(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
14 May 2009 (14.05.2009)

PCT

(10) International Publication Number
WO 2009/062036 A2

(51) International Patent Classification:
C07D 239/42 (2006.01)

(21) International Application Number:
PCT/US2008/082802

(22) International Filing Date:
7 November 2008 (07.11.2008)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
2575/CHE/2007 9 November 2007 (09.11.2007) IN
61/057,496 30 May 2008 (30.05.2008) US

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(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, NO, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2009/062036 A2

(54) Title: PROCESSES FOR PREPARING LEVOCETIRIZINE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

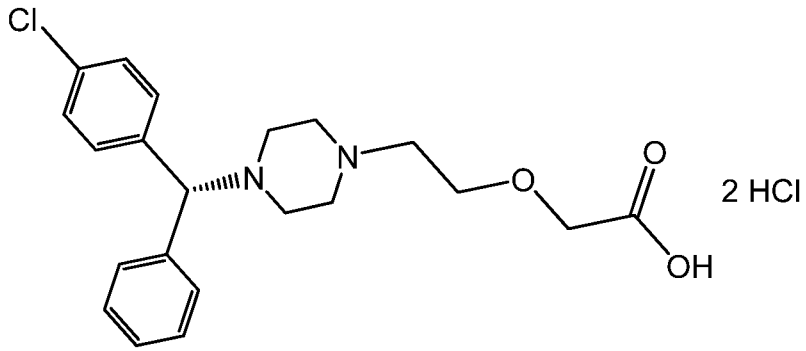
(57) Abstract: Processes for preparing levocetirizine dihydrochloride.

PROCESSES FOR PREPARING LEVOCETIRIZINE AND PHARMACEUTICALLY ACCEPTABLE SALTS THEREOF

INTRODUCTION

The present invention relates to processes for preparing levocetirizine and pharmaceutically acceptable salts thereof.

Levocetirizine dihydrochloride is the adopted name for a drug chemically described as (R)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid dihydrochloride, with molecular formula $C_{21}H_{25}ClN_2O_3 \bullet 2$ HCl and is represented by the structural Formula I.



Formula I

Levocetirizine dihydrochloride is a white, crystalline powder and is water soluble. It is used as an active and selective H1-receptor antagonist and is marketed under the brand name as XYZAL® tablets in 5 mg strength.

U.S. Patents Nos. 4525358, 5478941, and 7381821, and Great Britain Patent Nos. 2225320 and 2225321 described various processes for the synthesis of cetirizine and its enantiomers.

Great Britain Patent No. 2225321 described a process for the preparation of cetirizine in the levorotatory or dextrorotatory form or a mixture of thereof comprising the hydrolysis of enantiomerically pure or racemic [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]-acetonitrile.

Also, processes for preparing levocetirizine and dextrocetirizine from its racemic mixture or racemic intermediates were known in U.S. Patent No. 6977301, and International Application Publication Nos. WO 2005/073207 and WO 2006/094648.

According to the generally accepted procedure in the field of the synthesis of optically active chemicals, those synthetic routes are preferred which involve the use of optically active intermediate.

Literature records various processes wherein optically active intermediates have been employed for manufacturing levocetirizine, such as Great Britain Patent No. 2225321, U.S. Patent Nos. 5478941 and 6803465, and International Application Publication Nos. WO 2007/066162 and WO 2007/066163.

In some of the reported synthetic schemes, 1-(4-chlorophenyl)-phenylmethyl-piperazine served as the key intermediate in the synthesis of levocetirizine.

U.S. Patent No. 5478941 disclosed the preparation/introduction of optical center in the early phase of the synthesis i.e. R-(-)-1-(4-chlorophenyl)-phenylmethylamine followed by reaction with N,N-bis-(2-chloroethyl)4-methylbenzenesulfonamide to prepare optically active 1-[(4-chlorophenyl)-phenylmethyl]-4-[p-toluenesulphonyl]-piperazine, which was subsequently crystallized. According to the said process, p-toluenesulfonyl group was removed by stirring the protected intermediate with 30% HBr/acetic acid in presence of about four molar equivalents of 4-hydroxybenzoic acid which was added to prevent racemization. The crude product so obtained was further purified by recrystallization.

As per International Application Publication No. WO 2007/066163, the aforesaid process suffered from the disadvantages, such as the hydrolysis of the p-toluenesulphonyl group required harsh condition which resulted in racemization that could only be avoided by using further additives. Furthermore, the use of additive not only contaminated the product, but also constituted additional cost.

Similarly, International Application Publication No. WO 2004/065360 described a process for the preparation of levocetirizine, wherein enantiomerically pure intermediate,[2-[4-[(4-chlorophenyl)methyl]-1-piperazinyl]ethanol was used, which had been purified by using chiral chromatographic purification.

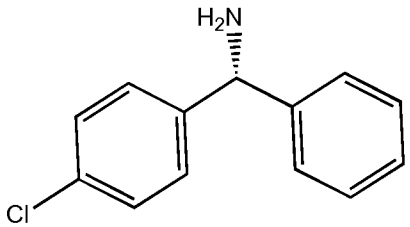
Thus, it is evident from the state of the art that only those protecting groups can be used at the nitrogen atom in position "4" of the piperazine ring of 1-(4-chlorophenyl)-phenylmethyl-piperazine, which can be removed under mild conditions without causing racemization of the optical center. Prior art also indicates that optically active 1-(4-chlorophenyl)-phenylmethyl-piperazine is transformed slowly into the corresponding racemic compound in acidic or basic solution even at room temperature.

In view of the demerits associated with these processes, it is desirable to develop a simpler route for the preparation of enantiomerically pure compounds, such as levocetirizine and its pharmaceutically acceptable salts, without or alleviating the use of expensive reagents, complicated and costly equipment, and without complicated operations (chiral chromatographic purification), thus which is economical and industrially viable.

