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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF TRAZODONE AND HYDROCHLORIDE SALT THEREOF

(57) Abrégé/Abstract:
The present invention provides an improved process for preparation of the substantially pure trazodone and its hydrochloride salt. The process comprises reaction of the compound- ? (as described) with the compound-III (as described) optionally in the presence of an inorganic base, and a catalyst; wherein in the said process the trazodone free base and/or its hydrochloride salt are isolated by precipitation at lower temperature. The improved process for the preparation of trazodone hydrochloride (the compound I) provides the product with total amount of alkylating substances (as described herein) as impurity in less than 10 ppm. The improved process for the preparation of trazodone hydrochloride (the compound I) provides the product with total amount of I-(3-chlorophenyl)-4-(3-chloropropyl) piperazine as an impurity in less than 2.5 ppm.

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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF TRAZODONE AND HYDROCHLORIDE SALT THEREOF

(57) Abstract: The present invention provides an improved process for preparation of the substantially pure trazodone and its hydrochloride salt. The process comprises reaction of the compound- II (as described) with the compound-Ill (as described) optionally in the presence of an inorganic base, and a catalyst; wherein in the said process the trazodone free base and/or its hydrochloride salt are isolated by precipitation at lower temperature. The improved process for the preparation of trazodone hydrochloride (the compound I) provides the product with total amount of alkylating substances (as described herein) as impurity in less than 10 ppm. The improved process for the preparation of trazodone hydrochloride (the compound I) provides the product with total amount of l-(3-chlorophenyl)-4-(3-chloropropyl) piperazine as an impurity in less than 2.5 ppm.

AN IMPROVED PROCESS FOR THE PREPARATION OF TRAZODONE AND HYDROCHLORIDE SALT THEREOF

FIELD OF THE INVENTION

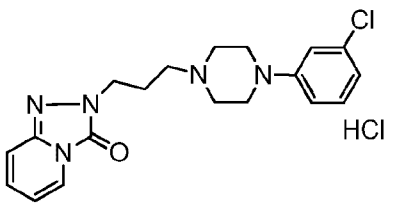
The present invention relates to an improved process for the preparation of 2-{3-[4-(3-chlorophenyl)piperazin-1-yl]propyl}[1,2,4]triazolo[4,3-*a*]pyridin-3(2*H*)-one, generically known as Trazodone, and its hydrochloride salt. In particular, the present invention provides an improved process for the preparation of Trazodone hydrochloride (referred to as the compound-I).

BACKGROUND OF THE INVENTION

The following discussion of the prior art is intended to present the invention in an appropriate technical context, and allows its significance to be properly appreciated. Unless clearly indicated to the contrary, reference to any prior art in this specification should not be construed as an expressed or implied admission that such art is widely known or forms part of common general knowledge in the field.

Trazodone is a serotonin-2 receptor antagonist/reuptake inhibitor that decreases extracellular gamma-amino-butyric acid (GABA) levels in the cerebral cortex through the blockade of 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors. This decrease is accompanied by an increase in 5-HTrelease. At higher doses, trazodone inhibits 5-HT transport and this inhibition of 5-HT uptake results in further increase in 5-HT levels. It is contemplated that this dual mechanism may be responsible for the anti-depressant properties of Trazodone. Moreover, the interaction between the GABAergic and serotoninergic systems may explain its sedative/anxiolytic properties. Trazodone is therefore a psychoactive compound with sedative and anti-depressant properties. It is rapidly absorbed from the upper gastro-intestinal tract and is extensively metabolized after oral administration. It is normally used to relieve symptoms of depression such as feelings of sadness, worthlessness, or guilt; loss of interest in daily activities; changes in appetite; tiredness; thoughts of death or suicide; and insomnia.

Trazodone in its salt form, particularly as hydrochloride salt, is represented by the following structural formula;



(I)

US patent No. 3,381,009 (the US'009 Patent) describes a process for the synthesis of trazodone which comprises condensation of [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one with 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine in the presence of sodium hydride and the solvent, dioxane. The said process requires stirring under reflux condition for about 20 hours.

The US'009 Patent also describes an alternative process for the synthesis of trazodone which comprises condensation of 2-(3-chloropropyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one with 1-(3-chlorophenyl)piperazine in the presence of triethyl amine and the solvent, dioxane.

The US'009 Patent further describes two more alternative processes for the preparation of trazodone, wherein one process comprises reaction of 2-(3-morpholinopropyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one with 3-chloroaniline; and the other comprises reaction of 2-(3-aminopropyl)-[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one with 3-chloro-N,N-bis(2-chloroethyl)aniline.

European Patent EP1108722B1 describes a process for preparation of Trazodone hydrochloride (compound-I) comprising treatment of Trazodone base with aqueous solution of hydrochloric acid.

US Published Patent Application No. 2009/209550 discloses the synthesis of deuterated compounds wherein deuterated 3-(4-(3-chlorophenyl)piperazin-1-yl)propan-1-ol is treated with

[1,2,4]triazolo[4,3-a]pyridin-3(2H)-one in Mitsonobou conditions that is the reaction is performed in the presence of triphenylphosphine and diethylazodicarboxylate as the reagents.

US Patent No.5,256,664 describes a process for the preparation of trazodone which comprises treatment of 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride with an aqueous solution of sodium hydroxide (NaOH) and extraction with methylene chloride. The organic layer was concentrated to produce an oily intermediate compound, 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine (free base) which is further reacted with [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one in the presence of sodium hydroxide and in isopropyl alcohol as the solvent under reflux conditions. The crude oily trazodone was purified using flash chromatography on silica gel. The purified trazodone in isopropyl alcohol was further treated with 2N HCL (hydrochloric acid) to produce trazodone hydrochloride with 47% of yield.

