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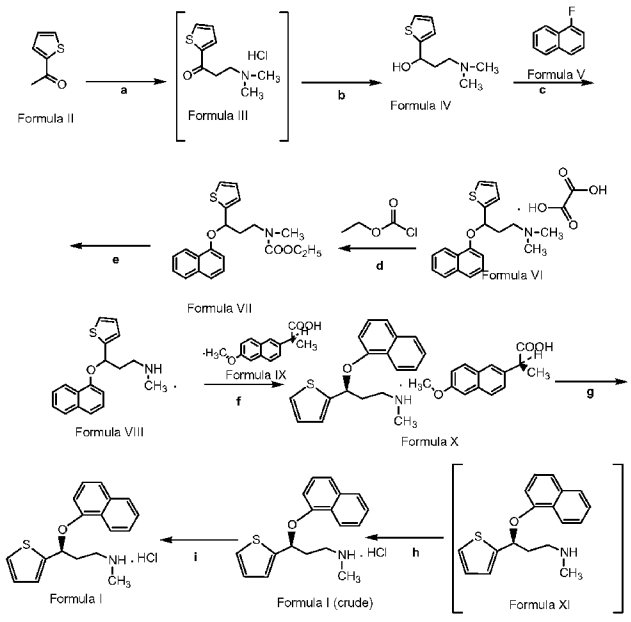
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(54) Title: PROCESS FOR PREPARING DULOXETINE



(57) Abstract: A process for preparing duloxetine or a salt thereof.

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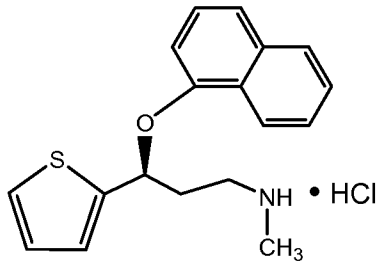
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PROCESS FOR PREPARING DULOXETINE

INTRODUCTION TO THE INVENTION

The present invention relates to a process for the preparation of duloxetine and its pharmaceutically acceptable salts. In an aspect, it relates to a process for preparing duloxetine and its pharmaceutically acceptable salts having low concentrations of impurities.

Duloxetine hydrochloride is the adopted name for a compound having the chemical name (+)-(*S*)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine hydrochloride and structurally represented by Formula I.



Formula I

Duloxetine is a selective serotonin and norepinephrine reuptake inhibitor for oral administration and is useful in the treatment of depression. Pharmaceutical products containing duloxetine hydrochloride as the active ingredient are commercially available in the market under the brand name CYMBALTA™ as capsules containing an equivalent of 20, 30 and 60 mg of duloxetine.

U.S. Patent No. 5,023,269 describes N-methyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propaneamine oxalate, its related compounds and processes for their preparation.

Processes for preparation of duloxetine, its pharmaceutically acceptable salts and its intermediates have been described in: U.S. Patent No. 5,362,886; European Patent No. 457559; International Application Publication Nos. WO 2006/071868, WO 2006/099468, and WO 2004/056795; U.S. Patent Application Publication Nos. 2006/0128791 and 2004/0249170; and *Drugs of the Future* 2000, 25(9) 907-916.

International Application Publication No. WO 2006/099433 discloses pharmaceutically acceptable salts of duloxetine containing less than 0.14% of (+)-

N-methyl-3-(1-naphtaleneyloxy)-3-(3-thienyl)propanamine (hereinafter designated as "DLX-ISO-3") impurity, and less than 0.04% of the R-enantiomer of duloxetine.

Like any other synthetic compound, duloxetine can contain extraneous compounds or impurities that can come from many sources. They can be unreacted starting materials, by-products of the reaction, products of side reactions, or degradation products. Impurities in duloxetine or any active pharmaceutical ingredient ("API") are undesirable and, in extreme cases, might even be harmful to a patient being treated with a dosage form containing the API.

Process impurities include unreacted starting materials, chemical derivatives of impurities contained in starting materials, synthetic by-products, and degradation products. The purity of the API produced in the commercial manufacturing process is clearly a necessary condition for commercialization. Impurities introduced during commercial manufacturing processes must be limited to very small amounts, and are preferably substantially absent. For example, the ICH Q7A guidance for API manufacturers requires that process impurities be maintained below set limits by specifying the quality of raw materials, controlling process parameters, such as temperature, pressure, time, and stoichiometric ratios, and including purification steps, such as crystallization, distillation, and liquid-liquid extraction, in the manufacturing process.

Enantiomeric purity of pharmaceutical compounds is important because the two isomers may exhibit different potency and certain isomers may actually be deleterious rather than simply inert. Therefore, there is a need to obtain the desired enantiomer of duloxetine hydrochloride which is free of its enantiomeric impurity, and also free of other process related impurities.

Therefore there is a need for a process, which is advantageous in preventing racemization, so as to increase the yields of the final product and also to yield an enantiomerically pure form of duloxetine and its pharmaceutically acceptable salts.

SUMMARY OF THE INVENTION

The present invention relates to a process for the preparation of duloxetine and its pharmaceutically acceptable salts. In an aspect, it relates to a process for the preparation of duloxetine and its pharmaceutically acceptable salts having low concentrations of impurities.

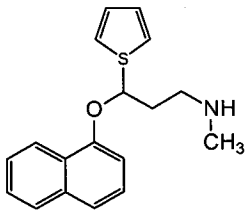
One aspect of the present invention provides a process for the preparation of duloxetine hydrochloride. In an embodiment, a process for the preparation of duloxetine hydrochloride comprises:

a) providing a solution comprising duloxetine; and

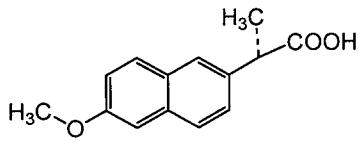
b) reacting the solution obtained of a) with less than about 1.5 molar equivalents of hydrochloric acid.

Another aspect of the present invention provides a process for the preparation of duloxetine from racemic duloxetine or an acid addition salt thereof. In an embodiment, a process for the preparation of duloxetine comprises:

a) reacting racemic duloxetine of Formula VIII or an acid addition salt thereof with (S)-6-methoxy-α-methyl-2 naphthalene acetic acid of Formula IX (hereinafter referred to as "naproxen") to give a salt represented by Formula X;

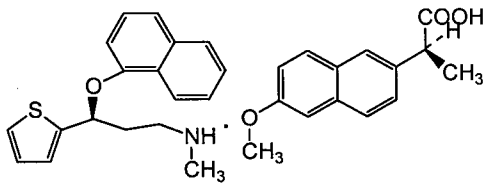


Formula VIII



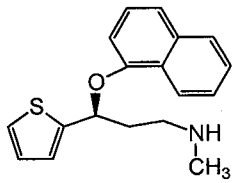
Formula IX

b) recovering the of salt duloxetine with naproxen of Formula X; and



Formula X

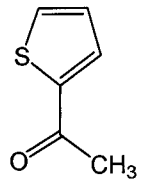
c) reacting the salt of Formula X with a suitable base to get duloxetine.



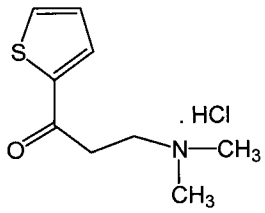
Formula XI

Yet another aspect of the present invention provides a process for the preparation of racemic duloxetine or an acid addition salt thereof. In an embodiment, a process for the preparation of racemic duloxetine or its acid addition salt comprises:

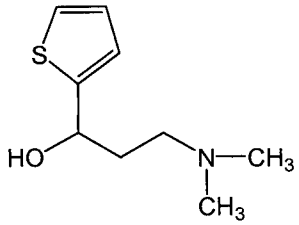
a) reacting 2-acetyl thiophene of Formula II with dimethylamine hydrochloride and paraformaldehyde to get 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride of Formula III, which is then reduced to give N,N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine of Formula IV;



Formula II

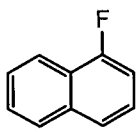


Formula III

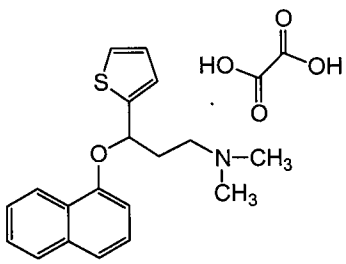


Formula IV

b) condensing N,N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine of Formula IV with 1-fluoronapthalene of Formula V to give N, N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine which can be converted to its oxalate salt of Formula VI;

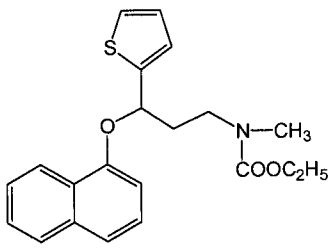


Formula V



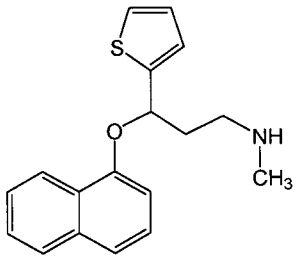
Formula VI

c) reacting N, N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate of Formula VI with ethylchloroformate to give N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII; and



Formula VII

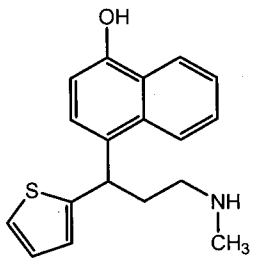
d) reacting N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII with a base to form racemic duloxetine of Formula VIII, which can be converted to its oxalate salt.



