London WC1X 8BT (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(54) Title: NOVEL ROTIGOTINE SALTS

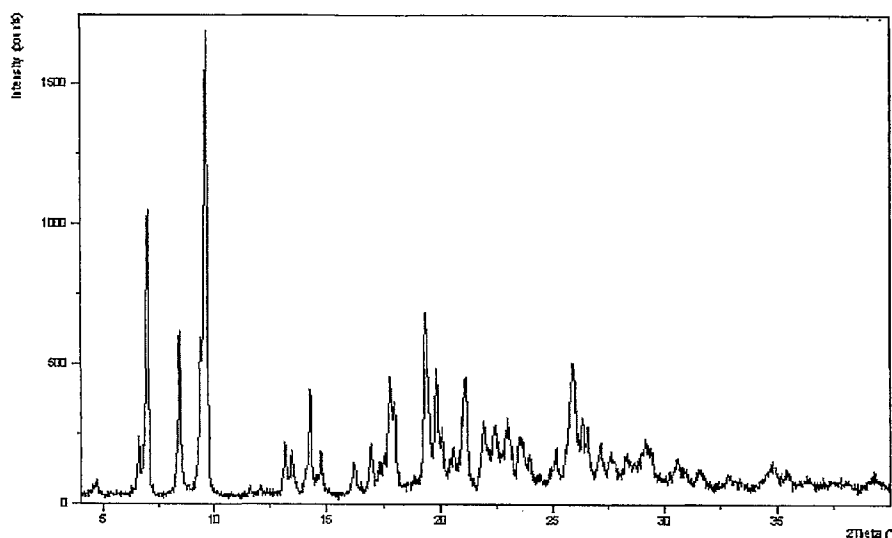


FIG. 1

(57) Abstract: The present invention relates to new salts of N,N-disubstituted aminotetralins, such as rotigotine hydrobromide, *p*-toluenesulfonate, heminaphthalene-1,5-disulfonate, tartrate, and phosphate. Also provided herein are methods of making the new salts and using them for the treatment of diseases that may be prevented, ameliorated or eliminated by the administration of a dopamine D2 receptor agonist or an antiparkinsonian agent.

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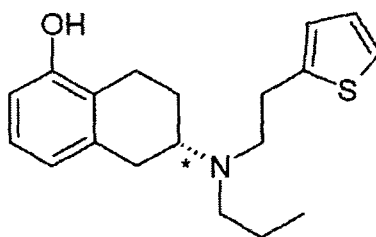
NOVEL ROTIGOTINE SALTS

FIELD OF THE INVENTION

[0001] The invention relates generally to new salt forms of nitrogen-disubstituted (N,N-disubstituted) aminotetralins. More specifically, the invention relates to new salts of rotigotine and processes for preparation and use of such salts in pharmaceutical applications.

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 one aspect, the present invention provides new pharmaceutically acceptable salts of rotigotine in solid form with good yield and high chemical and enantiomeric purity.

Surprisingly, it has been discovered that only a few salt forms of rotigotine are solids at room temperature, while most form oils. Thus, the following compounds, which may be isolated as solids, are disclosed for the first time: (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol hydrobromide, (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol *p*-toluenesulfonate, (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate, (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol tartrate, and (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol phosphate. In particular the formation of such salts allow for ease of manufacture by allowing the preparation and isolation of rotigotine from solution in high yields with good chemical and enantiomeric purity.

[0006] In another aspect, the present invention provides methods for preparing new pharmaceutically acceptable salts of rotigotine in solid form. The methods include contacting rotigotine base with an acid selected from hydrobromic acid, *p*-toluenesulfonic acid, naphthalene-1,5-disulfonic acid, tartaric acid, and phosphoric acid, to form the salt and crystallizing or precipitating the resulting salt from a suitable solvent or combination of solvents. Typically, suitable solvents include organic solvents and solvents including water (i.e., aqueous solvents). In particular, suitable solvents may be selected from an alcohol, ketone, ester, alkane, chlorinated alkane, ether, benzene derivative, water or a mixture of any two or more thereof. For example, the solvent can be selected from acetone, methyl ethyl ketone, cyclohexanone, 3-pentanone, ethyl acetate, *n*-propyl acetate, diethyl ether, diisopropyl ether, methanol, ethanol, propanol, heptane, nitromethane, dichloromethane, chloroform, 1,2-dichloroethane, benzonitrile, methyl benzoate, nitrobenzene, water, or a mixture of any two or more thereof. Preferably, the solvent is acetone, ethyl acetate or a mixture of acetone and isopropanol.

[0007] In another aspect, the invention provides compositions comprising a salt of rotigotine described herein. For example, pharmaceutical compositions may include a salt of rotigotine as described herein and a pharmaceutically acceptable carrier. Transdermal patches including a rotigotine salt as described herein are also provided.