SUMMARY

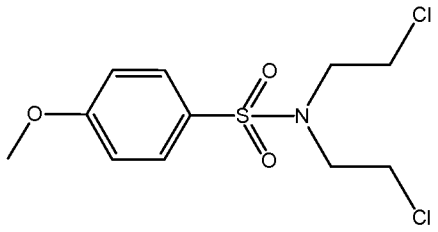
There are provided processes for preparing levocetirizine dihydrochloride of Formula I, which processes comprise at least one of the steps of:

(1) condensing (-)-4-chlorobenzhydrylamine of Formula VII



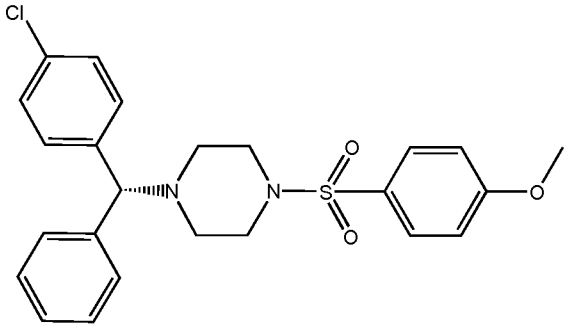
Formula VII

with N,N-bis-(2-chloroethyl)-4-methoxybenzenesulfonamide of Formula VI



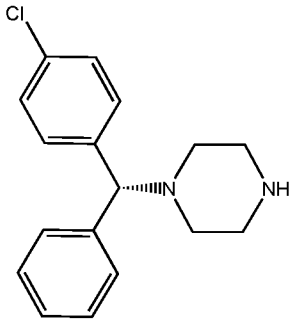
Formula VI

using a base in the presence of organic solvent(s) to afford (-)-1-[(4-chloro-phenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V;



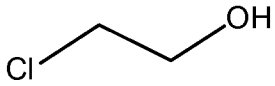
Formula V

(2) removing the 4-methoxyphenylsulfonyl group from the compound of Formula V using a deprotecting agent in the presence of organic solvent(s) to afford (-)-1-[(4-chlorophenyl)phenylmethyl]-piperazine of Formula IV;



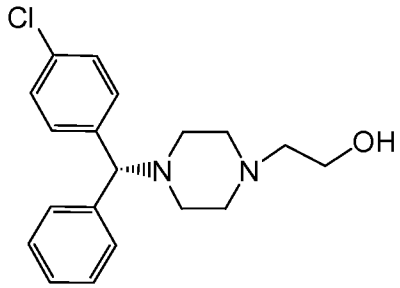
Formula IV

(3) condensing the compound of Formula IV with 2-chloroethanol of Formula III



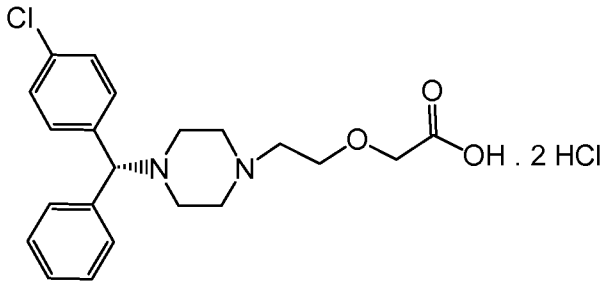
Formula III

using a base and optionally in the presence of organic solvent(s) to afford (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II.



Formula II

(4) reacting the compound of Formula II with sodium monochloroacetate using suitable reagents in the presence of organic solvent(s) at suitable temperatures to afford (+)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy] acetic acid dihydrochloride of Formula I



Formula I

(5) purifying the compound of Formula I by recrystallization or making a slurry in organic solvent(s).

There is also provided (-)-1-[(4-chloro-phenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V that is substantially pure of other process related impurities and optical impurities for use in a process for the manufacture of levocetirizine dihydrochloride.

There are provided processes for the preparation of (-)-1-[(4-chlorophenyl)phenylmethyl]-piperazine of Formula IV by deprotecting the (-)-1-[(4-chloro-phenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V, which process alleviates the use of an additive such as 4-hydroxybenzoic acid and any recrystallization or purification(s) steps with concomitant retention of the optical as well as chemical purity in compound of Formula IV.

There are provided a process for the preparation of substantially pure (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II.

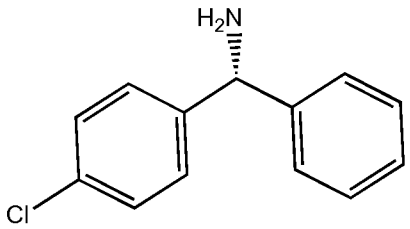
There are provided processes for the preparation of substantially pure (+)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride of Formula I starting from (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II, wherein the (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II is not purified by chiral chromatography.

There is provided substantially pure levocetirizine or its salts.

DETAILED DESCRIPTION

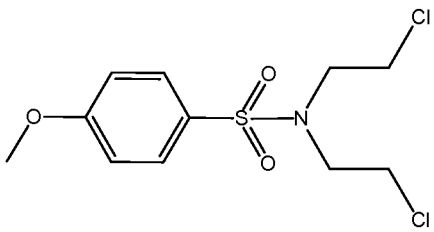
There are provided processes for preparing levocetirizine dihydrochloride of Formula I, which processes comprise at least one of the steps of:

(1) condensing (-)-4-chlorobenzhydrylamine of Formula VII



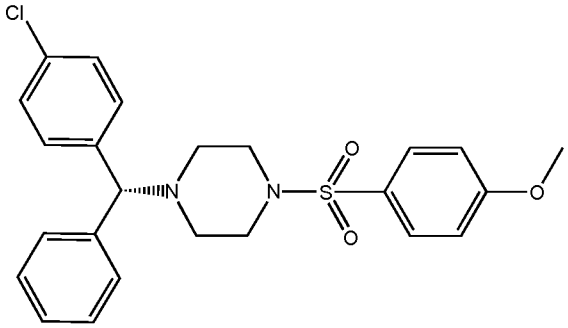
Formula VII

with N,N-bis-(2-chloroethyl)-4-methoxybenzenesulfonamide of Formula VI



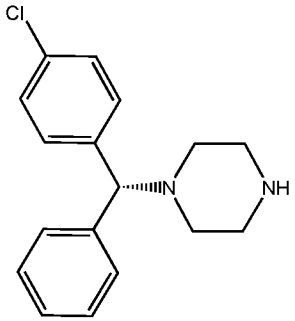
Formula VI

using a base in the presence of organic solvent(s) to afford (-)-1-[(4-chloro-phenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V;



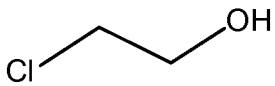
Formula V

(2) removing the 4-methoxyphenylsulfonyl group from the compound of Formula V using a deprotecting agent in the presence of organic solvent(s) to afford (-)-1-[(4-chlorophenyl)phenylmethyl]-piperazine of Formula IV;