Formula VIII

Still another aspect of the present invention provides substantially pure duloxetine and its pharmaceutically acceptable salts.

A further aspect of the present invention provides a process for the preparation of 4-(3-methylamino-1-thiophen-2-yl-propyl)naphthalene-1-ol hydrochloride represented by Formula Ib, useful as a reference standard for determining the purity of duloxetine hydrochloride by HPLC.



Formula Ib

A yet further aspect of the invention provides pharmaceutical compositions comprising substantially pure duloxetine hydrochloride prepared according to the process of the present invention along with one or more pharmaceutically acceptable carriers, excipients or diluents.

BRIEF DESCRIPTION OF THE DRAWINGS

Fig. 1 is a schematic representation of a process for the preparation of duloxetine according to an embodiment of the present invention.

Fig. 2 is an X-ray powder diffraction pattern of duloxetine hydrochloride prepared in Example 8.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of duloxetine and its pharmaceutically acceptable salts. In an embodiment, it relates to a

process for preparing duloxetine and its pharmaceutically acceptable salts having low concentrations of impurities.

As referred to herein, use of the term "racemic" in connection with duloxetine or its acid addition salt refers to a mixture of R- and S-isomers of the compound *N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine, or a salt thereof. Duloxetine is the officially adopted name of the single enantiomer S-(+)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine, and "R-(-)-duloxetine" is used herein to refer to the single enantiomer R-(-)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine.

One aspect of the present invention provides a process for the preparation of duloxetine hydrochloride. In an embodiment, the process for the preparation of duloxetine hydrochloride comprises:

a) providing a solution comprising duloxetine; and

b) reacting the solution obtained in step a) with less than about 1.5 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine.

Step a) involves providing a solution of duloxetine.

Duloxetine obtained using any of the processes described in the art can be used for the purpose of the present invention. The solution of duloxetine may be obtained by dissolving duloxetine in a suitable solvent, or such a solution may be obtained directly from a reaction in which duloxetine is formed.

When the mixture is prepared by dissolving duloxetine in a suitable solvent, any form of duloxetine such as any crystalline or amorphous form including any salts, solvates and hydrates may be utilized for preparing the solution.

Suitable solvents which can be used for dissolving duloxetine include but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, n-propanol, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; hydrocarbons such as toluene, xylene, n-heptane, cyclohexane, and the like; and mixtures thereof or their combinations with water in various proportions.

The temperatures for preparation of the solution can range from about 20 to 120 °C, depending on the solvent used. Any other temperature is also acceptable as long as the stability of duloxetine is not compromised.

The quantity of solvent used for preparing the mixture depends on the nature of solvent and the temperature adopted for preparing the mixture. The

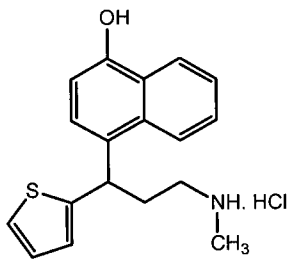
concentration of duloxetine in the solution may generally range from about 0.1 to about 1 g/ml in the solvent.

Step b) involves reacting the solution obtained in step a) with up to about 1.5 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine.

Hydrogen chloride used in the process can be in the form of aqueous hydrochloric acid, hydrogen chloride gas, alcoholic hydrochloride, ethyl acetate hydrochloride and the like.

The quantity of hydrogen chloride used is important for obtaining pure duloxetine hydrochloride free of impurities. Suitably, the molar ratio of hydrogen chloride to duloxetine can range from about 0.8 to 1.4, or from about 0.8 to about 1.2, or from about 0.9 to about 1.1, or from about 1 to about 1.2.

It has been found that if the molar ratio of hydrogen chloride to duloxetine is more than about 1.5, impurity formation is high, specifically, an impurity identified as 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol hydrochloride represented by Formula Ib (hereinafter referred to as "4-naphthol impurity") is formed in higher percentages.



Formula Ib

Suitable temperatures at which the hydrogen chloride can be added to the solution range form about 20 °C to about 80 °C, or from about 25 °C to about 35 °C. After the addition of hydrogen chloride, the reaction can be further maintained for about 30 minutes to about 5 hours, or longer, for the complete isolation of the desired product.

The isolated product is recovered from the reaction mixture by suitable techniques such as filtration by gravity or by suction, centrifugation, and the like.

The wet cake obtained may optionally be further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier and the like. The drying can be carried out at temperatures of about 35 °C to about 70 °C, with or without applying vacuum for any desired time periods, times from

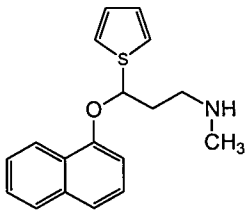
about 1 to 20 hours, or longer, frequently being suitable for obtaining a desired product purity.

Suitably, the duloxetine hydrochloride obtained above can be purified further in suitable solvents either by recrystallization or slurrying. Suitable solvents which can be used include, but are not limited to ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like, and mixtures thereof.

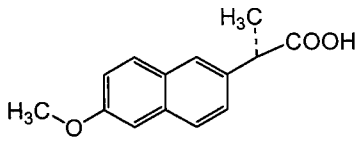
The duloxetine hydrochloride obtained using the process of the present invention is characterized by an X-ray powder diffraction pattern with peaks at approximately: 10.4, 14.8, 14.9, 17.0, 20.8, 21.2, and 24.0, ± 0.2 degrees 2 theta. X-ray powder diffraction patterns described herein were generated using a Bruker Axe, D8 Advance Powder X-ray Diffractometer with a Cu K alpha-1 radiation source. A characteristic XRPD pattern of the duloxetine hydrochloride is substantially in accordance with the pattern of Fig. 2.

Another aspect of the present invention provides a process for the preparation of duloxetine from racemic duloxetine or an acid addition salt thereof. In an embodiment, a process for the preparation of duloxetine comprises:

a) reacting racemic duloxetine of Formula VIII or its acid addition salt with (S)-6-methoxy-α-methyl-2 naphthalene acetic acid of Formula IX (hereinafter referred to as "naproxen") to give a salt represented by Formula X;

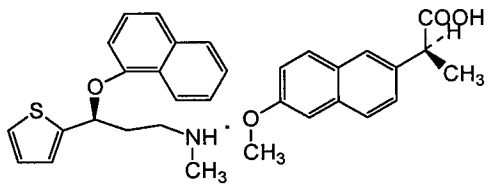


Formula VIII



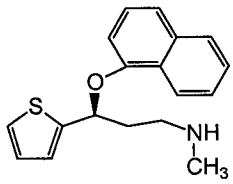
Formula IX

b) recovering of the of salt duloxetine with naproxen of Formula X; and



Formula X

d) reacting the salt of Formula X with a suitable base to get duloxetine.



Formula XI

Step a) involves reacting racemic duloxetine of Formula VIII or an acid addition salt thereof with naproxen to give a salt of duloxetine and naproxen represented by Formula X.

Suitable acid addition salts of racemic duloxetine which can be used as a starting material include, but are not limited to the hydrochloride, hydrobromide, para-toluenesulfonate, methanesulfonate, maleate, oxalate, succinate, mandalate and like.

When an acid addition salt of racemic duloxetine is used, the free base can be released from the salt by reacting it with a base before reacting it with naproxen.

Suitable bases that can used for conversion of the acid addition salt of racemic duloxetine to its free base include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions.

Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the corresponding base can be used. Any concentration is useful, which will convert the acid addition salt to the free base.

Suitable solvents which can be used for extraction of the free base from the aqueous solutions include, but are not limited to water immiscible solvents such as: halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform, and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; esters such as ethyl acetate, propyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof. The same solvents can be used to dissolve the free base, when the free base of racemic duloxetine is directly reacted with naproxen.

The molar ratio of naproxen to the racemic duloxetine used in the reaction can range from about 1 to 4, or about 1 to 2, or about 0.9.

Naproxen can be added either directly, or its solution in any of the solvents mentioned above for dissolution of the free base can be used.

