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(71) Applicants *(for all designated States except US)*: **FINETECH LABORATORIES LTD.** [IL/IL]; Technion City, P.O. Box 3557, 31032 Haifa (IL). **GUTMAN, Arie, L.** [IL/IL]; 9/22 Shindler Street, 34996 Haifa (IL). **NISNEVICH, Gennady** [IL/IL]; Netiv Hen 81/70, 32688 Haifa (IL).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: **TISHIN, Boris** [IL/IL]; 46/63 Leon Blum Street, 33852 Haifa (IL). **VILENSKY, Alexander** [IL/IL]; 46/43 Leon Blum steet, 38532 Haifa (IL). **POTYABIN, Pavel** [IL/IL]; 8 Victor Hugo Street, 35431 Haifa (IL).

(74) Agent: REINHOLD COHN AND PARTNERS; P.O.Box 4060, 61040 Tel-Aviv (IL).

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(54) Title: PROCESS FOR PRODUCTION OF HIGHLY PURE DONEPEZIL HYDROCHLORIDE

(57) Abstract: The present invention provides a process for the preparation of highly pure Donepezil hydrochloride having a liquid chromatography purity (relative area method) of more than 97%, with a content of each individual impurity not exceeding 0.02 area %, which process comprises forming Donepezil base in solution and treating the Donepezil base solution with HCl without prior isolation of Donepezil base; and optionally re-crystallizing the hydrochloride to give Donepezil hydrochloride of desired liquid chromatography purity. Donepezil base in solution may be obtained by intramolecular cyclization of 2-(3,4-dimethoxybenzyl)-3-(N-benzyl- 4-piperidine)propionic acid or a salt thereof.

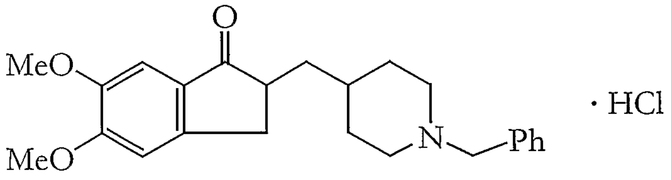
PROCESS FOR PRODUCTION OF HIGHLY PURE DONEPEZIL HYDROCHLORIDE

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of highly pure Donepezil hydrochloride.

BACKGROUND OF THE INVENTION

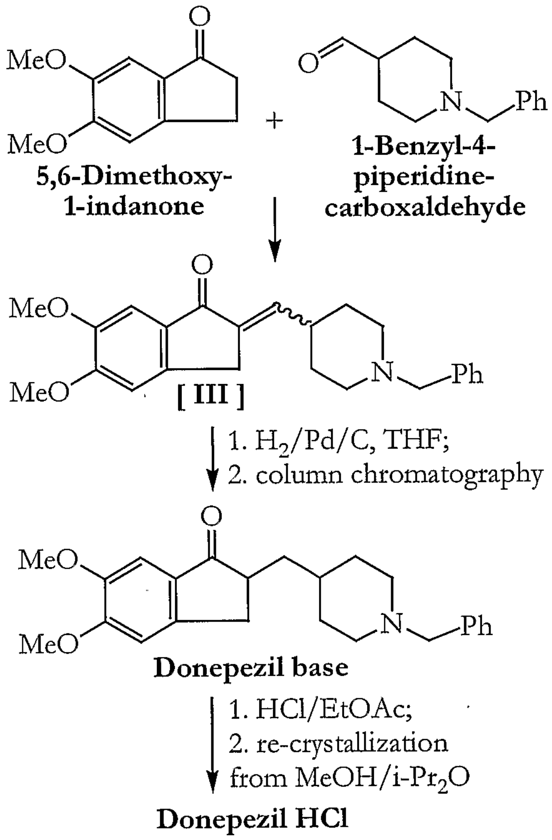
Donepezil hydrochloride, a reversible acetylcholinesterase inhibitor represented by the following formula



is an active ingredient marketed in the United States of America under a proprietary name ARICEPT (Applicant: Eisai Medical Research), useful as a therapeutic and ameliorating agent (tablets) for Alzheimer-type senile dementia, particularly as a prophylactic.

Donepezil hydrochloride is produced by first producing Donepezil, which is a free base, and then converting it into a hydrochloride. In other words, Donepezil base is used as a precursor for the production of Donepezil hydrochloride.

