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NEW IMPROVED PROCESS FOR PREPARATION OF LEVO-CETIRIZINE DIHYDROCHLORIDE AND KEY INTERMEDIATES THEREOF

KEYWORDS

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ABSTRACT A new synthesis for the preparation of optically pure (-)2-[2-(4-[(4-chlorophenyl) phenylmethyl)-1-piperazinyl]ethoxy-aceticacid (Levo-cetirizine) and its pharmaceutically acceptable salts by efficient and cost-effective process for obtaining greatly optically pure Levo-cetirizine in high yield under environmentally acceptable conditions. The present invention relates to a commercially viable, improved process and short route for the preparation of optically pure Levo-cetirizine by optical resolution of its key intermediate (±)1-[(4-chlorophenyl) phenylmethyl] piperazine using O,O'-Di-p-toluoyl-L-tartaric acid under environmentally acceptable conditions, thereby producing Levo-cetirizine and their pharmaceutical acceptable salts with simultaneous recovery of O,O'-Di-p-toluoyl-L-tartaric acid.

INTRODUCTION

Levo-cetirizine Dihydrochloride is a third-generation non-sedative antihistamine, developed from the second-generation antihistamine cetirizine. Chemically, levocetirizine is the active enantiomer of cetirizine. It is the R-enantiomer of the cetirizine racemate. Levocetirizine is an inverse agonist that decreases activity at histamine H1 receptors. This in turn prevents the release of other allergy chemicals and increased blood supply to the area, and provides relief from the typical symptoms of hay fever. It does not prevent the actual release of histamine from mast cells.

The manufacturers claim it to be more effective with fewer side effects than the second-generation drugs; however, there have been no published studies supporting this assertion. A study part funded by the manufacturer UCB concluded it may be more effective than some other second- and third-generation antihistamines, but didn't compare it to cetirizine1. Its pharmacological effects similar to cetirizine, for the treatment of respiratory system, skin and eyes, etc. of allergic diseases, such as allergic rhinoconjunctivitis, allergic dermatitis, allergic asthma and the like, having a fast onset of action, strong and long-lasting effect, but avoid the cetirizine sedation, drowsiness, etc. central nervous system side effects.

Cetirizine has one asymmetric carbon, therefore it may be resolved into enantiomers2-4. The pharmaceutically active enantiomer in the racemic cetirizine is the levocetirizine, which is the (R) enantiomer of cetirizine. A medicament comprising levocetirizine was launched in the first quarter of 2001 in Germany followed by a pan-European launch. Levocetirizine is also marketed as the dihydrochloride salt, under the brand name Xyzaal®. Cetirizine was disclosed in US 4,525,358 (EP 58146). Levocetirizine12 was specifically disclosed in GB2225321. The method of use of levocetirizine has been disclosed in US5,698,558 (EP 663828).

Levocetirizine may be obtained by resolution5,6 of the cetirizine enantiomers as generally suggested, e.g., in WO 94/06429. However, the effectiveness of such process is apparently not high and therefore it is preferred to make levocetirizine from an enantiopure intermediate[7,8].

Levocetirizine and its salts including its dihydrochloride are known and are effective in the treatment9 of allergies, including but not limited to, chronic and acute allergic rhinitis, allergic conjunctivitis, pruritus, urticaria and the like. Levocetirizine belongs to the second generation of Hl histamine receptor antagonists, which are believed to offer significant advantages over first generation compounds. Studies have shown that levocetirizine provides safe and effective symptomatic relief of seasonal allergies. Levocetirizine is used also for treating chronic idiopathic urticaria.

In European Patent Application No. 1,236,722, racemic l-(4-chlorophenyl)phenylmethyl-piperazine was acylated and the tertiary butoxycarbonylated derivative. The butoxycarbonyl derivative was resolved using D-(+)-0,0-dibenzoyl-tartaric acid10 as resolving acid and the primary product was obtained with an enantiomeric purity of 78%. Subsequently the protecting group was removed by hydrolysis and the base was recrystallized several times.