Hungarian patent application No. 201324 describes a process for the preparation of Trazodone comprising reaction of 1,2,4-triazolo-(4,3-a)-pyridine -3(2H)-one with 1-(3'-chloro-propyl)-4-(m-chlorophenyl)-piperazine-hydrochloride in the presence of an alkali-carbonate or powdered sodium-hydroxide wherein the reaction is carried out specifically in a polar aprotic solvent.

US Patent No. 8,133,893(the US'893 Patent) and US Patent No. 8,314,236 describe a process for the purification of trazodone and further conversion of the purified trazodone to its hydrochloride salt. The process described in the US'893 Patent essentially comprises;(a) preparing an organic phase comprising trazodone in at least one organic solvent; (b) preparing an aqueous phase comprising at least one basic compound and optionally, contains a phase transfer catalyst ; (c) mixing said aqueous phase with said organic phase to obtain a mixture; (d) heating said mixture at a temperature of at least 40^{o} C for at least 30 minutes; (e) recovering said trazodone; and, (f) optionally, treating said trazodone with hydrochloric acid to obtain trazodone hydrochloride. The said trazodone hydrochloride is obtained by the treatment with 12N HCl aqueous solution. In addition, the process of US'893 require azeotropic distillation of crude trazodone solution to remove residual water that was incurred from the aqueous phase.

It is evident from the above discussion of the processes for the synthesis of trazodone described in afore cited patent documents that the reported processes primarily requires longer reaction time. Further, the prior art processes involve additional purification methods such as column chromatography, or taking the compound in an organic solvent and washing it with basic aqueous solution; which render the process costlier. Also, these processes involve tedious workup procedures. In view of these drawbacks, there is a need to develop a simple, commercially advantageous and an industrially viable process for the preparation of trazodone and/or its salt such as Trazodone hydrochloride (the compound I) with improved yield and purity in shorter time duration.

Inventors of the present invention have developed an improved process that addresses the problems associated with the processes reported in the prior art. The process of the present invention does not involve use of any additional costly reagents. Moreover, the process does not require additional purification steps and critical workup procedure such as azeotropic distillation. Accordingly, the present invention provides a process for the preparation of trazodone or its salt, which is cost effective, environmentally friendly and commercially scalable for large scale operations.

SUMMARY OF THE INVENTION

In one aspect, the present invention relates to an improved process for the preparation of trazodone or its hydrochloride salt (the compound I), comprising reacting the compound-II (as described herein) with the compound-III (as described herein) optionally in the presence of an inorganic base, and a catalyst.

In one aspect, the present invention relates to an improved process for the preparation of trazodone or its hydrochloride salt (the compound I), comprising reacting the compound-II (as described herein) with the compound-III (as described herein) optionally in the presence of an inorganic base, and a catalyst; wherein in the said process the trazodone free base and/or its hydrochloride salt are isolated by precipitation at lower temperature.

In one aspect, the present invention relates to an improved process for the preparation of

trazodone or its hydrochloride salt (the compound I), comprising reacting the compound-II (as described herein) with the compound-III (as described herein) in the presence of an inorganic base and a phase transfer catalyst.

In one aspect, the present invention relates to an improved process for the preparation of trazodone or its hydrochloride salt (the compound I), comprising reacting the compound-II (as described herein) with the compound-III (as described herein) in the presence of an antioxidant as the catalyst.

In another aspect, the present invention relates to an improved process for the preparation of trazodone hydrochloride (compound I), comprising reacting the compound-II with the compound-III in the presence of an inorganic base and a phase transfer catalyst followed by treatment with an alcoholic solution of hydrogen chloride.

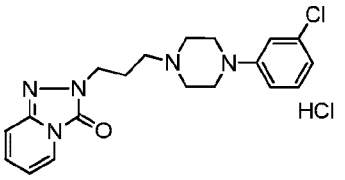
In another aspect, the present invention relates to an improved process for the preparation of trazodone hydrochloride (compound I), comprising isolation of pure trazodone free base or its hydrochloride salt in the absence of water.

According to another aspect of the present invention, there is provided an improved process for the preparation of trazodone hydrochloride (the compound I) wherein the product contains total amount of alkylating substances (as described herein) as impurities in less than 10 ppm.

According to another aspect of the present invention, there is provided an improved process for the preparation of trazodone hydrochloride (the compound I) wherein the product contains total amount of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine as an impurity in less than 2.5 ppm.

DETAILED DESCRIPTION OF THE INVENTION

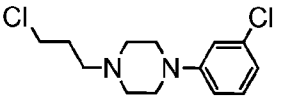
Accordingly, the present invention relates to an improved process for the preparation of trazodone hydrochloride (the compound I) represented by the following formula;



(Compound I)

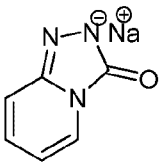
comprising the steps of,

(a) reacting the compound-II or its hydrochloride salt represented by the following formula;



Compound -II

with the compound-III having the following formula;



Compound-III

Optionally in the presence of an inorganic base and a catalyst in a solvent to obtain the compound I as a free base;

