The present invention relates to a novel racemic or optically active carbamate intermediate of formula (IV A). This novel racemic or optically active carbamate intermediate of formula (IV A) can be used to prepare drugs having antihistaminic activity such as cetirizine (IA), medizine (IB), chlorcyclizine (IC), cloczinize (ID), buclizine (IE) and enantiomers thereof such as levocetirizine (I). Further, disclosed herein is an improved process for the preparation of levocetirizine via a novel optically active intermediate i.e. compound of formula (IV). Also, disclosed herein is a novel process for the preparation of compound (II) and for crystallization of its salt.
AN IMPROVED PROCESS FOR THE PREPARATION OF ANTIHISTAMINE DRUGS VIA A NOVEL CARBAMATE INTERMEDIATE

Field of the Invention

The present invention relates to a novel racemic or optically active carbamate intermediate of formula (IVA).

\[ \text{(IVA)} \]

In another aspect of the present invention, this novel racemic or optically active carbamate intermediate of formula (IVA) can be used to prepare drugs having antihistaminic activity such as cetirizine (IA), meclizine (IB), chlorcyclizine (IC), clocinizine (ID), buclizine (IE) and enantiomers thereof such as levocetirizine (I).

\[ \text{(IA)} \]
\[ \text{(IB)} \]
\[ \text{(IC)} \]
\[ \text{(ID)} \]
\[ \text{(IE)} \]

Another aspect of the present invention is directed to an improved process for the preparation of levocetirizine of formula (I) and pharmaceutically acceptable salts thereof,
via a novel optically active carbamate intermediate of formula (IV).

The present invention is also related to a novel process for the preparation of compound (II),

comprising reacting the compound of formula (III)

with 2-chloroethanol in the presence of suitable base and suitable solvent to give compound (II). It also provides a novel process for crystallization of salt of compound (II) using suitable solvent thereby producing the salt with high optical purity.

Background of Invention
Cetirizine (IA), meclizine (IB), chlorcyclizine (IC), clocinizine (ID), buclizine (IE) and enantiomers thereof such as levocetirizine i.e. (-) cetirizine of formula (I) are known to possess antihistaminic activity. Furthermore, the administration of (-)-cetirizine is found to be pharmacologically advantageous over racemic cetirizine, as less side effects are experienced.

United Kingdom Patent No. GB2225321 discloses the preparation of 1-[(4-chlorophenyl)-phenylmethyl]piperazine of formula (III), which is a key intermediate in the process for the preparation of levocetirizine by resolving racemic 1-[(4-chlorophenyl)phenylmethyl]piperazine with an optically active tartaric acid to form diastereomeric salt. But, the problem with this method is that the desired compound of formula (III) is obtained in very low yield i.e. 13%.

U.S. Patent No. US 5,478,941 also describes the process for synthesizing optically active compounds of formula (III). The process involves the following steps:-
(a) reacting optically active 1-(4-chlorophenyl)-phenylmethylamine (V) with \( \text{N,N-bis-(2-chloroethyl)-4-methylbenzenesulphonamide} \) of formula (VII) in the presence of \( \text{N,N-diisopropyl ethyl amine} \) to yield compound of formula (VIII)
(b) treating the compound of formula (VIII) with 30% HBr in acetic acid in the presence of 4-hydroxybenzoic acid to obtain optically active piperazine derivative of formula (III).

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 group of compound (VIII). 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 (VII) 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.

US 6,803,465 describes synthesis of racemic compound of formula (IX) by the use of t-butyloxycarbonyl group as N-protecting group for racemic compound of formula (III). Racemic compound of formula (IX)
is resolved using O,O'-dibenzoyltartaric acid. This process has several drawbacks. First, it involves the use of expensive reagents like O,O'-dibenzoyltartaric acid and di-tertiary butyl dicarbonate. Secondly, resolution is performed at an advanced stage of process. Further, repeated recrystallization is required for the purification of diastereomeric salt to achieve the desired optical purity, thereby lowering the yield and making the process lengthy and uneconomical.