The disadvantage of the above mentioned process resides in the fact that the introduction and hydrolytic removal of the protecting group is costly and the yield is only about 30% calculated on the basis of the amount of racemic l-(4-chlorophenyl)-phenylmethyl-piperazine.

U.S. Patent No. US 5,478,941 also describes the process for synthesizing optically active 1-[(4-chlorophenyl)phenyl methyl]piperazine from (–)-(4-chlorophenyl) phenylmethylamine11. (–)-(4-chlorophenyl) phenylmethylamine is reacted with N,N-bis(2-chloroethyl) toluene-sulphonamide and then convert it into (-)1-[(4-chlorophenyl)phenylmethyl]piperazine by using hydrogen bromide in acetic acid(30%).

Main drawback of this process is the use of hydrogen bromide in acetic acid in the presence of 4-hydroxybenzoic acid for removal of toluenesulphonyl group10. This reagent (HBr in acetic acid) is extremely corrosive, irritating and toxic and thus requires special handling. Further, the use of 4-hydroxybenzoic acid produces impurities thereby requires purification before using in next step. If 4-methylphenylsulphonyl group present in the starting material is replaced by hydrogen, it results in a compound which is known to be extremely toxic due to the presence of a free amine group (nitrogen mustards). A significant amount of starting material remains unreacted on using this compound for cyclization.

GB 2,225,321 describes a process for the preparation of cetirizine in the levorotatory form, dextrorotatory form or a mixture thereof comprising the hydrolysis of enantiomerically pure [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetonitrile12. Enantiomerically pure [2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy]acetonitrile is prepared from 1-[(4-chlorophenyl)phenylmethyl]piperazine as starting material and L-tartaric acid12 as resoluting agent and then treating it with 2-(chloroethoxy)acetonitrile. This process is based on the use of levorotatory or dextrorotatory 1-[(4-chlorophenyl)phenyl methyl]piperazine as starting material. In that patent, the

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enantiomers of 1-[(4-chlorophenyl)phenylmethyl] piperazine are obtained by chemical resolution of the racemic form, using conventional methods, in particular, by salt formation with a suitably selected optical isomer of tartaric acid. Hydrolysis takes place in aqueous, alcoholic or aqueous-alcoholic medium by a base or by an acid; the acid thus obtained is converted to its dihydrochloride. The obtained optically active intermediate is further converted with chloroethoxyacetonitrile in 69% yield. EP 0617028 and EP 0955295 disclose a process for the preparation of optically active 1-[(4-chlorophenyl)phenylmethyl]piperazine and its conversion to cetirizine in the levorotatory form or dextrorotatory form or to derivative thereof. The drawback of the disclosed reaction is that it requires protection of N,N-bis(2-haloethyl)amine, and consequently deprotection of the intermediate obtained.

The major disadvantages of this process are, on the one hand, that the yield of the resolution step of the racemic 1-[(4-chlorophenyl)phenylmethyl] piperazine is extremely low (only 12.7%) and, on the other hand, that the optical purity of the dextrorotatory and levorotatory enantiomers so obtained is insufficient and does not allow the final product to be prepared with an optical purity greater than 95%.

Preparation of cetirizine in its levorotatory form proceeds in most known syntheses from enantiomerically pure 1-[(4-chlorophenyl)phenylmethyl]piperazine. Consequently it appears to be very desirable to provide new routes to prepare the enantiomers thereof with improved optical purity and good yields. Polymorphic form of crystalline levorotatory dihydrochloride salt of cetirizine and amorphous form thereof are disclosed in WO 2004/050647 and WO 2004/065360. Crystalline form is prepared by crystallization from ketone-containing solvent, such as acetone, methyl ethyl ketone, dimethylketone, 2-pentanone and mixtures thereof. Amorphous form was prepared by solvent evaporation. There still exists a need for an efficient synthesis of levocetirizine, new intermediates used in the process, suitable for large-scale production.