Suitable temperatures for conducting the reaction range from about 20 °C to 80 °C, or from about 25 °C to 35 °C. The reaction can be conducted for about 30 minutes to about 5 hours, or the reaction conditions can be maintained as long as required for the complete reaction to form the desired product.

Step b) involves recovering the salt of the duloxetine and naproxen.

The solid product obtained is recovered from the reaction mixture by suitable techniques such as decantation, filtration by gravity or by suction, centrifugation, and the like. The crystals so isolated can carry a small proportion of occluded mother liquor containing a higher percentage of impurities. If desired, the crystals can be washed on with a solvent to wash out the mother liquor.

The wet cake obtained can be optionally further dried. Drying can be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer and the like. The drying can be carried out at temperatures of about 35° C to about 70° C for any desired time period to achieve a desired result, times from about 1 to 20 hours, or longer, frequently being suitable.

Step c) involves reacting the salt with a suitable base to get pure duloxetine.

Suitable bases that can used include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions

Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the corresponding inorganic base can be used.

Suitable solvents which can be used for extracting duloxetine from the aqueous mixture include, but are not limited to: esters such as ethyl acetate, n-propyl acetate, n-butyl acetate, t-butyl acetate and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; ether solvents

such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof.

Suitably, the pH of the reaction mixture may range from about 7 to about 14, or from about 13 to about 14.

Suitable temperatures for conducting the reaction can range from about 10 °C to about 50 °C, or about 25 °C to 35 °C.

After reaction completion, the organic layer containing the free base is separated and may be progressed to further processing directly, or it can be concentrated to isolate the free base.

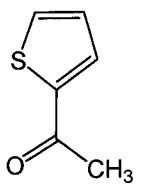
Suitably duloxetine obtained above can be converted to its pharmaceutically acceptable acid addition salts by reacting it with the corresponding acid in a suitable solvent.

Pharmaceutically acceptable acids that can be used include hydrochloric acid, hydrobromic acid, para-toluenesulfonic acid, methanesulfonic acid, oxalic acid, succinic acid, benzoic acid, and like.

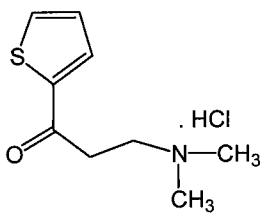
In one embodiment, the acid is hydrochloric acid and the acid addition salt of duloxetine is duloxetine hydrochloride.

Yet another aspect of the invention provides a process for the preparation of racemic duloxetine or an acid addition salt thereof. In an embodiment, a process for the preparation of racemic duloxetine or its acid addition salt comprises:

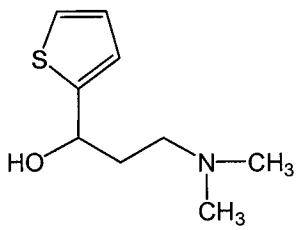
a) reacting 2-acetyl thiophene of Formula II with dimethylamine hydrochloride and paraformaldehyde to get 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride of Formula III which is then reduced to give N,N-dimethyl-3-hydroxy-3-(2-thienyl propanamine of Formula IV;



Formula II



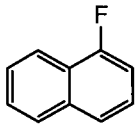
Formula III



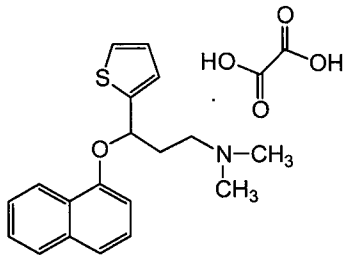
Formula IV

b) condensing N,N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine of Formula IV with 1-fluoronapthalene of Formula V to give N, N-dimethyl-3-(1-

naphthalenyloxy)-3-(2-thienyl) propanamine which can be converted to its oxalate salt of Formula VI;

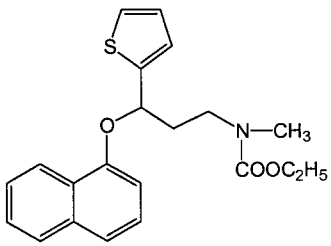


Formula V



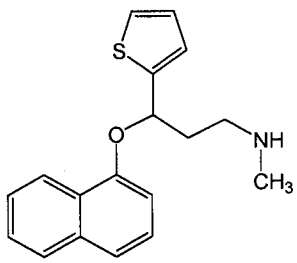
Formula VI

c) reacting N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate of Formula VI with ethylchloroformate to give N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII; and



Formula VII

d) reacting N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII with a base to form racemic duloxetine of Formula VIII, which can be converted to its oxalate salt.



Formula VIII

Step a) involves reaction of 2-acetyl thiophene of Formula II with dimethylamine hydrochloride and paraformaldehyde to get 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride of Formula III which is then reduced to give N,N-dimethyl-3-hydroxy-3-(2-thienyl propanamine of Formula IV.

Suitable organic solvents which can be used for the reaction include but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, n-butanol, and the like; ketones such as acetone, ethyl methyl ketone, methyl

isobutyl ketone, and the like; nitriles such as acetonitrile, propionitrile, and the like; halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform, and the like; and mixtures thereof in various proportions.

Suitably, the intermediate III is not dried, and is progressed to the next stage without drying the compound.

Suitable reducing agents which can be used for reducing the keto group of get 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride of Formula III include, but are not limited to, silanes, boranes, metal hydrides like sodium borohydride, lithium aluminium hydride, formates, hypophosphorous acid salts and the like.

Step b) involves condensation of N,N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine of Formula IV with 1-fluoronapthalene of Formula V to give N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine which can be converted to its oxalate salt of Formula VI.

Suitable organic solvents which can be used for the reaction include but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, n-butanol, and the like; ketones such as acetone, ethyl methyl ketone, methyl isobutyl ketone, and the like; aprotic polar solvents such as N.N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), dimethylacetamide (DMA) and the like; and mixtures thereof

Suitable bases which can be used include but are not limited to: inorganic bases such as lithium hydroxide, sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium tertiary butoxide and the like; organic bases such as methylamine, dimethylamine, triethylamine, di-isopropylamine N, N-di-isopropylethylamine, pyridine, butylamine, and the like; and mixtures thereof

Suitably, N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine obtained can be converted to its oxalate salt by reacting it with oxalic acid.

Step c) involves reaction of N, N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl) propanamine oxalate of Formula VI with ethylchloroformate and a suitable base to give methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid ethyl ester of Formula VII.

Suitably, the free base dimethyl-[3-naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine is released from the oxalate salt of Formula VI before reacting it witn ethyl chloroforamte.

Suitable bases that can be used for conversion of an oxalate salt compound of Formula VI to free base include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions.

Suitably, aqueous solutions containing about 5% to 50%, or about 10% to 20%, (w/v) of the corresponding inorganic base can be used. Any concentration is useful, which will convert the oxalate salt compound of Formula VI to the free base.

Suitable solvents which can be used include for extracting the free base include, but are not limited to water immiscible solvents such as: halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform, and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; esters such as ethyl acetate, propyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof.

Suitable temperatures for release of the free base can range from about 20 °C to about 80 °C, or from about 25 °C to about 35 °C. The reaction will be maintained until its completion, such as for about 30 minutes to about 10 hours, or longer.

After completing the reaction, the organic layer containing the free base is separated and may be progressed to further processing directly or it can be first concentrated to form a residue.

Suitably, the organic layer containing the free base obtained from previous step or the free base residue dissolved in a suitable solvent can be used for reacting with ethyl chloroformate in the presence of a base.

Suitably, the molar ratio of ethyl chloroformate to the starting material compound of Formula VI used in the reaction can range from about 0.5 to 8, or from about 2.0 to about 9.0.

Suitable solvents include but are not limited to: halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform, and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; ester solvents such as ethyl acetate, propyl acetate and the like; ether solvents such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof

Suitable bases that can used include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; organic bases such as methylamine, dimethylamine, triethylamine, di-isopropylamine, N, N-di-isopropylethylamine, pyridine, butylamine and the like; and mixtures thereof.

The amount of base that can be used in the reaction can vary depending upon the base used. Suitably, the molar ratio of base to the starting material compound of Formula VI can range from about 0.75 to 2, or about 1.

Suitably, ethyl chloroformate can be added to the reaction mixture over a prolonged time, such as about 20 minutes to about 5 hours, or about 1 to 2 hours, at temperatures ranging from about 20 °C to about 80°C, or 40 °C to about 60 °C, and can be maintained further until reaction completion, such as for about 2 to 10 hours, or about 4 to 6 hours.

After completion of the reaction, the reaction mixture is quenched with water and pH is adjusted to about 7 to 12, or about 8 to 9, by adding a suitable base.