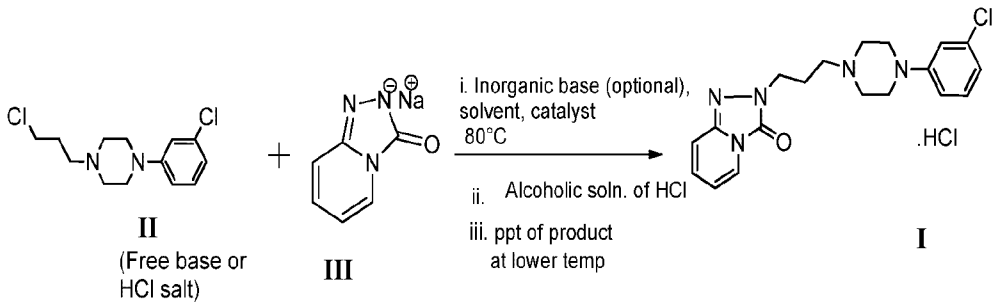
(b) treating the compound I as free base obtained in the above step (a) with an alcoholic solution of hydrogen chloride to obtain the corresponding hydrochloride salt (the compound I);

wherein, in the said process compound I as a free base and/or its hydrochloride salt (compound I) are isolated by precipitation at a lower temperature.

In the context of the present invention, the term "optionally" when used with respect to any element e.g. inorganic base; it is intended to mean that the subject element is present, or

alternatively, is absent. Both alternatives are intended to be within the scope of the present invention.

The process of the present invention as described above is depicted in the following Scheme I:



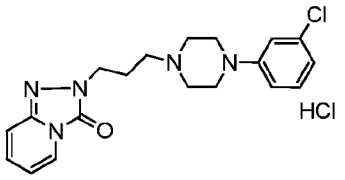
Scheme I

In an embodiment, the step (a) is carried out in the presence of an inorganic base; and the said inorganic base is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, cesium carbonate, calcium carbonate, sodium hydroxide and potassium hydroxide.

In an embodiment, the catalyst used in the process step (a) is a phase transfer catalyst or an antioxidant.

In an embodiment, the catalyst used in the process step (a) is a phase transfer catalyst.

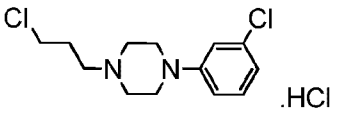
Accordingly, in an embodiment the present invention relates to a process for the preparation of trazodone or its hydrochloride salt (compound I) of the following formula,



(Compound I)

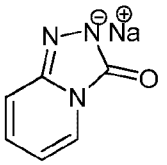
comprising the steps of,

(a) reacting the compound-II hydrochloride salt represented by the following formula;



Compound-II salt

with the compound-III having the following formula;



Compound-III

in the presence of an inorganic base and a phase transfer catalyst in a solvent to obtain the compound I as a free base;

(b) treating the compound I as free base obtained in the above step (a) with an alcoholic solution of hydrogen chloride to obtain the corresponding hydrochloride salt;

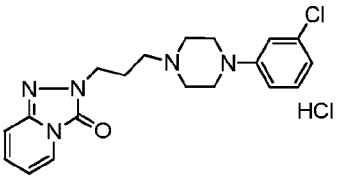
wherein, in the said process compound I as a free base and/or its hydrochloride salt (compound I) are isolated by precipitation at a lower temperature.

In an embodiment, the phase transfer catalyst is a quaternary ammonium salt selected from the group consisting of tricaprylyl methyl ammonium chloride (Aliquat 336), tetra-n-butyl ammonium bromide, triethylbenzylammonium chloride (TEBAC), cetyltrimethylammonium bromide (CTAB), cetylpyridiniumbromide, N-benzylquininiumchloride, tetra-n-butyl ammonium chloride, tetra-n-butyl ammonium hydroxide, tetra-n-butyl ammonium iodide, tetra-ethyl ammonium chloride, benzyltributyl ammonium chloride, benzyltriethylammoniumbromide, hexadecyltriethylammoniumchloride, tetramethylammonium chloride, hexadecyltrimethylammonium chloride and octyltrimethylammoniumchloride or a mixture thereof.

In anembodiment, the phase transfer catalyst is tetra-n-butyl ammonium bromideor triethylbenzyl Ammonium Chloride (TEBAC).

In an embodiment, the catalyst used in the process step (a) is an antioxidant.

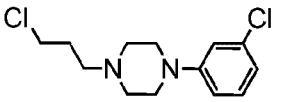
Accordingly, in an embodiment the present invention relates to a process for the preparation of trazodone or its hydrochloride salt (compound I) of the following formula,



(Compound I)

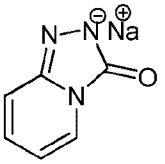
comprising the steps of,

(a) reacting the compound-II as free base represented by the following formula;



Compound-II

with the compound-III having the following formula;



Compound-III

in the presence of an antioxidant in a solvent to obtain the compound I as a free base;

(b) treating the compound I as free base obtained in the above step (a) with an alcoholic solution of hydrogen chloride to obtain the corresponding hydrochloride salt;

wherein, in the said process the compound I as a free base and/or its hydrochloride salt (compound I) are isolated by precipitation at a lower temperature.

In an embodiment, the antioxidant is selected from the group consisting of butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA), tertiary butylhydroquinone (TBHQ), propylgallate (PG), and hydroquinone monomethylether (MEHQ).

In an embodiment, the antioxidant used in step (a) is butylatedhydroxytoluene (BHT).

In an embodiment, the solvent used in step (a) of the process is selected from an alcohol such as ethyl alcohol, n-propyl alcohol, isopropyl alcohol, isobutyl alcohol and methanol; an ether such as ethyl ether or propylether; aromatic hydrocarbon solvents such as toluene, benzene or xylene; and other solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, dioxane, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide or dimethylacetamide.

In anembodiment, the solvent used in step (a) of the process is isopropyl alcohol (IPA).