European Patent No.58,146 describes the synthesis of 2-[2-(4-[(4.chlorophenyl) phenylmethyl)-1-piperazinyl]ethoxy-aceticacid and its dihydrochloride. In this synthesis, the starting substance is 1-[(4-chlorophenyl) phenylmethyl] piperazine, which is reacted with methyl (2-chloroethoxy)-acetate to give methyl 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl] ethoxy]-acetate13 in a yield of 27% This methyl ester is then subjected to hydrolysis with an inorganic base (sodium or potassium hydroride) to give the sodium or potassium salt, which is easily converted into the free acid, and then into levocetirizine dihydrochloride.

The major disadvantage of this synthesis is that the overall yield of 2-[2-[4-chlorophenyl) phenylmethyl-1-piperazinylethoxy]acetic acid dihydrochloride is only 10.6%, based on the amount of 1-[(4chlorophenyl)-phenylmethyl]-piperazine employed.

WO2009078627 relates to a method for preparing (L)-(-)-1-[(4-chlorophenyl) phenylmethyl]piperazine which is useful as an intermediate for preparing an antihistamine, levocetirizine. (±)-1-[(4-chlorophenyl)phenylmethyl]piperazine is allowed to a react with N-acetyl-L-phenylalanine14 to get (L)-(-)-1-[(4-chlorophenyl)phenyhnethyl]piperazine N- acetyl-L-phenylalanine salt.

The disadvantage of the above mentioned process is purification of (L)-(-)-1-[(4-chlorophenyl)phenyhnethyl]piperazine N- acetyl-L-phenylalanine salt is required. Optical purity of the salt varies from 80-99% even after purification. The resolution agent being used is costly and cannot be recovered.

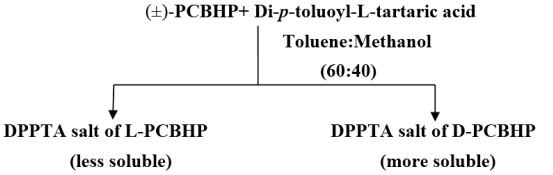
In view of the demerits associated with these processes, it is desirable to develop a simpler route for the preparation of enantiomerically pure compounds, such as levocetirizine and its pharmaceutically acceptable salts, without or alleviating the use of expensive reagents, complicated and costly equipment, and without complicated operations (chiral chromatographic purification), thus which is economical and industrially viable. We have tried various resoluting agents like, L-Mandelic acid, D-Mandelic acid, Camphor-10-sulphonic acid, L-Lactic acid, 4-nitro tartranilic acid, Dibenzoyl-L-Tartaric acid in numerous solvents and found that only Di-p-toluoyl-L-tartaric acid was useful as it gives better separation and overall loss during the process is in very minute quantity.

EXPERIMENTAL

Di-p-toluoyl-L-tartaric acid (DPTTA) is reacted with (±)-l-[(4-chlorophenyl) phenylmethyl]piperazine(PCBHP) in solvent mixture of Toluene and Methanol in (60:40) proportion and refluxed for few hours. Reaction mass is cooled to 40°C and solid precipitated is filtered off. The solid obtained is DPPTA salt of (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine, the solid obtained is purified two times in same solvent. Purified DPPTA salt of (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine is basified till pH 12-13 by using caustic lye in water and toluene. Layers are separated and basic aqueous layer is extracted with toluene. The basic aqueous layer was sent for simultaneous recovery of O,O'-Di-p-toluoyl-L-tartaric acid. Toluene is distilled under vacuum to get oily residue. n-Hexane was added to the residue and chilled to 0-5°C for few hours till solid precipitates. The precipitated solid is filtered and washed with n-hexane to get optically pure (-)-l-[(4-chlorophenyl) phenylmethyl]piperazine.

The basic aqueous layer was acidified with hydrochloric acid to pH 2 and extracted with terbutylmethylether(TBME). On concentrating the TBME solution gave a slightly coloured oil. It was dissolved in isopropyl alcohol(IPA) and heated to reflux. n-Heptane was added at reflux slowly to crystallize O,O'-Di-p-toluoyl-L-tartaric acid. It was cooled to room temperature and kept under stirring overnight. It was filtered to give pure O,O'-Di-p-toluoyl-L-tartaric acid.

Optically pure (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine is reacted with 2-chloroethanol in triethylamine and refluxed for few hours. Toluene is added after reaction is complete, water washing is given to the toluene and toluene is distilled out to get ethanol derivative of (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine.