[0008] The invention provides in another aspect, methods of treatment using rotigotine salts described herein. Thus, the methods include administering a rotigotine salt or composition as described herein to a subject suffering from a disease prevented, ameliorated or eliminated by the administration of a dopamine D2 receptor agonist or an antiparkinsonian agent. Such diseases include Parkinson's disease and restless legs syndrome.

BRIEF DESCRIPTION OF THE DRAWINGS

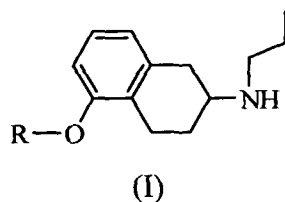
- [0009] FIG. 1 shows an X-ray powder diffraction pattern for rotigotine hydrobromide.
- [0010] FIG. 2 shows an X-ray powder diffraction pattern for rotigotine *p*-toluenesulfonate.
- [0011] FIG. 3 shows an X-ray powder diffraction pattern for rotigotine heminaphthalene-1,5-disulfonate.
- [0012] FIG. 4 shows an X-ray powder diffraction pattern for rotigotine phosphate.
- [0013] FIG. 5 shows an X-ray powder diffraction pattern for rotigotine tartrate.

DETAILED DESCRIPTION

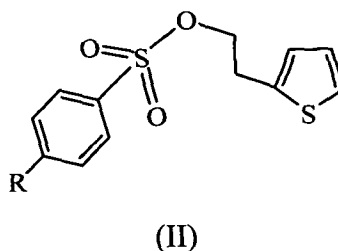
[0014] New solid acid addition salts of rotigotine are provided as well as methods of making and using such salts. Surprisingly, only a few salts of rotigotine may be prepared in solid form, a form advantageous for pharmaceutical usage. Screening of a number of potential salts yielded only the hydrobromide, toluenesulfonate, heminaphthalene-1,5-disulfonate, tartrate and phosphate salts as solids in addition to the known hydrochloride salt. The present salts may be prepared in high purity from rotigotine base, which may be prepared both by known methods (see, e.g., U.S. Patent No. 6,884,434) and by the following methods.

[0015] Processes for the preparation of N,N-disubstituted aminotetralins, specifically, for the preparation of enantiomerically enriched or enantiomerically pure rotigotine as the free base or as a pharmaceutically acceptable acid addition salt are provided herein. In one aspect, the processes include the step of:

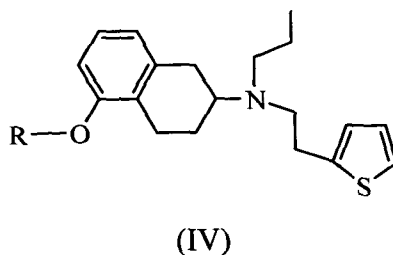
- a) reacting an enantiomerically enriched compound of Formula (I),



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

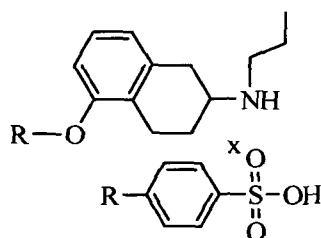


to provide a compound of Formula (IV),



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

[0016] Advantageously, unreacted starting aminotetralin precipitates from the reaction mixture as the salt of Formula (III):



(III)

[0017] Thus, the present processes may further comprise the following step:

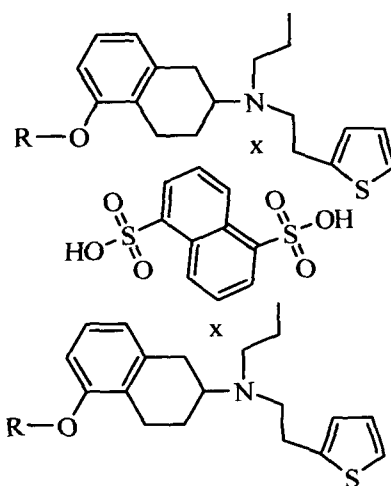
b) filtering the reaction mixture to isolate the precipitate comprising the salt having Formula (III). The filtrate will therefore comprise the product, the compound of Formula (IV).

[0018] 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 (I). 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 (I) to be extracted into an organic solvent such as dichloromethane or the like.

[0019] 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. When R is H, rotigotine heminaphthlene-1,5-disulfonate is produced.

[0020] 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.

[0021] The processes for preparing N,N-disubstituted aminotetralins 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.

