

**5,6,7,8-TETRAHYDRO-6-[N,N-BIS[(2-THIENYL)ETHYL]]AMINO-1-NAPHTHOL,
AND PREPARING METHOD AND USE THEREOF**

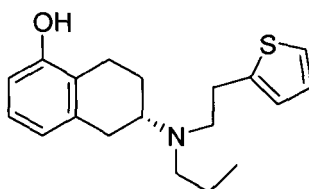
FIELD

5 The present disclosure belongs to the medical field, and more particularly relates to a reference compound for determining impurities in rotigotine or a preparation thereof, as well as method for preparing the same.

BACKGROUND

10 Parkinson's disease is a common degenerative disease of the nervous system for the middle-aged and elderly. Dopamine receptor agonist is an important class of drugs used in treating Parkinson's disease. Currently, the dopamine receptor agonist in clinical use comprises dopamine agonist drugs such as rotigotine, pramipexole, ropinirole, pergolide, and cabergoline, etc.

15 Rotigotine, (S)-5,6,7,8-tetrahydro-6-[propyl[2-(2-thienyl)ethyl]amino]-1-naphthol, is represented by a molecular formula of $C_{19}H_{25}NO$ and has the following structure. In May 2007, the U.S. FDA approved its listing under the trade name NeuPro for the adjuvant treatment of early secondary Parkinson's disease and advanced Parkinson's disease.



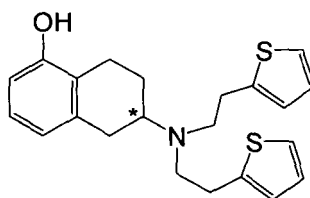
20 An impurity of a drug refers to a substance in the drug, which has no therapeutic effect but may influences the stability or efficacy of the drug, even may be harmful to human health. The source of the impurities mainly comprises the followings: firstly, the impurities that might have been introduced during the production process, including unreacted starting materials, chemical derivatives of impurities contained in the starting materials, synthesis by-products and degradation products; and secondly, the impurities that might have been produced during storage
25 when the drug physicochemical properties changed due to the external conditions. Adverse reactions produced in clinical use, in addition to being attributable to the pharmacological activity of the drug itself, sometimes may also be related to impurities present in the drug.

Therefore, normative research on the impurity is directly related to the quality and safety of marketed drugs.

By understanding the chemical structure and synthetic pathway of the impurities and by identifying the parameters which affect the content of impurities in the end product, management of impurities in medicinal active substance may be greatly enhanced. To monitor the impurities in the medicinal active substance, it is required to establish a quality standard to determine suitable separation and detection conditions, so as to control the impurities well. In the quality standard, the currently widely used impurity detection methods mainly comprise high performance liquid chromatography (HPLC) and like.

SUMMARY

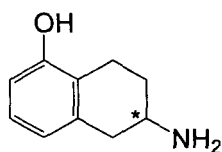
In one embodiment, the present disclosure provides a new, isolated compound as a reference compound for determining an impurity in rotigotine or a preparation thereof. The reference compound has a chemical name of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol and is represented by formula (I):



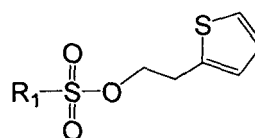
compound of formula (I)

in which (*) represents a chiral center, and the compound of formula (I) is a R or S configuration or a racemic mixture.

The compound of formula (I) may be prepared by the following method, which comprises: reacting a compound of formula (II) with a compound of formula (III), and purifying the resulting compound of formula (I),



compound of formula (II)



compound of formula (III)

in which the compound of formula (II) is a R or S configuration or a racemic mixture, and R₁ is methyl, trifluoromethyl, methylphenyl or nitrophenyl, preferably 4-methylphenyl or 4-nitrophenyl, more preferably 4-methylphenyl.

The compound of formula (I) may be used as a reference compound for qualitatively or quantitatively determining an impurity in rotigotine or a preparation thereof, particularly, by high pressure liquid chromatography analysis. The compound of formula (I) is dissolved in a solution to prepare a reference solution. Rotigotine or the preparation thereof is dissolved in a solution to prepare a test solution. HPLC chromatograms of the reference solution and the test solution are obtained by high pressure liquid chromatography analysis respectively. The retention time in the HPLC chromatograms of the reference solution and the test solution are compared to determine the test solution contains the compound of formula (I). More specifically, the peak areas of the compound of formula (I) in the HPLC chromatograms of the reference solution and the test solution are compared, and the content of the compound of formula (I) in rotigotine or the preparation thereof in weight percent is determined by an external standard method.