Dimethylformamide is added to the ethanol derivative and chill the reaction mass to 0-5°C. Caustic potash flakes are added in lots below 5°C. Temperature is raised to 7°C and sodium monochloroacetate is added in lots below 10°C, the temperature is raised to 32-34°C and maintained for 10hrs. After completion of the reaction water is added and three toluene washing are given to the aqueous layer to remove impurities. pH of aqueous layer is adjusted to 7-7.5 by using [1:1]hydrochloric acid. The aqueous layer is charcoalised and pH is further adjusted to 4-4.5 by using [1:1]hydrochloric acid and the Levo-cetirizine base liberated is extracted with methylene dichloride. The organic layer is washed with water and distill methylene dichloride under vacuum to get oily residue of Levo-cetirizine base. Acetone is added to the oily residue, charcoalised and pH is adjusted to 0-1 by purging dry HCl gas. The precipitated solid is stirred for 1hr and filtered. The final product thus obtained is washed with acetone and dried under vacuum to get pure Levo-cetirizine Dihydrochloride with optical purity above 99%.

REACTION SCHEME

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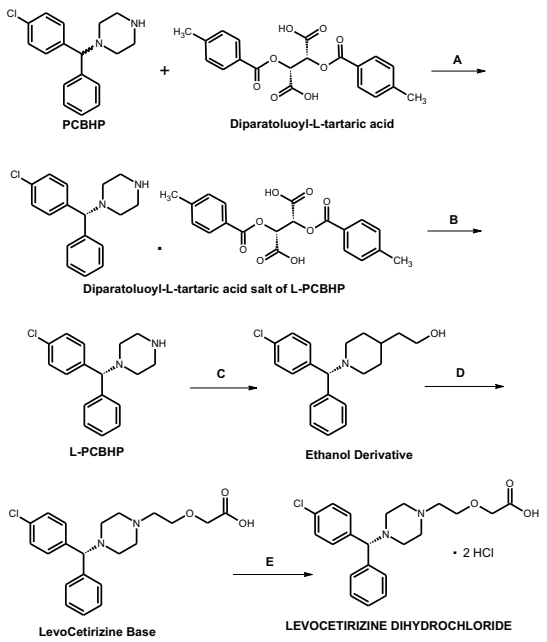

A-Toluene, Methanol, 65°C, 2hrs, 40°C, 1hr
B- NaOH, pH 11-12, Toluene, n-Hexane.
C- (2)-Chloroethanol, TEA, 90-95°C, 5hrs, Toluene
D- DMF, KOH, 0-5°C, SMCA, 5-10°C, 32-34°C, 10hrs, Toluene, dil. HCl, pH 4-4.5, MDC
E- Acetone, HCl gas, pH 0-0.5, RT, 1hr

EXAMPLES

1) Resolution of Racemic l-[(4-chlorophenyl) phenylmethyl] piperazine(PCBHP)

(–)-O,O′-Di-*p-toluoy*l-L-tartaric acid (DPPTA) (270.44gm, 0.7moles) is dissolved under mechanical stirring in 1.5 L Toluene and Methanol mixture(60:40) by gently heating it to 45-50°C. Meanwhile prepare (±)-l-[(4-chlorophenyl) phenylmethyl]piperazine(PCBHP) solution [PCBHP(200gm, 0.7moles) in 0.5 L Toluene:Methanol mixture] under mechanical stirring. Above prepared solution is slowly added to DPTTA solution dropwise within 30mins. The reaction mixture is heated to reflux for 2hrs, cool it to 40°C and maintain it for 1hr. The precipitated DPTTA salt of (-)PCBHP is filtered and wash with Tol:MeOH (60:40) mixture. The salt is purified two times with 1 L of the same mixture following the same procedure. DPTTA salt of (-)PCBHP is dried under vacuum. (Yield- 140gm 51.85%, M.P.=196-197°C, SOR -27°, c=1% DMF, Chiral purity- 95%)

