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A process for the preparation of Trazodone and its hydrochloride

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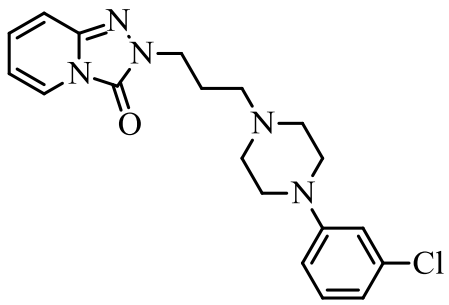
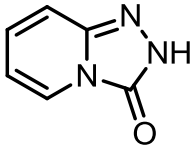
Field of the invention:

The present invention relates to a process for the preparation of Trazodone of formula-1 or its salts.



Formula-1.

The present invention also relates to a process for the preparation of [1,2,4] triazolo[4,3-a]pyridin-3(2H)-one or its salt of formula 4 by an ecofriendly process. The compound of formula 4 or its salt is a key intermediate for the preparation of Trazadone or Trazadone hydrochloride.

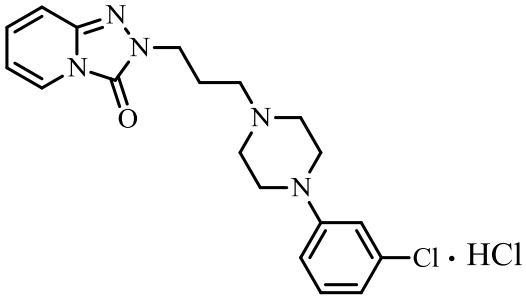


Formula 4.

Background of the invention:

Trazodone is chemically known as 2-[3-[4-(3-chlorophenyl)-1-piperazinyl]propyl]-1,2,4-triazolo [4,3-a]pyridin-3(2H)-one, is an antidepressant of Serotonin Antagonist Reuptake Inhibitor (SARI) class. It is indicated for the treatment of major depressive disorder (MDD). Trazodone decrease the extracellular gamma-amino-butyric acid (GABA) in cerebral cortex by blockade of 5-Hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptors on GABA neurons. Furthermore, a rise in 5-HT release occurs in response to the drop in GABA level. Trazodone is well absorbed after oral administration, without selective localization in any tissue.

Trazodone hydrochloride, represented by the given structural formula 1a, with a molecular weight of 408.32:

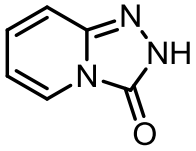


Formula-1a.

Brief description of the invention:

First embodiment of the present invention provides a preparation of Trazodone or its Hydrochloride salt.

Second embodiment of the present invention provides a process for the preparation of [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one of formula-4 or its salt water as used a solvent.



Formula 4.

Detailed Description of the invention:

The “suitable solvent” used in the present invention can be selected from but not limited to “hydrocarbon solvents” such as n-pentane, n-hexane, n-heptane, cyclohexane, petroleum ether, benzene, toluene, xylene and mixtures thereof; “ether solvents” such as dimethyl ether, diethyl ether, diisopropyl ether, methyl tert-butyl ether, 1,2-dimethoxyethane, tetrahydrofuran, 1,4-dioxane and mixtures thereof; “ester solvents” such as methyl acetate, ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate, tert-butyl acetate and mixtures thereof; “polar-aprotic solvents” such as dimethylacetamide, dimethylformamide, dimethylsulfoxide, N-

methylpyrrolidone (NMP) and mixtures thereof; “chloro solvents” such as dichloromethane, dichloroethane, chloroform, carbon tetrachloride and mixtures thereof; “ketone solvents” such as acetone, methyl ethyl ketone, methyl isobutyl ketone and mixtures thereof; “nitrile solvents” such as acetonitrile, propionitrile, isobutyronitrile and mixtures thereof; “alcohol solvents” such as methanol, ethanol, n-propanol, iso-propanol, n-butanol, iso-butanol, 2-butanol, tert-butanol, ethane-1,2-diol, propane-1,2-diol and mixtures thereof; “polar solvents” such as water; formic acid, acetic acid and the like or mixture of any of the afore mentioned solvents.

