Title: PROCESS FOR PREPARATION OF OLOPATADINE HYDROCHLORIDE

Abstract: Disclosed here is a process for preparation of compound 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydrodibenzo [b, e] oxepin - 2 - yl - acetic acid (Olopatadine) and its pharmaceutically acceptable salt comprising reacting compound of Formula (XII) where R¹ & R² independently represent H, or Cl - C₄ alkyl group; with 3-dimethylaminopropyldiene active metal halide of Formula (XIII) where X is Chlorine, bromine or iodine.
"PROCESS FOR PREPARATION OF OLOPATADINE HYDROCHLORIDE"

Field of Invention:
The present invention relates to an improved process for preparation of 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydrodibenz [b, e] oxepin -2 - yl - acetic acid and its pharmaceutical acceptable salts.

Background and Prior Art:
The compound 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydrodibenz [b, e] oxepin -2 - yl - acetic acid hydrochloride of formula - I having International Non - Proprietary Name Olopatadine Hydrochloride

![Chemical Structure](image)

Formula - 1

is a selective histamine H1 antagonist, which has mast cell stabilizing property and has been shown to affect the release of TNFa and various cytokines from conjunctival epithelial cell and is used for the treatment of allergic conjunctivitis.

Olopatadine hydrochloride was disclosed as dibenz [b, e] oxepin derivative in US Patent No 5,116,863 (herein after '863') 'in 1992, assigned to Kyowa Hakko Kogyo Co., Ltd. The patent discloses the preparation of Olopatadine through Wittig reaction by reacting 11 - oxo - 6, 11 - Dihydrodibenz [b, e] oxepin - 2 - acetic acid (Formula - II) with 3 - dimethylaminopropyl triphenyl phosphonium bromide hydro bromide (Formula - III) in presence of base n - butyl lithium and solvent tetrahydrofuran. The crude compound is passed through column chromatography to isolate pure olopatadine. The reaction sequence is as shown in scheme - 1,
In the above method, the preparation of olopatadine involves excess use of base and the Wittig reagent. The isolation of pure cis olopatadine employs the use of column chromatography. The final yield of the compound is low.

Another method disclosed in '863' is use of Grignard reagent for the preparation of Olopatadine hydrochloride. In this reaction, 11-oxo-6,11-Dihydrodibenz[b,e]oxepin-2-acetic acid (Formula - II) is converted to corresponding amide of Formula - IV by reacting the acid with thionyl chloride followed by reaction with 2-amino-2-methyl propanol, which is cyclised to get corresponding oxazoline derivative (Formula - V). Grignard reaction of the oxazoline derivative with 3-dimethylaminopropyl magnesium chloride yields the intermediate 11-(3-Dimethylamino-propyl)-2-(4,4-dimethyl-4,5-dihydro-oxazol-2-ylmethyl)-6,11-dihydrodibenz[b,e]oxepin-11-ol (Formula - VI), which on hydrolysis followed by dehydration with strong acid yields olopatadine (Formula - I). The reaction sequence is as per scheme - II.
The major disadvantages of the above process are the preparation of cyclised intermediate before Grignard reaction increasing the number of steps. Further, the isolation of pure compound employs the use of column chromatography.

J. Med. Chem. 35, 2074, (1992) discloses the preparation of olopatadine HCl as per the above scheme, wherein the separation of the Z / E diastereomer is disclosed. As per the disclosure, the diastereo selectivity of the dehydration step is poor and leads to the formation of predominantly undesired E’ isomer.

