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(71) **Applicant** *(for all designated States except US):* **RANBAXY LABORATORIES LIMITED** [IN/IN]; Head Office: 12th Floor, Devika Tower, 06 Nehru Place, New Delhi, Delhi 110019 (IN).

(72) **Inventors; and**

(75) **Inventors/Applicants** *(for US only):* **JAYACHANDRA, Suresh, Babu** [IN/IN]; C-237, Phase - I, Sushant Lok, Gurgaon, Haryana 122002 (IN). **GAHLOT, Udaibhan, Singh** [IN/IN]; Sukhadia Colony, Moya Bus Stand, TB, Hospital, Bari, Udaipur, Rajasthan 313025 (IN). **SINGH, Tarun, Kumar** [IN/IN]; 485, Eldeco II, Abhishek, SGPGI Road, Lucknow, Uttar Pradesh 226015 (IN). **KHANDURI, Chandra, Has** [IN/IN]; D-1952, Palam Vihar, Gurgaon, Haryana 122017 (IN).

(74) **Common Representative: RANBAXY LABORATORIES LIMITED;** c/o Dr. B. Vijayaraghavan, Intellectual Property Dept., 600 College, Road East, Suite 2100, Princeton, New Jersey 08540 (US).

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(54) **Title:** PROCESS FOR THE PREPARATION OF AN ANTIPSYCHOTIC AGENT

(57) **Abstract:** The present invention provides a process for the preparation of an antipsychotic agent useful for the treatment of schizophrenia.

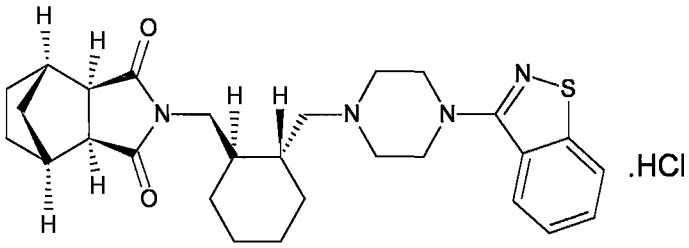
PROCESS FOR THE PREPARATION OF AN ANTIPSYCHOTIC AGENT

Field of the Invention

A process for the preparation of an antipsychotic agent useful for the treatment of schizophrenia is provided.

Background of the Invention

The present invention provides a process for the preparation of lurasidone hydrochloride. Lurasidone hydrochloride is chemically (3aR,4S,7R,7aS)-2-{(lR,2R)-2-[4-(l,2-benzisothiazol-3-yl)piperazin-l-ylmethyl]cyclohexylmethyl}hexahydro-4,7-methano-2H-isoindole-l,3-dione hydrochloride having the structure as represented by Formula I.