The term “base” used in the present invention refers to inorganic bases selected from “alkali metal carbonates” such as sodium carbonate, potassium carbonate, lithium carbonate, cesium carbonate and the like; “alkali metal bicarbonates” such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate and the like; “alkali metal hydroxides” such as sodium hydroxide, potassium hydroxide, lithium hydroxide and the like; “alkyl metals” such as n-butyl lithium and like; “metal hydrides” such as lithium hydride, sodium hydride, potassium hydride and the like; “alkali metal phosphates” such as disodium hydrogen phosphate, dipotassium hydrogen phosphate; ammonia such as aqueous ammonia, ammonia gas, methanolic ammonia and like and “organic bases” selected from but not limited to methyl amine, ethyl amine, diisopropyl amine, diisopropylethyl amine (DIPEA), diisobutylamine, triethylamine, tert.butyl amine, pyridine, 4-dimethylaminopyridine (DMAP), N-methyl morpholine (NMM), nmethyl pyridine (NMP), 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,5-diazabicyclo[4.3.0] non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO), imidazole; “alkalimetal alkoxides” such as sodium methoxide, sodium ethoxide, potassium methoxide,potassium ethoxide, sodium tert.butoxide, potassium tert.butoxide and the like; “alkali metal amides” such as sodium amide, potassium amide, lithium amide, lithiumdiisopropyl amide (LDA), sodium bis(trimethylsilyl) amide (NaHMDS), potassiumbis(trimethylsilyl)amide, lithium bis(trimethysilyl) amide (LiHMDS) and

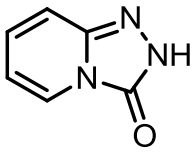
the like; or mixtures thereof.

First embodiment of the present invention provides a preparation of Trazodone or its hydrochloride salt comprises:

a) reacting 1-(3-chlorophenyl)-4-(3-chloropropyl) piperazine formula-5 or its salt with a [1,2,4] triazolo[4,3-a]pyridin-3(2H)-one formula-4 or its salt in the presence of a base optionally in the presence of a catalyst in a solvent,
b) treating the Trazodone obtained in step-a) with base,
c) isolating the Trazodone from step-b),
d) converting Trazodone to Trazodone hydrochloride by reacting with hydrochloric acid source in a solvent.

Solvent used in step-a) is selected from hydrocarbon solvents, ether solvents, ester solvents, polar-aprotic solvents, chloro solvents, ketone solvents, nitrile solvents, alcohol solvents or mixture thereof; base in step-a) or step-b) can be selected from the base defined as above; isolating Trazodone in step-c) refers to the solvent removal by known techniques which are selected from but not limited to removal by distillation, by decanting, by filtration, cooling the clear solution to lower temperatures to precipitate the solid followed by filtration of the reaction; the hydrochloric acid source can be selected from but not limited to concentrated hydrochloric acid, dry hydrochloric acid, hydrochloric acid gas, aqueous hydrochloric acid, methanolic hydrochloric acid, ethanolic hydrochloric acid, isopropyl alcohol- hydrochloric acid, ethyl acetate- hydrochloric acid, 1,4-dioxane- hydrochloric acid and the like.

Second embodiment of the present invention provides a process for the preparation of [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one of formula-4 or its salt



Formula 4

comprising:

a) reacting the 2-chloropyridine compound of formula 2 with semicarbazide of formula-3 or its hydrochloride salt in presence of water to provide [1,2,4]triazolo[4,3-a]pyridin-3(2H)-one,

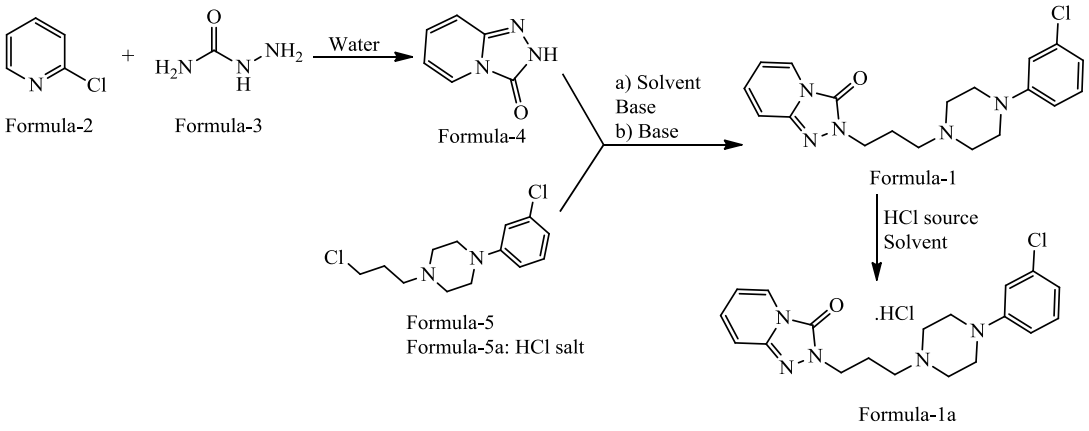
b) optionally converting to its salt.

wherein salt in step-b) is obtained treating with metal source.

Metal source is selected from alkali or alkaline hydroxides or carbonates.

Further the present invention surprisingly noticed that the Trazodone hydrochloride obtained according to the present invention is free of halo alkyling impurities.