PCT application WO2006 129781 discloses the preparation of olopatadine hydrochloride wherein Methyl 2-(4-(2-chlorobenzyloxy)phenyl)acetate is iodinated using iodine and silver sulfate to give methyl 2-(4-(2-chlorobenzyloxy)-3-iodophenyl)acetate; which is coupled with but-3-yn-1-ol in presence of Copper iodide and palladium catalyst results methyl 2-(4-(2-chlorobenzyloxy)-3-(4-hydroxybut-1-ynyl)phenyl)acetate; which on palladium catalyzed cyclization yields methyl [(11Z)-1-(3-hydroxypropylidene)-6,1 1-dihydrodibenzo[b,e]oxepin-2-yl]acetate; which is converted to Olopatadine via mesylate salt followed by treatment with dimethylamine and basic hydrolysis.
Another PCT application WO2007105234 discloses one pot process for the preparation of olopatadine hydrochloride using Grignard reaction. The compound 11-oxo-6, 11-Dihydrodibenz [b, e] oxepin - 2 - acetic acid is reacted with Grignard reagent of 1- halo - 3 - dimethylamino propane which is heated with dilute hydrochloric acid (1:1) to get Olopatadine hydrochloride. The reaction sequence is as per scheme - III:

![Chemical Structures](image)

Scheme - III

The drawback in the process is, longer time for Grignard reaction and lower yield of desired cis - olopatadine hydrochloride.

Another PCT application No. WO2007119120 describes the preparation of olopatadine hydrochloride by employing Grignard reaction, wherein 11-oxo-6, 11-Dihydrodibenz [b, e] oxepin - 2 - acetic acid is reacted with 3 - dimethylamino propyl magnesium chloride at 25 - 30°C for 15 hours. The work up is carried out by decomposition with ammonium chloride followed by treatment with hydrochloric acid to isolate olopatadine hydrochloride.

The drawback in the process is longer time required during Grignard reaction and formation of olopatadine hydrochloride.
The patent application JP2009114166 discloses the preparation of Olopatadine hydrochloride involving Grignard reaction, wherein tert-butyl ester of 11-oxo-6,11-dihydrodibenz[b,e]oxepin-2-yl acetic acid (Formula - VIII) is reacted with 3-dimethylaminopropylmagnesium chloride yields tert-butyl ester of 11-hydroxy-11-(3-dimethylaminopropyl)-6,11-dihydrodibenz[b,e]oxepin-2-yl acetic acid (Formula - IX), which is decomposed by heating in presence of solvent and acid to give racemic olopatadine of Formula - X. The compound of Formula - X obtained is isomerized by heating in presence of solvent and hydrochloric acid, with simultaneous removal of water yields required isomer Cis - Olopatadine hydrochloride of Formula - I. The reaction sequence is as shown in scheme - IV.

The drawback of the process involves difficulty in preparation of tertiary butyl ester, isomerisation of racemic isomer to required cis olopatadine and azeotropic removal of water during isomerisation.
Another PCT application WO2009044838 describes the preparation of olopatadine hydrochloride by dehydrating tertiary alkyl ester of 11-hydroxy-11-(3-dimethylamino propyl)-6,11-dihydrodibenz[b,e]-oxepin-2-yl-acetic acid of Formula - IX with a dehydrating agent such as acetic anhydride, propionic anhydride, butyric anhydride, anhydrous trifluoroacetic acid, anhydrous trichloroacetic acid, thionyl chloride, phosphorus oxychloide, phosphorous pentachloride, phosphorus trichloride to result into a mixture of (E,Z) - 11 - (3 - dimethylamino propylidene) - 6,11-dihydrodibenz[b,e] oxepin-2-yl-acetic acid alkyl ester (Formula - XI). The compound of Formula XI is further isomerised to Z-isomer from E-isomer in an organic solvent and hydrochloric acid where the reaction proceeds with deesterification reaction of compound of Formula XI simultaneously. After isomerization cools the reaction solution to deposit crystals, and filtered the precipitated crystals, and compound of Formula - I is isolated as acid addition salt corresponding to acid used. The reaction sequence is as shown in the following scheme - V.
The drawback of the process mentioned is the use of dehydrating agents which are either costly or hazardous and industrially non-friendly to use on commercial scale.