Suitable bases that can used for adjusting reaction mixture pH include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and

mixtures thereof. These bases can be used in the form of solids or in the form of aqueous solutions

Suitably aqueous solutions containing about 5% to about 50%, or about 10% to about 20%, (w/v) of the corresponding inorganic base can be used. Any concentration is useful, which will provide the required pH values.

Finally the organic layer is separated and concentrated to form a residue. The residue can be further purified by crystallizing from a suitable solvent.

Suitable solvents useful for the purification include but are not limited to: hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; esters such as ethyl acetate, propyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof.

Step d) involves reacting N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII with a base to form racemic duloxetine of Formula VIII, which can be converted to its oxalate salt.

Suitable bases that can used in the reaction include but are not limited to: alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; carbonates of alkali metals such as sodium carbonate, potassium carbonate and the like; bicarbonates of alkali metals such as sodium bicarbonate, potassium bicarbonate, and the like; ammonia; and mixtures thereof.

Suitable solvents which can be used for the reaction include but are not limited to: ketonic solvents such as acetone, ethyl methyl ketone, methyl isobutyl ketone and the like; nitrile solvents such as acetonitrile, propionitrile and the like; aprotic polar solvents such as N,N-dimethylformamide (DMF), dimethylsulfoxide (DMSO), N,N-dimethylacetamide (DMA) and the like; and mixtures thereof

Suitable temperatures for conducting the reaction range from about 50 °C to about 120 °C, or from about 100 °C to about 110 °C. The reaction is maintained until completion, such as for about 2 hours to about 20 hours, or longer.

After completion, the reaction mixture is quenched with water and the product is extracted using a suitable solvent.

Suitable solvents useful for extraction include but are not limited to: hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; ester solvents such as ethyl acetate, propyl acetate and the like; ether

solvents such as diethyl ether, diisopropyl ether, methyl tertiary-butyl ether and the like; and mixtures thereof.

Finally, the organic layer is separated and may be progressed to further processing directly or it can be concentrated to form a residue.

Suitably, an organic layer containing the free base obtained from previous step or the free base residue dissolved in a suitable solvent can be used for reacting with oxalic acid to form an oxalate salt.

Suitably, the molar ratio of oxalic acid to the free base compound of Formula IV, used in the reaction can range from about 0.75 to 2, or about 1.

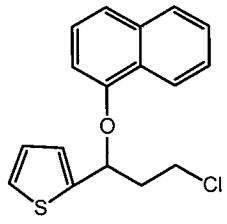
Suitable temperatures for the formation of the oxalate salt range form about 20 °C to about 80 °C, or from about 50 °C to about 60 °C. The reaction conditions can be maintained until reaction completion, such as for about 30 minutes to about 10 hours, or more.

After completing the reaction, the product is isolated by methods such as filtration by gravity or by suction, centrifugation, and the like.

N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl) propanamine of Formula VII obtained from the above process can comprise process related impurities. These impurities are removed by crystallizing from a suitable solvent.

Suitable solvents useful for the purification include but are not limited to: alcohols such as methanol, ethanol, isopropanol, butanol and the like; hydrocarbons such as toluene, xylene, n-hexane, n-heptane, cyclohexane and the like; ester solvents such as ethyl acetate, propyl acetate and the like; ether solvents such as diethyl ether, diisopropyl ether, methyl tertiarybutyl ether and the like; and mixtures thereof.

In one embodiment, methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid ethyl ester of Formula VII obtained by the present invention contains less than about 0.15 % by weight of the 2-[3-chloro-1- (naphthalenyloxy-propyl] thiophene of compound of Formula VIIa, as determined by high performance liquid chromatography (HPLC).



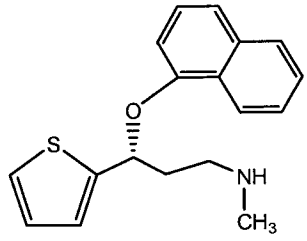
Formula VIIa

Still another aspect of the present invention provides substantially pure duloxetine.

By "substantially pure duloxetine" it is meant that duloxetine or any of the pharmaceutically acceptable salts of duloxetine prepared in accordance with the present invention contains less than about 0.5%, or less than about 0.1%, by weight of the corresponding impurities like the R-enantiomer of duloxetine, 4-napthol impurity of duloxetine, and DLX-ISO-3 impurities, as characterized by a high performance liquid chromatography ("HPLC") chromatogram obtained from a mixture comprising the desired compound and one or more of the said impurities.

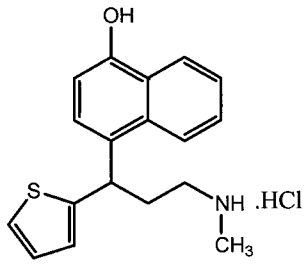
The pharmaceutically acceptable salts of duloxetine refer to salts prepared from pharmaceutically acceptable non-toxic acids including inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, and organic acids such as acetic acid, tartaric acid, methanesulfonic acid and the like.

"R-enantiomeric of duloxetine" refers to (-)-(R)-*N*-methyl-γ-(1-naphthyloxy)-2-thiophenepropylamine of Formula Ia;



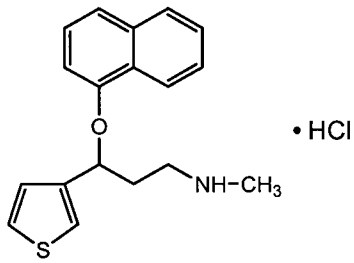
Formula Ia

"4-Naphthol duloxetine" refers to 4-(3-methylamino-1-thiophen-2-yl-propyl)-naphthalen-1-ol hydrochloride compound of Formula Ib;



Formula Ib

DLX-ISO-3 impurity" refers to (+)-N-methyl-3-(1-naphtaleneyloxy)-3-(3-thienyl)propanamine hydrochloride of Formula Ic.



Formula Ic

Duloxetine having a reduced level of impurities typically also contains residual solvents. For purposes of the present invention, any residual solvents in purified duloxetine are also considered as impurities. Residual solvents can be quantified by application of chromatographic techniques, such as gas chromatography.

Duloxetine hydrochloride of Formula I obtained by the process of the present invention has: a residual methanol content less than about 500 ppm, or less than about 100 ppm; a residual acetone content less than about 1000 ppm, or less than about 300 ppm; a residual isopropyl alcohol content less than about 2000 ppm, or less than about 1000 ppm; a residual ethyl acetate content less than about 500 ppm, or less than about 200 ppm; a residual cyclohexane content less than about 500 ppm, or less than about 200 ppm; and a residual toluene content less than about 500 ppm, or less than about 200 ppm.

Duloxetine hydrochloride obtained according to the process of the present invention has a particle size distribution D_{50} less than about 100 µm.

The D_{10}, D_{50} and D_{90} values are useful ways for indicating a particle size distribution. D_{90} refers to at least 90 volume percent of the particles having a size smaller than the said value. Likewise D_{10} refers to 10 volume percent of the particles having a size smaller than the said value. D_{50} refers to 50 volume percent

of the particles having a size smaller than the said value. Methods for determining D_{10}, D_{50} and D_{90} include laser diffraction, such as using equipment from Malvern Instruments Ltd. of Malvern, Worcestershire, United Kingdom.

Duloxetine hydrochloride obtained according to an embodiment of the present invention has: D_{10} less than 50 μm, or less than 20 μm; D_{50} less than 100 μm, or less than 50 μm; and D_{90} less than 300 μm, or less than 200 μm. There is no specific lower limit for any of the D values.

A further aspect of the present invention provides a process for the preparation of 4-(3-methylamino-1-thiophen-2-yl-propyl)naphthalene-1-ol hydrochloride compound of Formula Ib ("4-napthol duloxetine impurity") and its use as a reference standard for identifying the purity of duloxetine hydrochloride by HPLC. The process comprises keeping duloxetine free base in contact with hydrochloric acid in ethyl acetate for a prolonged time, such as, for example, about 30 hours or about 40 hours, or longer. Hydrochloric acid used in the process can be in the form of aqueous hydrochloric acid, hydrochloric acid gas, alcoholic hydrochloride, ethyl acetate hydrochloride and the like. Suitable temperatures for preparation of the compound range from about 10 °C to about 50 °C.

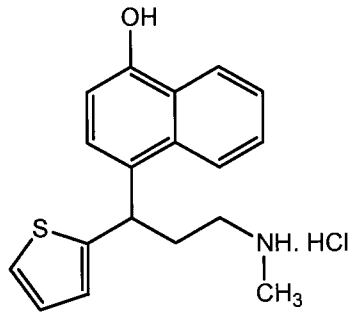
A compound in a relatively pure state can be used as a "reference standard." A reference standard is similar to a reference marker, which not only is used for qualitative analysis, but is also used to quantify the amount of the compound of the reference standard in an unknown mixture, as well. The management of process impurities is greatly enhanced by understanding their chemical structures and synthetic pathways, and by identifying the parameters that influence the amount of impurities in the final product.