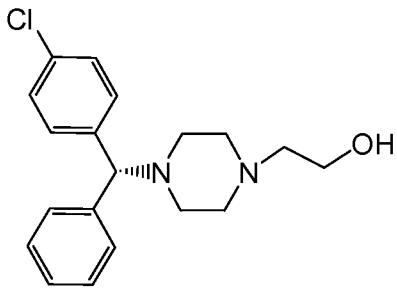
Formula IV

(3) condensing the compound of Formula IV with 2-chloroethanol of Formula III



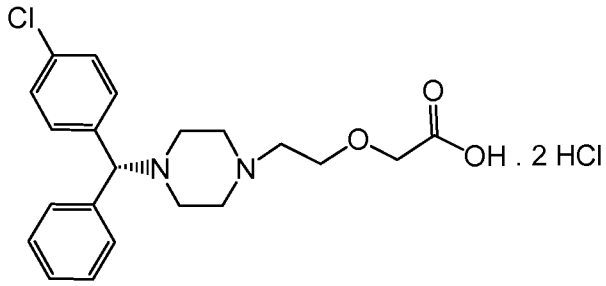
Formula III

using a base and optionally in the presence of organic solvent(s) to afford (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II.



Formula II

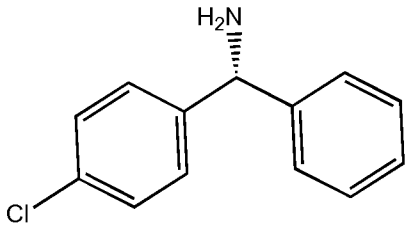
(4) reacting the compound of Formula II with sodium monochloroacetate using suitable reagents in the presence of organic solvent(s) at suitable temperatures to afford (+)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride of Formula I



Formula I

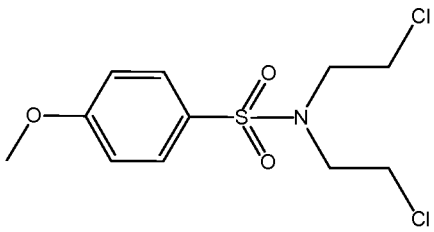
(5) purifying the compound of Formula I by recrystallization or making a slurry in organic solvent(s).

Step (1) involves condensing (-)-4-chlorobenzhydrylamine of Formula VII



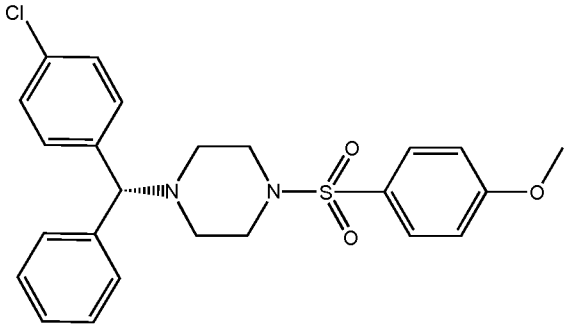
Formula VII

with N,N-bis-(2-chloroethyl)-4-methoxybenzenesulfonamide of Formula VI



Formula VI

using a base optionally in the presence of organic solvent(s) to afford (-)-1-[(4-chloro-phenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V;



Formula V

Suitable bases for Step (1) include organic bases, inorganic bases, and mixtures thereof. Suitable inorganic bases include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Suitable organic bases include methylamine, dimethylamine, triethylamine, N-ethyl diisopropylamine, butyl amine, and N-methyl morpholine. For example, the base is N,N-diisopropylethylamine.

In Step (1), the molar equivalent of base per compound of Formula VI, *i.e.*, (-)-4-chlorobenzhydryl amine, may be about 2–4.

Suitable solvents for Step (1) include and are not limited to: alcohols, such as, for example, methanol, ethanol, and isopropyl alcohol; halogenated solvents, such as, for example, dichloromethane, dichloroethane, and chloroform; hydrocarbon solvents, such as, for example, toluene, xylene, cyclohexane, and heptane; ketones, such as, for example, acetone, methyl isobutyl ketone, methyl ethyl ketone, and n-butanone; esters, such as, for example, ethyl acetate, n-propyl acetate, and isopropyl acetate; and mixtures thereof. For example, a solvent comprises methanol.

Suitable temperatures for conducting the reaction of Step (1) may range from about 30 °C to about 140°C or the reflux temperature of the solvent used. The reaction may be carried out for a desired time period to achieve the desired product yield and purity, for example, from about 30 minutes to about 10 hours, or longer.

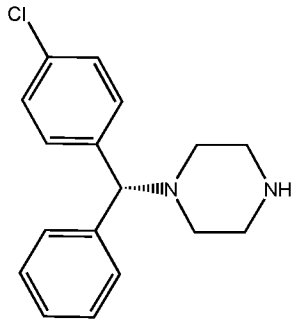
The completion of the reaction can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). The reaction mass is cooled after completion of the reaction, methanol is added, cooled to ambient temperature to precipitate out the product, which is further cooled to less than about 10 °C, aged for sufficient time to ensure complete precipitation of the compound.

The separated compound may be recovered from the reaction mixture by removal of solvent, by gravity filtration, filtration by suction or by centrifugation, followed by washing the compound with a suitable solvent, which may the same solvent used during precipitation of the product to wash out mother liquors occluded in the product.

The recovered product may optionally be further dried. Drying may be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, rotatory dryer, and the like. Drying may be carried out at temperatures from about 25 °C to about 75 °C with or without vacuum and in the presence or absence of an inert atmosphere like nitrogen, argon, neon, and helium. Drying may be carried out for a desired time period to achieve the desired product purity. Drying times from about 1 to about 15 hours, or longer, are frequently adequate.

The compound may optionally be recrystallized from a suitable solvent, which includes: alcohols such as methanol, ethanol, and isopropyl alcohol; halogenated solvents, such as dichloromethane, dichloroethane, and chloroform; hydrocarbon solvents, such as, toluene, xylene, cyclohexane, and heptane; ketones, such as, acetone, methyl isobutyl ketone, methyl ethyl ketone, and n-butanone; esters, such as, for example, ethyl acetate, n-propyl acetate, and isopropyl acetate; and mixtures thereof.