Japanese application JP2007031363 describes the preparation of olopatadine hydrochloride wherein 2-(Bromomethyl) benzonitrile is reacted with methyl 2-(4-hydroxyphenyl)acetate in presence of potassium carbonate followed by hydrolysis of the ester with sodium hydroxide to get methyl 2-(4-hydroxyphenyl)acetate; which is cyclized with acetic anhydride results in 11-oxo-6,11-Dihydrodibenz[b,e]oxepin-2-acetic acid; Wittig reaction of the acid formed with (3-dimethylaminopropyl) triphenyl phosphonium bromide hydro bromide in presence of n-Butyl lithium gives Olopatadine; which is treated with hydrochloric acid and water to give Olopatadine hydrochloride.

The major drawbacks of the prior art processes include:

- Longer time required for Grignard reaction;
- Poor yield of the desired isomers;
- Need of isomerisation for getting increased yield of cis isomer;
- the use of column chromatography to isolate the pure form of the compound;
- Requires hazardous or costly chemicals for dehydration of the intermediate to get olopatadine.

There remains a need for an improved process for preparing olopatadine and its pharmaceutically acceptable salt that requires less time for reaction, reduces number of steps in a convenient and cost efficient manner with the use of cost effective reagent which are industrial friendly and easy to handle at commercial scale.

The present inventors have come out with an improved process which ameliorates the problems in the prior art for the preparation of olopatadine starting with the protected 11-oxo-6,11-Dihydrodibenz[b,e]oxepin-2-acetic acid compound of Formula-II.

**Objectives of the invention:**

The present invention tackles the problem of providing process for the preparation of (Z)-11-[(3-Dimethylamino)propylidene]-6,11-dihydrodibenz[b,e]oxepin-2-acetic acid compound of Formula-II.
acetic acid and its pharmaceutically acceptable salt, which overcomes the problems in the prior art.

The objective of the present invention is to prepare \((Z) - \text{11 - [(3 - Dimethylamino) propylidene]} - 6, 11\)-dihydrodibenz \([b, e]\) oxepin - 2 - acetic acid of higher purity.

Another objective of the present invention is to prepare \((Z) - \text{11 - [(3 - Dimethylamino) propylidene]} - 6, 11\)-dihydrodibenz \([b, e]\) oxepin - 2 - acetic acid by an industrially useful and cost effective process.

Yet another objective of the present invention is to prepare the pharmaceutically acceptable salt of \((Z) - \text{11 - [(3 - Dimethylamino) propylidene]} - 6, 11\)-dihydrodibenz \([b, e]\) oxepin - 2 - acetic acid with good yield.

**Summary of the invention:**

Accordingly the present invention provides a process for the preparation of compound \(11\) - \((Z) - [3 - (Dimethylamino) propylidene] - 6, 11\)-dihydro dibenz \([b, e]\) oxepin - 2 - acetic acid of Formula I and its pharmaceutically acceptable salt comprises a step of:

a) reacting compound of Formula - XII

![Formula I](image-url)
Formula - XII

where \( R^1 \) & \( R^2 \) independently represent \( H \), or \( C_1 - C_4 \) alkyl group;
b) with 3-dimethylaminopropyl magnesium halide of Formula - XIII

Where \( X \) is Chlorine, bromine or iodine.

Wherein;
a. reacting compound of Formula XII with 3-dimethylaminopropyl magnesium halide of formula XIII by Grignard reaction in presence of solvent at temperature of\(-10^\circ \) to \( 30^\circ \)C;
b. decomposing the reaction mixture with dilute acid at temperature of \( 0^\circ \)C to \( 5^\circ \)C followed by stirring, adjusting the pH of reaction mixture with suitable base and extracting the reaction mass with toluene;
c. adjusting pH of toluene layer with dilute hydrochloric acid solution followed by separating aqueous layer and heating upto \( 80^\circ \)C - \( 100^\circ \)C;
d. adjusting pH of aqueous solution with metal hydroxide to \( 6.8 - 7.2 \) and extracting with chlorinated solvent to isolate olopatadine;
e. treating olopatadine in presence of solvent with dry hydrochloric acid gas at temperature of \( 60^\circ \)C to \( 90^\circ \)C to isolate crude olopatadine hydrochloride and
f. purifying isolated crude olopatadine hydrochloride.