The detection or quantification of the reference standard serves to establish the level of purity of the API or intermediates thereof. Use of a compound as a standard requires recourse to a sample of the substantially pure compound.

Regulatory authorities require declarations that the active agent is acceptable for administration to humans and that the particular formulation, which is to be marketed, is free from impurities at the time of release and has an appropriate shelf life. While submitting these declarations, drug manufacturers must include analytical records to demonstrate that impurities are absent from the

drug at the time of manufacture, or are present only at a negligible level, and that the storage stability, i.e., shelf-life of the drug is acceptable.

These details are usually obtained by testing the drug against an external standard, or reference marker, which is a pure sample of a potential impurity or a potential degradation product. 4-naphthol duloxetine is useful as a reference marker compound in identifying the purity of the duloxetine hydrochloride.



Formula Ib

A still further aspect of the invention provides a pharmaceutical composition comprising substantially pure duloxetine hydrochloride along with one or more pharmaceutically acceptable excipients.

The pharmaceutical composition comprising substantially pure duloxetine hydrochloride and their combination with a pharmaceutically acceptable carrier of this invention may be further formulated as solid oral dosage forms such as, but not limited to, powders, granules, pellets, tablets, and capsules; liquid oral dosage forms such as but not limited to syrups, suspensions, dispersions, and emulsions; and injectable preparations such as but not limited to solutions, dispersions, and freeze dried compositions. Formulations may be in the form of immediate release, delayed release or modified release. Further, immediate release compositions may be conventional, dispersible, chewable, mouth dissolving, or flash melt preparations, and modified release compositions that may comprise hydrophilic or hydrophobic, or combinations of hydrophilic and hydrophobic, release rate controlling substances to form matrix or reservoir or combination of matrix and reservoir systems. The compositions may be prepared by direct blending, dry granulation or wet granulation or by extrusion and spheronization. Compositions may be presented as uncoated, film coated, sugar coated, powder coated, enteric coated or modified release coated. Compositions of the present invention may further comprise one or more pharmaceutically acceptable excipients.

Pharmaceutically acceptable excipients that find use in the present invention include, but are not limited to: diluents such as starch, pregelatinized starch, lactose, powdered cellulose, microcrystalline cellulose, dicalcium phosphate, tricalcium phosphate, mannitol, sorbitol, sugar and the like; binders such as acacia, guar gum, tragacanth, gelatin, polyvinylpyrrolidone, hydroxypropyl cellulose, hydroxypropyl methylcellulose, pregelatinized starch and the like; disintegrants such as starch, sodium starch glycolate, pregelatinized starch, crospovidone, croscarmellose sodium, colloidal silicon dioxide and the like; lubricants such as stearic acid, magnesium stearate, zinc stearate and the like; glidants such as colloidal silicon dioxide and the like; solubility or wetting enhancers such as anionic or cationic or neutral surfactants; complex forming agents such as various grades of cyclodextrins, resins; release rate controlling agents such as hydroxypropyl cellulose, hydroxymethyl cellulose, hydroxypropyl methylcellulose, ethyl cellulose, methyl cellulose, various grades of methyl methacrylates, waxes and the like. Other pharmaceutically acceptable excipients that are of use include but are not limited to film formers, plasticizers, colorants, flavoring agents, sweeteners, viscosity enhancers, preservatives, antioxidants and the like.

In the compositions of present invention duloxetine is a useful active ingredient in the range of 20 mg to 30 mg, or 30 mg to 60 mg, per dosage unit.

Certain specific aspects and embodiments of this invention are described in further detail by the examples below, which examples are provided only for the purpose of illustration and are not intended to limit the scope of the appended claims in any manner.

EXAMPLE 1

PREPARATION OF 3-DIMETHYLAMINO-1-(2-THEINYL)-1-PROPANONE HYDROCHLORIDE (FORMULA IV)

10 kg of 2-acetyl thiophene of Formula II, 7.4 kg of dimethylamine hydrochloride and 2.7 kg of paraformaldehyde were charged into a clean and dry reactor containing 20 liters of isopropyl alcohol followed by stirring for 10 minutes at 25 °C. 0.48 liters of 36% aqueous hydrochloric acid was added to the reaction mixture and heated to 77 °C. The reaction mixture was maintained for 8 hours at

77-79 °C. After completion of the reaction, the reaction mass was cooled to 25 °C followed by stirring for 2 hours. The separated compound 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride of Formula III was centrifuged and the wet cake was washed with 5 liters of isopropyl alcohol.

The above obtained wet solid was dissolved in 60 liters of water and the solution cooled to 11 °C. 2.4 kg of sodium borohydride was added slowly in 3 equal lots at 10 °C over 2 hours, 45 minutes. The reaction mixture was heated to 20 °C and stirred for 1 hour, 45 minutes at 19-25 °C. 14.3 liters of 48 % aqueous sodium hydroxide solution was added and the reaction mixture was stirred at 30 °C for 2 hours. The separated solid was centrifuged and the wet cake was washed with 40 liters of water. The wet solid was dried at 50 °C under a vacuum of 550 mm Hg for about 5.5 hours to afford 11.5 kg of the title compound.

Purity By HPLC: 99.62 %.

EXAMPLE 2

PREPARATION OF N,N-DIMETHYL-3-(1-NAPHTHALENYLOXY)-3-(2-THIENYL) PROPANAMINE OXALATE (FORMULA VI)

25.5 kg of N,N-dimethyl-3-hydroxy-3-(2-thienyl) propanamine of Formula IV was taken into a clean and dry reactor containing 76.5 liters of dimethylsulfoxide. 17.1 kg of potassium tertiary butoxide was added and the mixture was stirred for about 10 minutes, followed by addition of 22.18 kg of 1-fluoronaphthalene. The reaction mixture was heated to 90 °C and maintained for 9 hours. The reaction mixture was cooled to 30 °C and 153 liters of water was added and stirred for 20 minutes. The reaction mixture was extracted with 256 liters of ethyl acetate in two equal lots and the total organic layer was washed with 102 liters of water. 17.4 kg of oxalic acid was added to the organic layer and the mixture heated to 60 °C and stirred for 60 minutes. The solution was cooled to 30 °C for 30 minutes. The formed solid was centrifuged and washed with 25.5 liters of ethyl acetate. The wet solid was dried at 60 °C under vacuum for 5 hours to afford 51 kg of title compound.

Purity by HPLC: 99.66 %.

EXAMPLE 3

PREPARATION OF METHYL-[3-(NAPHTHALEN-1-YLOXY)-3-THIOPHEN-2-YL-PROPYL]-CARBAMIC ACID ETHYL ESTER (FORMULA VII)

13 kg of dimethyl- [3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-amine oxalate of Formula VI was taken into a clean reactor containing 130 liters of toluene and 65 liters of water, and stirred for 15 minutes. The pH of the reaction mixture was adjusted to 8.2 by adding 52 liters of 10% aqueous sodium bicarbonate solution over a period of 3 hours, 45 minutes. The resultant reaction suspension was stirred for 25 minutes and the organic layer was separated. The organic layer was washed with 26 liters of water and dried over sodium sulphate. 3.276 kg of triethyl amine was added to the organic layer and the resultant reaction mixture was heated to 43 °C. 14.0 kg of ethyl chloroformate was added slowly to the reaction mixture at 55 °C. The resultant reaction mixture was stirred for 4 hours followed by cooling to 30 °C. 26 liters of water was charged and reaction solution pH was adjusted to about 9.1 using 11 liters of 10% aqueous sodium hydroxide solution. The organic layer was separated and washed with 26 liters of water. The total organic layer was distilled completely at about 90 °C under vacuum of about 550 mm Hg to afford the title compound as a residue.

39 liters of n-hexane was charged to the above obtained residue and heated to 69 °C for complete dissolution. The clear solution thus obtained was cooled to 8 °C and stirred for 2 hours. The solid that separated was filtered through a Nutsche filter and washed with 6.5 liters of n-hexane. Solid obtained was dried at 50 °C under a vacuum of about 550 mm Hg for 3 hours, 20 minutes to yield 9.7 kg of the title compound.

Purity by HPLC: 98.737.