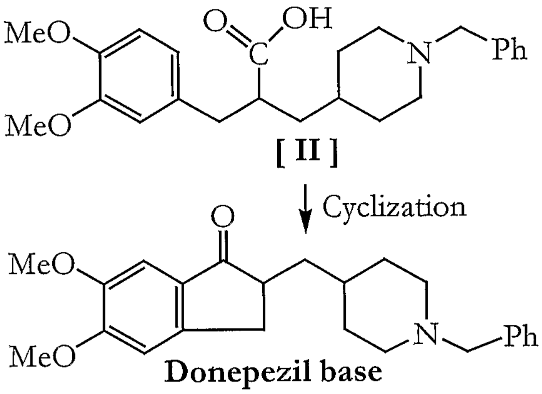
A synthetic route to Donepezil is shown in Scheme 1 and comprises the condensation of 5,6-dimethoxy-1-indanone with 1-benzyl-4-piperidinecarboxaldehyde followed by reduction of the obtained compound **[III]** and column chromatography of the crude Donepezil base on silica gel. Donepezil hydrochloride was prepared from the resulting purified Donepezil base by treating the base with HCl/EtOAc and re-crystallizing the resulting solid from MeOH/i-Pr_2O (H. Sugimoto et al., J. Med. Chem., 1995, v. 38, 481 and Eisai Co., U.S. 5,100,901).



Scheme 1

Recently it was proposed to use crystallization for purification of crude Donepezil base obtained after the reduction of compound **[III]** (Eisai Co., U.S. 6,245,911).

An alternative process disclosed in WO00/09483 for preparing Donepezil base is shown in Scheme 2 and comprises the steps of (a) intramolecular cyclization of the compound **[II]** to yield Donepezil base and (b) isolating the resulting Donepezil base, following crystallization:



Scheme 2

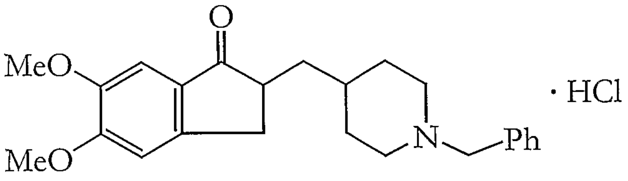
An additional process for production of Donepezil hydrochloride involves reacting a Donepezil intermediate with halogenated benzyl to obtain a Donepezil quaternary ammonium salt, hydrogenation of the quaternary ammonium salt to produce Donepezil base, followed by addition of HCl to produce Donepezil hydrochloride (US 6,252,081).

It should be noted that all the known procedures for preparing Donepezil hydrochloride involve the isolation and handling of intermediate Donepezil base prior to converting it into Donepezil hydrochloride. There are several disadvantages in such two-step processes. These include increased cycle time due to increased handling requirements, increased air emissions if drying of the Donepezil base is required, and increased total volume of solvent needed. Further, in the prior art, the desired compound is purified by column chromatography, which requires a large amount of solvent and the column is discarded after use, and is thus very disadvantageous in production cost. In addition, the large amount of the used solvent is evaporated into the atmosphere, and therefore, the column chromatography is preferably not used from the viewpoint of working environment or environmental protection.

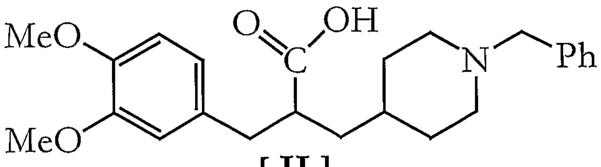
SUMMARY OF THE INVENTION

In view of the foregoing, there is a need in the art to provide a scalable industrial process for synthesizing highly pure Donepezil hydrochloride, without the need for isolation, chromatography and re-crystallization of the intermediate Donepezil base. It is a further need in the art to provide a process for synthesizing Donepezil hydrochloride having a liquid chromatography (hereinafter abbreviated "LC") purity (relative area method which measures the area under a LC peak) of higher than 97%, preferably higher than 98%, more preferably higher than 99% and even more preferably higher than 99.9 % and a content of each individual impurity not exceeding 0.02 % (by area).

Thus, the present invention provides according to a first aspect thereof, a process for preparing highly pure Donepezil hydrochloride represented by the following formula



wherein the obtained salt has a liquid chromatography (LC) purity (relative area method) of higher than 97% and a content of each individual impurity not exceeding 0.02 % (by area), which process comprises: intramolecular cyclization of 2-(3,4-dimethoxybenzyl)-3-(N-benzyl-4-piperidine)propionic acid **[II]**



[II]

or its salt to form Donepezil base, treating the donepezil base with HCl without isolating Donepezil base to form Donepezil hydrochloride; and optionally crystallizing the Donepezil hydrochloride to give the salt of desired LC purity.

In a preferred embodiment Donepezil hydrochloride prepared by the method of the present invention has a liquid chromatography (LC) purity (relative area method) of at least 99.9%.