In an embodiment, the alcoholic solution of hydrogen chloride used in step (b) of the process is selected from the group consisting of isopropyl alcohol hydrochloride (IPA.HCl), ethanolic HCl and methanolic HCl.

In an embodiment, the alcoholic solution of hydrogen chloride used in step (b) of the process is isopropyl alcohol hydrochloride (IPA.HCl).

In an embodiment, trazodone free base as obtained in step (a) of the process is isolated by precipitation at lower temperature.

In an embodiment, trazodone hydrochloride (compound I) as obtained in step (b) of the process is isolated by precipitation at lower temperature.

In an embodiment, trazodone free base in step (a); and/or trazodone hydrochloride in step (b) of the process is isolated by precipitation at lower temperature of about 5 ^{o}C.

The term 'lower temperature" referred to in the step (a)and step (b) of the above process can range from 0 ^{o}C to 10^{o}C.In the context of the present invention the term "lower temperature" can be used interchangeably with the term "lower temperature of about 5°C".

In a specific embodiment, process for the preparation of trazodone hydrochloride (compound I) comprises the steps of,

(1) dissolving the compound II (as its hydrochloride salt)in a solvent, in the presence of an inorganic base;

(2) adding the compound III and a phase transfer catalyst to the reaction mixture of step (1);

(3) stirring the reaction mixture of the above step (2) at a temperature of about 85 ^{o}C;

(4) filtering the hot reaction mixture of the above step (3),and stirring the reaction mixture at a temperature of about 70 ^{o}C;

(5) filtering the reaction mixture of the step (4), and cooling the filtrate to a lower temperature of about 5 °C to obtain a precipitated product;

(6) isolating the precipitated product obtained in the step (5) and treating it with an alcoholic solution of hydrogen chloride at a temperature of about 60 °C;

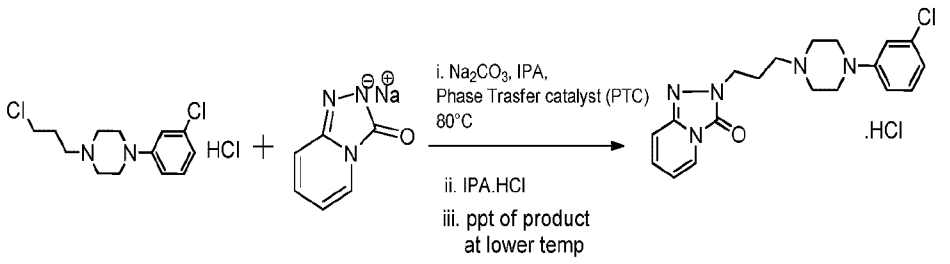
(7) cooling the reaction mixture of step (6) to a lower temperature of about 5 °C to obtain a precipitated product;

(8) isolating the precipitated product obtained in the above step (7)and dissolving it in an alcoholic solvent;

(9) treating the reaction mixture of the above step (8) with carbon powder and stirring it at reflux temperature; and

(10) cooling the reaction mixture of the above step (9) to a lower temperature of about 5 °C, and isolating the precipitated trazodone hydrochloride (compound I).

The process of the present invention as per a specific embodimentis illustrated in the following Scheme-II,



II **III** **I**

Scheme-II

The solvent used in the step-(1) of the above process (as depicted in the Scheme II) is selected from an alcohol such as ethyl alcohol, n-propyl alcohol, isopropyl alcohol, isobutyl alcohol and methanol; an ether such as ethyl ether or propylether; aromatic hydrocarbon solvents such as

toluene, benzene or xylene; and other solvents such as acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, dioxane, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide or dimethylacetamide.

In an embodiment, the solvent used in step-(1) of the above process (as depicted in the Scheme II) is selected from the group consisting of ethyl alcohol, n-propyl alcohol, isopropyl alcohol, isobutyl alcohol and methanol.

In an embodiment, the solvent used in step-(1) of the above process (as depicted in the Scheme II) is isopropyl alcohol (IPA).

The inorganic base used in the step-(1) of the above process (as depicted in the Scheme II) is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, cesium carbonate, calcium carbonate, sodium hydroxide and potassium hydroxide.

In an embodiment, in the process (as depicted in the Scheme II) of the present invention, the inorganic base is used in an amount ranging from 1.5 to 2.5 equivalents with reference to the compound II.

The phase transfer catalyst used in the step-(2) of the above process (as depicted in the Scheme II) is a quaternary ammonium salt selected from the group consisting of tricaprylyl methyl ammonium chloride (Aliquat 336), tetra-n-butyl ammonium bromide, triethylbenzylammonium chloride (TEBAC), cetyltrimethyl- ammonium bromide (CTAB), cetylpyridiniumbromide,N-benzylquininiumchloride, tetra-n-butyl ammonium chloride, tetra-n-butyl ammonium hydroxide, tetra-n-butyl ammonium iodide, tetra-ethyl ammonium chloride, benzyltributylammonium chloride, benzyltriethylammoniumbromide, hexadecyltriethylammoniumchloride, tetramethylammonium chloride, hexadecyltrimethylammonium chloride and octyltrimethylammonium chloride, or a mixture thereof.

In anembodiment, the phase transfer catalyst used in the step-(1) of the process (as depicted in the Scheme II) is selected from tetra-n-butyl ammonium bromideor triethylbenzylammonium

chloride (TEBAC).

In an embodiment, in the process (as depicted in the Scheme II) of the present invention, the phase transfer catalyst (PTC) is used in an amount ranging from 1 % to 5% with reference to the compound-II.

The term 'temperature of about 85°C' referred to in the step (3) of the above process (as depicted in the Scheme II) can range from 80 °C to 90°C.