WO 2007/066163 discloses a process for the preparation of benzyl protected (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine, followed by replacement with 2,2,2-trichloroethyl chloroformate and finally isolated as its hydrochloride salt. Optically pure (-)-l-[(4-chlorophenyl)phenylmethyl]piperazine is isolated in the form of its hydrochloride salt with poor over all yield of about -50% yield. As referred herein the racemization occurs during the alkaline hydrolysis of ethoxycarbonyl group when used as a protecting group in the preparation of piperazine ring.

The most important drawback of WO '163 is that process is quite lengthy and involves the use of 2, 2, 2- trichloroethyl chloroformate which is costly, inflammable and carcinogenic. As a result the process is not commercially viable and environment friendly.

WO 2009/065622 discloses the process for synthesizing optically active compounds of formula (III) by reacting compound of formula (V) with compound of formula (X);

\[
\begin{align*}
X & \quad \text{N} \quad \text{O} \\
\text{Z} & \quad \text{X}
\end{align*}
\]

wherein Z is C₃₋C₂₀ cycloalkyl group, C₇₋C₂₀ aralkyl group, C₆₋C₂₀ aryl/alkylaryl group, each of which groups can be substituted by one to four halogen, alkoxy, amino and/or nitro groups; followed by alkaline hydrolysis. The leaving group X may be represented by halogen or sulphonyl group such as mesyloxy, besyloxy, anisylsulfonyloxy or tosyloxy group. The yield obtained by following the said process is poor, which is only 53%. The challenge remains to obtain highly optically pure levocetirizine of pharmaceutical grade purity in good yield.
Thus, there is a need to develop the process for the preparation of levocetirizine of formula (I), which is cost effective, safe and environment friendly. It appears to be desirable to provide an improved route for preparing levocetirizine or salt thereof.

Object and Summary of the Invention

The object of present invention is a novel racemic or optically active carbamate intermediate of formula (IVA).

\[
\begin{align*}
\text{(IVA)}
\end{align*}
\]

In another object of the present invention, this novel racemic or optically active carbamate intermediate of formula (IVA) can be used to prepare drugs having antihistaminic activity such as cetirizine (IA), meclizine (IB), chlorcyclizine (IC), clocinizine (ID), buclizine (IE) and enantiomers thereof such as levocetirizine (I).

Further object of the present invention is to improve upon limitations in the prior art by providing an improved process for the preparation of levocetirizine of formula (I).

\[
\begin{align*}
\text{(I)}
\end{align*}
\]

It is another object of the present invention to provide an improved process for the preparation of levocetirizine of formula (I) via a novel optically active carbamate intermediate of formula (IV).

Further object of the present invention is to provide the process for the preparation of the optically active compound of formula (IV) comprising reacting compound of formula (VI)
with an optically active L-(4-chlorophenyl)phenylmethylamine (V) in the presence of suitable base,

followed by basic hydrolysis of compound of formula (IV) in a suitable solvent to yield optically active piperazine derivative of formula (III), which is a key intermediate in the process for the preparation of levocetirizine.

Compound of formula (III) can be optionally converted into acid addition salts thereof. It is then treated with 2-chloroethanol in the presence of a suitable base and suitable solvent to obtain compound of formula (II).

The compound of formula (II) is converted into acid addition salts thereof. The salt of compound (II), thus obtained is crystallized by heating in suitable solvent and then cooling to produce the salt in good yield with enhanced optical purity, which subsequently give levocetirizine or pharmaceutically acceptable salt thereof.

The above and other objects are further attained and supported by the following embodiments described herein. However, the scope of the invention is not restricted to describe embodiments herein after.

Detailed Description of the Invention
While this specification concludes with claims particularly pointing out and distinctly claiming that, which is regarded as the invention, it is anticipated that the invention can be more readily understood through reading the following detailed description of the invention and study of the included examples.

The present invention relates to a novel racemic or optically active carbamate intermediate of formula (IVA).

![IVA](image)

In another aspect of the present invention, this novel racemic or optically active carbamate intermediate of formula (IVA) can be used to prepare drugs having antihistaminic activity such as cetirizine (IA), meclizine (IB), chlorcyclizine (IC), clocinizine (ID), buclizine (IE) and enantiomers thereof such as levocetirizine (I).