According to a second aspect, the present invention provides a scalable industrial process for the preparation of pure Donepezil hydrochloride having a liquid chromatography purity (relative area method) of higher than 97 %, preferably higher than 98%, more preferably higher than 99% and even more preferably higher than 99.9%, and with a content of each individual impurity not exceeding 0.02 % (by area),

which process comprises forming Donepezil base in solution and treating the Donepezil base solution with HCl without prior isolation of Donepezil base; and optionally re-crystallizing the hydrochloride salt to give Donepezil hydrochloride of desired liquid chromatography purity.

Donepezil base in solution may be obtained by intramolecular cyclization of 2-(3,4-dimethoxybenzyl)-3-(N-benzyl- 4-piperidine)propionic acid **[II]** or a salt thereof, as described above or by any other process which affords highly pure Donepezil base as end product, without prior isolation and purification.

The term "industrial process" mentioned above refers to commercial production scale in the range of 1 kilogram and more.

DETAILED DESCRIPTION OF THE INVENTION

The described invention provides a process for the preparation of highly pure Donepezil hydrochloride by cyclization of a compound of formula **[II]** or a salt thereof.

Preferably, the cyclization of compound **[II]** is carried out under Friedel-Crafts reaction conditions, optionally with previous derivatization of the carboxylic group to a halocarbonyl group, preferably chlorocarbonyl group.

Preferably, the cyclization in the process of the present invention is carried out in the presence of protic acids or Lewis acids or a mixture of protic and Lewis acids. Examples of such acids are trifluoromethanesulfonic acid, methanesulfonic acid, polyphosphoric acid, fluoro- or chlorosulfonic acid, sulfuric acid, hydrogen fluoride and hydrogen chloride. Examples of Lewis acids are zinc chloride, zinc bromide, aluminum chloride, aluminum bromide, titanium chloride, boron fluoride, phosphorus pentoxide, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride and sulfuryl chloride.

The cyclization may be carried out in the presence of a solvent. Preferably, the solvent is a halogenated solvent. Examples of halogenated solvents are dichloromethane, chloroform, dichloroethane, tetrachloroethane, chlorobenzene, dichlorobenzene and mixtures thereof. Alternatively, the solvent is nitromethane, nitroethane, nitrobenzene, ether and mixtures thereof.

Preferably, the compound **[II]** or its salt has liquid chromatography purity (relative area method) of at least 97 %. More preferably, the compound **[II]** or its salt has liquid chromatography purity (relative area method) of at least 98 %. Most preferably, the compound **[II]** or its salt has liquid chromatography purity (relative area method) of at least 99 %.

The present invention will be described in more detail with the aid of the following non-limiting examples.

EXAMPLES

The liquid chromatography (LC) purity was determined by separating a sample by high performance liquid chromatography (HPLC) under the following conditions, and calculating the area percentage thereof.

HPLC conditions:

Column: Intersil 5 mm ODS-2 150 x 4.6 mm (Metachem)

Mobile phase: acetonitrile/water/70 % aq. perchloric acid 30 : 70 : 0.1 (v/v)

Flow rate: 0.7 mL/min

Column temperature: 36 °C

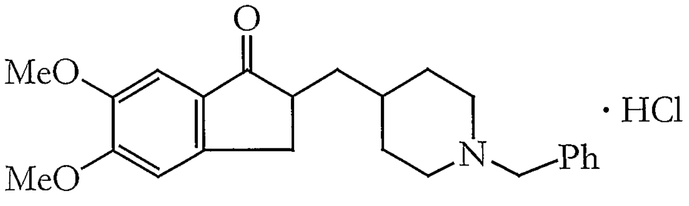
Detection: UV 230 nm

Example 1: Preparation of Highly Pure Donepezil Hydrochloride

A 100 L glass reactor equipped with a mechanical stirrer, a dropping funnel, a thermometer and a condenser connected to a bubbler was charged with phosphorus pentoxide (1.53 Kg) and methanesulfonic acid (14.6 Kg) and filled with argon. The mixture was stirred at 70 - 80 °C until complete homogenization. Dichloromethane (12 L) and 2-(3,4-dimethoxybenzyl)-3-(N-benzyl-4-piperidine)propionic acid **[II]** (2.75 Kg) were added to the mixture at 15 - 30 °C. The obtained mixture was stirred under reflux conditions for 3 hour. The cold reaction mixture was poured into ice (40 Kg). The mixture was basified to pH 9-10 with 40 % aq. potassium hydroxide at 10 - 15 °C. The organic layer was separated and the aqueous layer was extracted with dichloromethane. The combined organic extracts were dried over sodium sulfate and concentrated to the volume of 7 – 8 L. The concentrated solution was added dropwise to the stirred 10 wt. % solution of hydrogen chloride in ethyl acetate (3.40 Kg) while maintaining the temperature at 0 - 3 °C. The mixture was stirred for 1 hour at 0 - 15 °C and evaporated under reduced pressure to obtain crystals, which were recrystallized from methanol/isopropyl ether to obtain 2.45 Kg (85 %) of Donepezil hydrochloride with HPLC purity (relative area method) of more than 99.9 % and a content of any individual impurity not exceeding 0.02 area %.