The term 'lower temperature of about 5°C' referred to in the step (5), step (7) and step (10) of the above process (as depicted in the Scheme II) can range from 0°C to 10°C.

The term 'isolating the precipitated product' referred to in the step (6), step (8) and step (10) corresponds to the steps involving filtration, washing and drying.

The 'alcoholic solution of hydrogen chloride' used in the step (6) of the above process (as depicted in the Scheme II) is selected from the group consisting of isopropyl alcohol hydrochloride (IPA.HCl), ethanolic HCl and methanolic HCl.

In anembodiment, the alcoholic solution of hydrogen chloride used in the process is isopropyl alcohol hydrochloride (IPA.HCl).

The 'alcoholic solvent' used in the steps (6) and (8) of the process(as depicted in the Scheme II) is an alcohol selected from the group consisting of methanol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol and isobutyl alcohol.

In an embodiment, the alcohol used in step-(8) of the process (as depicted in the Scheme II) is methanol.

The process of the present invention as illustrated in the above Scheme-II comprises reaction of the compound II (as its HCl salt) and compound III in the presence of an inorganic base selected

from sodium carbonate or potassium carbonate, and a phase transfer catalyst (PTC) catalyst selected from tetra-n-butyl ammonium bromide or triethylbenzylammonium chloride (TEBAC) in isopropyl alcohol as the solvent. The reaction mixture was heated to a temperature of 80-85°C for 8-12 hours and filtered. The filtrate was distilled out under reduced pressure up to 4.75 volumes, and cooled to a lower temperature of about 0-5 °C and maintained for 2h. The precipitated product was isolated by filtration and the wet cake was dissolved in 3 volume of IPA (isopropyl alcohol) and acidified with IPA HCl at a temperature about 50-60 °C. The reaction mixture was cooled to 0-5 °C and the precipitated product was isolated by filtration. To the dry product, added 6 volume of methanol, heated to reflux until dissolution of product and further treated with carbon powder. The reaction mixture was filtered and the filtrate was cooled to 0-5 °C. The precipitated product, trazodone hydrochloride (compound I) was isolated and the said compound was obtained in a yield of about 85% and purity of about $\geq$ 99.9% (HPLC).

In an another embodiment, process for the preparation of trazodone hydrochloride (compound I) comprises the steps of,

(i) dissolving the compound II (free base) in a solvent;

(ii) adding the compound III and an antioxidant to the reaction mixture of step (i);

(iii) stirring the reaction mixture of the above step (ii) at a temperature of about 85 ^{o}C;

(iv) filtering the hot reaction mixture and stirring the reaction mixture at temperature of about 70 ^{o}C;

(v) filtering the reaction mixture of the step (iv), and cooling the filtrate to a lower temperature of about 5 ^{o}C to obtain a precipitated product;

(vi) isolating the precipitated product obtained in the step (v), and treating it with an alcoholic solution of hydrogen chloride at a temperature of about 60 ^{o}C;

(vii) cooling the reaction mixture of step (vi) to a lower temperature of about 5 ^{o}C to obtain a precipitated product;

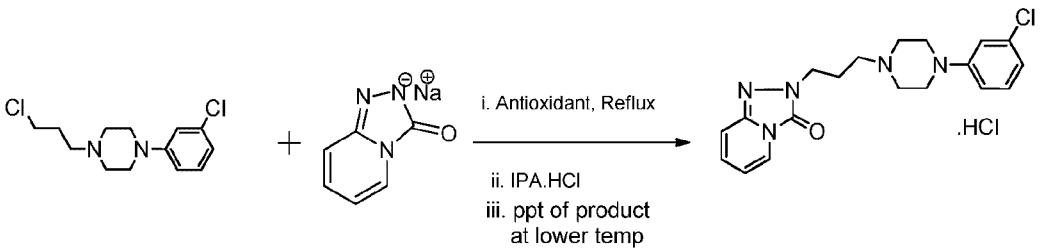
(viii) isolating the precipitated product obtained in the above step (vii), and dissolving it in

an alcoholic solvent;

(ix) treating the reaction mixture of the above step (viii) with carbon powder and stirring it at reflux temperature; and

(x) cooling the reaction mixture of the above step (ix) to a lower temperature of about 5 °C, and isolating the precipitated trazodone hydrochloride (compound I).

The process of the present invention as per the afore described specific embodiment is illustrated in the following Scheme-III,



II (free base) **III** **I**

Scheme-III

The solvent used in the step-(i) of the above process (as depicted in the Scheme III) is the same as that described in respect of step (1) of the process for the preparation of trazodone hydrochloride as depicted in the above Scheme III.

In an embodiment, the solvent used in step-(i) of the above process (as depicted in the Scheme III) is isopropyl alcohol (IPA).

The antioxidant used in the step-(ii) of the above process (as depicted in the Scheme III) is selected from the group consisting of butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA), tertiary butylhydroquinone (TBHQ), propyl Gallate (PG), hydroquinone monomethylether (MEHQ).

In an embodiment, the antioxidant used in the step-(ii) of the process (as depicted in the Scheme III) is butylatedhydroxytoluene (BHT).

In an embodiment, in the process (depicted in Scheme III) of the present invention, the antioxidant is used in an amount ranging from 0.01 to 0.1 mole equivalent with reference to the compound-II.

In an embodiment, in the process (as depicted in the Scheme III) of the present invention, the antioxidant is used in an amount of 0.02 mole equivalent with reference to the compound-II.

