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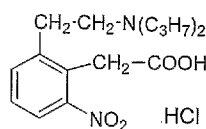


WO 2007/010557 A2

(54) Title: PROCESS FOR THE PREPARATION OF HIGHLY PURE ROPINIROLE



(I)



(II)

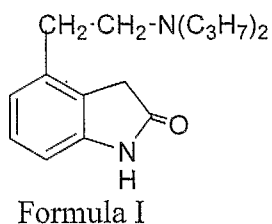
(57) Abstract: The present invention relates to highly pure Ropinirole or salt thereof and a process for preparing highly pure Ropinirole of structural Formula (I), by reducing nitro compound of formula (II), and cyclizing the resulting amino compound in situ using palladium on carbon in the presence of aqueous alcoholic medium.

**TITLE OF THE INVENTION**

PROCESS FOR THE PREPARATION OF HIGHLY PURE ROPINIROLE

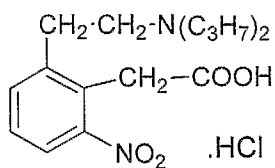
**FIELD OF THE INVENTION**

The field of the invention relates to highly pure ropinirole or salt thereof and a process for preparing highly pure ropinirole of structural Formula I,

**BACKGROUND OF THE INVENTION**

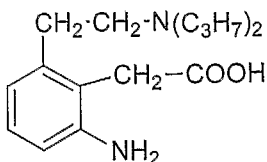
Ropinirole of Formula-I chemically known as 4-[2-(di-n-propylamino)-ethyl]-2(3H)-indolone and is useful in the treatment of Parkinsons disease. Ropinirole has been first disclosed in US patent 4,452,808.

In general, the synthetic approach reported in the literature for the preparation of Ropinirole involves the reduction of 2-nitro-6-(2-di-n-propylaminoethyl)-phenylacetic acid hydrochloride of Formula II followed by in situ cyclization.



There are significant drawbacks to this approach as the reduction of nitro group of 2-nitro-6-(2-di-n-propylaminoethyl)-phenyl acid hydrochloride of formula II to

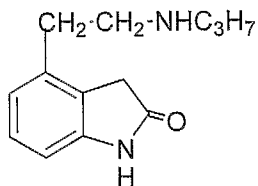
the corresponding amino compound 2-amino-6-(2-di-n-propylaminoethyl)-phenylacetic acid of Formula III or salt thereof,



Formula III

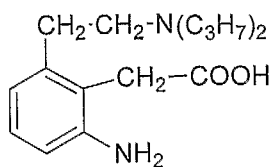
and further conversion to ropinirole results in the formation of many impurities, of which, the following impurities along with other unidentified impurities are difficult to remove:

- a) 4-[2-(n-propylamino)-ethyl]-2(3-H)-indolone or salt thereof



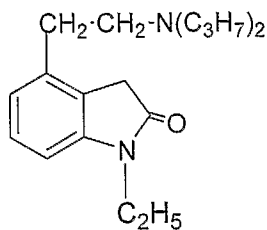
Formula IV

- b) 2-amino-6-(2-di-n-propylaminoethyl)-phenylacetic acid or salt thereof



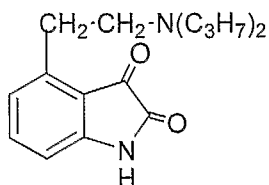
Formula III

- c) 4-[2-(di-n-propylamino)-ethyl]-2(3-ethyl)-indolone or salt thereof



Formula V

- d) 4-[2-(di-n-propylamino)-ethyl]1H-indole-2,3-dione



Formula VI

These impurities are further carried into ropinirole. The prior art approach is not suitable from commercial point of view because the desired ropinirole is not obtained in high purity and requires purification by tedious and cumbersome purification processes. The presence of significant quantity of unreacted amino compound in final product even after using 100 times by volume of acetonitrile for recrystallization makes the process uneconomical and unviable.

The inventors have observed that during the cyclization of amino compound of formula III, only 80-85% conversion of amino compound is achieved. The unreacted amino compound leads to formation of impurities which are very difficult to remove from ropinirole. In order to achieve a high efficiency of the reaction for industrial synthesis of ropinirole, it is necessary to increase the conversion of amino compound and minimizes the formation of impurities.

Thus, the present invention provides a process for the preparation of highly pure ropinirole where starting material converts to final product in more than 97%.