Step (2) involves removing the 4-methoxyphenylsulfonyl group from the compound of Formula V using a deprotecting agent in the presence of organic solvent(s) to afford (-)-1-[(4-chlorophenyl)phenylmethyl]-piperazine of Formula IV;



Formula IV

Suitable deprotecting agents for Step (2) include and are not limited to acids, such as, for example, hydrochloric acid and hydrobromic acid in their aqueous medium or purged in organic acids, such as, for example, acetic acid. For example, the deprotecting agent comprises hydrobromic acid.

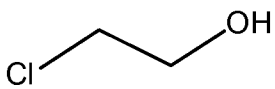
For Step (2), suitable solvents include and are not limited to: alcohols, such as, for example, methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, and tertiary-butyl alcohol; ketones, such as, for example, acetone, methyl ethyl ketone, and methylisobutylketone; halogenated solvents, such as, for example, dichloromethane, dichloroethane, and chloroform; hydrocarbon solvents, such as, for example, toluene, xylene, and cyclohexane; esters, such as, for example, ethyl acetate, isopropyl acetate, and tertiary butyl acetate; acetic acid and mixtures of acetic acid and acetic anhydride; water; and mixtures thereof in various proportions. For example, a solvent comprises glacial acetic acid.

Suitable temperature for conducting the reaction may range from about 15 °C to about 90 °C, or the reflux temperature of the solvent used. The reaction may be carried out for a desired time period to achieve the desired product yield and purity. For example, the reaction time may be from about 30 minutes to about 10 hours.

The completion of the reaction can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). The reaction mass is cooled to a lower temperature of about less than 40 °C. The reaction mass is diluted with water and washed with a suitable water immiscible solvent such as, an aliphatic or aromatic hydrocarbon for example, hexane, heptane, benzene, toluene, xylene etc. or a halogenated hydrocarbon such as, chloroform, dichloromethane, chlorobenzene or an ester such as, for example; ethyl acetate, isopropyl acetate, n-butyl acetate or an ether such as, for example diethyl ether, diisopropyl ether or a ketone such as methyl ethyl ketone, methyl isobutyl ketone or any suitable solvent as desired, to remove unreacted starting materials if any and to remove impurities.

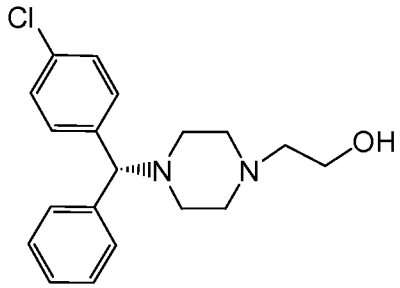
The product may be recovered by basification of the aqueous reaction mass to a pH of above 7.0, followed by extraction of the product into a suitable water immiscible solvent such as benzene, toluene, xylene, dichloromethane, chloroform ethyl acetate. The organic layer obtained upon extraction followed by separation from the aqueous layer may be washed with water, followed by removal of the solvent by distillation. The residue left after solvent removal is triturated with water and the separated solid is aged for suitable time and filtered to remove the solvent, washed with water to remove the occluded mother liquors and dried.

Step (3) involves condensing the compound of Formula IV with 2-chloroethanol of Formula III



Formula III

using a base and optionally in the presence of organic solvent(s) to afford (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol of Formula II.



Formula II

In Step (3), the molar equivalent of 2-chloroethanol per Formula IV may be about 1–5.

The bases suitable for Step (3) include and are not limited to sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium methoxide, potassium teritarybutoxide, pyridine, N-methylmorpholine, diisopropylamine, triethylamine, diisopropylethylamine, and mixtures thereof. For example, the base comprises triethylamine.

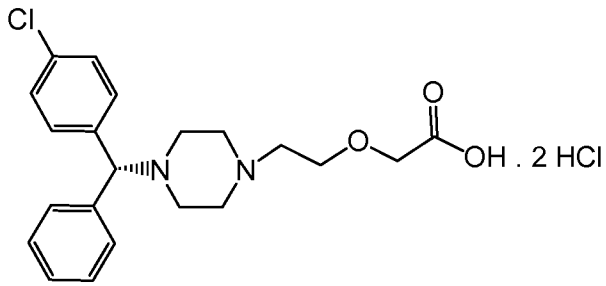
The solvents suitable for Step (3) include and are not limited to: alcohols, such as, for example, methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, and tertiary-butyl alcohol; ketones, such as, for example, acetone, methyl ethyl ketone, and methylisobutylketone; hydrocarbon solvents, such as, for example, toluene, xylene, cyclohexane, and the like; esters, such as, for example, ethyl acetate, isopropyl acetate, tertiary butyl acetate, and the like; nitriles, such as, for example, acetonitrile and propionitrile; aprotic polar solvents, such as, for example, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and N-methylpyrrolidinone; and mixtures thereof; and their combinations with water in various proportions.

Suitable temperatures for conducting the reaction of Step (3) may range from about 15 °C to about 120 °C, or the reflux temperature of the solvent used. The reaction of Step (3) may be carried out for a desired time period to achieve the

desired product yield and purity. For example, the reaction time may be from about 30 minutes to about 10 hours.

The completion of the reaction can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). After completion of the reaction the reaction mass may be cooled to a lower temperature and quenched with water, the compound is extracted with a suitable water immiscible solvent such as benzene, toluene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, ethyl acetate, isopropyl acetate or n-butyl acetate. Solvent is removed from the organic extract by distillation resulting in thick syrupy oil.

Step (4) reacting the compound of Formula II with sodium monochloroacetate using suitable reagents in the presence of organic solvent(s) at suitable temperatures to afford (+)-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy] acetic acid dihydrochloride of Formula I.



Formula I

The molar equivalent of sodium monochloroacetate per the compound of Formula II may be about 1–5.

Suitable bases for Step (4) include organic bases, inorganic bases, and mixtures thereof. Suitable inorganic bases include sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Suitable organic bases include methylamine, dimethylamine, triethylamine, N-ethyldiisopropylamine, butylamine, and N-methylmorpholine. For example, a base comprises potassium carbonate.