The term 'higher temperature of about 85 ^{o}C' referred to in the step (iii) of the above process (as depicted in the Scheme III) can range from 80 ^{o}C to 90 ^{o}C.

The term 'lower temperature of about 5^{o}C' referred to in the step (v), step (vii) and step (x) of the above process (as depicted in the Scheme III) can range from 0^{o}C to 10^{o}C.

The term 'isolating the precipitated product' referred to in the step (vi), step (viii) and step (x) of the process (as depicted in the Scheme III) corresponds to the steps involving filtration, washing and drying.

The term 'alcoholic solution of hydrogen chloride' referred to in the step (vi) of the above process (as depicted in the Scheme III) is selected from the group consisting of isopropyl alcohol hydrochloride (IPA.HCl), ethanolic HCl and methanolic HCl.

In an embodiment, the alcoholic solution of hydrogen chloride used in the process (as depicted in the Scheme III) is isopropyl alcohol hydrochloride (IPA.HCl).

The 'alcoholic solvent' used in the steps (vi) and (viii) of the process(as depicted in the Scheme III) is an alcohol such as methanol, ethyl alcohol, n-propyl alcohol, isopropyl alcohol and isobutyl alcohol.

In an embodiment, the alcohol used in step-(viii) of the process (as depicted in the Scheme III) is methanol.

The process of the present invention as illustrated in the above Scheme-III comprises reaction of the compound II (free base) and the compound III in the presence of an antioxidant as the catalyst selected from the group consisting of butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA), tertiary butylhydroquinone (TBHQ), propyl Gallate (PG) and hydroquinone monomethylether (MEHQ);in isopropyl alcohol as the solvent. The reaction mixture was heated to a temperature of 80-85°C for 8-12 hours and filtered. The filtrate was distilled out under reduced pressure up to 4.75 volumes, and cooled to a lower temperature of about 0-5 °C and maintained for 2h. The precipitated product was isolated by filtration and the wet cake was dissolved in 3 volume of methanol and acidified with IPA HCl at a temperature about 50-60 °C. The reaction mixture was cooled to 0-5 °C and the precipitated product was isolated by filtration. To the dry product, added 6 volume of methanol, heated to reflux until dissolution of product, and further treated with carbon powder. The reaction mixture was filtered, and the filtrate was cooled to 0-5 °C. The precipitated product, trazodone hydrochloride (compound I) was isolated and the said compound was obtained in a yield of about 76% and purity of about ≥ 99.9% (HPLC).

The compound II and the compound III used in the process of the present invention can be prepared by any method reported in the prior art; for instance, the said compounds II and III can be prepared by the process described in US Patent No 4,252,806 (US'806 Patent) and US 4,465,683 (US'683 Patent) respectively. The process for the preparation of compound-II as described in the patent US'806 comprises condensation of 1-(3-chlrophenyl) piperazine with 1-bromo-3-chloropropane;and the process for the preparation of compound III as described in the US'683 Patent comprises condensation of 2-chloropyridine with semicarbazide hydrochloride.

It is evident from the processes for the synthesis of trazodone or trazodone hydrochloride reported in the prior art that the yield of trazodone hydrochloride obtained by the said processes was found to be around 75%, and the purity was 99%, whereas process of the present invention provided the desired compound, trazodone hydrochloride (compound I) in a yield of about 85% and purity of about ≥ 99.9%.

Further, it is reported in the US Patent No. 8,133,893 (US'893 patent) that alkylating substances

such as 2,2-dichloroethylamine, 1-bromo-3-chloropropane that are used in the synthesis of trazodone are genotoxic. The US'893Patent also identifies other potential hazardous alkylating substances namely N-(3-chlorophenyl)-N'-(3-chloropropyl)-piperazine, 2-(3-chloropropyl)-s-triazolo-[4,3-a]-pyridin-3-one, 3-chloro-N,N'-dichloroethyl-aniline, 2-{3-[bis-(2-chloroethyl)-amino]-propyl}-2H-[1,2,4]-triazolo[4,3-a]pyridin-3-one, 2,2-dibromoethylamine, 1,3-dichloropropane, and a mixture thereof, that may be present as impurities in trazodone or trazodone hydrochloride. The US'893 patent describes a process for the purification of trazodone in order to lower the content of these alkylating substances in the final product to below 15 ppm. It is described in the US'893 patent that trazodone was prepared by the process as per disclosed in US 3,381,009. The purification process described in the US'893 Patent essentially comprises preparation of an organic phase containing trazodone, and of an aqueous phase containing a basic compound; and further mixing the two phases by which the said aqueous phase is added to the said organic phase resulting in lowering the content of the specified alkylating substances to below 15 ppm.

Accordingly, in another aspect, the present invention relates to an improved process for the preparation of trazodone hydrochloride (compound I) wherein the product contains total amount of alkylating substances (as described herein) as impurity below 10 ppm.

In an embodiment, the product obtained by process of the present invention contains total amount of alkylating substances (as described herein) as impurity below 5 ppm.

The alkylating substances referred to herein as impurities that can be present in the product, trazodone or trazodone hydrochloride include 1-3(chlorophenyl)-4-(3- chloropropyl) piperazine, 2,2-dichloroethylamine and 1-bromo-3-chloro propane.

In an embodiment, the process of the present invention controls the level of the specified alkylating substances as impurity during the reaction itself. The process of the present invention does not require any additional purification methods such as a method involving giving basic aqueous solution wash to the organic phase containing trazodone. The product i.e. trazodone hydrochloride containing total amount of alkylating substances (as described herein)as impurity

below 5 ppm, is obtained by the process of the present by reducing the temperature to about 5 ^{o}C of the reaction mixture containing the product, and isolating the precipitated product by filtration. Since the instant process does not involve any additional purification step, the overall yield of the process increased to around 85%.