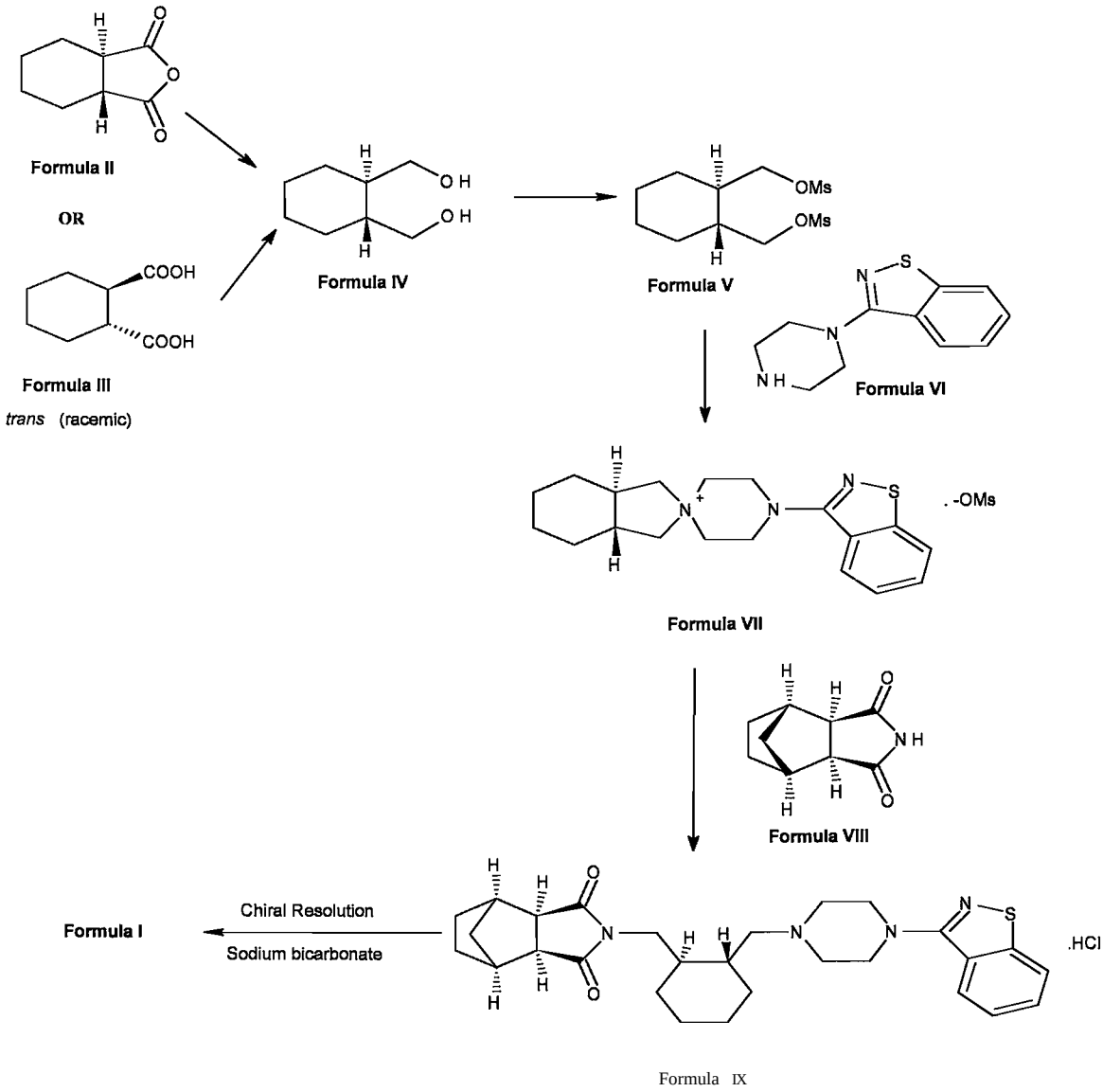


Formula I

Lurasidone hydrochloride is marketed in the United States under the brand name Latuda® for the treatment of schizophrenia.

U.S. Patent No. 5,532,372 describes preparation of lurasidone hydrochloride using racemic ***trans*** 1,2-cyclohexane dicarboxylic acid of Formula III as intermediate as depicted in Scheme I.

Scheme I



The process described in U.S. Patent No. 5,532,372 involves use of racemic *trans* 1,2-cyclohexane dicarboxylic acid of Formula III as an intermediate. The *trans* intermediate of Formula III may further exist as (R,R) *trans* and (S,S) *trans* isomers. In the process described in U.S. Patent No. 5,532,372, resolution of free base of Formula IX was carried out using a chiral resolving agent in the last step to obtain lurasidone followed by subsequent conversion of lurasidone into lurasidone hydrochloride.

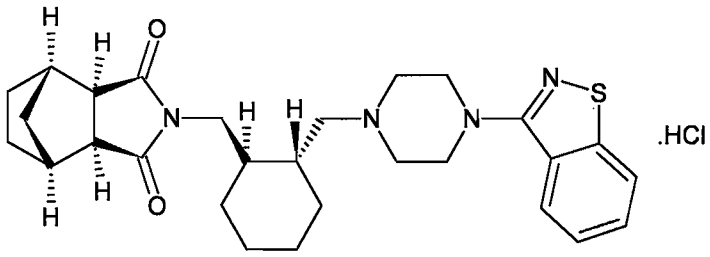
The present inventors have observed that chiral resolution of free base of an intermediate of Formula IX is difficult due to the presence of six chiral centers. This affects the overall yield and the cost of manufacturing. Thus, there exists a need for the development of a simple, cost-effective, and industrially advantageous process for the preparation of lurasidone hydrochloride which overcomes the difficulties of the prior art process.

Summary of the Invention

The present invention provides an easy, cost-effective and industrially advantageous process for the preparation of highly pure lurasidone hydrochloride which involves separating the racemic *trans* 1, 2-cyclohexane dicarboxylic acid of Formula III into its R,R *trans* and S,S *trans* isomers and then using the desired *trans* R,R isomer for the preparation of lurasidone hydrochloride. Since the process of the present invention involves separating the undesired S,S *trans* isomer in the initial stages of the manufacturing process, no undesired isomers due to reaction with *trans* (S,S)-isomer are formed in the subsequent steps.

Lurasidone hydrochloride prepared by the process of the present invention is a highly pure, easy to filter, free-flowing solid having small average particle size.

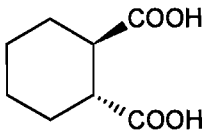
A first aspect of the present invention provides a process for the preparation of lurasidone hydrochloride of Formula I



Formula I

comprising the steps of:

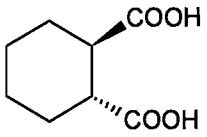
i) Resolving *trans* (racemic)-!, 2-cyclohexane dicarboxylic acid of Formula III



Formula III

trans **(racemic)**

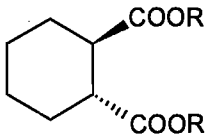
into *trans* (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia



Formula Ilia

trans **(R,R)-isomer**

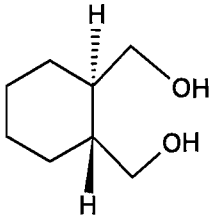
ii) Converting *trans* (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia into *trans* (R,R)-dicarboxylate intermediate of Formula X, wherein R is Ci-C_4 alkyl or benzyl;