The details of one or more embodiments of the present invention are set forth in the description below. Other features, objects and advantages of the invention will be apparent from the appended examples and claims.

Description of the invention:
The present invention describes an improved process for the preparation of 11-(Z)-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[b,e]oxepin-2-yl acetic acid of Formula I and its pharmaceutically acceptable salt.

In one embodiment of the present invention the compound 11-(Z)-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[b,e]oxepin-2-yl acetic acid of Formula I is prepared by carrying out Grignard reaction of the carboxamido compound of 11-oxo-6,11-Dihydrodibenzo[b,e]oxepin-2-carboxylic acid of Formula XII

\[
\text{Formula - XII}
\]

Where \( R^1 \) and \( R^2 \) independently represent hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl, and

\[
\text{Formula - XIII}
\]

Where \( X \) is chlorine, bromine or iodine,

in presence of an organic solvent.

The Grignard reaction is carried out in presence of solvent at temperature ranging from -10°C to 30°C. The solvent used for Grignard reaction is selected from toluene, tetrahydrofuran and hexane, wherein the most preferred solvent for the Grignard reaction is tetrahydrofuran. The temperature range for Grignard reaction is maintained between -10°C to 30°C; wherein the preferred temperature range is -5°C to 10°C and the most preferred temperature range is from 0°C to 5°C.

The compound of Formula XII used for the Grignard reaction is selected from where \( R^1 \) and \( R^2 \) independently represent hydrogen, methyl, ethyl, n-propyl, iso-propyl, n-butyl and
iso-butyl group. The preferred compound used for Grignard reaction is where both R₁ and R₂ are methyl group viz. N, N-dimethyl-2-(ll-oxo-6, 11-dihydrodibenz[b, e]oxepin-2-yl) acetamide. The preferred Grignard reagent of Formula XIII used for the Grignard reaction is 3 - dimethylaminopropyl magnesium chloride.

In accordance with the above embodiment, the compound N, N-dimethyl-2-(1 ll-oxo-6, 11-dihydrodibenz[b, e]oxepin-2-yl) acetamide is charged in flask containing solvent tetrahydrofuran. Under nitrogen atmosphere the mixture is cooled to -5 - 10°C and the compound 3 - dimethylaminopropyl magnesium chloride is charged maintaining the temperature between -5 to 5°C. After complete addition of the reagent the reaction mass is maintained at 0 - 5°C under stirring for 1 to 4 hours. The preferred time of Grignard reaction is between 1 to 2 hours. After the completion of reaction the reaction mass is decomposed by adding water and followed by concentrated hydrochloric acid or with dilute 1:1 hydrochloric acid maintaining the temperature at 0 - 5°C. Raised the temperature of the reaction solution to 25 - 35°C and maintained the reaction solution under stirring at 25 - 35°C for 1 to 3 hours. Adjusted the pH of the reaction solution to 9 - 10 with a suitable base. The suitable base is selected from ammonium hydroxide, sodium hydroxide and potassium hydroxide; wherein the preferred base used for pH adjustment is ammonium hydroxide. Charged toluene and extracted the organic compound in toluene. Separated the toluene layer and adjusted the pH of the solution to acidic using dilute 1:1 hydrochloric acid. Separated the aqueous layer and heated with simultaneous distillation to 80 - 100°C. Maintained the reaction solution at 80 - 100°C for 4 to 6 hours for complete hydrolysis of amide. The preferred temperature for hydrolysis of amide functional group is 90 - 95°C.