2) Preparation of (-)[l-[(4-chlorophenyl) phenylmethyl] piperazine]PCBHP

140gm of DPTTA salt of (-)PCBHP is added to 2 L water and adjust pH 12-13 by using caustic flakes. The aqueous layer is extracted with 0.4 L Toluene two times. The organic layer is washed with water and dried over sodium sulphate. Toluene is distilled out under vacuum below 60°C to get oily residue. n-Hexane is added to the oily residue and chilled to 0-5°C and maintain for 5hrs, the precipitated (-)[l-[(4-chlorophenyl)phenylmethyl]piperazine] is filtered and washed with chilled n-hexane. (-)PCBHP is dried under vacuum below 45°C. The basic aqueous layer was sent for simultaneous recovery of O,O'-Di-p-toluoyl-L-tartaric acid.

(Yield-55gm 92.44%, M.P.= 95-96°C, SOR -19.3°, c=1% toluene, Chiral purity-99.8%)

3) Preparation of (-)-2-[4-[(4-Chlorophenyl)phenylmethyl]-1-piperazinyl]ethanol (Ethanol derivative)

(50gm, 0.17moles) of (-)PCBHP is added to (25gm, 0.25moles) triethylamine along with (17.5gm, 0.22moles) 2-chloroethanol at room temperature. The reaction mixture is heated to 80-85°C for 2hrs and then at 90-95°C for 3hrs, after the reaction is complete checked on TLC. The reaction mass is cooled to room temperature, 0.25 L water and 0.175 L Toluene is added. Stir it for 30min, settle and separate layers. Take aqueous layer and extract with 0.15 L Toluene two times. Combine the total organic layer and wash with 0.175 L water three times. Organic layer is dried on sodium sulphate and toluene is distilled out under vacuum below 60°C, degas well for 1hr to get 68gm of ethanol derivative. (Yield- 56gm 97.0%, SOR -22°, c=1% tolene, Optical purity-99.5%)

4) Preparation of Levo-cetirizine Dihydrochloride

(50gm, 0.15moles) of ethanol derivative is dissolved in 0.135 L Dimethyl formamide at room temperature and chill the reaction mass to 0-5°C. Add (25gm, 0.44moles) caustic potash flakes in lots below 5°C. Raise the temperature to 7°C and add (27gm, 0.23moles) sodium monochloroacetate in lots below 10°C. Raise the temperature to 32-34°C and maintain for 10hrs, after the reaction is complete checked on TLC 0.56 L water is added along with 0.10 L toluene. Stir for 30mins, settle and seprate layers. Take aqueous layer and wash with 0.10 L toluene two times. To the aqueous layer (1:1)hydrochloric acid is added till pH 7-7.5. The aqueous layer is charcoalised at 40°C and cool to room temperature. (1:1)hydrochloric acid is added till pH 4-4.5, the aqueous layer is extracted three times with 0.165 L methylene dichloride each. Organic layer is washed two times with 0.15 L water. Methylene dichloride is distilled under vacuum below 40°C, degass well for 1hr. 0.5 L Acetone is added and charcoalised at the same temperature. Cool the reaction mass at room temperature and pH is adjusted to 0-0.5 by purging dry hydrochloric gas. The precipitated solid is stirred at room temperature for 1hr, filtered and wash with acetone. Dry the product at 50°C under vacuum to give 60gm of pure Levocetirizine Dihydrochloride. (Yield- 60gm 85.71%, M.P.-217-221°C, SOR +12, c=1% water)

5) Recovery and purification of O,O'-Di-p-toluoyl-L-tartaric acid

The basic layer from example 2 was acidified with (1:1)hydrochloric acid to pH 2.0 and this acidic aqueous layer was extracted with tertiary-butylmethylether(TBME). The TBME layer was distilled out under vacuum below 40°C to give crude oil of O,O'-Di-p-toluoyl-L-tartaric acid. Crude O,O'-Di-p-toluoyl-L-tartaric acid was dissolved in 0.54 L isopropyl alcohol(IPA) and heated to 80-85°C for 1hr, to this refluxing IPA solution add 1.25 L n-Heptane slowly for 1hr. O,O'-Di-p-toluoyl-L-tartaric acid slowly crystallizes at 50°C. The solution was allowed to cool to room temperature gently and maintain it was 10-12hrs at RT. The white precipitated solid was filtered and was with chilled n-Heptane to give 215gm pure O,O'-Di-p-toluoyl-L-tartaric acid. (Yield- 215gm 79.5%, M.P.-169-170°C, SOR -137°, c=1% ethanol)