## **SUMMARY OF THE INVENTION**

In one general aspect there is provided a highly pure ropinirole or a salt thereof.

In another general aspect there is provided substantially pure ropinirole or a salt thereof having amino compound less than 0.05%.

In another general aspect there is provided highly pure ropinirole or a salt thereof having impurity (a) and (c) each less than 0.05%.

In another general aspect there is provided highly pure ropinirole or a salt thereof having total impurities less than 0.15 %.

In another general aspect there is provided a process for the preparation of substantially pure ropinirole or a salt thereof. The process includes reducing nitro compound of Formula II with a reducing agent to produce amino compound of Formula III, cyclizing the resulting amino compound in situ using palladium on carbon in the presence of aqueous alcoholic medium and isolating the substantially pure ropinirole or a salt thereof by simple isolation method of extraction and acid base treatment. The reducing agent may be palladium on carbon.

The details of one or more embodiments of the inventions are set forth in the description below. Other features, objects and advantages of the inventions will be apparent from the description and claims.

## **DETAILED DESCRIPTION OF THE INVENTION**

The inventors have developed an efficient process for the preparation of substantially pure ropinirole or a salt thereof, by reducing nitro compound of Formula II with a reducing agent to produce amino compound, 2-amino-6-(2-di-n-propylaminoethyl)-phenylacetic acid of Formula III and cyclizing in situ the

amino compound of Formula III in aqueous alcoholic medium and isolating substantially pure ropinirole or a salt thereof by simple isolation method of extraction and acid base treatment.

In general, the 2-nitro-6-(2-di-n-propylaminoethyl)-phenylacetic acid hydrochloride of formula II may be treated with a reducing agent in the presence of alcoholic solvent. The reaction is performed in an autoclave at a temperature between 25° -50°C and preferably at 35° -40°C under hydrogen pressure of 3.0 kg/cm<sup>2</sup> for 5 hours. It is advantageous to add some water in the reaction mass to complete cyclization of the resulting amino compound i.e. up to 98% conversion. The progress of reaction is monitored by HPLC.

The reducing agent includes any reducing agent which is capable of carrying out the reduction of the nitro group, including, for example, palladium on carbon, and the like and preferably palladium on carbon is used.

The alcoholic solvent may include one or more of primary, secondary and tertiary alcohol having from one to six carbon atoms. The alcoholic solvent may include one or more of methanol, ethanol, n-propanol, isopropanol, isobutanol, n-butanol and t-butanol. In particular, the alcoholic solvent is preferably ethanol. Mixtures of all of these solvents are also contemplated.

After completion of reaction, solvent (aqueous alcohol) is removed under vacuum and product may be slurred in acetonitrile, isopropyl ether, ethyl acetate and chlorinated solvent such as methylene chloride, chloroform and the like. Further the resulting solid (crude ropinirole) may take in water and basified with sodium hydroxide and product is extracted in organic solvent such as isopropyl ether, ethyl acetate and chlorinated solvent such as methylene chloride, chloroform and the like. The organic layer is optionally distilled to 60-70% with respect to its original volume. The hydrochloride salt of Ropinirole is prepared by treating the

organic layer with ethanolic-HCl at ambient temperature. The product is isolated in high purity and high yield. The compound can be optionally recrystallized from alcohol to improve colour if required. The product so obtained is having purity greater than 99.5% by HPLC, and preferably greater than 99.8%. The major advantages realized in the present invention are:

- High purity
- Completion of cyclization reaction up to 97%
- Avoid use of costly solvent for recrystallization.

The present invention is further illustrated by the following examples which are provided merely to be exemplary of the inventions and is not intended to limit the scope of the invention. Certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

### Examples

#### Preparation of 4-[2- (di-n-propylamino) ethyl] - 2 (3H)-indolone hydrochloride

2-Nitro-6(2-di-n-propylaminoethyl)-phenylacetic acid hydrochloride (100g) was dissolved in absolute alcohol (4.0 lit.) and charged into hydrogenator under nitrogen. Palladium on carbon( 10%, 50% wet, 12.5 g) was charged to the filtered reaction mass at 35° - 40°C and hydrogen pressure was maintained at 3.0 kg/cm<sup>2</sup> and was stirred for 5 hours at temperature 35° - 40°C. DM water (400 ml) was added and reaction mass was further stirred for 20 hours at hydrogen pressure 5 - 6 kg/cm<sup>2</sup> at temperature 40°-45°C. After completion of reaction, the reaction mass was filtered and ethyl alcohol was recovered completely under vacuum at temperature 40°-45°C. Ethyl alcohol (300 ml) was added and recovered under same conditions. Ethyl alcohol (300 ml) was added to the dried mass and stirred for 30-45 min at 40° - 45°C then cooled at 15-20°C and stirred at 15° - 20 °C for