![IA](image) ![I](image) ![IB](image)

![IC](image) ![ID](image) ![IE](image)

According to the present invention, the compounds and reactions involving the optically active compounds are also applicable to their racemic mixture.

The present invention is directed to an improved process for the preparation of levocetirizine of formula (I) and pharmaceutically acceptable salts thereof *via* a novel optically active carbamate intermediate of formula (IV).
The present invention discloses a process, which does not involve use of expensive and toxic reagents. Further, the removal of carbamate group is carried out under mild conditions with less racemization, thus making the process environment friendly.

The process for the preparation of levocetrizine (I) as depicted in Scheme-1 using the novel optically active intermediate carbamate of formula (IV) comprises of following steps:

a) Reacting the optically active 1-(4-chlorophenyl)phenylmethylamine (V)

\[
\text{(V)}
\]

with the compound of formula (VI)

\[
\text{(VI)}
\]

wherein \(X\) is a leaving group. The said leaving group can be selected from the group comprising of halogen, or sulphonyloxy group such as mesyloxy, besyloxy, anisylsulfonyloxy, tosylloxy group, preferably \(X\) is chloro; in the presence of a suitable base to yield the optically active compound of formula (IV).

\[
\text{(IV)}
\]

Suitable base is selected from the group comprising of \(N,N\)-diisopropylethylamine, triethylamine, pyridine and the like. The preferred base is \(N,N\)-diisopropylethylamine. The optically active 1-(4-chlorophenyl)phenylmethylamine (V) is prepared by resolution of racemic 1-(4-chlorophenyl)phenylmethylamine by
means of optically active tartaric acid according to the method described by R. Clemo

b) Hydrolyzing the compound of formula (IV) with suitable base in a suitable
solvent to yield optically active piperazine derivative of formula (III), which is a key
intermediate in the process for the preparation of levocetirizine.

\[
\begin{align*}
\text{Cl} & \quad \text{N}^0 \\
\text{\textbullet-\textbullet} & \quad \text{\textbullet-\textbullet} \\
(III)
\end{align*}
\]

Suitable base is selected from inorganic bases. Inorganic base is selected from the
group comprising of hydroxides, carbonates and bicarbonates of alkali and alkaline
earth metals. Examples include potassium hydroxide, sodium hydroxide, sodium
carbonate, potassium carbonate and like. The preferred base is potassium hydroxide.
Solvent is selected from group comprising of organic solvents. The organic solvent is
selected from group comprising of alcohols, dimethyl sulphoxide, dimethylformamide, acetonitrile and like. Preferably, isopropyl alcohol is used for the
reaction. This deprotection step is carried out at a temperature ranging from 60-90°C,
preferably at 80-85°C.

c) Optionally, the compound of formula (III) can be converted into acid addition
salts thereof in a suitable solvent. The acid addition salts can be prepared using the
acids selected from the group comprising of organic or inorganic acids. Inorganic
acids include hydrochloric acid, hydrobromic acid and hydroiodic acid and the like.
The organic acids include oxalic acid, succinic acid and like. Preferably, it is isolated
as oxalate salt. The oxalate salt of compound (III) is obtained in high yield with high
purity and can be easily handled and stored. Solvent used for salt formation is selected
from alcohols. Alcohol is selected from the group comprising of methanol, ethanol,
isopropyl alcohol and the like. Free compound (III) is made available for further
reaction by neutralizing its salt using suitable base such as sodium hydroxide,
potassium hydroxide, or their carbonates and bicarbonates, preferably sodium
hydroxide.

d) Treating compound (III) with 2-chloroethanol in the presence of suitable base
and suitable solvent to obtain compound (II).
The base is selected from organic base. The organic base is selected from the group comprising of potassium tert-butoxide, dimethylamine, triethylamine, diisopropyl ethylamine, pyridine and like. The preferred organic base is triethylamine. Suitable solvent is selected from the group comprising of aliphatic or aromatic hydrocarbon and the like. Aliphatic hydrocarbon is selected from group comprising of hexane, heptane, octane etc. Aromatic hydrocarbon is selected from group comprising of toluene, xylene, chlorobenzene etc. The preferred solvent is toluene.