In various embodiments, the isolated compound of formula (I) has a purity of at least 95%, preferably, the isolated compound of formula (I) has a purity of at least 98%; and more preferably, the isolated compound of formula (I) is free of any other compounds or impurities.

In a further embodiment, the present disclosure also provides a high-purity rotigotine, containing the compound of formula (I) in an amount less than 0.5 weight percent.

BRIEF DESCRIPTION OF THE DRAWINGS

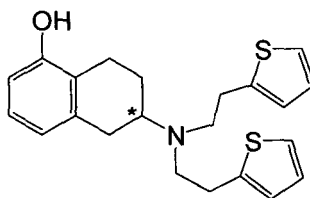
Fig.1 is a high resolution mass spectrum of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol.

Fig. 2-1 is an HPLC chromatogram of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol.

Fig. 2-2 is an HPLC chromatogram of rotigotine.

DETAILED DESCRIPTION

One embodiment of the present disclosure provides a compound of formula (I):

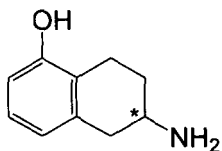


compound of formula (I)

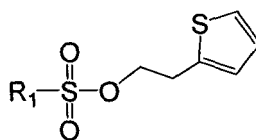
wherein (*) represents a chiral center, and the compound of formula (I) is a R or S configuration or a racemic mixture.

5 In a further embodiment, the compound as used herein is isolated, i.e., the compound is at least 80%, preferably at least 90%, even more preferably at least 95%, and most preferably at least 99% pure, as judged by GC or HPLC.

Another embodiment of the present disclosure provides a method for preparing a compound of formula (I), comprising: reacting a compound of formula (II) with a compound of formula
10 (III),



compound of formula (II)



compound of formula (III)

wherein the compound of formula (II) is a R or S configuration or a racemic mixture, and R₁ is methyl, trifluoromethyl, methylphenyl or nitrophenyl; and purifying the compound of
15 formula (I).

In one preferred embodiment of the present disclosure, R₁ is 4-methylphenyl or 4-nitrophenyl.

In another preferred embodiment of the present disclosure, R₁ is 4-methylphenyl.

Another embodiment of the present disclosure provides the use of a compound of formula (I)
20 as a reference compound for determining an impurity in rotigotine or a preparation thereof.

A further embodiment of the present disclosure provides a method for determining the content of an impurity in rotigotine or a preparation thereof by high pressure liquid chromatography analysis, wherein the compound of formula (I) is used as a reference compound, comprising: preparing a reference solution of the compound of formula (I) in a pre-determined
25 concentration; preparing a test solution containing rotigotine or a preparation thereof; obtaining HPLC chromatograms of the reference solution and the test solution by high pressure liquid chromatography analysis respectively; comparing respective retention times in the HPLC

chromatograms of the reference solution and the test solution to ascertain that the test solution contains the compound of formula (I); and determining the content of the compound of formula (I) in rotigotine or the preparation thereof in weight percentage by an external standard method.

Yet another embodiment of the present disclosure provides a high-purity rotigotine, comprising rotigotine and a compound of formula (I) in an amount less than 0.5 weight percent.

EXAMPLES

The present disclosure will be further illustrated by the following examples and test examples, which will not limit the scope of the present invention in any way.

Example 1

Preparation of 5,6,7,8-Tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol

5.0 g of 5,6,7,8-tetrahydro-6-amino-1-naphthol, 3.0 g of 2-(2-thienyl)ethyl 4-methylbenzenesulfonate, 4.8 g of sodium carbonate and 100 ml of xylene were mixed to form a mixture, and the mixture was refluxed for 48 h. The mixture was cooled to room temperature, and washed with an appropriate amount of water. Active carbon was added to decolorize the mixture. The mixture was filtered and left standing. An organic phase was reserved and concentrated under vacuum to obtain a residue. The residue was purified by column chromatography to obtain 1.7 g of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol. Attributions of nuclear magnetic resonance (NMR) spectra of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol were shown in Table 1. A high resolution mass spectrum of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol was shown in Fig. 1.