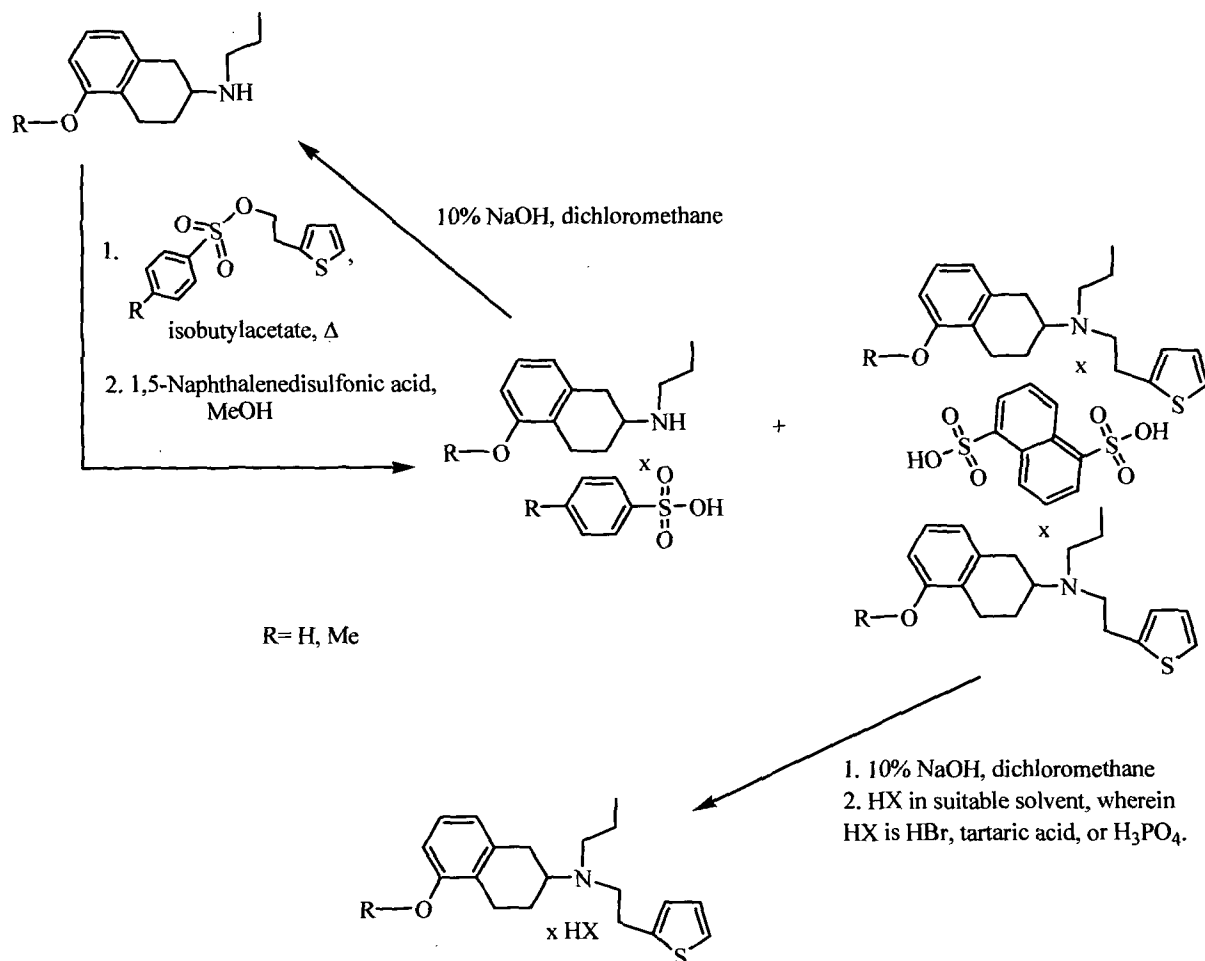
[0022] The free base from step (e) may be converted to a pharmaceutically acceptable salt. Thus, processes of the invention may further include.

f) contacting the enantiomerically enriched or enantiomerically pure compound of Formula (IV) from step (e) with a pharmaceutically acceptable acid and isolating the resulting salt. In some embodiments, the compound is rotigotine and the salt is the hydrochloride, hydrobromide, *p*-toluenesulfonate, heminaphthalene-1,5-disulfonate, tartrate and phosphate salt of rotigotine.

[0023] The synthetic processes described herein possess several advantages over prior art procedures. First, the present methods avoid the use of a large excess of alkylation agent, which is commonly greater than three-fold molar excess with respect to the starting 2-aminotetralins. Not only is this cheaper and more efficient, but extensive purification of the final product is avoided, thus simplifying the procedure. Second, the present methods avoid the use of temperatures higher than 120 °C for prolonged periods of time and thus avoid increased amounts of impurities that are problematic to remove from the final product. Finally, the unreacted starting material is readily recovered in a salt form that simplifies workups and subsequent purification of the product, which remains in the filtrate after the reaction.