(e) Converting the compound of formula (II) into acid addition salts thereof in the presence of suitable solvent. The acid addition salts can be prepared using the acids selected from the group comprising of inorganic acids and organic acids such as hydrochloric acid, hydrobromic acid, oxalic acid and like. The preferred acid is hydrochloric acid. Solvent is selected from ketones. Ketone is selected from group comprising of acetone, methyl ethyl ketone, diethyl ketone, methyl isobutyl ketone and like. The preferred solvent used is acetone. Selection of solvent is critical. It has been observed that the use of isopropyl alcohol leads to the salt which is difficult to handle as it is sticky in nature and results in salt having comparatively low purity. While acetone gives the salt which is free flowing. Due to better physical characteristics, the activities such as filtration etc are convenient on large scale.

(f) Crystallizing the salt of compound (II) thus obtained using suitable solvent at temperature of 40-70°C, thereby producing salt. During hydrolysis of carbamate, racemization to some extent occurs. If such compound is continued till the final stage, it would not pass in optical purity required for pharmaceutical grade. Hence, enhancement in chemical and optical purity is required. Compound of formula (II) being in oil form, is difficult to purify. It has been found that the formation and crystallization of salt of compound (II) increases the chemical purity as well as optical purity with good yield. Such steps are required to obtain the final API i.e.
levocetirizine of pharmaceutical grade. Suitable solvent used for crystallization of salt of compound (II) is selected from group comprising of ketones or their mixtures with water. Ketone is selected from group comprising of acetone, diethyl ketone, methyl isobutyl ketone, methyl ethyl ketone and the like. The preferred solvent is aqueous acetone. The temperature for carrying out crystallization is 40-70°C. Preferably, the crystallization is carried out at temperature of 50-55°C. At this temperature the salt gets dissolved, and on further cooling provides the salt of compound of formula (II) with enhanced optical purity of more than 99.5%. Preferably, hydrochloride salt of compound of formula (II) is obtained with optical purity 99.8%. Compound (II) can be obtained as free base by neutralizing its salt with base such as aqueous ammonia in toluene.

(g) Reacting compound of formula (II) with a compound of formula (XI)

\[
\begin{align*}
\text{Y} & \quad \text{OZ} \\
\text{(XI)}
\end{align*}
\]

wherein Y is halogen and Z represents hydrogen or alkali metal such as sodium; in the presence of organic solvent and base. The base is selected from the group comprising of hydrides, hydroxides, alkoxide of alkali metal or alkaline earth metal to yield levocetirizine. The preferred base is alkali metal hydroxide such as potassium hydroxide. Organic solvent is selected from the group comprising of ethers, amides, nitriles and dimethyl sulphoxide. Amide is selected from the group comprising of dimethyl formamide, dimethyl acetamide and the like. The preferred solvent is amide such as dimethylformamide.

(h) Optionally, converting levocetirizine into pharmaceutically acceptable salts thereof. Preferably, it is converted into its dihydrochloride salt.
We have also found that cyclization reaction between optically active l-(4-chlorophenyl)phenylmethylamine (V) and N, N-bis(2-chloroethyl) carbamic acid ethyl ester under basic condition produces N-carboethoxy piperazine derivative in 50% w/w (with respect to compound (V)) yield with 74% purity. Further, deprotection of ethoxycarbonyl derivative produces the compound of formula (III) with higher degree of racemization thereby reducing the chiral purity of final API i.e. levocetirizine. This racemization cannot be controlled by either lowering the reaction temperature or decreasing the molar equivalent of potassium hydroxide.

Serendipitously, it was found that isobutyloxy carbonyl derivative provides the superior results as compared with ethoxycarbonyl derivative. Quantitative yield of the reaction was obtained along with 90% purity of the reaction product, which makes the synthetic sequence commercially viable. Surprisingly, with isobutyloxycarbonyl derivative, racemization occurs comparatively to lesser extent.