Impurity of Formula VIIa: 1.10 %

EXAMPLE 4

PREPARATION OF OXALATE SALT OF RACEMIC DULOXETINE OF FORMULA VIII:

9.7 kg of methyl- [3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid ethyl ester of Formula VII and 29 liters of dimethylsulfoxide were taken into a clean and dry reactor. 7.37 kg of potassium hydroxide dissolved in 19 liters of

water was added slowly to the reaction mixture over about 35 minutes at a temperature below 50 °C. The reaction mixture was heated to 110 °C and stirred for 9.5 hours. The reaction mixture was cooled to 50 °C and 97 liters of water was added to it. The resultant reaction suspension was stirred for 15 minutes and extracted with ethyl acetate in two lots of 97 liters and 48 liters at 50 °C. The total organic layer was washed with 38 liters of water in two equal lots at 50 °C. 3.3 kg of oxalic acid was added to the organic layer and the reaction mixture was heated to 58 °C. The resultant mixture thus obtained was stirred for 40 minutes and then cooled to 35 °C. The resultant slurry was stirred for 1.5 hours. The solid that separated was centrifuged and the wet cake was washed with 10 liters of ethyl acetate. The solid obtained was dried at 60 °C under a vacuum of about 550 mm Hg for 9 hours to yield 9.5 kg of crystalline solid.

9.5 kg of N-methyl-3-(1-napthalenyloxy)-3-(2-thienyl) propanamine oxalate obtained above was taken into a clean and dry reactor containing 48 liters of methanol. The reaction mixture was heated to 60 °C and stirred for 40 minutes. The reaction mass was cooled to 30 °C followed by stirring for 45 minutes. The separated solid was centrifuged and the solid was washed with 10 liters of methanol. The solid obtained was suction dried for 2 hours at 550 mm Hg vacuum to yield 13 kg of the title compound.

Purity by HPLC: 98.67%.

EXAMPLE 5

PREPARATION OF (+)-N- METHYL-3- [1-NAPTHALEN-1-YLOXY)-3-THIOPHEN-2-YL-PROPYL]-AMINE NAPROXEN SALT (FORMULA X)

39 liters of ethyl acetate, 78 liters of water and 7.8 kg of racemic oxalate salt of racemic duloxetine prepared above were taken into a clean and dry reactor. The pH of the reaction solution was adjusted to 9.75 by the addition of 5.5 liters of 15% aqueous ammonia. The resultant suspension was stirred for about 30 minutes followed by separation of organic and aqueous layers. The aqueous layer was extracted with 31.2 liters of ethyl acetate in two equal lots. The combined organic layer was distilled completely below 60 °C under vacuum to obtain a residue.

To the above-obtained residue 2.75 liters of toluene was added followed by stirring for 10 minutes. 4.21 kg of naproxen was charged followed by stirring for 2 hours at 30 °C. The resultant reaction mixture was heated to 50 °C followed by stirring for 1 hour. The resultant reaction mass was cooled to 30 °C and maintained for 50 minutes followed by filtration of separated solid through a Nutsche filter. The filtered solid was washed with 2.75 liters of toluene followed by suction drying for 30 minutes. The obtained solid was dried at 60 °C for 50 minutes under a 550 mm Hg vacuum to yield 4.7 kg of the title compound.

Purity by HPLC: 99.86 %.

Chiral purity by HPLC: 91.73 %.

EXAMPLE 6

PREPARATION OF DULOXETINE HYDROCHLORIDE (FORMULA I)

9 kg of the salt of duloxetine with naproxen of Formula X was taken into a clean and dry reactor containing 135 liters of water. The pH of the reaction solution was adjusted to about 13.4 by the addition of 11.35 liters of 10% sodium hydroxide solution at 30 °C. The resultant reaction suspension was stirred for about 15 minutes. 67.5 liters of cyclohexane was charged into the reaction mass followed by heating the reaction mass to 60 °C and stirring for 15 minutes. The organic layer was separated and the aqueous layer was extracted into 22.5 liters of cyclohexane. The combined organic layer was washed with 45 liters of water. The solvent was distilled completely at about 600-700 mm Hg vacuum at a temperature below 60 °C for 11 hours to afford a crude solid.

49.5 liters of acetone was taken into the reactor containing above obtained crude solid and stirred for 15 minutes at 30 °C. 3.83 liters of 14.5% w/v hydrogen chloride in isopropanol was added at 25 °C followed by stirring for 4 hours at 30 °C. The separated solid was filtered through a Nutsche filter under nitrogen pressure and the solid was washed with 9.9 liters of acetone. The solid obtained was press dried for 50 minutes followed by drying at 60 °C at 600-700 mm Hg for 4 hours to yield 4 kg of the title compound.

EXAMPLE 7

PURIFICATION OF DULOXETINE HYDROCHLORIDE (FORMULA I)

2 kg of duloxetine hydrochloride was taken into a clean and dry reactor containing 18 liters of Isopropyl alcohol. The reaction mixture was heated to 85 °C for 1 hour, 40 minutes followed by addition of 2 liters of isopropyl alcohol and 0.1 kg carbon and maintained for 15 minutes. The suspension was filtered through a candy filter and a micron filter followed by washing the carbon cake with 2 liters of isopropyl alcohol. The resultant filtrate was cooled to 25-30 °C and stirred for 3 hours. The separated solid was centrifuged and the wet cake was washed with 2 liters of isopropyl alcohol and spin dried for 30 minutes followed by drying at 55 °C for 4 hours to yield 1.58 kg of the title compound.

Purity by HPLC: 99.97 %.

Chiral purity by HPLC: 99.25%.

4-napthol duloxetine impurity: less than 0.0055%.

DLX-ISO-3 impurity: 0.08%.

Residual solvent content: methanol 41 ppm; acetone not detected, isopropanol 497 ppm; ethyl acetate 73 ppm; toluene 111 ppm.

Particle size distribution: D_{10} 17 μm, D_{50} 69 μm, D_{90} 191 μm.

EXAMPLE 8

PREPARATION OF DULOXETINE HYDROCHLORIDE USING METHYL ISOBUTYL KETONE AS SOLVENT

4 g of duloxetine was dissolved in 40 ml of methyl isobutyl ketone followed by cooling to 0 °C. pH of the solution was adjusted to 2 by the addition of 1.6 ml of 12 N hydrochloric acid under stirring, and maintained under stirring for 5 hours. Separated solid was filtered and washed with 5 ml of methyl isobutyl ketone and the solid obtained was dried at 45 °C for 10 hours to afford 1.6 g of the title compound.

EXAMPLE 9

PREPARATION OF 4-NAPTHOL DULOXETINE IMPURITY OF DULOXETINE HYDROCHLORIDE (FORMULA 1b)

25 g of duloxetine was charged into a round-bottom flask containing 250 ml of ethyl acetate and stirred for about 30 minutes. 10 ml of 36 % aqueous hydrochloric acid was charged to the reaction mass and stirred for about 4 hours at 28° C. The reaction mass was kept without stirring for about 10 hours (overnight). Then the reaction mass was further stirred for 16 hours. The solid was filtered and the solid cake was washed with ethyl acetate (25 ml). The solid was dried at 50 °C under a vacuum of about 650 mm Hg for 3 hours to get 10 g of product.

Purity by HPLC: 96.7%.

^{1}H NMR (400 MHz, DMSO, δ in ppm): 2.5 (m, 5H), 2.9 (m, 2H), 5.1 (m, 1H), 6.9-7.1 (m, 3H), 7.3-7.6 (m, 4H), 8.2 (m, 2H), 9.1 (broad s, NH_2^+), 10.2 (broad s, OH).

Mass: m/z 298.1.

EXAMPLE 10

ANALYSIS OF 2-[3-CHLORO-1-(NAPHTHALENYLOXY-PROPYL] THIOPHENE IN METHYL-[3-(NAPHTHALEN-1-YLOXY)-3-THIOPHEN-2-YL-PROPYL]-CARBAMIC ACID ETHYL ESTER OF FORMULA VI

The amount of 2-[3-chloro-1-(naphthalenyloxy-propyl] thiophene of Formula VIIa in methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid ethyl ester of Formula VI is determined using HPLC. The HPLC analysis conditions are described in Table 1.