RESULTS AND DISCUSSION

To confirm the elemental composition of Levo-cetirizine Dihydrochloride, it was subjected to CHN analysis and the values obtained were compared with the theoretical values calculated from the molecular formula C21H25ClN2O3.2HCl of Levo-cetirizine Dihydrochloride (Table-I).

Table-I: Elemental Composition data of Levo-cetirizine Dihydrochloride

Molecular Formula	Formula Weight	Elemental Composition Found(Calculated)			
$C_{21}H_{25}ClN_2O_3.2HCl$	461.81	C	H	N	O
		54.94 (54.62)	5.74 (5.89)	6.07 (6.07)	11.09 (10.39)

Mass spectrum of Levo-cetirizine Dihydrochloride shows a molecular Ion Peak at 389.08 which is the value obtained theoretically after the protonation of one hydrogen atom in the calculated molecular mass of 388.89 using the molecular formula C21H25ClN2O3. The UV spectrum of Levo-cetirizine

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Dihydrochloride in 0.1 M Hydrochloric Acid at concentration of 20ppm exhibits peak maxima at 231 nm. Assignment of various frequencies obtained from the FTIR spectrum to their corresponding functional groups is depicted in Table-II. The assignment of the chemical shifts and the number of protons in the molecule has been described in Table-III and Table-IV.

Table-II: FTIR data of Levo-cetirizine Dihydrochloride

Wave Number (cm^{-1})	Functional group / Band assignment
3416.05	Hydroxyl(-OH) stretching
2983.98,2949.26	Aliphatic C-H stretch
1740	Acid C=O stretching
1435.09	Aromatic C=C Stretch
1319.35	Carboxylate C-O stretch
1055.1	Alkoxy C-O stretch
808.2	Para disubstituted aromatic bending
758.05	Monosubstituted aromatic bending

Table-III: 1H-NMR data of Levo-cetirizine Dihydrochloride

Chemical shift (δppm)	Multiplicity	H atoms	Assignment
3.33-3.39	Multiplet	6H	Aliphatic proton
3.55	Multiplet	4H	Aliphatic proton(>N-C**H**$_2$-C**H**$_2$-O)
3.74-3.77	Triplet	2H	Aliphatic proton
4.06	Singlet	2H	Aliphatic proton(-O-C**H**$_2$-COOH)
5.22	Singlet	1H	Aliphatic proton(Ar2-C**H**-N<)
7.21	Singlet	1H	Aromatic proton
7.24	Singlet	1H	Aromatic proton
7.30-7.42	Multiplet	5H	Aromatic proton
7.44	Multiplet	2H	Aromatic proton

Table-IV: 13C-NMR data of Levo-cetirizine Dihydrochloride

Chemical shift (δppm)	Position of Carbon
48.53, 49.10	Piperazinyl group
56.14	-**C**H2-N
64.02, 67.65	-**C**H2-O-**C**H2-
74.88	Ar2-**C**H-N<
128.03, 129.58, 129.88, 130.02, 130.06	Aromatic ring carbons
132.46, 133.62, 135.22	Quaternary ring carbons
174.55	>**C**=O

CONCLUSION

1. (–)-O,O′-Di-p-toluoyl-L-tartaric gives better separation of enantiomers.

2. Process is easy and no need to use expensive reagents, complicated and costly equipment, and without complicated operations (chiral chromatographic purification), thus making it economical and industrially viable.

3. O,O'-Di-*p*-toluoyl-L-tartaric acid was recovered and can be reused during the process thus fulfilling the principle of Green Chemistry.

4. The elemental analysis, UV, FTIR, ^{1}H-NMR, ^{13}C-NMR and Mass spectral analysis of Levo-cetirizine Dihydrochloride confirms the chemical structure as per literature[15].

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