After complete hydrolysis, cooled the reaction solution to 0 - 20°C and adjusted the pH with metal hydroxide solution to 6.8 to 7.2. The metal hydroxide used for pH adjustment is selected from sodium hydroxide, potassium hydroxide and calcium hydroxide. The preferred metal hydroxide used is potassium hydroxide. The aqueous solution is extracted several times with chlorinated solvent to isolate mixture of E & Z isomer of 11 - [3 -(Dimethylamino) propylidene] - 6, 11 - dihydro dibenz[b, e]oxepin -2 - yl - acetic acid of Formula - X. The chlorinated solvent used for the extraction of compound of Formula - X is selected from dichloromethane, dichloroethane, trichloroethane, tetrachloroethane
and chlorobenzene. The preferred chlorinated solvent used for extraction is dichloromethane and chlorobenzene; wherein the most preferred solvent used is dichloromethane. The combined extract is concentrated under reduced pressure to get the compound (E,Z)-11-[3-(Dimethylamino)propylidene]-6,11-dihydrodibenzo[b,e]oxepin-2-yl acetic acid of Formula-X having HPLC purity of E:Z ratio 65:35. The reaction sequence can be represented as below in Scheme-VI.

![Scheme-VI](image)

The compound N,N-dimethyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl) acetamide of Formula XII can be prepared as per the known methods for the preparation of carboxamide from the corresponding carboxylic acid. For the present invention the compound N,N-dimethyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl) acetamide of Formula XII is prepared from 11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-acetic acid of Formula-II, where the compound of Formula-II is reacted with thionyl chloride in dichloromethane to get acid chloride which on reaction with dimethyl amine gas results in the formation of N,N-dimethyl-2-(11-oxo-6,11-dihydrodibenzo[b,e]oxepin-2-yl) acetamide of Formula XII which is used for the present invention.
In another embodiment of the present invention, the compound olopatadine having mixture of E & Z isomer is taken in solvent selected from chlorobenzene and n - butanol for the preparation of pharmaceutically acceptable salt of Formula - I. The preferred solvent used for the preparation of pharmaceutically acceptable salt of Formula - I is chlorobenzene.

In accordance with the above embodiment for the preparation of pharmaceutically acceptable salt, the isolated racemic compound is taken in chlorobenzene and heated to raise the temperature to 60 - 90°C; wherein the preferred temperature for the preparation of salt is 80 - 85°C. After attaining the temperature started passing dry hydrochloric acid gas for 5 - 8 hours maintaining the temperature at 80 - 85°C to complete the salt formation and cooled the reaction mass to 20 - 30°C. The solid crude olopatadine hydrochloride salt thus obtained is filtered, washed with cooled acetone and dried.

The preparation of hydrochloride salt of compound of Formula - 1 at temperature range of 60 - 90°C is done to isolate the required cis isomer of the compound in almost pure form from the mixture of cis and trans compound of Formula - X. At the preferred temperature the hydrochloride of desired cis isomer formed, separates out as solid from the reaction solution and the Trans isomer remains soluble in the solvent.

The dried crude olopatadine hydrochloride is purified in solvent selected from acetone, isopropanol, tetrahydrofuran and water or mixture thereof to isolate pure olopatadine hydrochloride having HPLC purity of more than 99.00% of Cis - olopatadine hydrochloride and less than 0.1% to nil of Trans isomer. The preferred solvent for purification is mixture of acetone and water.
The present invention is further illustrated in detail with reference to the following example. It is desired that the example be considered in all respect as illustrative and are not intended to limit the scope of the claimed invention.

**Examples:**

**Example 1:**

**Step I: Preparation of N, N-dimethyl-2-(1 l-oxo-6, 11-dihydrodibenz [b, e] oxepin-2-yl) acetamide.**

Charged 200 gm of 11-oxo-6, 11-dihydrodibenz [b, e] oxepin-2-acetic acid) in 1000 ml of dichloromethane. Charged 82.0 ml of thionyl chloride maintaining temperature at 25 - 30°C. Raised the temperature of the reaction mass to reflux and maintained five hours. Cooled the reaction mass to 0°C and started passing of dimethyl amine gas in the reaction mass to attain pH of 9.5 to 10.0 maintaining the temperature at 0 - 20 °C. Concentrated the reaction mass under vacuum to remove solvent dichloromethane. Charged 400 ml of DM water and cooled the water slurry of the product to 20 - 30°C and maintained under stirring for one hour. Filtered the solid product N, N-dimethyl-2-(1 l-oxo-6, 11-dihydrodibenz [b, e] oxepin-2-yl) acetamide and dried till constant weight.