45 min. and filter. The wet cake was slurred in acetonitrile (500 ml) and stirred for 30 min at 35° - 40°C then cooled to 15 – 20°C. The cooled mass was filter and slurry washed with di- isopropyl ether (300 ml). The wet cake was added to D M water (120 ml), sodium hydroxide solution 2 % (400 ml) and isopropyl ether (900 ml) were added and stirred at 15° - 20°C for 10 -15 min. The organic layer was separated and aqueous layer was extracted with isopropyl ether (2 x 250 ml). The combined organic layer was washed with chilled sodium hydroxide solution 1%, (200 ml) filtered by brine (200 ml) and heat to recover isopropyl ether (60 - 70%) was recovered under vacuum. The reaction mass was cooled at 15° -20°C and pH was adjusted to 1.5 – 2.5 with ethanolic hydrochloric acid (20 - 25%, 30 ml) and was stirred 30-40 min at 20° -25°C. The product obtained was centrifuged and slurry washed with absolute alcohol (200 ml). The wet material was dried under vacuum for 7 - 8 hr to obtain 57 g (66.80%) of title compound having purity of 99.30% by HPLC

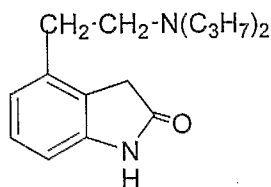
**Purification of 4-[2-(Di-n-propylamino) ethyl] 2(3H) indolone hydrochloride**

Crude ropinirole hydrochloride (250 g) was added in the mixture of di-isopropyl ether (2.5 lit), purified water (500 ml) and sodium hydroxide solution (4%, 2.0 lit) at 20°-25°C. The reaction mass was stirred for 30-35 min. at 20°– 25°C. The organic layer was separated and aqueous layer was extracted (two times) with di-isopropyl ether (2 x 650 ml). The combined organic layer was washed with water (500 ml) and the solvent was recovered under vacuum. The residue left was dissolved in absolute alcohol (300 ml), cooled at 5-10°C and pH was adjusted to 1.0 – 2.0 using ethanolic hydrochloric acid (260 ml). The reaction mass was stirred at 15-20°C for 30- 40 minutes and filtered. The wet cake was slurried in absolute alcohol (500 ml), filtered and dried under vacuum at 65-70°C to obtain 222 g; (88.80%) of title compound having purity of 99.91 % by HPLC



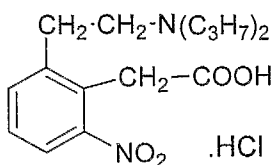
**WE CLAIM:**

1. An improved process for the preparation of Ropinirole of Formula I or salt thereof,



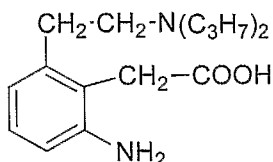
Formula I

which comprises reducing nitro compound of Formula II,



Formula II

with a reducing agent to produce amino compound of Formula III,



Formula III

cyclizing the resulting amino compound in situ using palladium on carbon in the presence of aqueous alcoholic medium,

distilling the solvent completely,

washing crude Ropinirole with organic solvent,

dissolving in dilute sodium hydroxide solution,

and treating with ethanolic-hydrochloric acid to prepare Ropinirole hydrochloride.

2. The process according to claim 1 wherein alcoholic aqueous medium is methanol/ ethanol/ isopropanol and water or mixture of
3. The process according to claim 2 wherein alcoholic aqueous medium is mixture of ethanol and water.
4. The process according to claim 1 wherein reaction is conducted at a temperature of 25° - 60°C.
5. The process according to claim 4 wherein reaction is preferably conducted at a temperature of 30° -50°C.
6. The process according to claim 1 wherein organic solvent is isopropyl ether, ethyl acetate and chlorinated solvents such as methylene chloride, chloroform or mixture thereof.
7. The process according to claim 1 wherein Ropinirole hydrochloride is recrystallized from alcohols.
8. The process according to claim 7 wherein ropinirole hydrochloride is further recrystallized from absolute ethanol.

Dated day 17<sup>th</sup> of July, 2006

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