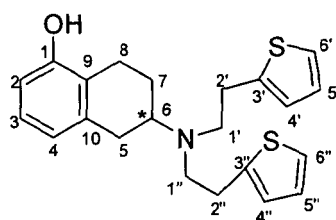
Table 1 Attributions of NMR Spectra of

5,6,7,8-Tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol

No.	¹ H-NMR	¹³ C-NMR	No.	¹ H-NMR	¹³ C-NMR
1	-----	153.4	2'	2.55	25.3
2	6.65	111.7	3'	-----	142.6
3	6.95	126.1	4'	6.80	124.4
4	6.52	121.4	5'	6.92	126.8
5	3.04, 2.79	32.5	6'	7.11	123,3

6	2.74	69.6	1''	2.74	56.7
7	1.57, 1.81	30.1	2''	2.55	25.7
8	2.85, 2.88	23.6	3''	-----	142.6
9	-----	122.7	4''	6.80	124.7
10	-----	138.2	5''	6.92	126.6
1'	2.74	52.5	6''	7.11	123,4

The numbering of the carbon atoms in the NMR structure of
 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol were as follows:



5 Example 2

Preparation of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol

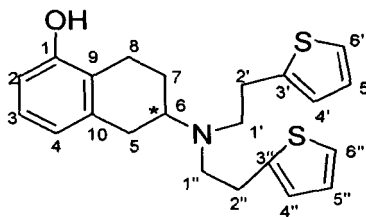
5.0 g of (S)-5,6,7,8-tetrahydro-6-amino-1-naphthol, 3.0 g of 2-(2-thienyl)ethyl
 4-methylbenzenesulfonate, 4.8 g of sodium carbonate and 100 ml of xylene were mixed to form
 a mixture, and the mixture was refluxed for 48 h to 50 h. The mixture was cooled to room
 temperature, and washed with an appropriate amount of water. Active carbon was added to
 decolorize the mixture. The mixture was filtered and left standing. An organic phase was
 reserved and concentrated under vacuum to obtain a residue. The residue was purified by column
 chromatography to obtain 1.7 g of
 (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol. Attributions of nuclear
 magnetic resonance (NMR) spectra of
 (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol were shown in Table 2.

Table 2 Attributions of NMR Spectra of

(S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol					
No.	¹ H-NMR	¹³ C-NMR	No.	¹ H-NMR	¹³ C-NMR
1	-----	153.5	2'	2.56	25.6
2	6.66	111.9	3'	-----	142.9
3	6.97	126.4	4'	6.80	124.6
4	6.56	121.6	5'	6.91	126.6

5	3.04, 2.79	32.3	6'	7.11	123,3
6	2.74	67.9	1''	2.75	56.9
7	1.57, 1.83	30.1	2''	2.56	25.7
8	2.85, 2.90	23.5	3''	-----	142.9
9	-----	122.9	4''	6.80	124.6
10	-----	138.2	5''	6.91	126.6
1'	2.75	52.7	6''	7.11	123,3

The numbering of the carbon atoms in the NMR structure of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol were as follows:



Example 3

5 Preparation of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol

5.0 g of (S)-5,6,7,8-tetrahydro-6-amino-1-naphthol, 3.3 g of 2-(2-thienyl)ethyl 4-methylbenzenesulfonate, 4.8 g of sodium carbonate and 100 ml of xylene were mixed to form a mixture, and the mixture was refluxed for 48 h to 50 h. The mixture was cooled to room temperature, and washed with an appropriate amount of water. Active carbon was added to decolorize the mixture. The mixture was filtered and left standing. An organic phase was reserved and concentrated under vacuum to obtain a residue. The residue was purified by column chromatography to obtain 1.5 g of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol.

Example 4

15 Preparation of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol

5.0 g of (S)-5,6,7,8-tetrahydro-6-amino-1-naphthol, 2.2 g of 2-(2-thienyl)ethyl methanesulfonate, 4.8 g of sodium carbonate and 100 ml of xylene were mixed to form a mixture, and the mixture was refluxed for 48 h to 50 h. The mixture was cooled to room temperature, and washed with an appropriate amount of water. Active carbon was added to decolorize the mixture. The mixture was filtered and left standing. An organic phase was reserved and concentrated under vacuum to obtain a residue. The residue was purified by column chromatography to obtain 1.3 g of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol.

Test Example 1**Use of 5,6,7,8-Tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol as Reference Compound for Determining the Content of Impurity in Rotigotine****Sample Preparation:**

5 An appropriate amount of rotigotine was weighed and dissolved in an acetonitrile-0.05% methanesulfonic acid solution (20:80) to prepare a solution with a concentration of 1 mg/ml as a test solution. An appropriate amount of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol was weighed precisely and dissolved in an acetonitrile-0.05% methanesulfonic acid solution (20:80) to prepare a solution, 10 which was diluted quantitatively to prepare a solution with a concentration of 0.001 mg/ml as a reference solution.