Yield = 204 - 210 gm

**Step - II: Preparation of 11 - (Z) - [3-(dimethylamino) propyldiene]-6, 11-dihydrodibenz [b, e] oxepin-2-acetic acid (Olopatadine).**

Charged 190 gm of N, N-dimethyl-2-(1 l-oxo-6, 11-dihydrodibenz [b, e] oxepin-2-yl) acetamide in 570 ml of tetrahydrofuran. Cooled the reaction mass to 0 - 5°C and charged 340 gm dimethylaminopropyl magnesium chloride, maintained for one hour at 0-5°C. Decomposed the reaction mass adding 570 ml of DM water to the reaction mass stirred and added 570 ml of cone, hydrochloric acid maintaining temperature at 0 to 5 °C. Stirred and raised the temperature of the decomposed reaction mass to 25 - 35°C. Adjusted pH of the decomposed reaction mass to 9 - 10 with ammonium hydroxide solution maintaining temperature at 0 to 5°C. Extracted aqueous layer with 3 X 570 ml of toluene. Combined the toluene layers and extracted with dilute 1:1 hydrochloric acid (3 X 380 ml). Combined the acidic aqueous layer and heated for 5 - 10 hours at 90 - 95 °C. Cooled the reaction to 10 - 20°C and adjusted pH with potassium hydroxide solution (475 g of KOH in 380 ml water) to 6.8 - 7.2 and stirred for 30 minutes at 10 to 15°C. Charged
dichloromethane and extracted aqueous layer with 5 X 15V of dichloromethane. Combined all dichloromethane layers and concentrated under reduced pressure to isolate racemic mixture of E and Z isomer of olopatadine.
Yield = 120 - 125 gm.

**Step III: Preparation of 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydro dibenz [b, e] oxepin -2 - yl - acetic acid hydrochloride [Cis - Olopatadine hydrochloride].**
Charged 1250 ml of chlorobenzene to 120 gm of olopatadine. Raised the temperature of the reaction mixture to 80 - 85°C and started passing dry hydrochloric acid gas for 5 hours. Stopped passing hydrochloric acid gas and cooled the reaction mixture to 25 - 30°C and maintained 2.0 hours at 25 - 30°C. Filtered the solid separated and washed with cooled acetone to isolate crude 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydro dibenz [b, e] oxepin -2 - yl - acetic acid hydrochloride (Cis - Olopatadine HCl). Dried the solid till constant weight.
Yield = 90.0 gm

**Step - IV: Purification of crude 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydro dibenz [b, e] oxepin -2 - yl - acetic acid hydrochloride:**
To 375 ml of acetone, charged 75 gm of crude cis - olopatadine hydrochloride and raised the temperature of the reaction to attain reflux. Charged DM water (112. 5 ml) to the slurry at reflux temperature to get clear solution. Charcoalised the clear solution and filtered through charcoal bed. Charged filtrate in the flask and raised the temperature to reflux. Diluted the filtrate with acetone (125 ml) at reflux temperature. After the addition maintained the reaction mass at reflux temp for 30 minutes. Cooled the reaction mass to 0 -5°C and maintained for two hours. Filtered the white solid and dried till constant weight to get pure cis - olopatadine hydrochloride.
Yield = 60 gm
We claim,

1. A process for preparation of compound 11 - (Z) - [3 - (Dimethylamino) propylidene] - 6, 11 - dihydrodibenz [b, e] oxepin -2 - yl - acetic acid (Olopatadine) of Formula I and its pharmaceutically acceptable salt

Formula – I

comprising a step of;
reacting compound of Formula – XII

Formula - XII

where R¹ & R² independently represent H, or C₁ - C₄ alkyl group;
with 3-dimethylaminopropyl magnesium halide of Formula - XIII

Formula - XIII

where X is Chlorine, bromine or iodine.