Formula X

frans(R,R)-isomer

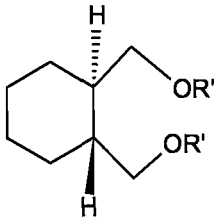
iii) Converting *trans* (R,R)-dicarboxylate intermediate of Formula X into *trans* (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI;



Formula XI

***trans*(R,R)-isomer**

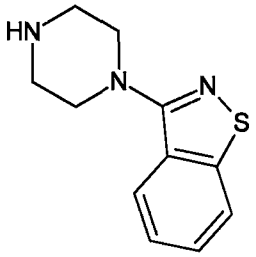
iv) Converting *trans* (R,R)- 1,2-bis(hydroxymethyl)cyclohexane of Formula XI into an intermediate of Formula XII



Formula XII
fraAjs(R,R)-isomer

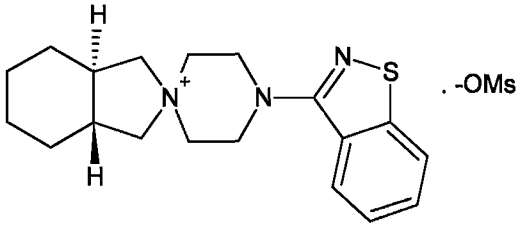
wherein R' is a leaving group;

v) Reacting intermediate of Formula XII with 3-(l-piperazinyl-l,2-benzisothiazole) of Formula VI



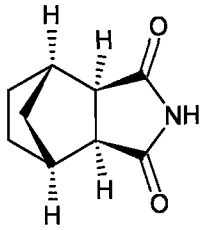
Formula VI

to obtain *trans* (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila;



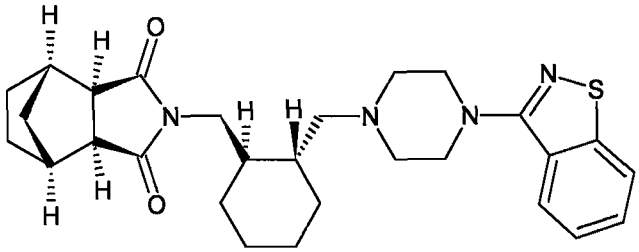
Formula Vila
irans(R,R)-isomer

vi) Reacting *trans* (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila with bicyclo[2.2.l]heptane-2-exo-3-exo-dicarboximide intermediate of Formula VIII



Formula VIII

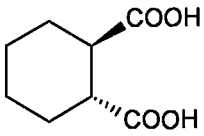
to obtain lurasidone of Formula XIII; and



Formula XIII

vii) Treating lurasidone of Formula XIII with hydrogen chloride to obtain lurasidone hydrochloride of Formula I.

A second aspect of the present invention provides use of ***trans*** (R,R)-1,2-cyclohexane dicarboxylic acid of Formula Ilia



Formula Ilia

trans **(R,R)-isomer**

for the preparation of lurasidone hydrochloride of Formula I.

Detailed Description of the Invention

Various embodiments and variants of the present invention are described hereinafter.

The term "ambient temperature", as used herein, refers to a temperature in the range of about 20°C to about 35°C.

The term "contacting", as used herein, refers to dissolving, slurrying, stirring or a combination thereof.

Racemic ***trans*** 1,2-cyclohexane dicarboxylic acid of Formula III, to be used for the preparation of lurasidone hydrochloride of Formula I of the present invention, may be obtained by methods known in the literature such as the one disclosed in U.S. Patent No. 5,532,372, which is incorporated herein by reference. It may be obtained as a solution directly from a reaction in which it is formed and used as such without isolation or it may be isolated and then used in the next step.

Racemic ***trans*** 1,2-cyclohexane dicarboxylic acid of Formula III may be resolved into (R,R) ***trans*** 1,2-cyclohexane dicarboxylic acid of Formula Ilia and (S,S) ***trans*** 1,2-cyclohexane dicarboxylic acid using a chiral resolving agent selected from the group comprising (R)-l-phenylethyl amine, alpha-methylbenzylamine, l-(l-naphthyl)-ethylamine, sec-butylamine l-amino-2-methylbutane, N,N-dimethyl-l-phenylethylamine, 1-cyclohexylethylamine, 2-(methoxymethyl)-pyrrolidine, l-(4-nitrophenyl)-ethylamine, 2-amino-l-butanol, l-amino-2-propanol, cinchonidine, brucine, strychnine, cinchonine, N-methyl-ephedrine or alpha-phenyl-glycinol. In a preferred embodiment, the resolving agent used is (R)-l-phenylethyl amine.

Resolution may be carried out using a solvent selected from the group comprising alcohols, ketones, alkyl acetates, chlorinated hydrocarbons, ethers, nitriles or hydrocarbons. Examples of alcohols are methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol or n-pentanol. Examples of ketones are acetone, methyl ethyl ketone or methyl isobutyl ketone. Examples of alkyl acetates are ethyl acetate or isopropyl acetate. Examples of chlorinated hydrocarbons are dichloromethane or chloroform. Examples of ethers are diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofiiran or dioxane. Examples of nitriles are acetonitrile or propionitrile. Examples of hydrocarbons are benzene, xylene, toluene, hexanes, heptane or pentane.