Chromatographic Condition:

Stearyl bonded silica was used as a filler. A 0.05% methanesulfonic acid solution (0.5 ml of methanesulfonic acid was taken and diluted with water to 1000 ml) was used as a mobile phase 15 A, acetonitrile/0.05% methanesulfonic acid (0.5 ml of methanesulfonic acid was taken and diluted with acetonitrile to 1000 ml) was used as a mobile phase B, and gradient elution was carried out according to the following table. The column temperature was 30°C. The detection wavelength was 220 nm. Theoretical plate number calculated by the rotigotine peak should not be less than 5000. 10 µl of the reference solution and 10 µl of the test solution were taken and 20 injected into a high performance liquid chromatograph respectively.

Mobile Phase Gradient

Time (min)	Mobile PhaseA (%)	Mobile PhaseB (%)
0-2	95	5
35	40	60
35-38	40	60

Figs. 2-1 and 2-2 are HPLC chromatograms of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol and rotigotine respectively. As calculated by the external standard method, in each of 3 batches of rotigotine, the content of 5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol was lower than 0.5% in weight 25 percent.

Test Example 2

**Use of (S)-5,6,7,8-Tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol as
Reference Compound for Determining the Content of Impurity in Preparation
of Rotigotine Microspheres**

Sample Preparation:

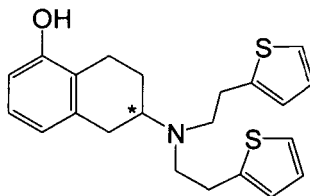
- 5 An appropriate amount of a rotigotine sustained release microspheres (equivalent to about 10 mg of rotigotine) were taken, weighed precisely and placed in a 10 ml volumetric flask. 5 ml of acetonitrile was added to dissolve the rotigotine to prepare a solution, which was diluted with a 0.01 mol/L hydrochloric acid solution to the scale so as to prepare a 10 ml solution of rotigotine. The 10 ml solution of rotigotine was shaken up and placed in a centrifuge tube. The
10 centrifugal tube was centrifuged at a rotation speed of 13000 revolutions per minute for 5 minutes. The supernatant was taken and used as a test solution. An appropriate amount of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]]amino-1-naphthol was weighed precisely and dissolved in an acetonitrile-0.05% methanesulfonic acid solution (20:80) to prepare a solution, which was diluted quantitatively to prepare a solution with a concentration of 0.005 mg/ml as a
15 reference solution.

Chromatographic Condition: the same as that in Test Example 1

As calculated by the external standard method, in each of 3 batches of rotigotine microspheres, the content of (S)-5,6,7,8-tetrahydro-6-[N,N-bis[(2-thienyl)ethyl]] amino-1-naphthol was lower than 0.5% in weight percent.

WHAT IS CLAIMED IS:

1. A compound of formula (I):

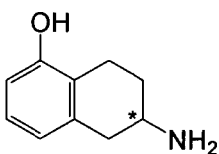


compound of formula (I)

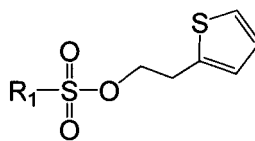
wherein (*) represents a chiral center, and the compound of formula (I) is a R or S configuration or a racemic mixture.

2. A method for preparing a compound of formula (I) of claim 1, comprising:

reacting a compound of formula (II) with a compound of formula (III),



compound of formula (II)



compound of formula (III)

wherein the compound of formula (II) is a R or S configuration or a racemic mixture, and R_1 is methyl, trifluoromethyl, methylphenyl or nitrophenyl; and purifying the compound of formula (I).

3. The method of claim 2, wherein R_1 is 4-methylphenyl or 4-nitrophenyl.

4. The method of claim 3, wherein R_1 is 4-methylphenyl.

5. Use of a compound of formula (I) of claim 1 as a reference compound for determining an impurity in rotigotine or a preparation thereof.

6. A method for determining the content of an impurity in rotigotine or a preparation thereof by high pressure liquid chromatography analysis, wherein the compound of claim 1 is used as a reference compound.

7. The method of claim 6, comprising:

preparing a reference solution of the compound of formula (I) in a pre-determined concentration;

preparing a test solution containing rotigotine or a preparation thereof;

obtaining HPLC chromatograms of the reference solution and the test solution by high pressure liquid chromatography analysis respectively;

5 comparing respective retention times in the HPLC chromatograms of the reference solution and the test solution to ascertain that the test solution contains the compound of formula (I) of claim 1; and

determining the content of the compound of claim 1 in rotigotine or the preparation thereof in weight percentage by an external standard method.

8. A high-purity rotigotine, comprising rotigotine and a compound of claim 1 in an amount
10 less than 0.5 weight percent.