The trazodone hydrochloride obtained by the process of the present invention is substantially pure, particularly in terms of the presence of certain alkylating substances as impurities, for instance the quantification by LCMS method indicates the content of 1-3(chloro phenyl)-4-(3-chloro propyl) piperazine, which is a known genotoxic substance, is present below 2.5 ppm, whereas as the other undesired alkylating substances namely 2,2-dichloroethylamine and 1-bromo-3-chloro propane are not detected in the final product.

According to another aspect of the present invention, there is provided an improved process for the preparation of trazodone hydrochloride (the compound I) wherein the product contains total amount of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine as impurity below 2.5 ppm.

In an embodiment, the product obtained by process of the present invention contains total amount of 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine as impurity below 2.5 ppm.

The invention is further illustrated by the following examples which are provided to be exemplary of the invention and do not limit the scope of the invention. While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Example-1

A round bottom flask was charged with the compound II (HCl salt) (100gm, 0.323M), sodium carbonate (65 g, 0.613 moles) and 600 mL of isopropyl alcohol (IPA).To this reaction mixture was added the compound III (50.8 g, 0.337 moles) and tetra-n-butylammonium bromide (5 g, 5 % w/w). The reaction mixture was stirred for 12 hours at temperature around 80-85°C. The hot

reaction mixture was filtered and the cake was washed with (0.5 volume) IPA. The filtrate was distilled off up to 4.75 volume and cooled to lower temperature around 0-5°C and maintained for 2hours.The precipitated product was filtered and washed with (0.5 volume) of chilled IPA. The obtained crude product was dissolved in 3 volume of IPA and heated the mass to 55-60°C to get clear solution. To this clear solution was added IPA HCl to adjust pH in the range of 2.0 to 2.5 at 55-60°C. The reaction mass was cooled to temperature of around 0°C and maintained for 2 hours at 0-5°C. The precipitated product was filtered and the wet cake was washed with 0.5 volume of chilled IPA, suck dried the product using vacuum. To this dried compound was added methanol (575 mL) and heated to reflux until mass becomes clear solution. Added 6 g of carbon to this methanol solution and stirred for 30 min at reflux temperature. This solution was filtered through the bed of celite and washed with 60 mL of hot methanol. The combined filtrate was distilled out under vacuum up to 2 - 3 volumes. The solution was cooled to lower temperature about 0-5°C and maintained for 2hours. The precipitated product was filtered and washed with 30 mL of chilled methanol. The product was dried to get trazodone hydrochloride in 83%yield and purity of 99.98% (HPLC).

Impurities analysis:

Impurity chemical name	**Impurity Quantificationby LCMS**
Bis(2-chloroethyl) amine or 2,2-dichloroethylamine (Known to be genotoxic substance)	Not detected
1-Bromo-3-chloro propane	Not detected
1-3(chloro phenyl)-4-(3- chloro propyl) piperazine (Known to be genotoxic substance)	<2.5 ppm

Example-2:

A round bottom flask was charged with the compound II (HCl salt)(100gm, 0.323M), potassium carbonate (84.24 g, 0.613 moles) and 600 mL of isopropyl alcohol (IPA). To this stirring reaction mixture was added the compound III (50.8 g, 0.337 moles) and tetra-n-butylammonium bromide (5 g, 5 % w/w). The reaction mixture was stirred for 12 hours at a temperature of around 80-85°C. The hot reaction mixture was filtered and the cake was washed with (0.5 volume) IPA.

The filtrate was distilled off up to 4.75 volumes and cooled to lower temperature around 0-5°C and maintained for 2 hours. The precipitated product was filtered and washed with (0.5 volume) of chilled IPA. The obtained crude product was dissolved in 3 volume of IPA and heated the mass to 55-60°C to get clear solution. To this clear solution was added IPA HCl to adjust pH in the range of 2.0 to 2.5 at 55-60°C. The reaction mass was cooled to temperature around 0°C and maintained for 2 hours at 0-5°C. The precipitated product was filtered and the wet cake was washed with 0.5 volume of chilled IPA, suck dried the product using vacuum. To this dried compound was added methanol (575 mL) and heated to reflux until the mass becomes clear solution. Added 6 g of carbon to this methanol solution and stirred for 30 min at reflux temperature. This solution was filtered through the bed of celite™ and washed with 60 mL of hot methanol. The combined filtrate was distilled out under vacuum up to 2 - 3 volumes. The solution was cooled to lower temperature of about 0-5°C and maintained for 2hours. The precipitated product was filtered and washed with 30 mL of chilled methanol. The product was dried to get trazodone hydrochloride having yield of 83% and purity of 99.98% (HPLC).

Example-3

A round bottom flask was charged with the compound II (100gm, 0.323M), sodium carbonate (65 g, 0.613 moles) and 600 mL of isopropyl alcohol (IPA). To this stirring reaction mixture was added the compound III (50.8 g, 0.337 moles) and triethylbenzylammonium chloride (TEBAC) (5 g, 5 % w/w). The reaction mixture was stirred for 12 hours at a temperature of around 80-85°C. The hot reaction mixture was filtered and the cake was washed with (0.5 volume) IPA. The filtrate was distilled off up to 4.75 volumes and cooled to lower temperature around 0-5°C and maintained for 2 hours. The precipitated product was filtered and washed with chilled IPA (0.5 volumes). The obtained crude product was dissolved in 3 volume of IPA and heated the mass to 55-60°C to get clear solution. To this clear solution was added IPA HCl to adjust pH in the range of 2.0 to 2.5 at 55-60°C. The reaction mass was cooled to temperature of around 0°C and maintained for 2 hours at 0-5°C. The precipitated product was filtered and the wet cake was washed with 0.5 volume of chilled IPA, suck dried the product using vacuum. To this dried compound was added methanol (575 mL) and heated to reflux until the mass becomes clear solution. Added 6 g of carbon to this methanol solution and stirred for 30 min at reflux temperature. This solution was filtered through the bed of celite™ and washed with 60 mL of hot