Resolving agent may be added at a temperature of about 0°C to -100°C. The reaction mixture may be stirred for about 30 minutes to about 2 hours, warmed to ambient temperature and stirred for about 2 hours to about 10 hours followed by isolation.

Isolation may be accomplished by filtration and drying. Drying may be carried out using any suitable method such as drying under reduced pressure, drying under atmospheric pressure, air drying or drying with aeration of inert gas such as nitrogen. Drying may be carried out at a temperature of about 40°C to about 80°C for about 2 hours to about 10 hours.

The salt of *trans* 1,2-cyclohexane dicarboxylic acid of Formula III with the resolving agent may be further purified by crystallization from the solvent selected from the group consisting of alcohols, hydrocarbons, ketones, alkyl acetates, chlorinated hydrocarbons, ethers, nitriles and mixtures thereof. Examples of alcohols are methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol, and n-pentanol. Examples of hydrocarbons are benzene, xylene, toluene, hexane, heptanes, and pentane. Examples of ketones are acetone, methyl ethyl ketone, and methyl isobutyl ketone. Examples of alkyl acetates are ethyl acetate, and isopropyl acetate. Examples of chlorinated hydrocarbons are dichloromethane and chloroform. Examples of ethers are diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran, and dioxane. Examples of nitriles are acetonitrile and propionitrile. In a preferred embodiment, salt of (R,R) *trans* 1,2-cyclohexane dicarboxylic acid of Formula Ilia with the resolving agent is purified by crystallization from a solvent mixture comprising an alcohol and a hydrocarbon.

Crystallization may be carried out by dissolving the salt of *trans* 1,2-cyclohexane dicarboxylic acid of Formula III with the resolving agent at a temperature of about 60°C to about 100°C. The solution may be cooled to about -10°C to an ambient temperature, stirred for about 30 minutes to about 2 hours, filtered and dried. The crystallization step may be repeated if required. The solid material thus obtained may be dissolved in about IN hydrochloric acid solution, extracted with a solvent and isolated to obtain *trans* (R,R)-1,2-cyclohexane dicarboxylic acid of Formula Ilia. In a preferred embodiment, purification is carried out by crystallization from ethanohtoluene mixture. In another preferred embodiment, purification is carried out by crystallization from ethanohtoluene mixture (1:1) mixture.

Conversion of (R,R) *trans* 1,2-cyclohexane dicarboxylic acid of Formula Ilia into dicarboxylate intermediate of Formula X may be carried out by contacting with a Ci-C_4

alcohol or benzyl alcohol in the presence of sulphuric acid. Examples of **C1-C4** alcohols are methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, and sec-butanol. The reaction mixture may be stirred at about 25°C to 60°C for about 1 hour to 24 hours and concentrated. Isolation may be accomplished by adding de-ionized water, solvent extraction and concentration.

In a particular embodiment, ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia may be converted into ***trans*** (R,R)-l,2-dimethyl cyclohexane dicarboxylate of Formula X by contacting with methanol in the presence of sulphuric acid. The reaction mixture may be stirred at about 40°C for about 18 hours. The reaction mixture may be concentrated under reduced pressure at about 50°C. De-ionized water may be added. Isolation of ***trans*** (R,R)-l,2-dimethyl cyclohexane dicarboxylate may be accomplished by solvent extraction and concentration.

Conversion of dicarboxylate intermediate of Formula X into ***trans*** (R,R)-1,2-bis(hydroxymethyl)cyclohexane of Formula XI may be carried out by adding a reducing agent selected from the group comprising diisobutyl aluminum hydride, lithium aluminium hydride, lithium borohydride, sodium borohydride, calcium borohydride, and lithium triethylborohydride, in an inert atmosphere. A solvent selected from the group comprising hydrocarbons or ethers may be added. Examples of hydrocarbons are benzene, xylene, toluene, hexane, heptanes or pentane. Examples of ethers are diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran, diglyme or dioxane. The reducing agent may be added drop-wise at a temperature of about -10°C to 10°C. The reaction mixture may be warmed to an ambient temperature and stirred for about 2 hours to 10 hours. About IN hydrochloric acid solution may be added at about -5°C to 40°C. The reaction mixture may be stirred for about 10 hours to 15 hours. Isolation may be accomplished by filtration and concentration.

In a preferred embodiment, conversion of dicarboxylate intermediate of Formula X into ***trans*** (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI may be carried out using diisobutyl aluminum hydride in a hydrocarbon solvent. In a more preferred embodiment, conversion of dicarboxylate intermediate of Formula X into ***trans*** (R,R)-1,2-bis(hydroxymethyl)cyclohexane of Formula XI may be carried out using diisobutyl aluminum hydride in toluene.