The solvents suitable for Step (4) include and are not limited to: alcohols, such as, for example, methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol and tertiary-butyl alcohol; ketones, such as, for example, acetone, methyl ethyl ketone, and methylisobutylketone; hydrocarbon solvents, such as, for example, toluene, xylene, cyclohexane, and the like; esters, such as, for example, ethyl acetate, isopropyl acetate, and tertiary butyl acetate; nitriles, such as, for example, acetonitrile, propionitrile, and the like; aprotic polar solvents, such as, for example, dimethylsulfoxide, N,N-dimethylformamide, dimethylacetamide, and N-methylpyrrolidinone; and mixtures thereof; and their combinations with water in various proportions. For example, a solvent comprises N,N-dimethylformamide

Suitable temperature for conducting the reaction of Step (4) may range from about 0 °C to about 90 °C, or the reflux temperature of the solvent used. The reaction may be carried out for a desired time period to achieve the desired product yield and purity. For example, the reaction time for Step (4) may be from about 30 minutes to about 10 hours.

Suitable acids for acidification may be aqueous hydrochloride (5%-36%), hydrochloride in methanol, hydrochloride in isopropyl alcohol, hydrochloride in acetone, dry hydrochloride gas, and mixtures thereof.

The completion of the reaction can be monitored by thin layer chromatography (TLC) or high performance liquid chromatography (HPLC). After completion of the reaction the reaction mass is quenched with water, and washed with a suitable water immiscible solvent such as, an aliphatic or aromatic hydrocarbon for example; hexane, heptane, benzene, toluene, xylene etc. or a halogenated hydrocarbon such as, chloroform, dichloromethane, chlorobenzene or an ester such as, for example; ethyl acetate, isopropyl acetate, n-butyl acetate or an ether such as, for example diethyl ether, diisopropyl ether or a ketone such as methyl ethyl ketone, methyl isobutyl ketone or any suitable solvent as desired, to remove unreacted starting materials if any and to remove impurities.

The aqueous reaction mass after removal of the undesired compounds, is acidified with diluted aqueous hydrochloric acid to a pH of less than 4.5 and the product is extracted with a suitable water immiscible solvent such as benzene, toluene, xylene, dichloromethane, chloroform, 1,2-dichloroethane, ethyl acetate, isopropyl acetate or n-butyl acetate, followed by carbon treatment with activated charcoal and removal of the solvent. Solvent may be removed by evaporation, distillation, distillation may be carried out atmospherically or under reduced pressure to yield the desired compound in the form of freebase as thick syrupy oil, which may optionally be converted to an acid additional salt using a pharmaceutically acceptable acid.

The syrupy oil obtained upon removal of the solvent may be converted to a hydrochloride salt by treating a solution of the compound in a suitable solvent such as acetone, methyl ethyl ketone, toluene, and ethyl acetate, preferably acetone, at a suitable temperature of from about 25 to 50 oC with hydrochloric acid.

The hydrochloride salt separated out is further maintained at about 25-35 oC for about 30 min. to 2.0 hrs, the product may be recovered from the reaction mass by filtration or centrifugation and may be washed with the same solvent to remove mother liquors trapped in the compound.

The recovered product may optionally be further dried. Drying may be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, rotatory dryer, and the like. Drying may be carried out at temperatures from about 25 °C to about 75 °C with or without vacuum and in the presence or absence of an inert atmosphere like nitrogen. Drying may be carried out for a desired time period to achieve the desired product purity. Drying times from about 1 to about 15 hours, or longer, are frequently adequate.
The product may be purified if desired by conventional methods such as recrystallisation, purification by slurry or by regeneration of base followed by conversion to hydrochloride salt.

Step (5) involves purifying the compound of Formula I by recrystallization or making a slurry in organic solvent(s).

Recrystallization involves providing a solution of crude levocetirizine or a salt thereof in a suitable solvent or mixture of solvents and then crystallizing the solid from the solution.

Suitable organic solvents in which levocetirizine or a salt may be dissolved for purification include and are not limited to: C_1–C_5 ketones, such as, for example, acetone, ethyl methyl ketone and butanone; alcohols, such as, for example, ethanol, methanol, and isopropanol; ethers, such as, for example, tetrahydrofuran and 1,4-dioxane, ethyl acetate; water; and mixtures thereof in various proportions without limitation. For example, the organic solvent comprises water and acetone.

Suitable temperatures for forming a solution for recrystallization may range from about 25 °C to about 75 °C, or from about 50 °C to about 60 °C, or about reflux temperature of the solvent used.

The concentration of the levocetirizine or its salt in the solvent(s) may range from about 15 % to about 95 %. The solution may be prepared at an elevated temperature if desired to achieve a higher solute concentration. Any temperature is acceptable for the dissolution as long as a clear solution of the levocetirizine or salt is obtained and the temperature is not detrimental to the drug substance chemically or physically. Further processing of the solution, if desired, is achieved by adjusting the temperature. A higher temperature for dissolution will allow the precipitation from solutions with higher concentrations of levocetirizine, resulting in better economies of manufacture. Crystal formation from the solution may be promoted by cooling the solution.

The recovered product may optionally be further dried. Drying may be suitably carried out in a tray dryer, vacuum oven, air oven, fluidized bed drier, spin flash dryer, flash dryer, rotatory dryer, and the like. Drying may be carried out at temperatures from about 25 °C to about 75 °C with or without vacuum and in the

presence or absence of an inert atmosphere like nitrogen, argon, neon, and helium. Drying may be carried out for a desired time period to achieve the desired product purity. Drying times from about 1 to about 15 hours, or longer, are frequently adequate.

The present invention includes enantiomerically pure (-)-1-[(4-chlorophenyl) phenylmethyl]-4-[(4-methoxyphenyl)sulfonyl] piperazine of Formula V, that is substantially pure of other process related impurities and optical impurities.

The present invention includes processes for preparing a compound of Formula IV by deprotecting a compound of Formula V, without using 4-hydroxy benzoic acid, wherein, the optical purity, as well as chemical purity, is retained in the compound of Formula IV without performing any additional step of recrystallization or purification(s).

The present invention includes processes for the preparation of substantially pure compound of Formula II from compound of Formula IV, which does not require any purification, by techniques like chiral chromatographic separation or salt formation or recrystallization.

The present invention includes substantially pure levocetirizine or its salts. As used in this instance, substantially pure refers to chemical and optical purity of levocetirizine greater than 99 %, preferably 99.5 %, and more preferably 99.8 % by weight.