methanol. The combined filtrate was distilled out under vacuum up to 2 - 3 volumes. The solution was cooled to lower temperature of about 0-5°C and maintained for 2hours. The precipitated product was filtered and washed with 30 mL of chilled methanol. The product was dried to get trazodone hydrochloride in 83% yield and purity of 99.98% (HPLC).

Example-4

A round bottom flask was charged with the compound II (HCl salt) (100 g), 628 mL of DM water, 152 mL of toluene and aqueous sodium hydroxide solution (23 g of Sodium hydroxide by dissolved in 76 mL of DM water). The reaction mixture was stirred and the organic layer was separated.

The combined organic layers (Toluene layers) washed with DM water. Evaporated the solvent completely under vacuum below 70-75°C to provide the compound II (free base) i.e. 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine (free base).

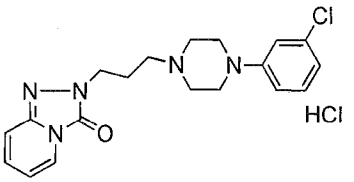
Example-5

A round bottom flask was charged with the compound II (free base) obtained from (example-4) in 800 mL of isopropyl alcohol (IPA) and the compound-III (53.3 gm). To this reaction mixture was added BHT (1.55 g) at 30-35°C. The reaction mixture was stirred at reflux temperature for 14-16 hours. The hot reaction mixture was filtered and the cake was washed with IPA. The filtrate was distilled off up to 4.7 volume and cooled to lower temperature around 0-5°C and maintained for 2hours. The precipitated product (Trazodone free base) was filtered and washed with (500 ml) of chilled IPA. The obtained crude product was dissolved in 300 ml of methanol and heated the mass to 55-60°C to get clear solution. To this clear solution was added IPA HCl to adjust pH in the range of 2.0 to 2.5 at 55-60°C.The reaction mass was cooled to temperature of around 0°C and maintained for 2 hours at 0-5°C. The precipitated product was filtered and the wet cake was washed with 50 ml of chilled methanol, suck dried the product using vacuum. To this dried compound was added methanol (600 ml) and heated to reflux until mass becomes clear solution. Added 5 g of carbon to this methanol solution and stirred for 30 min at reflux temperature. This solution was filtered through the bed of celite and washed with 50 mL of hot methanol. The combined filtrate was distilled out under vacuum up to 2 - 3 volumes. The solution was cooled to lower temperature about 0-5°C and maintained for 2 hours. The

precipitated product was filtered and washed with 100 mL of chilled methanol. The product was dried to get trazodone hydrochloride in 76% yield and purity of 99.98% (HPLC).

We Claim:

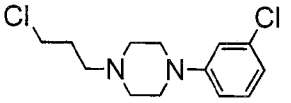
1. A process for the preparation of trazodone or its hydrochloride salt (the compound I) of the following formula,



(Compound I)

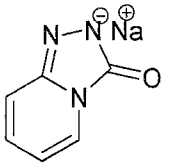
comprising the steps of,

(a) reacting the compound-II or its hydrochloride salt represented by the following formula;



Compound-II

with the compound-III having the following formula;



Compound-III

in the presence of an inorganic base and a catalyst in a solvent to obtain the compound I as a free base;

(b) treating the compound I as free base obtained in the above step (a) with an alcoholic solution of hydrogen chloride to obtain the corresponding hydrochloride salt (the compound I);

wherein, in the said process the compound I as the free base and/or the compound I is isolated by precipitation at lower temperature ranging from 0°C to 10°C.

2. The process as claimed in claim 1, wherein the catalyst is an antioxidant.

3. The process as claimed in claim 1, wherein the inorganic base is selected from the group consisting of sodium carbonate, potassium carbonate, sodium bicarbonate, cesium carbonate, calcium carbonate, sodium hydroxide and potassium hydroxide.

4. The process as claimed in claim 2, wherein the antioxidant is selected from the group consisting of butylatedhydroxytoluene (BHT), butylatedhydroxyanisole (BHA), tertiary butylhydroquinone (TBHQ), propylgallate (PG), and hydroquinone monomethylether (MEHQ).

5. The process as claimed in claim 4, wherein the antioxidant is butylatedhydroxytoluene (BHT).

6. The process as claimed in claim 1, wherein the solvent is selected from the group consisting of ethyl alcohol, n-propyl alcohol, isopropyl alcohol, isobutyl alcohol, methanol; ethyl ether, propylether, toluene, benzene, xylene, acetone, methyl ethyl ketone, methyl isobutyl ketone, acetonitrile, dioxane, tetrahydrofuran, dimethylformamide, dimethyl sulfoxide and dimethylacetamide.

7. The process as claimed in claim 6, wherein the solvent is selected from the group consisting of ethyl alcohol, n-propyl alcohol, isopropyl alcohol, isobutyl alcohol and methanol.

8. The process as claimed in claim 1, wherein the said compound I or its free base contains total amount of alkylating substances as impurity below 10 ppm.

9. The process as claimed in claim 8, wherein the alkylating substance is 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine, present as an impurity below 2.5 ppm.