The hydroxyl group of *trans* (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI may be converted into a leaving group by reaction with a halide or a sulphonyl compound to obtain a intermediate of Formula XII. Examples of halides are thionyl chloride and thionyl bromide. Examples of sulphonyl compounds are alkyl- or aryl-sulphonyl halides selected from the group comprising of methane sulphonyl chloride, ethane sulphonyl chloride, p-toluene sulphonyl chloride, and benzene sulphonyl chloride. An organic or inorganic base may be added. Examples of organic bases are triethylamine, ammonia, and pyridine. Examples of inorganic bases are hydroxides, carbonates and bicarbonates of alkali and alkaline earth metals such as sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, and potassium hydroxide. Conversion may be carried out in the presence of a solvent selected from the group comprising of chlorinated hydrocarbons such as dichloromethane or chloroform or in pyridine at a temperature of about -10°C to about 10°C. The reaction mixture may be further stirred at ambient temperature for about 1 hour to 8 hours. De-ionized water may be added. Organic layer may be concentrated at a temperature of about 35°C to 60°C. Precipitation of the hydroxyl protected intermediate may be achieved by adding an ether solvent such as diethyl ether, diisopropyl ether, methyl butyl ether, tetrahydrofuran, diglyme or dioxane, stirring for about 30 minutes to 2 hours followed by isolation.

In a preferred embodiment, *trans* (R,R)-l,2-iw(hydroxymethyl)cyclohexane may be converted into *trans* (R,R)-l,2-Z>w(methanesulfonylmethyl)cyclohexane using methane sulphonyl chloride in the presence of triethylamine. Addition of methane sulphonyl chloride may be carried out at a temperature of about -10°C to 10°C in a chlorinated solvent. Reaction mixture may be stirred at ambient temperature for about 1 hour to 8 hours. De-ionized water may be added. Organic layer may be concentrated at about 45°C under reduced pressure. Precipitation of *trans* (R, R)-l,2-Z>/s(methanesulfonylmethyl)cyclohexane may be achieved using di-isopropyl ether. The reaction mixture may be stirred at an ambient temperature for about 30 minutes to 2 hours followed by isolation.

trans (R,R)-l,2-bis(methanesulfonylmethyl)cyclohexane may be converted to *trans* (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila by contacting with 3-(l-piperazinyl-l,2-

benzisothiazole) of Formula VI in a nitrile or amide solvent in the presence of a base. Examples of nitriles are acetonitrile and propionitrile. Examples of amide solvents are N,N-dimethyl formamide and N,N-diethylformamide. Examples of bases are carbonates, bicarbonates and hydroxides of alkali and alkaline earth metals such as sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, and potassium hydroxide. The reaction mixture may be refluxed for about 15 hours to 2 days, filtered and concentrated at about 40°C to 80°C under reduced pressure. Precipitation may be achieved by adding a ketone solvent, a hydrocarbon solvent or mixtures thereof. Examples of ketones are acetone, methyl ethyl ketone, and methyl isobutyl ketone. Examples of hydrocarbons are benzene, xylene, toluene, hexane, heptanes, and pentane. The reaction mixture may be stirred for about 10 minutes to 1 hour followed by isolation.

trans (R,R)-3a,7a-octahydroisoindolium-2-spiro-r-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila may be reacted with bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide of Formula VIII in the presence of a catalyst and a base. The catalyst may be selected from crown ethers such as dibenzo-18-crown-6 or 18-crown-6. Examples of bases are carbonates, bicarbonates and hydroxides of alkali and alkaline earth metals such as sodium carbonate, potassium carbonate, sodium bicarbonate, lithium hydroxide, sodium hydroxide, and potassium hydroxide. Hydrides of alkali metals such as sodium hydride and potassium hydride may also act as base. The reaction may be carried out in a hydrocarbon solvent selected from the group comprising benzene, xylene, toluene, hexane, heptanes, and pentane. The reaction mixture may be refluxed for about 1 hour to 2 days, filtered and concentrated at about 40°C to 100°C under reduced pressure. Precipitation of lurasidone may be carried out by adding an alcohol selected from methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol or n-pentanol followed by isolation.

Lurasidone may be converted into lurasidone hydrochloride by drop-wise addition of hydrogen chloride to a solution of lurasidone in a solvent. The solvent may be selected from the group comprising alcohols, alkyl acetates, ketones, and hydrocarbons. Examples of alcohols are methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, sec-butanol, and n-pentanol. Examples of alkyl acetates are ethyl acetate and isopropyl acetate. Examples of ketones are acetone, methyl ethyl ketone, and methyl isobutyl

ketone. Examples of hydrocarbons are benzene, xylene, toluene, hexane, heptanes, and pentane. Conversion of lurasidone into lurasidone hydrochloride may be carried out by purging hydrogen chloride gas or by adding aqueous hydrochloric acid in a solvent selected from iso-propanol, ethyl acetate, toluene, and water at ambient temperature to about 80°C. The reaction mixture may be stirred at ambient temperature to the reflux temperature of the solvent for about 10 minutes to 1 hour followed by isolation.

When aqueous hydrogen chloride is used for the conversion of lurasidone into lurasidone hydrochloride, the concentration of aqueous hydrogen chloride may vary from 0.1% to 36%.

In a preferred embodiment, lurasidone may be converted to lurasidone hydrochloride by contacting a solution of lurasidone in ethyl acetate with 6% to 8% aqueous hydrogen chloride at about 40°C, stirring at ambient temperature for about 30 minutes to 5 hours followed by isolation.