Levocetirizine and its pharmaceutically acceptable salts described herein and/or prepared in accordance with the processes described herein may contain less than about 0.5 %, or less than about 0.1 %, by weight of process, optical, or structural impurities as characterized by high performance liquid chromatography (HPLC) and chiral HPLC.

Levocetirizine dihydrochloride of Formula I may be analyzed by the HPLC, for example, by a method using a column LICROSPHER® silica, 250×4.0 mm ID, 5 µm or equivalent. The parameters are given in Table 1.

Table 1

Flow rate	0.8 mL/min
Detector	230 nm
Injection load	20 µl
Temperature	ambient
Run Time	45 min
Diluent	Mix 2N H_2SO_4, water, and acetonitrile in the ratio of 0.4, 6.6 and 93 respectively
Sample Preparation	Dilute 20 mg of the substance in the diluent to 100 mL.
Mobile phase	Mobile phase: a mixture of dilute sulphuric acid, 0.01M tetra-n-butyl ammonium hydrogen sulphate, and acetonitrile in the ratio of 50:20:930 respectively.

Levocetirizine dihydrochloride of Formula I may also be analyzed by a second HPLC method using a column INERTSIL® silica 250×4.6 mm ID, 5 µm particle size or equivalent. The parameters are given in Table 2.

Table 2

Flow rate	1 mL/min
Detector	230 nm
Injection load	10 µl
Temperature	ambient
Run Time	30 min
Sample Preparation	Take 50.0 mg of test sample into a 100 mL volumetric flask, dissolve, and dilute

	it to volume with mobile phase. Take 10 mL of above solution in a 100 mL volumetric flask and dilute the volume with the mobile phase.
Mobile phase	Mix 0.4 volumes of 2N sulphuric acid, 6.6 volumes of water, and 93 volumes of acetonitrile.

The optical purity of levocetirizine dihydrochloride of Formula I may be analyzed by chiral HPLC using a column CHIRALPAK® AD (4.6×250 mm). The parameters are given in Table 3.

Table 3

Flow rate	1 mL/min
Detector	230 nm
Injection load	10 µl
Temperature	ambient
Run Time	30 min
Sample Preparation	Dissolve accurately about 25 mg of test sample in 25 mL of methanol and approximately 50 µl of thionyl chloride.
Mobile phase	Mix methanol, acetonitrile, and diethylamine in the ratio of 95:5:0.1

The processes as described herein can produce the desired compound levocetirizine hydrochloride of Formula I with high yield and purity.

The present invention includes pharmaceutical compositions comprising a therapeutically effective amount of substantially pure levocetirizine or a pharmaceutically acceptable salt thereof, containing less than about 0.20% of any individual impurity, together with one or more pharmaceutically acceptable

excipients. Suitable excipients for pharmaceutical compositions are well known in the art.

Certain specific aspects and embodiments will be explained in greater detail with reference to the following examples, which are provided by way of illustration only and should not be construed as limiting the scope of the invention in any manner.

EXAMPLE 1: PREPARATION OF (-)1-[(4-CHLOROPHENYL)PHENYLMETHYL]-4-[(4-METHOXYPHENYL)SULFONYL] PIPERAZINE

In a clean and dry reactor N,N-diisopropylethylamine (22 kg), (-)-4-chloro benzhydrylamine (12.5 kg), and N,N-dichloroethyl-4-methoxybenzenesulfonamide (19.8 kg) are charged under stirring and the reaction mixture is heated to about 125 °C to about 130 °C. The reaction mass is maintained under reflux at the same temperature for about 10 hours. After completion of the reaction, the reaction mass is cooled from about 80 °C to about 90 °C. Methanol (50 L) is charged into the reactor and cooled to about 0 °C to about 5 °C, and the reaction mass is maintained at the same temperature for about 30 to about 60 minutes. The separated solid is then centrifuged and the wet material in centrifuge is washed with methanol (12.5 L). The material is spin-dried for about 30 to about 60 minutes. The wet cake is further dried at about 60 °C to about 70 °C for about 3 to about 4 hours to afford 23.8 kg of the title compound.

Yield: 90.83%, Purity by HPLC: 99.0%.

EXAMPLE 2: PREPARATION OF (-)-1-[(4-CHLOROPHENYL)PHENYLMETHYL] PIPERAZINE

(-)-1-[(4-chlorophenyl)phenylmethyl]-4-[(4-methoxyphenyl)sulfonyl] piperazine (22.0 kg) is slowly added to a solution of hydrobromic acid in glacial acetic acid (91.0 kg) in a clean and dry reactor, and the contents are heated to about 70–75 °C and maintained at the same temperature for about 3 hours. After completion of the reaction, the reaction mass is cooled to about 25–35 °C. Water (115 L) is slowly charged into the reactor at a temperature of about 25 °C to about 30 °C and stirred for about 10–15 minutes. The reaction mass is washed with toluene (2×45 L) at room temperature followed by cooling of the aqueous layer to 0–5 °C

and then the pH of the aqueous layer is adjusted to about 12.0 to about 14.0 at below 35 °C using 40 % sodium hydroxide (67 L). The reaction mass is then extracted with toluene (3×70 L) at about 40 °C to about 45 °C. The combined organic layer is washed with water (2×25 L) and distilled off completely. To the residue so obtained, water (115 L) is charged at about 25 °C to about 35 °C and stirred at the same temperature for about 2–4 hours. The separated solid is then centrifuged and the wet material in the centrifuge is washed with water (25 L). The material is spin-dried for about 30 to about 60 minutes. The cake is further dried at about 30 °C to about 35 °C for about 10 hours to afford 12.8 kg of the title compound.
Yield: 92.7%, Purity by HPLC: 98.9%, Chiral purity by HPLC: 99.87

EXAMPLE 3: PREPARATION OF (-)-2-[4-[(4-CHLOROPHENYL) PHENYL METHYL]-1-PIPERAZINYL] ETHANOL
A mixture of 2-chloroethanol (7.95 kg), (-)-1-[(4-chlorophenyl)phenylmethyl]-piperazine (23 kg) and triethylamine (9.58 kg) are charged in a clean and dry reactor and heated to about 80–85 °C for about 45–60 minutes. The reaction mass is further heated to about 90–95 °C and stirred at the same temperature for about 45–60 minutes. The reaction mass is further heated to about 96–105 °C for about 4 hours. After completion of the reaction, the reaction mass is cooled to about 65–75 °C and water (144 L) is charged and stirred for about 15 minutes. The reaction mass is then extracted with toluene (68 L), subsequently washed with toluene (2×23 L), and the combined organic layer is washed with water (3×68 L). The solvent is distilled off completely under vacuum at below 100 °C and cooled to 50–55 °C to afford 24 kg oily residue of the title compound.
Yield: 90.49%, Purity by HPLC: 97.83%.