[0024] Thus, in certain embodiments, the processes of the invention may be represented as in Scheme I.

Scheme I



[0025] In another aspect, the invention provides compositions comprising a salt of rotigotine described herein. For example, pharmaceutical compositions may include a salt of rotigotine as described herein and a pharmaceutically acceptable carrier. Transdermal patches including a rotigotine salt as described herein are also provided. In some embodiments of the compositions and transdermal patches, the rotigotine salt is present in a therapeutically effective amount for treating a disease that may be prevented, ameliorated, or eliminated by administration of a dopamine D2 receptor agonist or antiparkinsonian agent, e.g., Parkinson's disease. Methods of preparation or construction of a transdermal formulation, including with suitable excipients are known in the art, e.g., see US 6,884,434 or WO 94/07468.

In yet another aspect, the invention provides pharmaceutical formulations comprising a therapeutically effective amount of rotigotine, as described above, or a mixture of any two or more thereof, preferably in the form of a transdermal patch. The use of the salts of rotigotine in

transdermal formulations may benefit from the addition of a pharmaceutically acceptable base in the preparation of the transdermal patch to aid the formation of the free base *in situ*. In the transdermal patch rotigotine can be used as rotigotine in the salt forms as described above, or as rotigotine free base. If rotigotine free base is used then either the free base of rotigotine is added, after being formed directly prior to addition to the formulation from the rotigotine salt forms described above, or converted to the free base *in situ* during the preparation of the transdermal patch by adding a pharmaceutically acceptable base, such as potassium hydroxide or sodium hydroxide, such as described in US 6,884,434.

[0026] The invention provides in another aspect, methods of treatment using rotigotine salts described herein. Thus, the methods include administering a rotigotine salt or composition as described herein to a subject suffering from a disease prevented, ameliorated or eliminated by the administration of a dopamine D2 receptor agonist or an antiparkinsonian agent. Such diseases include Parkinson's disease and restless legs syndrome.

Definitions of terms used herein are provided below.

[0027] 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%.

[0028] 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%.

[0029] As used herein, benzene derivatives useful as solvents include organic solvents having one or more phenyl groups such as benzene, toluene, xylene, halogenated benzenes (e.g., chlorobenzene), benzonitrile, nitrobenzene, methyl benzoate, and the like.

[0030] 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.

[0031] 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 – Synthesis of (S)-6-(Propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate

[0032] (-)-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 when 1.91 g (5.30 mmol) of 1,5-naphthalenedisulfonic acid was added, and 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, 43.2% yield based on starting 2-aminotetralin) of (S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate.

Example 2 – Synthesis of (-)-5-Hydroxy-N-(n-propyl)-2-aminotetralin

[0033] 2.62 g (6.96 mmol) of (-)-5-hydroxy-N-n-propyl-2-aminotetralin toluenesulfonate was suspended in a mixture of 10% NaOH (30 mL) and dichloromethane (30). The mixture was stirred for 30 minutes; the organic layer was separated, and the aqueous layer was washed again with dichloromethane (30 mL). The combined organic layers were dried with Na₂SO₄, filtered and evaporated to yield 1.41 g (6.87 mmol) of (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (rotigotine base).

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

[0034] The free base of rotigotine, (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (50 mg), was dissolved in acetone (2 mL) at room temperature. To the clear solution HBr acid (8,6µL) was added drop wise. The solution was stirred at room temperature overnight and EtOAc (1 mL) was

added drop wise without crystallization. Solvent was partially removed under reduced pressure and crystallization occurred. The resulting product was collected by filtration; 35 mg of white crystalline product was obtained and analyzed by X-ray powder diffraction (XRPD) (FIG. 1). Characteristic diffraction peak positions 2θ : (6.6, 7.0, 8.5, 9.4, & 9.7 ± 0.2 and further characterized by 4.7, 11.6, 12.1, 13.2 & 14.3 ± 0.2)

Example 4 - Synthesis of (S)-6-(Propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol *p*-toluenesulfonate

[0035] The free base of rotigotine, (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (50 mg) was dissolved in EtOAc (2 mL) at room temperature. To the clear solution *p*-toluenesulphonic monohydrate acid (30 mg) was added to give a hazy solution. The solution was stirred at room temperature overnight to provide a white crystalline product. The product was collected by filtration to give 22 mg of white crystals that were analyzed by XRPD (FIG. 2). Characteristic diffraction peak positions 2θ : (6.8, 9.4, 10.4, 12.2, 13.6, & 17.8 ± 0.2 and further characterized by 8.5, 11.1, 12.8, 13.9 & 16.6 ± 0.2).