The present invention depicted in the following scheme-1 as follows:



Scheme-1

An embodiment of the present invention provides a method of treating a patient in need thereof comprising administering to the said patient a therapeutically effective amount of Trazodone Hydrochloride obtained according to the present invention.

In an aspect of the third embodiment of the present invention provides a method of treatment of major depressive disorder (MDD) by using Trazodone Hydrochloride according to the present invention.

Trazodone hydrochloride produced by the present invention can be further micronized or milled to get desired particle size to achieve desired solubility profile based on different forms of pharmaceutical composition requirements. Techniques that may be used for particle size reduction includes but not limited to single or multi-stage micronization using cutting mills, pin/cage mills, hammer mills, jet mills, fluidized bed jet mills, ball mills and roller mills. Milling/micronization may be performed before drying or after drying of the product.

The best mode of carrying out the present invention was illustrated by the below mentioned examples. These examples are provided as an illustration only and hence, should not be construed as a limitation on the scope of the invention.

Examples:

Example 1: Preparation of (1,2,4)triazolo(4,3-a)pyridine-3(2H)-one

Semicarbazide hydrochloride (196 g) was added to the mixture of 2-Chloropyridine (100 g) and water (300 ml) at 25-35°C. Heated the reaction mass to 95±3°C and stirred at same temperature. Further heated the reaction mixture to 105±5°C and stirred at same temperature. Reaction mixture was cooled to 25-35°C and stirred. Filtered the precipitated solid and washed with water at 25-35°C. Water was added to the obtained compound at 25-35°C. The mixture was heated to 60-70°C and stirred. Mixture was cooled to 25-35°C and stirred at same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 75 g.

Example 2: Preparation of 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride

1-(3-chlorophenyl)piperazine hydrochloride (100 g) was added to aqueous sodium hydroxide solution {42.8 g of sodium hydroxide in 500 ml water) solution at 25-35°C and stirred. 1-bromo-3-chloropropane (203 gr) was added to the reaction mass at 25-35°C. Stirred the reaction mass at 30-35°C. Cyclohexane was added to the reaction mixture. Organic and aqueous layers were separated. Aqueous layer extracted with

cyclohexane. Combined the organic layers and aqueous hydrochloric acid solution was added at 25-30°C and stirred. Filtered the precipitated solid and washed with cyclohexane. Methanol was added to the obtained solid at 25-35°C and stirred. Water was added to the above mixture. Heated the mixture to 60-70°C and stirred. Cooled the mixture to 0-10°C and stirred at same temperature. Filtered the solid, washed with mixture of water and methanol, dried to get the title compound.

Yield: 115 g.

Example 3: Preparation of 2-(3-(4-(3-chlorophenyl)piperazin-l-yl)propyl) [l,2,4]triazolo [4,3-a]pyridin-3(2H)-one

Sodium carbonate (30.81 g) was added to the mixture of [l,2,4]triazolo[4,3-a] pyridin-3(2H)-one (14.4 g) and isopropyl alcohol (180 ml) at 25-30°C and stirred. 1-(3-chlorophenyl)-4-(3-chloropropyl)piperazine hydrochloride (30 g) and Tetrabutylammonium Bromide (1.5 g) was added to the reaction mixture at 25-30°C. Heated the reaction mixture to 80-85°C and stirred at the same temperature. Cooled the reaction mixture to 60-70°C. A solution of sodium methoxide (2.61 g) in isopropyl alcohol (30 ml) was added to the reaction mixture and stirred at the same temperature. Filtered the mixture and washed with isopropyl alcohol at 60-70°C. The solution of sodium methoxide (0.52 g) in isopropyl alcohol (15 ml) was added to the above filtrate and stirred. The mixture was cooled to 35-45°C and stirred, further cooled the mixture to 10±3°C and stirred. Filtered the solid washed with chilled isopropyl alcohol. Water was added to the obtained compound, heated the mixture to 55-65°C and stirred. The mixture was cooled to 30-40°C and stirred the same temperature. Filtered the solid, washed with water and dried to get the title compound.

Yield: 28.5 g.

Example 4: Preparation of Trazodone hydrochloride

Dissolved 2-(3-(4-(3-chlorophenyl)piperazin-l-yl)propyl)[l,2,4]triazolo[4,3-a]pyridin-3(2H)-one (20 g) in isopropyl alcohol (160 ml) at 65-75°C. Activated carbon was added to the reaction mixture and stirred at same temperature. Filtered the mixture

through hyflow bed and washed with isopropyl alcohol. The obtained filtrate was cooled to 36°C, then added aqueous hydrochloride in to the mixture and stirred. Cooled the mixture to 30±3°C and stirred. Filtered the precipitated solid washed with isopropyl alcohol. The obtained compound was slurried in mixture of solvent isopropyl alcohol and water. Filtered the solid, washed with isopropyl alcohol and dried to get the title compound.

Yield: 19 g.

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