2. The process as claimed in claim 1, wherein said process comprising the steps of;
   a) reacting compound of Formula XII with 3-dimethylaminopropyl magnesium halide of formula XIII by Grignard reaction in presence of solvent at temperature of -10° to 30°C;
b) decomposing the reaction mixture with dilute acid at temperature of 0°C to 5°C followed by stirring, adjusting the pH of reaction mixture with suitable base & extracting the reaction mass with toluene;

c) adjusting pH of toluene layer with dilute hydrochloric acid solution followed by separating aqueous layer and heating upto to 80°C - 100°C;

d) adjusting pH of aqueous solution with metal hydroxide to 6.8 - 7.2 and extracting with chlorinated solvent to isolate olopatadine;

e) treating olopatadine in presence of solvent with dry hydrochloric acid gas at temperature of 60°C to 90°C to isolate crude olopatadine hydrochloride and

f) purifying isolated crude olopatadine hydrochloride.

3. The process as claimed in claim 2; wherein the solvent used for Grignard reaction is selected from tetrahydrofuran, toluene, and hexane.

4. The process as claimed in claim 3; wherein the preferred solvent used for Grignard reaction is tetrahydrofuran.

5. The process as claimed in claim 2; wherein the base used for the pH adjustment at step (b) is selected from ammonium hydroxide, potassium hydroxide, sodium hydroxide.

6. The process as claimed in claim 5; wherein the preferred base is ammonium hydroxide.

7. The process as claimed in claim 2; wherein the metal hydroxide used in step (d) is selected from sodium hydroxide, potassium hydroxide and calcium hydroxide.

8. The process as claimed in claim 2; wherein the chlorinated solvent used in step (d) is selected from dichloromethane, dichloroethane, trichloroethane, tetrachloroethane and chlorobenzene.

9. The process as claimed in claim 2; wherein the solvent used in step (e) for hydrochloride salt formation is selected from chlorobenzene and n-butanol.
10. The process as claimed in claim 2; wherein the preferred solvent used in step (e) for hydrochloride salt formation is chlorobenzene.

11. The process as claimed in claim 2; wherein the preferred temperature of the hydrochloride salt formation is 80°C - 85°C.

12. The process according to any of the above claims; wherein the compound is cis-olopatadine hydrochloride.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D313/12

ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic database consulted during the international search (name of database and, where practical, search terms used)

EPO-Internal, WPI Data, BEI LSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>WO 2007/105234 A2 (USV LTD [IN]; TARUR VENKATASUBRAMANIAN RADHA [IN]; BHISE NANDU BABAN [ ]) 20 September 2007 (2007-09-20) page 12 - page 13; claim 26</td>
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<td>X</td>
<td>EP 0 235 796 A2 (KYOWA HAKKO Kogyo KK [JP] ) 9 September 1987 (1987-09-09) page 7 page 25; compound 22</td>
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X Further documents are listed in the continuation of Box C.

X See patent family annex.

* Special categories of cited documents:

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Date of the actual completion of the international search

2 March 2011

Authorized officer

Lewis, Sara

Form PCT/ISA/210 (second sheet) (April 2005)
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<td>OHSHIMA E ET AL: &quot;SYNTHESIS AND ANTIALLERGIC ACTIVITY OF II- (AMINOALKYLIDENE) -6, 11-DIHY</td>
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<td>DRODBENZUB, E 3/4 OXEPIN DERIVATIVES&quot; , JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN</td>
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<td>XP000615220, ISSN : 0022-2623 , DOI : 10.1021/JM00089A020 page 2076</td>
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