Table 1

Column	ACE C18, 250 x 4.0mm x 5.0 µ.
Flow rate	0.8 ml
Detector	215 nm
Injection load	5 µl
Sample Preparation	5 mg sample was dissolved in diluent and diluted to 10 ml.
Temperature	Ambient

<table>
<tr><td>Run Time</td><td>60 minutes</td></tr>
<tr><td>Diluent</td><td>Mobile phase B</td></tr>
<tr><td>Mobile phases</td><td>Buffer preparation: dissolve 1.36 g of KH_2PO_4 in 1000 ml of milli-Q water, then add 2.0 gm of sodium-1-octane sulphonate and adjust the pH to 5.0 with dilute KOH.
Mobile phase A: Degassed buffer.
Mobile Phase B: Degassed mixture of acetonitrile and water in the ratio of 8:2.</td></tr>
<tr><td>Gradient program</td><td>
<table>
<tr><th>Interval (min)</th><th>Flow</th><th>Mobile phase A (percent v/v)</th><th>Mobile phase A (percent v/v)</th></tr>
<tr><td>0.01</td><td>1.0</td><td>60.0</td><td>40.0</td></tr>
<tr><td>10.0</td><td>1.0</td><td>60.0</td><td>40.0</td></tr>
<tr><td>20.0</td><td>1.0</td><td>50.0</td><td>50.0</td></tr>
<tr><td>35.0</td><td>1.0</td><td>20.0</td><td>80.0</td></tr>
<tr><td>45.0</td><td>1.0</td><td>10.0</td><td>90.0</td></tr>
<tr><td>55.0</td><td>1.0</td><td>10.0</td><td>90.0</td></tr>
<tr><td>60.0</td><td>1.0</td><td>60.0</td><td>40.0</td></tr>
<tr><td>65.0</td><td>1.0</td><td>60.0</td><td>40.0</td></tr>
</table>
</td></tr>
</table>

RRT for 2-[3-chloro-1-(naphthalenyloxy-propyl] thiophene impurity: 1.28 (methyl-[3-(naphthalen-1-yloxy)-3-thiophen-2-yl-propyl]-carbamic acid ethyl ester = 1).

EXAMPLE 11

ANALYSIS OF R- DULOXETINE HYDROCHLORIDE, 4-NAPTHOL DULOXETINE AND ALPHA NAPHTOL IMPURITIES IN DULOXETINE HYDROCHLORIDE

The R-duloxetine hydrochloride impurity is determined using HPLC. The HPLC analysis conditions are as described in Table 2.

Table 2

Column	Chiralcel OD-H
Detector	230 nm
Flow	1.0 ml/min
Column temp	Ambient
Load	10 µl
Sample Preparation	5 mg of sample was dissolved in ethanol and diluted to 10 ml
Run time	35 minutes
Mobile phase	A mixture of 80 volumes of N-hexane, 20 volumes of ethanol and 0.5 volumes of diethylamine

RRT for R-enantiomeric impurity: 1.36 (duloxetine = 1).

The "DLX-ISO3" impurity content was analyzed by HPLC with the parameters in Table 3.

Table 3

Column	Symmetry C8, 250 × 4.6 mm × 5 µm
Flow rate	1.2 ml/ minute
Detector	215 nm
Injection load	10 µl
Sample Preparation	10 mg of sample was dissolved in acetonitrile and diluted to 10 ml.
Temperature	40 °C
Run Time	45 Minutes
Diluent	Acetonitrile:Mobile phase=2:8
Mobile phase	Buffer Preparation: dissolve 10 ml of TEA in 1000 ml milli-Q water, pH adjusted to 4.0 with dil. H_3PO_4. Mobile phase: Degassed mixture of buffer, tetrahydrofuran and methanol in the ratio 7:2:1.

RRT for DLX-ISO-3 impurity: 1.21 (duloxetine = 1).

The "4-naphthol impurity" was analyzed by HPLC with the parameters in Table 4.

Table 4

<table>
<tr><td>Column</td><td>ACE C18, 250 × 4.0 mm × 5 μm</td></tr>
<tr><td>Flow rate</td><td>1.0 ml/ minute</td></tr>
<tr><td>Detector</td><td>215 nm</td></tr>
<tr><td>Injection load</td><td>5 μl</td></tr>
<tr><td>Sample Preparation</td><td>5 mg of sample was dissolved in mobile phase B and diluted to 10 ml.</td></tr>
<tr><td>Temperature</td><td>Ambient</td></tr>
<tr><td>Gradient conditions</td><td>
<table>
<tr><th>Interval (min)</th><th>Flow</th><th>Mobile phase A (percent v/v)</th><th>Mobile phase B (percent v/v)</th></tr>
<tr><td>0.00</td><td>1.0</td><td>100</td><td>0</td></tr>
<tr><td>2.5</td><td>1.0</td><td>100</td><td>0</td></tr>
<tr><td>15.00</td><td>1.0</td><td>85</td><td>15</td></tr>
<tr><td>30.0</td><td>1.0</td><td>55</td><td>45</td></tr>
<tr><td>40.0</td><td>1.0</td><td>10</td><td>90</td></tr>
<tr><td>55.0</td><td>1.0</td><td>10</td><td>90</td></tr>
<tr><td>15.0</td><td>1.0</td><td>85</td><td>15</td></tr>
<tr><td>60.0</td><td>1.0</td><td>100</td><td>0</td></tr>
<tr><td>65.0</td><td>1.0</td><td>100</td><td>0</td></tr>
</table>
</td></tr>
<tr><td>Mobile phase</td><td>Mobile phase A: Mix 900 ml of buffer and 100 ml of methanol, filter and degas through a filter having porosity 0.45 μ. Mobile phase B: Mix 500 ml of buffer and 200 ml of acetonitrile and 300 ml of methanol, filter and degas through a filter having porosity of 0.45 μ.</td></tr>
</table>

RRT for 4-napthol duloxetine impurity: 0.75 (duloxetine = 1).

EXAMPLE 12

DETERMINATION OF RESIDUAL SOLVENTS IN DULOXETINE HYDROCHLORIDE

The residual solvents and organic volatile impurities are analyzed by a gas chromatography (GC) method using a gas chromatograph equipped with flame ionization detector (FID) and column AT-624 or equivalent, with the parameters given in Table 5.

Table 5

Column length	30 meters
ID	0.53 mm
Film thickness	3.0 μm
Detector temperature	260 °C
Injector temperature	100 °C
Split ratio	1:5
Carrier gas	2.2 psi (Helium)
Sample size	1.0 μl
Sample Preparation	200 mg of sample was dissolved in 1-methyl-2-pyrrolidone and diluted to 10 ml.
Column oven temperature	Initially held at 40 °C for 10 minutes, then increased to 165 °C at a rate of 10°C per minute and held at 165°C for 5 minutes, again increased to 250 °C at a rate of 35 °C per minute and held at 250 °C for 16 minutes.

CLAIMS:

1. A process for preparing duloxetine hydrochloride, comprising reacting hydrogen chloride with duloxetine, in a ratio of up to about 1.5 molar equivalents of hydrogen chloride per molar equivalent of duloxetine.

2. The process of claim 1, wherein about 0.8 to about 1.2 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine, are reacted.

3. The process of claim 1, wherein about 0.8 to about 1.4 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine, are reacted.

4. The process of claim 1, wherein about 0.9 to about 1.1 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine, are reacted.

5. The process of claim 1, wherein about 1 to about 1.2 molar equivalents of hydrogen chloride, per molar equivalent of duloxetine, are reacted.

6. A process for preparing duloxetine or a salt thereof, comprising reacting N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine with naproxen to form a naproxen salt.

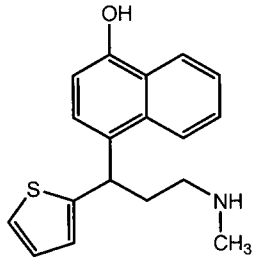
7. The process of claim 6, further comprising reacting a naproxen salt with a base to form duloxetine.

8. A process for preparing duloxetine or a salt thereof, comprising reacting an acid addition salt of N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine with naproxen to form a naproxen salt.

9. The process of claim 8, further comprising reacting a naproxen salt with a base to form duloxetine.

10. The process of claim 8 wherein said acid addition salt is selected from hydrochloride, hydrobormide, para-toluenesulfonate, methanesulfonate, maleate, oxalate, succinate and mandalate.

11. Duloxetine or a salt thereof containing about 0.0055 to about 0.15 weight percent of a compound having a formula:



or a salt thereof.

12. A process for preparing duloxetine or a salt thereof, comprising:

a) reacting 2-acetyl thiophene with dimethylamine hydrochloride and paraformaldehyde to form 3-dimethylamino-1-(2-theinyl)-1-propanone hydrochloride, reducing to form N,N-dimethyl-3-hydroxy-3-(2-thienyl)propanamine, reacting with 1-fluoronaphthalene to form N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine, and reacting with oxalic acid to form a salt;

b) reacting N,N-dimethyl-3-(1-naphthalenyloxy)-3-(2-thienyl)propanamine oxalate with ethylchloroformate to form N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl)propanamine; and

c) reacting N-ethoxycarbonyl-N-methyl-3-(1-naphthanlenyloxy)-3-(2-thienyl)propanamine with a base to form N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine.

13. The process of claim 12, further comprising reacting N-methyl-gamma-(1-naphthyloxy)-2-thiophenepropylamine with naproxen to form a naproxen salt.