The process described above in the present invention is demonstrated in the examples illustrated below. These examples are provided as illustration only and therefore should not be construed as limitation of the scope of the invention.
Example 1

Preparation of Compound (IV)

To a solution of (4-chlorophenyl)phenyl methylamine (V, 75 g) in N,N-diisopropyl ethylamine (133.50 g), N,N-bis(2-chloroethyl) isobutyl carbamate (VI, 100.1 g) was added at 25-30 °C. The reaction mixture was heated to 128-130°C for 12-14h while maintaining the same temperature. The progress of reaction was monitored using HPLC. After the completion of reaction, the reaction mixture was cooled to 25-30°C. A mixture of dichloromethane (630 ml) and water (375 ml) was added and allowed to stir for 15 min. The layers were separated. To the organic layer, 250 ml of water was added. The pH of the reaction mixture was adjusted to 5.0-5.5 by adding cone. HCl (-30 ml) and then allowed to stir for 15 min. After separating the organic layer, 2% NaHCO₃ solution (dissolving 5 g NaHCO₃ in 250 ml water) was added with stirring. The organic layer was then separated and washed with water (250 ml). Finally, it was distilled out to obtain the residual mass as oil in quantitative yield.

Example 2

Preparation of Compound (I)

Compound (IV, obtained above) was taken in 630 ml of isopropyl alcohol. 90.78 g KOH was added to the reaction mixture at 25-30°C. The heterogeneous reaction mixture was heated at 80-85 °C for 9h. The progress of reaction was monitored using HPLC. After the completion of reaction, the reaction mixture was cooled to 25-30°C. The reaction mass was filtered at 25-30°C and washed with IPA (124 ml). The filtrate was distilled out under reduced pressure at 55-60°C. A mixture of dichloromethane (508 ml) and water (628 ml) was added to the above reaction mass and allowed to stir for 15 min. The organic layer was separated. To this organic layer, water (508 ml) was added. The pH of the reaction mixture was adjusted to 0-1.0 by adding cone. HCl (68 ml) at 25-30°C and allowed to stir for 15 min. After separating the aqueous layer, 380 ml of dichloromethane was added to acidic aqueous layer. The pH of the reaction mixture was adjusted to 11-12 by adding 30% NaOH solution at 25-30°C and stirred for 15 min. The aqueous layer was separated and extracted with dichloromethane (75 ml). The combined organic layer was washed with water (250 ml). The reaction mixture was concentrated under vacuum to give the title compound with 75% yield.
Example 3
Preparation of oxalate salt of Compound (III)

A solution of compound (III, obtained above) in IPA (508 ml) was heated to 40-45°C. To this, oxalic acid (78.13 g) was added. The reaction mixture was allowed to reflux to 80-85°C for 30 min and then cooled at 20-30°C and stirred for 5h. The solid thus obtained was filtered and washed with IPA (124 ml). The title compound was then dried under vacuum at 50-55°C for 12h. The title compound (115.0 g) was obtained with 71.65% yield.

Example 4
Preparation of Compound (II) from its oxalate salt

A solution of oxalate salt of compound (III, 75 g) in water (300 ml) was heated to 65-70°C. After adding NaOH solution (28.8 g dissolved in 28.8 ml water), the reaction mixture was allowed to stir at 65-70°C for 30 min. After cooling, dichloromethane (225 ml) was added to the reaction mixture. It was stirred for another 30 min and filtered and washed with DCM (75 ml). From the filtrate, the organic layer was separated. Aqueous layer was further extracted with DCM (75 ml). The organic layer was washed with water (150 ml). The organic layer was concentrated under vacuum to yield the title compound. The title compound (III) thus obtained can be used such as for next step without purification.