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

[0036] The free base of rotigotine, (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (0.60 g) was dissolved in a mixture of acetone and isopropanol. To the solution, 0.35 g of 1,5-naphthalenedisulfonic acid was added at 60°C, and the resulting mixture was cooled and stirred at room temperature for 20 hours. The product was filtered, washed with 2-PrOH (8 mL) and dried under reduced pressure to yield 0.56 g of (S)-6-(propyl-(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate. The product was analyzed by XRPD (FIG. 3). Characteristic diffraction peak positions 2θ : (5.6, 9.1, 10.3, 14.8 & 16.6 ± 0.2 and further characterized by 8.7, 11.1, 13.8, 15.2 & 17.4 ± 0.2).

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

[0037] The free base of rotigotine, (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (50 mg) was dissolved in acetone (2 mL) at room temperature. To the clear solution, H_3PO_4 (9.1 μL) was added drop-wise. The solution was stirred at room temperature overnight and EtOAc (1 mL) was added drop-wise without crystallization. Solvent was removed under reduced pressure and oily

product was obtained. Oily product was dissolved in EtOAc (3 mL) and crystallization occurred while stirring in ice bath. Obtained product was collected by filtration; 53 mg of off white product was obtained and analyzed by XRPD (FIG. 4). Amorphous product was obtained.

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

[0038] The free base of rotigotine, (-)-5-hydroxy-N-(n-propyl)-2-aminotetralin (50 mg) was dissolved in 2 ml of acetone at room temperature. To the clear solution, tartaric acid (24 mg) was added. The solution was stirred at room temperature overnight and 1 mL of EtOAc was added drop wise without crystallization. Solvent was partially removed under reduced pressure and crystallization occurred. Obtained product was collected by filtration; 10 mg of white product was obtained and analyzed by XRPD (FIG. 5). Characteristic diffraction peak positions 2θ (8.5, 9.6, 9.9, 14.5 & 18.0 ± 0.2 and further characterized by 4.8, 7.0, 13.2, 14.8 & 16.6 ± 0.2).

[0039] 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.

[0040] 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 compound selected from the group consisting of
(S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol hydrobromide,
(S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol *p*-toluenesulfonate,
(S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol heminaphthalene-1,5-disulfonate,
(S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol tartrate, and
(S)-6-(propyl(2-thiophen-2-yl)ethyl)amino)-5,6,7,8-tetrahydronaphthalen-1-ol phosphate.
2. A method of preparing a compound of claim 1 comprising contacting rotigotine base with an acid selected from the group consisting of hydrobromic acid, *p*-toluenesulfonic acid, naphthalene-1,5-disulfonic acid, tartaric acid, and phosphoric acid, to form the corresponding rotigotine salt and crystallizing or precipitating the rotigotine salt from a suitable solvent or combination of solvents.
3. The method of claim 2 wherein the solvent is selected from an alcohol, ketone, ester, alkane, chlorinated alkane, ether, benzene derivative, water or a mixture of any two or more thereof.
4. The method of claim 3 wherein the solvent is selected from acetone, methyl ethyl ketone, cyclohexanone, 3-pentanone, ethyl acetate, *n*-propyl acetate, diethyl ether, diisopropyl ether, methanol, ethanol, propanol, heptane, nitromethane, dichloromethane, chloroform, 1,2-dichloroethane, bezonitrile, methyl benzoate, nitrobenzene, water, or a mixture of any two or more thereof.
5. The method of claim 2 wherein the solvent is selected from acetone, ethyl acetate or a mixture of acetone and isopropanol.
6. The method of any one of claims 2-5 wherein the solvent comprises water.
7. A composition comprising a compound of claim 1 and a pharmaceutically acceptable carrier.
8. A transdermal patch comprising a compound of claim 1.

9. A method comprising administering the compound of claim 1 to a subject suffering from a disease prevented, ameliorated or eliminated by the administration of a dopamine D2 receptor agonist or an antiparkinsonian agent.
10. The method of claim 9 wherein the disease is Parkinson's disease.
11. A method comprising administering the composition of claim 7 or 8 to a subject suffering from a disease prevented, ameliorated or eliminated by the administration of a dopamine D2 receptor agonist or an antiparkinsonian agent.
12. The method of claim 11 wherein the disease is Parkinson's disease.