14. The process of claim 13, further comprising reacting a naproxen salt with a base to form duloxetine.

15. The process of claim 14, further comprising reacting hydrogen chloride with duloxetine, in a ratio of up to about 1.5 molar equivalents of hydrogen chloride per molar equivalent of duloxetine, to form duloxetine hydrochloride.

16. Duloxetine hydrochloride prepared according to claim 1 having a particle size distribution D_{10} of less than about 50 µm.

17. Duloxetine hydrochloride prepared according to claim 1 having a particle size distribution D_{50} of less than about 100 µm.

18. Duloxetine hydrochloride prepared according to claim 1 having a particle size distribution D_{90} of less than about 300 µm.

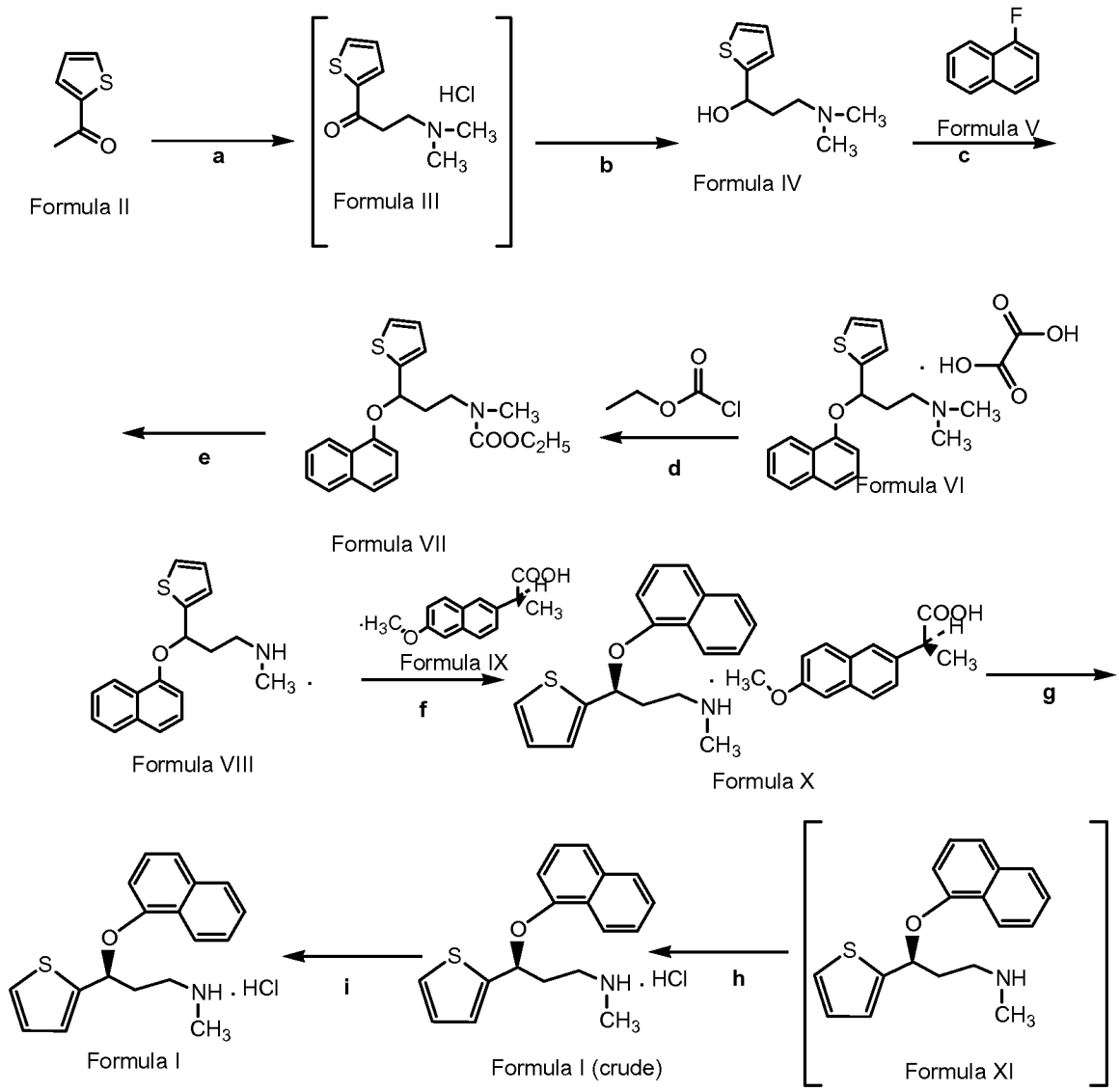
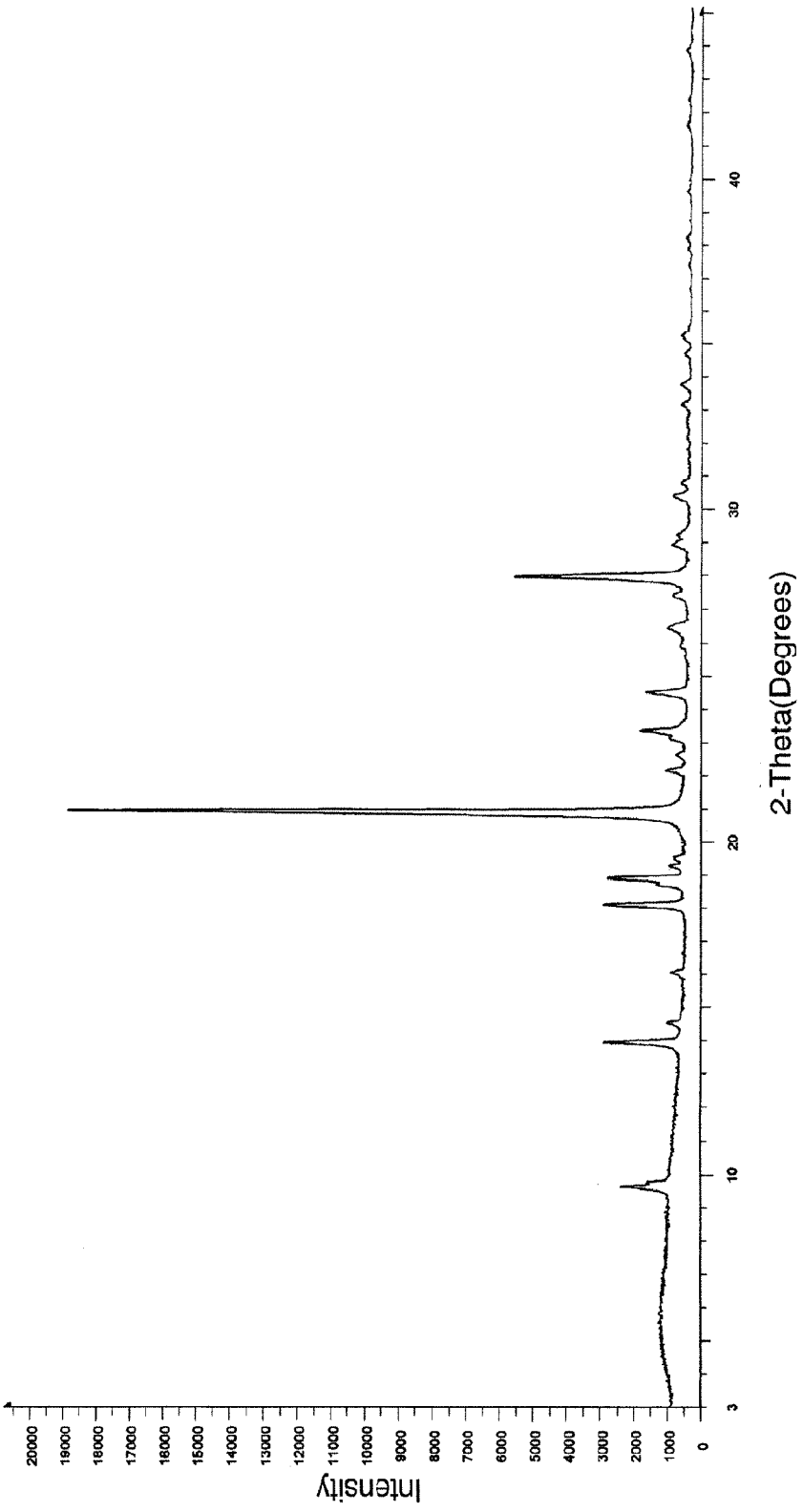

Formula II
a
HCl
Formula III
b
Formula IV
Formula V
c
Formula VI
d
e
Formula VII
Formula IX
f
Formula VIII
g
Formula X
Formula XI
h
i
Formula I (crude)
Formula I

Fig. 1

Fig. 2


Intensity
20000
19000
18000
17000
16000
15000
14000
13000
12000
11000
10000
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
3
10
20
30
40
2-Theta(Degrees)