Example 5
Preparation of Compound (II) & its hydrochloride salt

Compound III (obtained in example 2) was taken in toluene (300 ml). To this, 2-chloroethanol (23.29 g) and triethylamine (72.12 ml) were added and then heated to 110-115°C for 3h. After cooling the reaction mass to 75-80°C, the remaining 15.52 g of 2-chloroethanol was added. The temperature of the reaction mixture was further raised to 110-115°C and maintained at this temperature for 4h. The progress of reaction was monitored by HPLC. After the completion, it was allowed to cool to 25-30°C and followed by the addition of water (150 ml) and stirred for 10 min. After separating the organic layer, it was washed with water (75 ml) and then 112.5 ml of water was added to the organic layer. The pH of the reaction mixture was adjusted to 1.0-2.0 using cone. HCl (~28 ml). After stirring, the aqueous layer was separated. To the aqueous layer, dichloromethane (225 ml) was added and adjusted the pH to 9.5-10.0 using liquid ammonia. The organic layer was separated, washed with water (150
ml) and concentrated to yield an oily mass of title compound. This oily mass was taken in acetone (750 ml) and heated at 40-45°C to get clear solution. The reaction mixture was cooled to 25-30°C and cone. HCl (45.8 ml) was added. It was allowed to stir for 12h at 25-30°C. The solid thus obtained was washed with acetone (75 ml) and dried under vacuum to yield 68.61 g hydrochloride salt of title compound with 49.4% yield (with respect to compound (V)).

Example 6

Crystallization of Hydrochloride salt of Compound (II)

48.0 g of Hydrochloride salt of compound (II) was taken in 288 ml aqueous acetone (13%). The reaction mixture was heated to 50-55°C to get the clear solution and allowed to stir for 30 min while maintaining the same temperature. Acetone (192 ml) was added to the hot solution. The reaction mixture was allowed to cool at 0-5°C and stirred at the same temperature for 4h. Solid thus obtained was filtered and washed with chilled acetone (48 ml). Solid was then dried under vacuum at 50-55°C for 12h to get the title compound of yield 83.3% (with respect to compound (IV)) with optical purity 99.8%.

Example 7

Preparation of Compound (I): Levocetirizine

To a solution of hydrochloride salt of compound (II, 36 g) in 108 ml of water, 180 ml toluene was added. The pH of the biphasic system was adjusted to 8.5-9.0 using liq. ammonia and stirred for 15 min. To this, sodium chloride (9.0 g) was added and stirred for another 30 min. After separating the organic layer, aqueous layer was extracted with toluene (36 ml). The combined organic layers were concentrated to get oily residue. A homogeneous solution of residue in DMF (57.6 ml) was cooled to 0-5°C and then added sodium chloroacetate powder (XI, 16.6 g) and KOH (10+5.3 g, added in lots). After addition, the reaction mixture was stirred at 5-10°C for 2h. The progress of reaction was monitored by HPLC. After the completion, water (360 ml) was added and stirred for 10 min. The pH of the reaction mixture was adjusted to 9.3-9.8 using cone. HCl. Ethyl acetate (144 ml) was added and stirred for another 15 min. The aqueous layer was separated and washed with ethyl acetate (3 x 144 ml). The pH of solution was adjusted to 4.3-4.8 using cone. HCl (-7.2 ml). Dichloromethane (180 ml) was added to the aqueous layer and stirred for 30 min. Then the organic layer was separated and washed with water (3 x 36 ml). The reaction mixture was concentrated
under vacuum to yield the title compound. The compound (I) thus obtained can be used such as for next step without purification.

**Example 8**

**Preparation of Levocetirizine dihydrochloride**

To a homogenous solution of compound (I, obtained above) in acetone (432 ml), cone. HCl (16.5 ml) was added. The reaction mixture was seeded with crystals of levocetirizine dihydrochloride (0.36 g) and allowed to stir for 12 h at 25-30°C. The reaction mixture was then cooled to 10-15°C and stirred for 2h. Solid thus obtained was filtered and washed with acetone (36 ml). To this, 2% aqueous acetonitrile (144 ml) was added and heated to 45-50°C with stirring for 30 min. The reaction mass was then cooled to 25-30°C over a period of 2h. It was further cooled to 10-15°C and stirred at the same temperature for 30 min. The solid thus obtained was filtered and washed with acetone (36 ml). The solid was dried under vacuum at 50-55°C to give the title compound of yield 71%.