Lurasidone hydrochloride prepared by the process of the present invention is a highly pure, easy to filter, free-flowing solid having small average particle size.

In the foregoing section, embodiments are described by way of examples to illustrate the processes of invention. However, these are not intended in any way to limit the scope of the present invention. Several variants of the examples would be evident to persons ordinarily skilled in the art which are within the scope of the present invention.

Methods

HPLC purity was determined using Water alliances, Model 2695 instrument.

EXAMPLES

Example 1: Preparation of *trans* fR..RH.2-Cyclohexane Dicarboxylic Acid

To a suspension of racemic *trans* 1,2-cyclohexane dicarboxylic acid (65 g) in ethanol (650 mL) was added (R)-l-phenylethyl amine (50.7 mL) at about -70°C. The reaction mixture was stirred for about 90 minutes, warmed to ambient temperature and stirred for about 5 hours. Precipitates were filtered, washed with ethanol (25 mL) and dried under reduced pressure at about 40°C to obtain crude salt *of trans* (R,R)- 1,2-cyclohexane dicarboxylic acid (96.5 g).

The salt ***of trans*** (R,R)-l,2-cyclohexane dicarboxylic acid, obtained above, was dissolved in ethanol:toluene (1:1) mixture (1.4 L) at about 80°C. The solution was cooled to about 0°C to about 5°C over a period of about 60 minutes to about 90 minutes, filtered and dried under reduced pressure at about 45°C. Crystallization was repeated twice. Solid material, thus obtained, was dissolved in about IN hydrogen chloride (250 mL) and extracted two times with ethyl acetate (600+300 mL). Organic layers were combined, washed with brine and concentrated at about 45°C under reduced pressure to obtain ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid as colorless crystals.

Yield: 30%

Example 2: Preparation ***of trans*** (R,RV1.2-Dimethyl Cyclohexane Dicarboxylate

Sulphuric acid (9 mL) was added to a solution of ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid (18 g) in methanol (180 mL). The reaction mixture was stirred at about 40°C for about 18 hours. The reaction mixture was concentrated at about 50°C under reduced pressure. De-ionized water (150 mL) was added. The reaction mixture was extracted twice with ethyl acetate (150 + 100 mL). The organic layers were combined, washed with brine and concentrated under reduced pressure at about 50°C to obtain ***trans*** (R,R)-l,2-dimethyl cyclohexane dicarboxylate as an oil.

Yield: 97%

Example 3: Preparation of ***trans*** (Tl.RV1.2-Bis(HvdroxymethvDCyclohexane

trans (R,R)-l,2-dimethyl cyclohexane dicarboxylate (20 g) was dissolved in toluene (200 mL) at about 0°C to about -5°C in an inert atmosphere. Diisobutyl aluminum hydride (248.5 ml, 20% solution in toluene) was added drop-wise into the above solution. The reaction mixture was warmed to an ambient temperature and stirred for about 6 hours. The reaction was quenched by drop-wise addition of about IN HC1 (125 mL) at about -5°C to about 40°C. The reaction mixture was further stirred for about 13 hours to get freely filterable inorganic solids. The solids were filtered out and the filtrate was concentrated under reduced pressure to obtain ***trans*** (R,R)-1,2-bis(hydroxymethyl)cyclohexane as an oil.

Yield: 74%

Example 4: Preparation of ***trans*** (R,RH.2-Z?/s(MethanesulfonylmethvDCyclohexane

Methane sulfonyl chloride (23.85 g) was added to a solution of (R,R) ***trans*** 1,2-£/s(hydroxymethyl)cyclohexane (10.0 g) and triethylamine (15.45 g) in chloroform (100 mL) at about 0°C to about 5°C. The reaction mixture was stirred at an ambient temperature for about 5 hours. De-ionized water (120 mL) was added. The organic layer was separated and concentrated under reduced pressure at about 45°C. Diisopropyl ether (120 mL) was added. The reaction mixture was stirred at ambient temperature for about 60 minutes, filtered and dried under reduced pressure at about 40°C to obtain ***trans*** (R,R)-l,2-bis(methanesulfonylmethyl)cyclohexane.

Yield: 90.8%

Example 5: Preparation of ***trans*** (R,Rl-SaJa-Octahydroisoindolium^-Spiro -1'-[4'-(1,2-Benzoisothiazole-3-YD]Piperazine Methane Sulfonate

3-(l-Piperazinyl-l,2-benzisothiazole) (13.2 g) and sodium carbonate (6.5 g) were added to a solution of ***trans*** (R,R)-l,2-bis(methanesulfonylmethyl)cyclohexane (18 g) in acetonitrile (180 mL) at ambient temperature. The reaction mixture was refluxed for about 30 hours, filtered and washed with acetonitrile (2x25 mL). The combined filtrate was concentrated at about 60°C under reduced pressure. Acetone (40 mL) was added to the residue and the reaction mixture was stirred at about 40°C until the product precipitated out. Hexane (50 mL) was added. The reaction mixture was stirred for about 30 minutes at ambient temperature, filtered and dried under reduced pressure at about 45°C for about 8 hours to obtain ***trans*** (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate.