EXAMPLE 4: PREPARATION OF (+)-2-[4-[(4-CHLOROPHENYL) PHENYL METHYL]-1-PIPERAZINYL] ETHOXY ACETIC ACID DIHYDROCHLORIDE
Caustic potash flakes (6.8 kg) are slowly added to a mixture of N,N-dimethyl-formamide (40 L) and (-)-2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethanol (13 kg) in a clean and dry reactor at about 0–5 °C. The reaction mass is stirred at about 5–10 °C for about 1–1.5 hours. Sodium monochloroacetate (7.1

kg) is added at about 5–10 °C into the reactor and the reaction mixture is stirred at the same temperature for about 1–1.5 hours. The temperature is then raised to about 25 °C to about 35 °C and stirred for about 10 hours. After the completion of the reaction, water (145 L) is charged and stirred for about 15 minutes. The reaction mass is then washed with toluene (4×25L) at about 40–45 °C. The pH of the aqueous layer is then adjusted to about 4.0 to about 4.5 with 36 % hydrochloric acid (11 L) at about 25–35 °C. The aqueous layer is then extracted with dichloro methane (2×41 L). The combined dichloromethane layer is washed with saturated sodium chloride solution (2×41 L) and water (2×40 L). The organic layer is then treated with charcoal at reflux temperature, filtered through hyflow and washed hyflow with dichloromethane (83 L). The organic layer is distilled off initially at atmospheric condition and then under vacuum at about 650±50 mmHg at below 60 °C. The residue is cooled to about 40–50 °C and acetone (202 L) is charged. Hydrochloric acid (36 %, 7.8 L) is slowly added at about 40–45 °C in about 1–1.5 hr and it is stirred at the same temperature for about 1–1.5 hr. The reaction mass is then cooled to about 25–35 °C and stirred for about 30–60 minutes at the same temperature. The separated solid is then centrifuged and washed with acetone (15 L). The material is spin-dried for about 30–60 minutes. The wet cake is initially air dried and further dried at about 60–70 °C for about 4 hours then cooled to 25–30 °C, pulverized to afford 10.5 kg of the title compound. Yield: 55.70%, Purity by HPLC: 99.78%.

EXAMPLE 5: PURIFICATION OF (+)-2-[4-[(4-CHLOROPHENYL) PHENYL METHYL]-1-PIPERAZINYL] ETHOXY ACETIC ACID DIHYDROCHLORIDE

Water (2.3 L), acetone (64L) and (+)-2-[4-[(4-Chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid dihydrochloride (10.5 kg) are charged in a clean dry reactor and the reaction mixture is heated to reflux for about 4–5 hours. The reaction mass is then cooled to about 25–35 °C and maintained at the same temperature for about 30–60 minutes. The separated solid is centrifuged and washed with acetone (27L). The material is spin-dried for about 30–60 minutes. The wet cake is further dried at about 60–70 °C for about 4–5 hours, cooled to 25–35 °C and then pulverized, to afford 9.2 kg of the title compound.
Yield: 87.6%, Purity by HPLC: 99.5%, Purity by Chiral HPLC: 99.8

EXAMPLE 6: Levorotatory (-)-1-[(4-chlorophenyl)phenylmethyl]-4-[(4-methylphenyl) sulfonyl]piperazine.

3.4 g (0.0156 mole) of levorotatory (-)-(4-chlorophenyl)phenylmethylamine (prepared in accordance with Example 1.1 of U.S. Patent No. 5478941) and 5.1 g (0.0172 mol) of N,N-bis(2-chloroethyl)-4-methylbenzenesulfonamide (prepared in Example 2.3 of U.S. Patent No. 5478941) in 6 mL (4.4 g or 0.0343 mol) of ethyldiisopropylamine are mixed in a 25 mL round-bottomed flask. The mixture is heated under reflux (127 °C) for 4 hours and then cooled, with stirring, to 86 °C and 13.8 mL of methanol are added at once. The mixture is then cooled in an ice bath and still stirred for 1 hour. The precipitate which forms is filtered off, washed with 10 mL of methanol and dried under vacuum at 40 °C. The product is recrystallized from a 3:1 (v/v) mixture of methanol and acetone. 6 g of levorotatory (-)-1-[(4-chlorophenyl)phenylmethyl]-4-[(4-methylphenyl)sulfonyl]piperazine are obtained.

M.P: 171.1 °C. Yield: 87.2%.

$[\alpha]_D^{25}$: -40.68 ° (c=1, toluene)

Optical purity: 100%

Analysis for $C_{24}H_{25}ClN_2O_2S$ in %:

Calc.: C 65.37, H 5.71, N 6.35, Cl 8.04, S 7.27

Found: C 65.95, H 5.80, N 6.60, Cl 8.12, S 7.33

EXAMPLE 7: Levorotatory (-)-1-[(4-chlorophenyl)phenylmethyl]piperazine.

370 g (0.839 mol) of levorotatory (-)-1-[(4-chlorophenyl)phenylmethyl]-4-[(4-methylphenyl)sulfonyl]piperazine (prepared in accordance with Example 3.A1 of U.S. Patent No. 5478941) and 405 g of 4-hydroxybenzoic acid are added to 1 liter of a 30% solution of hydrobromic acid in acetic acid. The suspension is stirred for 17 hours at 25 °C. 2 liters of water are then added thereto and the suspension is cooled in an ice bath. The precipitate which forms is filtered and washed with 750 mL of water. 2 liters of toluene and 0.9 liters of a 50 % aqueous solution of sodium hydroxide are then added to the filtrate. The organic phase is decanted off and washed with 100 mL of water and then once again with 1 liter of a saturated aqueous solution of sodium chloride. The organic phase is dried over

sodium sulfate, filtered and the solvent evaporated off under reduced pressure. The residue is recrystallized from 600 mL of boiling hexane. The solution is filtered while hot, so as to remove any slightly insoluble material and the filtrate is then allowed to crystallize, first at ambient temperature, and then for 24 hours in an ice bath. The crystals are filtered off, washed with hexane and dried under vacuum at 40°C to afford 204.15 g of levorotatory (-)-1-[(4chlorophenyl) phenylmethyl]piperazine.