While this invention has been described in detail with reference to certain preferred embodiments, it should be appreciated that the present invention is not limited to those precise embodiments. Rather, in view of the present disclosure, which describes the current best mode for practicing the invention, many modifications and variations would present themselves to those skilled in the art without departing from the scope and spirit of this invention.
We claim:

1. A process for preparing levocetirizine of formula (I) using an optically active compound of formula (IV) comprising the steps of:

   a. reacting the optically active (4-chlorophenyl)phenylmethylamine (V)

   with compound of formula (VI)

   wherein X is a leaving group, in the presence of a suitable base to yield the optically active compound of formula (IV);
b. hydrolyzing the compound of formula (IV) with a suitable base in a suitable organic solvent to yield optically active piperazine derivative of formula (III);

\[
\begin{align*}
\text{(III)} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{N} \\
\text{NH}
\end{array}
\end{align*}
\]

c. optionally, converting the compound of formula (III) into acid addition salts thereof and treating it with a suitable base to obtain compound of formula (III);

d. reacting the compound of formula (III) obtained from step (b) or (c) with 2-chloroethanol in the presence of a suitable base and suitable solvent to obtain compound of formula (II);

\[
\begin{align*}
\text{(II)} & \quad \begin{array}{c}
\text{Cl} \\
\text{N} \\
\text{N} \\
\text{OH}
\end{array}
\end{align*}
\]

e. converting the compound of formula (II) into acid addition salts thereof in presence of a suitable solvent and crystallizing the resultant in the presence of suitable solvent and then cooling, followed by treatment with a base to obtain compound of formula (II);

f. reacting the compound of formula (II) with compound of formula (XI)

\[
\begin{align*}
\text{(XI)} & \quad \begin{array}{c}
Y \\
\text{OZ}
\end{array}
\end{align*}
\]

wherein Y is halogen and Z is hydrogen or alkali metal;
in the presence of organic solvent and base to yield levocetirizine;
g. optionally, converting levocetirizine into pharmaceutically acceptable salt thereof.

2. The process according to claim 1, wherein the leaving group X in step (a) is selected from the group comprising of halogen or sulphonyloxy group.

3. The process according to claim 2, wherein the X group is chloro.

4. The process according to claim 1, wherein the base used in step (a) is selected from the group comprising of N, N-diisopropylethylamine, triethylamine and pyridine.

5. The process according to claim 4, wherein the base used is N, N-diisopropylethylamine.

6. The process according to claim 1, wherein the base used in step (b) is an inorganic base selected from a group comprising of hydroxides, carbonates and bicarbonates of alkali and alkaline earth metals.

7. The process according to claim 6, wherein the base used is potassium hydroxide.

8. The process according to claim 1, wherein the solvent used in step (b) is selected from organic solvents comprising of alcohols, dimethyl sulphoxide, dimethylformamide and acetonitrile.

9. The process according to claim 8, wherein the solvent used is isopropanol.

10. The process according to claim 1, wherein the step (b) is carried out in temperature range of 60-90°C.

11. The process according to claim 1, wherein the acid addition salt of compound (III) in step (c) is an oxalate salt.

12. The process according to claim 1, wherein the solvent used in step (d) is selected from the group comprising of aliphatic or aromatic hydrocarbon.

13. The process according to claim 12, wherein the aromatic hydrocarbon is selected from group comprising of toluene, xylene, chlorobenzene and so forth.

14. The process according to claim 13, wherein the aromatic hydrocarbon is toluene.

15. The process according to claim 1, wherein the base used in step (d) is an organic base selected from the group comprising of potassium tert-butoxide, dimethylamine, triethylamine, diisopropylethylamine and pyridine.
16. The process according to claim 15, wherein the base is triethylamine.

17. The process according to claim 1, wherein the solvent used in step (e) for crystallization of salt of compound (II) is selected from the group comprising of ketones or their mixtures with water.

18. The process according to claim 17, wherein the ketone is selected from the group comprising of acetone, diethyl ketone, methyl isobutyl ketone and methyl ethyl ketone.

19. The process according to claim 17, wherein the solvent used is aqueous acetone.

20. The process according to claim 1, wherein the crystallization in step (e) is carried out at temperature of 40-70°C.

21. The process according to claim 1, wherein the salt obtained after crystallization in step (e) is having optical purity more than 99.5%.