Yield: 88%

Example 6: Preparation of Lurasidone

Method A:

Bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (7.5 g), potassium carbonate (7.5 g) and dibenzo-18-crown-6 (0.15 g) were added to a solution of ***trans*** (R,R)-3a,7a-octahydroisoindolium-2-spiro -1'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate (15 g) in xylene (150 mL). The reaction mixture was refluxed for about 25 hours, filtered and concentrated at about 70°C under reduced pressure. Sticky residue was

obtained. Isopropanol (30 mL) was added. The reaction mixture was cooled to ambient temperature, stirred for about 5 hours, filtered, washed with isopropanol (15 mL) and dried at about 45°C under reduced pressure for about 15 hours to obtain lurasidone.

Yield: 76.8%

Method B:

Bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide (7.5 g), potassium carbonate (7.5 g) and dibenzo-18-crown-6 (0.15 g) were added to a solution of ***trans*** (R,R)-3a,7a-octahydroisoindolium-2-spiro-1'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate (15 g) in toluene (150 mL). The reaction mixture was refluxed for about 12 hours, filtered and concentrated at about 55°C to 60°C under reduced pressure. Sticky residue was obtained. Denatured spirit (75 mL) was added. The reaction mixture was heated to about 40°C, maintained for about 1 hour, cooled to ambient temperature and stirred for about 6 hours. The solid was filtered, washed with denatured spirit (20 mL) and dried at about 45°C under reduced pressure for about 15 hours to obtain lurasidone free base.

Yield: 86.35%

HPLC Purity: 98.41%

Example 7: Preparation of Lurasidone Hydrochloride

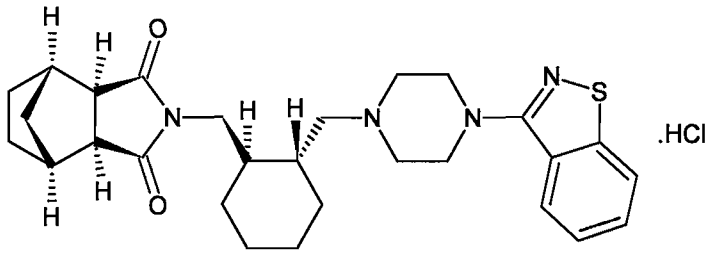
About 7% aqueous hydrochloric acid (5 mL) was slowly added to a reaction mixture containing lurasidone (1.0 g) in ethyl acetate (25 mL) at about 40°C. The reaction mixture was stirred at ambient temperature for about 2 hours, filtered and dried at about 45°C under reduced pressure to obtain lurasidone hydrochloride.

Yield: 93%

HPLC Purity: 98.98%

We Claim:

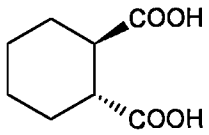
1. A process for the preparation of lurasidone hydrochloride of Formula I



Formula I

comprising the steps of:

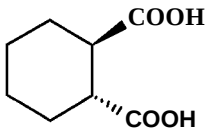
i) Resolving ***trans*** (racemic)-l,2-cyclohexane dicarboxylic acid of Formula III



Formula III

trans **(racemic)**

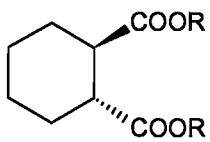
into ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia;



Formula Ilia

trans **(R,R)-isomer**

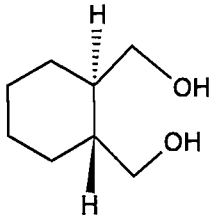
ii) Converting ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia into ***trans*** (R,R)-dicarboxylate intermediate of Formula X, wherein R is C_1-C_4 alkyl or benzyl;



Formula X

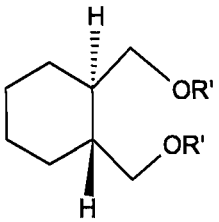
trans(R, **R)-isomer**

iii) Converting ***trans*** (R,R)-dicarboxylate intermediate of Formula X into ***trans*** (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI;



Formula XI
fra/7s(R,R)-isomer

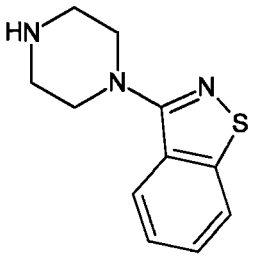
iv) Converting ***trans*** (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI into an intermediate of Formula XII



Formula XII
f/a/7s(R,R)-isomer

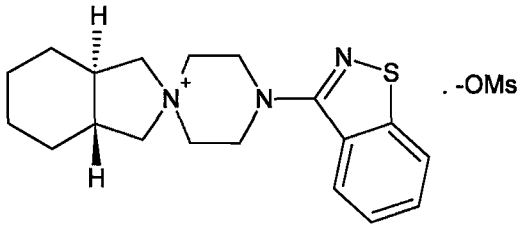
wherein R' is a leaving group;

v) Reacting intermediate of Formula XII with 3-(1-piperazinyl-1,2-benzisothiazole) of Formula VI



Formula VI

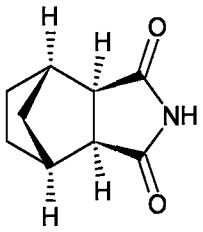
to obtain ***trans*** (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila;