M.P.: 90.5 °C. Yield: 84.8%

$[\alpha]_D^{25}$: 90.5 ° (c=1, methanol).

Optical purity: ≥99.8%.

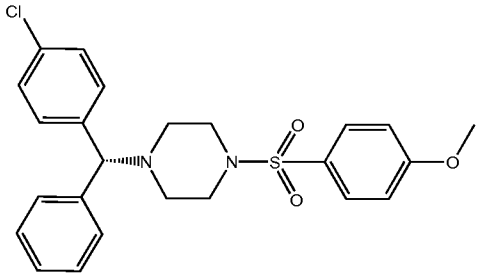
Analysis for $C_{17}H_{19}ClN_2$ in %:

Calc.: C 71.19, H 6.68, N 9.77, Cl 12.36

Found: C 71.19, H 6.84, N 9.55, Cl 11.48

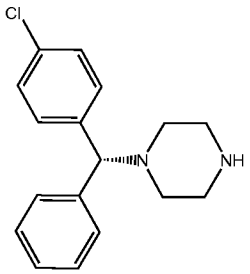
CLAIMS:

1. A process for the preparation of levocetirizine or a pharmaceutically acceptable salt thereof, comprising deprotecting a compound of Formula V



Formula V

with a deprotecting agent in the absence of 4-hydroxybenzoic acid to obtain the compound of Formula IV;

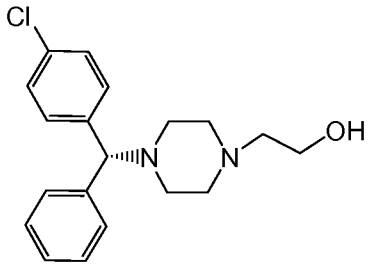


Formula IV

and converting the compound of Formula IV to levocetirizine or a pharmaceutically acceptable salt thereof.

2. The process according to claim 1, wherein a deprotecting agent comprises hydrobromic acid.

3. The process according to any of claims 1–2, further comprising condensing the compound of Formula IV with 2-chloroethanol in the presence of a base to produce a compound of Formula II.



Formula II

4. The process according to claim 3, wherein condensing is carried out in the presence of a solvent.

5. The process of claim 4, wherein a solvent is N,N-dimethylformamide.

6. The process according to claim 3, wherein condensing is carried out in the absence of solvent.

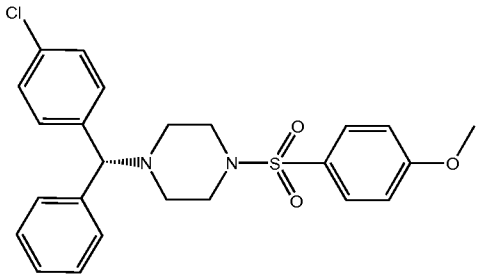
7. The process according to any of claims 3–6, wherein a base is triethylamine or caustic potash.

8. The process according to any of claims 3–7, further comprising reacting a compound of Formula II with sodium monochloroacetate in the presence of a base and a solvent to afford (-)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid.

9. The process according to claim 8, further comprising converting (-)-[2-[4-[(4-chlorophenyl) phenylmethyl]-1-piperazinyl] ethoxy] acetic acid to a pharmaceutically acceptable salt.

10. The process according claim 9, wherein a pharmaceutically acceptable salt is a dihydrochloride salt.

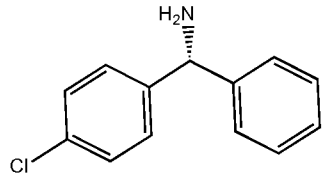
11. A process for the preparation of a compound of Formula V,



Formula V

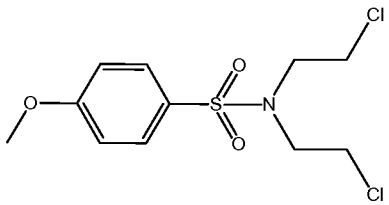
which comprises:

condensing (-)-4-chlorobenzhydryl amine of Formula VII or a salt thereof



Formula VII

with N,N-bis-(2-chloroethyl)-4-methoxybenzenesulfonamide of Formula VI,



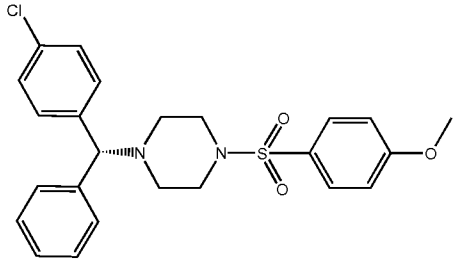
Formula VI

in the presence of a base and an organic solvent to afford (-)-1-[(4-chlorophenyl)phenylmethyl]-4-(4-methoxyphenylsulfonyl)-piperazine of Formula V.

12. The process of claim 11, wherein a base is present at about 2–4 molar equivalents per equivalent of (-)-4-chlorobenzhydryl amine.

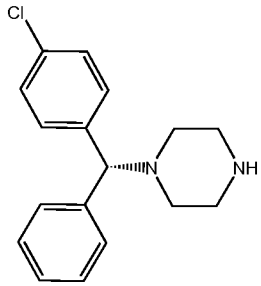
13. The process of claim 11 or 12, wherein a base comprises N,N-diisopropylethylamine.

14. A compound of Formula V.



Formula V

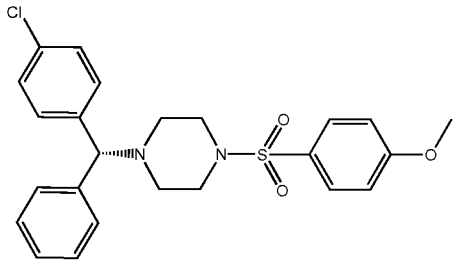
15. A process for the preparation of a compound of Formula IV,



Formula IV

which comprises:

deprotecting the compound of Formula V



Formula V

with a deprotecting agent in the absence of 4-hydroxybenzoic acid.

16. A process according to claim 15, wherein a deprotecting agent comprises hydrobromic acid in glacial acetic acid.