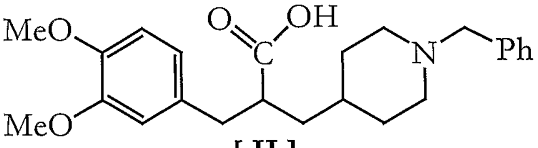
CLAIMS:

1. A process for the preparation of highly pure Donepezil hydrochloride represented by the following formula



having a liquid chromatography purity (relative area method) of more than 97%, with a content of each individual impurity not exceeding 0.02 area %, which process comprises:

intramolecular cyclization of 2-(3,4-dimethoxybenzyl)-3-(N-benzyl-4-piperidine)propionic acid **[II]**



[II]

or its salt to form Donepezil hydrochloride, upon treatment of the solution with HCl and without isolation of Donepezil base.

2. The process of claim 1 further comprising the step of re-crystallizing the hydrochloride salt of Donepezil to give Donepezil salt of desired liquid chromatography purity.

3. The process of claim 1 or 2 wherein the intramolecular cyclization is performed in the presence of a protic acid, a Lewis acid or a mixture thereof.

4. The process of claim 3, wherein said intramolecular cyclization is performed in the presence of a protic acid selected from the group consisting of trifluoromethanesulfonic acid, methanesulfonic acid, polyphosphoric acid, fluoro- or chlorosulfonic acid, sulfuric acid, hydrogen fluoride and hydrogen chloride.

5. The process of claim 3, wherein said intramolecular cyclization is performed in the presence of a Lewis acid selected from the group consisting of zinc chloride, zinc bromide, aluminum chloride, aluminum bromide, titanium chloride, boron fluoride, phosphorus pentoxide, phosphorus oxychloride, phosphorus pentachloride, phosphorus trichloride, thionyl chloride and sulfuryl chloride.

6. The process of claim 1 or 2, wherein said intramolecular cyclization is performed in the presence of a solvent.

7. The process of claim 6, wherein said solvent is a halogenated solvent.

8. The process of claim 7, wherein said halogenated solvent is selected from the group consisting of dichloromethane, chloroform, dichloroethane, tetrachloroethane, chlorobenzene, dichlorobenzene and mixtures thereof.

9. The process of claim 6, wherein said solvent is selected from the group consisting of nitromethane, nitroethane, nitrobenzene, ether and mixtures thereof.

10. The process of claim 1, wherein the carboxylic group of compound **[II]** is derivatized to a halocarbonyl group prior to carrying out the intramolecular cyclization.

11. The process of claim 1, wherein said Donepezil base is treated with HCl to form a Donepezil hydrochloride-containing solution that is subsequently evaporated under reduced pressure to obtain Donepezil hydrochloride crystals, where said crystals are re-crystallized from methanol/isopropyl ether.

12. The process of claim 1, wherein Donepezil hydrochloride has a LC purity of more than 98%.

13. The process of claim 1, wherein Donepezil hydrochloride has a LC purity of more than 99%.

14. The process of claim 1, wherein Donepezil hydrochloride has a LC purity of more than 99.9%.

15. Donepezil hydrochloride having a LC purity of more than 99.9%, with a content of each individual impurity not exceeding 0.02%, prepared by the process of claim 1.

16. A process for the preparation of highly pure Donepezil hydrochloride having a liquid chromatography purity (relative area method) of higher than 97%, and with a content of each individual impurity not exceeding 0.02 % (by area), which process comprises forming Donepezil base in solution and treating the Donepezil base solution with HCl without prior isolation of Donepezil base; and optionally re-crystallizing the hydrochloride salt to give Donepezil hydrochloride of desired liquid chromatography purity.

17. The process of claim 16, wherein Donepezil base in solution is obtained by intramolecular cyclization of 2-(3,4-dimethoxybenzyl)-3-(N-benzyl-4-piperidine)propionic acid **[II]** or a salt thereof.

18. The process of claim 16, wherein Donepezil hydrochloride has a liquid chromatography purity higher than 98%, more preferably higher than 99% and even more preferably higher than 99.9%.

19. Donepezil hydrochloride having a LC purity of more than 99.9%, with a content of each individual impurity not exceeding 0.02%, prepared by the process of claim 16.