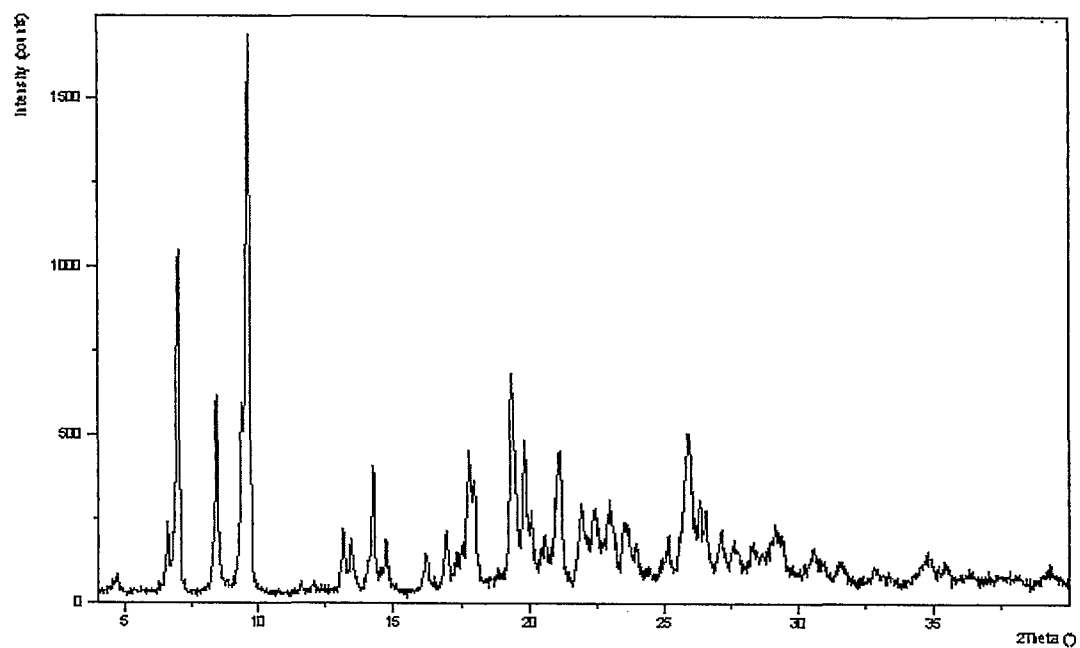


FIG. 1

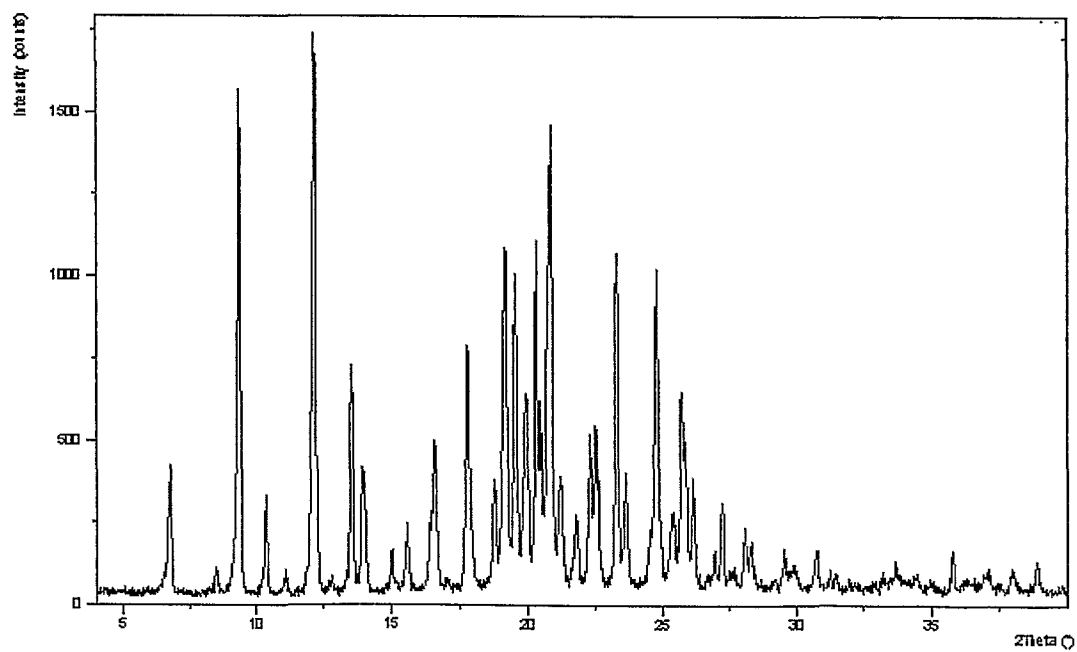


FIG. 2

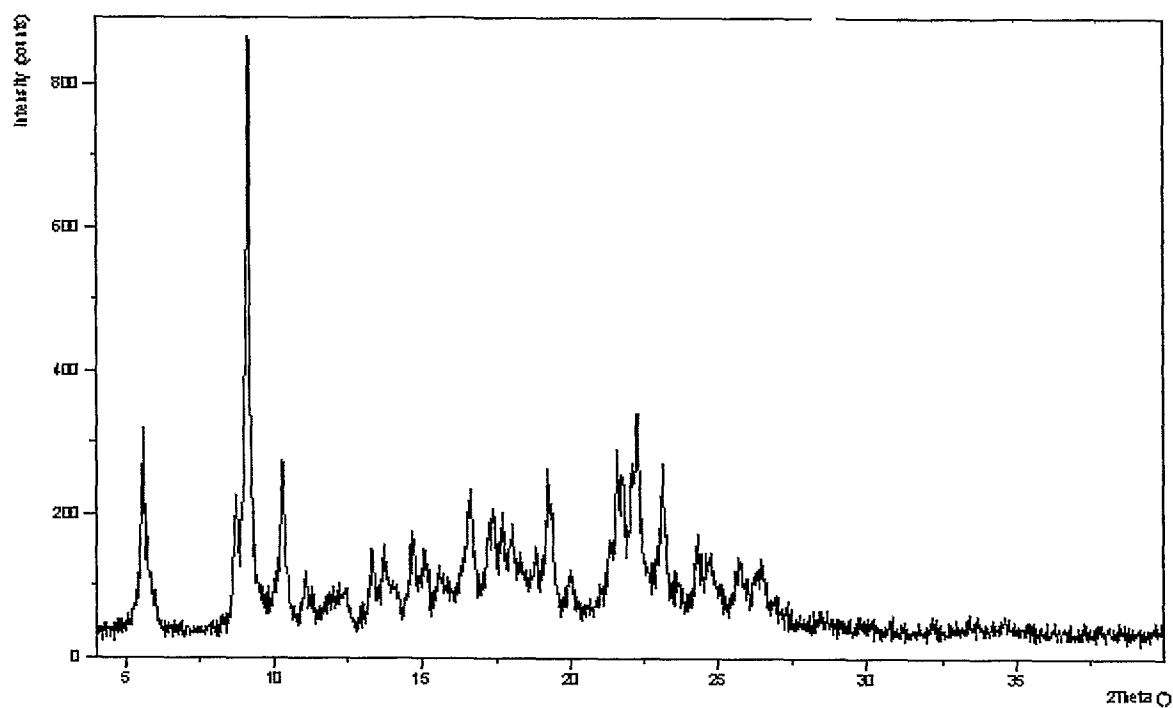


FIG. 3

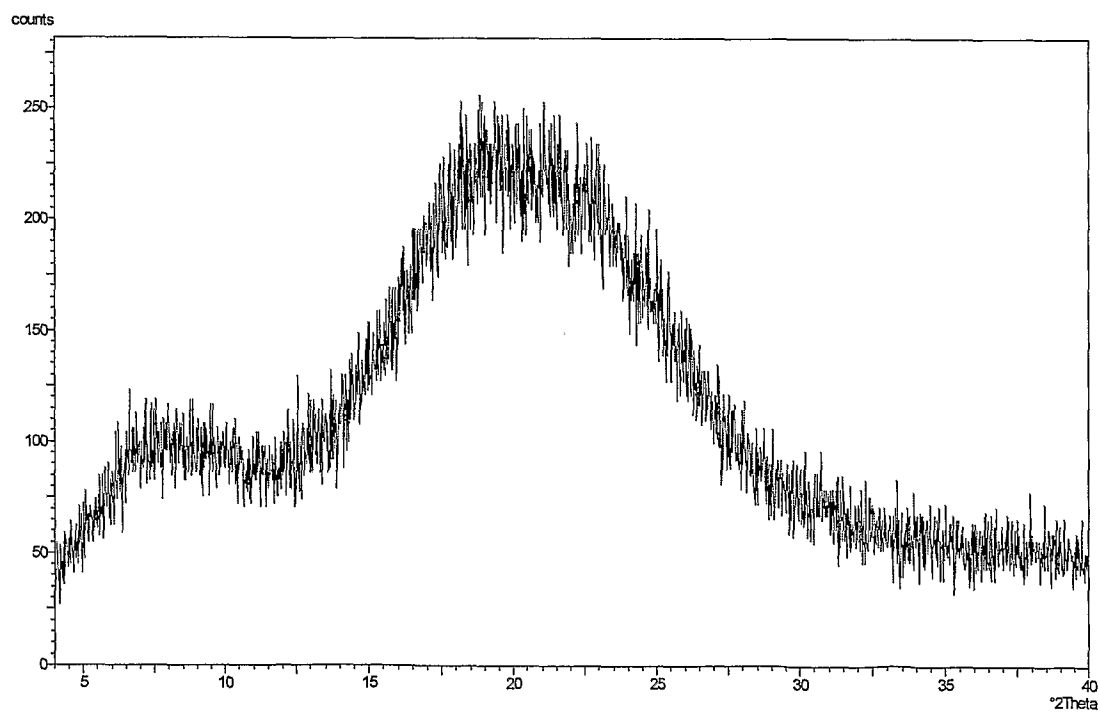


FIG. 4

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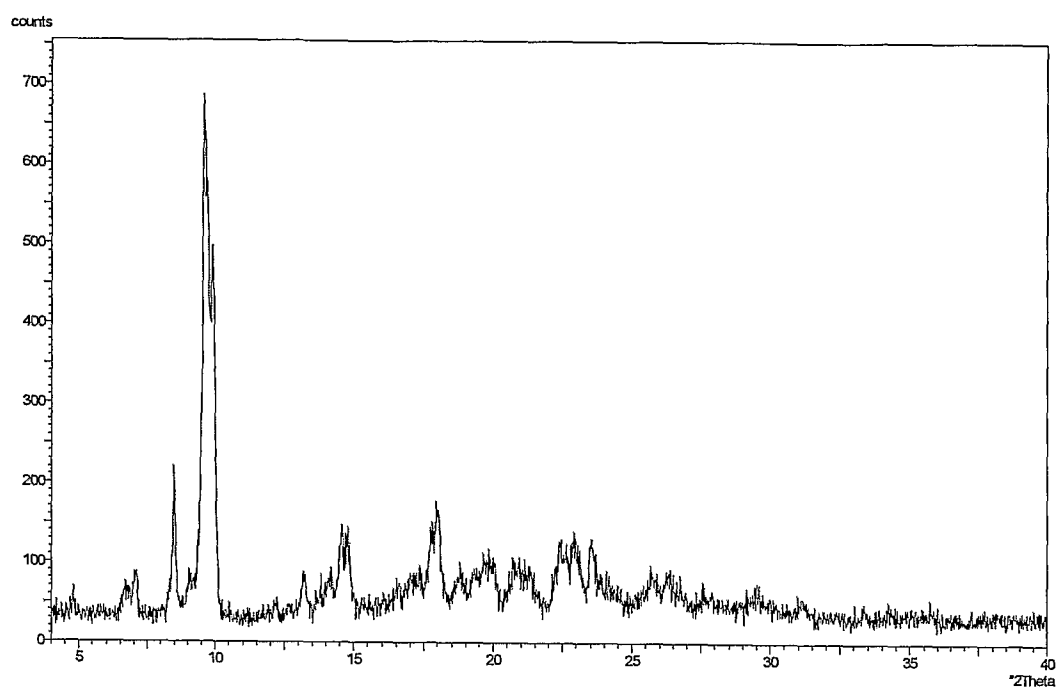


FIG. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB2008/003741

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D333/20 A61K31/381 A61P25/16

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 A61K A61P

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, BEILSTEIN 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 02/15903 A (SANOL ARZNEI SCHWARZ GMBH [DE]; RIMPLER STEPHAN [DE]; GRAPATIN SABINE) 28 February 2002 (2002-02-28) page 6, line 30 - page 7, line 3	1,7,9-12
X	US 6 884 434 B1 (MULLER WALTER [DE] ET AL) 26 April 2005 (2005-04-26) cited in the application examples 3-7	8-12