22. The process according to claim 21, wherein the salt is hydrochloride having optical purity of about 99.8%.

23. A compound of formula (IVA) in racemic or optically active form.

24. Use of racemic or optically active compound of formula (IVA) for preparing drugs exhibiting antihistaminic activity.

25. Use of the racemic or optically active compound of formula (IVA) according to claim 24, wherein the drugs are cetirizine, meclizine, chlorcyclizine, clocinizine, buclizine and enantiomers thereof.
26. Use of the racemic or optically active compound of formula (IVA) according to claim 25, wherein the drug is levocetirizine.

27. A process for the preparation of racemic or optically active carbamate intermediate of formula (IVA) comprising reacting the racemic or optically active 1-(4-chlorophenyl)phenylmethylamine with compound of formula (VI)

\[
\text{(VI)}
\]

wherein \(X\) is a leaving group;
in the presence of a suitable base to yield the racemic or optically active compound of formula (IVA).

\[
\text{(IVA)}
\]

28. The process according to claim 27, wherein the optically active carbamate of formula (IV) is

\[
\text{(IV)}
\]

29. A process for preparing an antihistaminic drug using racemic or optically active compound of formula (IVA).

\[
\text{(IVA)}
\]
30. A process according to claim 29, wherein the antihistaminic drug is levocetirizine.

31. A process according to claim 29, wherein the process comprising the steps of:
   a. hydrolyzing the compound of formula (IV)

   ![Formula IV]

   with a suitable base in a suitable organic solvent to yield optically active piperazine derivative of formula (III):

   ![Formula III]

   b. optionally, converting the compound of formula (III) into acid addition salts thereof and treating it with a suitable base to obtain compound of formula (III);

   c. reacting the compound of formula (III) obtained from step (a) or (b) with 2-chloroethanol in the presence of a suitable base and suitable solvent to obtain compound of formula (II):

   ![Formula II]

   d. converting the compound of formula (II) into acid addition salts thereof in the presence of suitable solvent and crystallizing the salt thus
obtained in the presence of suitable solvent and then cooling, followed by
treatment with a base to obtain compound of formula (II);

e. reacting the compound of formula (II) with compound of
formula (XI)

\[
Y \begin{array}{c}
\text{O} \\
\text{Z}
\end{array}
\]

(XI)

wherein Y is halogen and Z is hydrogen or alkali metal; in the presence of
organic solvent and base to yield levocetirizine;

f. optionally, converting levocetirizine into pharmaceutically
acceptable salt thereof.
## A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D295/088  C07D295/205

ADD.

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

- **C07D**

## 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 data base consulted during the international search (name of data base and, where practical, search terms used):

- EPO-Internal, WPI Data, BIOSIS, EMBASE, CHEMABS Data

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
<thead>
<tr>
<th>Category*</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>wo 2010/057515 AI (SYNTHON BV [NL]; ZHU JIE [NL]; FJ RET JUDITH JANNEKE [NL]) 27 May 2010 (2010-05-27) the whole document</td>
<td>1-31</td>
</tr>
<tr>
<td>A</td>
<td>US 2 819 269 A (WESTON ARTHUR W ET AL) 7 January 1958 (1958-01-07) the whole document in particular example III</td>
<td>1-31</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of Box C.

* Special categories of cited documents:

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "E" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- "Z" document member of the same patent family

### Date of the actual completion of the international search

**16 April 2012**

### Date of mailing of the international search report

**02/05/2012**

**Name and mailing address of the ISA:**

European Patent Office, P.B. 5818 Patentlaan 2

NL - 2280 HV RIJWELK

Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016

**Authorized officer:**

Papathoma, Sofia

---

Form PCT/ISA/210 (second sheet) (April 2005)
<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td>WO 2010057515 A1</td>
<td>27-05-2010</td>
<td>NL 1037485 A</td>
<td>28-05-2010</td>
</tr>
<tr>
<td>WO 2010057515 A1</td>
<td>27-05-2010</td>
<td>DE 60210696 T2</td>
<td></td>
</tr>
<tr>
<td>US 2819269 A</td>
<td>07-01-1958</td>
<td>NONE</td>
<td></td>
</tr>
</tbody>
</table>