Formula Vila

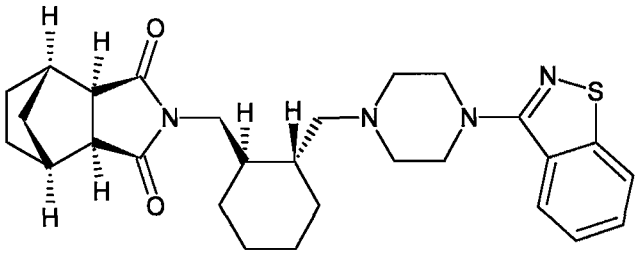
*trans(R,*R)-isomer

vi) Reacting *trans* (R, R)-3a,7a-octahydroisoindolium-2-spiro -r-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila with bicyclo[2.2. l]heptane-2-exo-3-exo-dicarboximide intermediate of Formula VIII



Formula VIII

to obtain lurasidone of Formula XIII; and



Formula XIII

vii) Treating lurasidone of Formula XIII with hydrogen chloride to obtain lurasidone hydrochloride of Formula I.

2. The process according to claim 1, wherein resolution is carried out using a chiral resolving agent.

3. The process according to claim 1, wherein the resolution is carried out at a temperature of about 0°C to -100°C.

4. The process according to claim 1, wherein the salt of *trans* 1,2-cyclohexane dicarboxylic acid of Formula III with the resolving agent is further purified by crystallization from a solvent selected from alcohols, hydrocarbons, ketones, alkyl acetates, chlorinated hydrocarbons, ethers, nitriles, or mixtures thereof.

5. The process according to claim 1, wherein conversion of *trans* (R,R)-1,2-cyclohexane dicarboxylic acid of Formula Ilia into *trans* (R,R)-dicarboxylate intermediate of Formula X is carried out in a **C1-C4** alcohol or benzyl alcohol.

6. The process according to claim 1, wherein conversion of *trans* (R,R)-1,2-cyclohexane dicarboxylic acid of Formula Ilia into *trans* (R,R)-dicarboxylate intermediate of Formula X is carried out at about 40°C.

7. The process according to claim 1, wherein conversion of *trans* (R,R)-dicarboxylate intermediate of Formula X into *trans* (R,R)-l,2-bis(hydroxymethyl)cyclohexane of Formula XI is carried out by adding a reducing agent in a hydrocarbon or ether solvent.

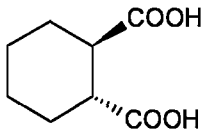
8. The process according to claim 1, wherein conversion of *trans* (R,R)-1,2-bis(hydroxymethyl)cyclohexane of Formula XI into *trans* R,R intermediate of Formula XII by reaction with a halide or sulphonyl compound in the presence of a base in a chlorinated hydrocarbon or pyridine.

9. The process according to claim 1, wherein *trans* R,R intermediate of Formula XII is reacted with 3-(l-piperazinyl-l,2-benzisothiazole) of Formula VI in the presence of a base in a nitrile or amide solvent to obtain *trans* (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila.

10. The process according to claim 1, wherein the reaction of *trans* (R,R)-3a,7a-octahydroisoindolium-2-spiro-l'-[4'-(l,2-benzoisothiazole-3-yl)]piperazine methane sulfonate of Formula Vila with bicyclo[2.2.1]heptane-2-exo-3-exo-dicarboximide intermediate of Formula VIII is carried out in the presence of a base in a hydrocarbon solvent.

11. The process according to claim 1, wherein a solution of lurasidone in ethyl acetate is treated with 7% aqueous hydrochloric acid.

12. Use of ***trans*** (R,R)-l,2-cyclohexane dicarboxylic acid of Formula Ilia



Formula Ilia

***trans* (R,R)-isomer**

for the preparation of lurasidone hydrochloride.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051500

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D417/12
ADD.

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

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 practicable, search terms used)
EPO-Internal , CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 532 372 A (SAJI IKUTARO [JP] ET AL) 2 July 1996 (1996-07-02) cited in the application Columns 14-16: reference examples I-(a), I-(b); columns 30-32, examples I-(a) to **I-(e)**.	1-12
Y	BERKESSEL ET AL.: "Enantiomerically Pure [beta]-Amino Acids: A Convenient Access to Both Enantiomers of trans-2-Aminocyclohexanecarboxylic Acid", EUR. J. ORG. CHEM., 1 January 2002 (2002-01-01), pages 2948-2952, XP55027946, Abstract; page 2949: left column, paragraph 1, lines 6-11 and scheme 2; page 2950: 1st paragraph, figure 3, last paragraph.	1-12

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2012	22/06/2012

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Weisbrod, Thomas

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2012/051500

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
L	"Chapter 16. IV" In: Anderson : "Practical Process Research & Development" , 2000, Academic Press , San Diego, XP002676468, ISBN : 0120594757 pages 341-342 , Page 342 , "Tips: Guidelines for assymmetric synthesis": tip 5 of 5. Cited as common general knowledge. -----	1-12

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2012/051500

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 5532372 A	02-07-1996	NONE	