A	US 4 564 628 A (HORN ALAN S [NL]) 14 January 1986 (1986-01-14) column 7 - column 8; examples I-IV	1,7,9-12
A	STAHL ET AL.: "Salt selection" "POLYMORPHISM", 22 May 2006 (2006-05-22), pages 309-332, XP002514558 page 319; table 12.2	2-6



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

17 February 2009

Date of mailing of the international search report

06/05/2009

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Lewis, Sara

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB2008/003741

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.:
because they relate to subject matter not required to be searched by this Authority, namely:
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:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers allsearchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an 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 reportcovers 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.:

1-12 (part)

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.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-12 (part)

Hydrobromide salt of (S)-rotigotine base and the corresponding processes for its preparation, compositions and uses;

2. claims: 1-12 (part)

p-Toluenesulfonate salt of (S)-rotigotine base and the corresponding processes for its preparation, compositions and uses;

3. claims: 1-12 (part)

Heminaphthalene-1,5-disulfonate salt of (S)-rotigotine base and the corresponding processes for its preparation, compositions and uses;

4. claims: 1-12 (part)

Tartrate salt of (S)-rotigotine base and the corresponding processes for its preparation, compositions and uses;

5. claims: 1-12 (part)

Phosphate salt of (S)-rotigotine base and the corresponding processes for its preparation, compositions and uses.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/GB2008/003741

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