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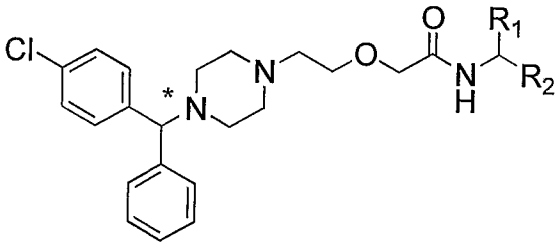
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

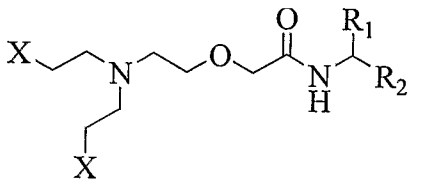
— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

[Continued on next page]

(54) **Title:** A PROCESS FOR THE SYNTHESIS OF 2-[2-[4-[(4-CHLOROPHENYL)PHENYL METHYL]-1-PIPERAZINYL] ETHOXY ACETIC ACID



(IIa)



(VIIIa)

(57) **Abstract:** TAbstract A process for the preparation of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid of formula (Ia) and pharmaceutically acceptable salts thereof, and compounds of formula (IIa) and (VIIIa), wherein R1 = H or C1-C4 alkyl; R2 = aryl or heteroaryl or R1 and R2 together with the carbon to which they are attached form a C3-C8 cycloalkyl group and X is a suitable leaving group for example, chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group are described.

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— *of inventorship (Rule 4.17(iv))*

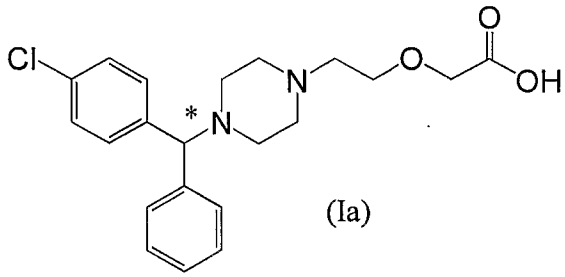
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A process for the synthesis of 2-[2-[4-[(4-chlorophenyl)phenylmethyl]-1-piperazinyl]ethoxy acetic acid

FIELD OF THE INVENTION

The present invention relates to a process for the preparation of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid of formula (Ia) and pharmaceutically acceptable salts thereof,

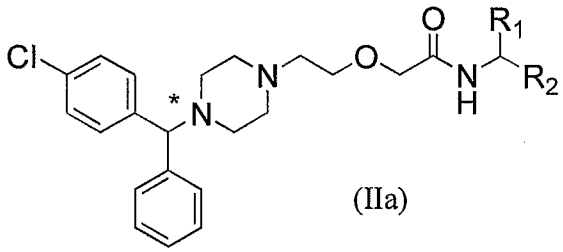


(Ia)

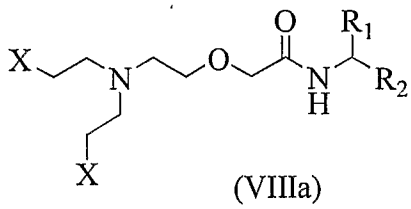
wherein the asterisk indicates the centre of asymmetry of the molecule.

The compound of formula (Ia) may exist in the levorotatory form, the dextrorotatory form or a mixture of the levorotatory and dextrorotatory forms or pharmaceutically acceptable salts thereof.

The present invention also relates to a novel compound of formula (IIa) and (VIIIa),



(IIa)



(VIIIa)

wherein R_1 = H or C_1-C_4 alkyl;

R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group and X is a suitable leaving group for example, chlorine,

bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group.

BACKGROUND

The dihydrochloride of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, also known as Cetirizine, is known as a medicament for the treatment of allergic syndromes, such as chronic and acute allergic rhinitis, allergic conjunctivies, pruritus, urticaria etc. Its pharmacological and medicinal properties have been described in the literature, C. De. Vos et. Al., Ann. Allergy 59, 278, 1987; L. Juhlin et. Al, J. Allergy Clin. Immunol., 80, 80,599 (1987).

The levorotatory isomer of cetirizine, i..e Levocetirizine is also approved for allergic rhinitis and chronic idiopathic urticaria.

European Patent No. 58,146 describes the synthesis of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid and its dihydrochloride. Patent discloses the synthesis wherein the starting substance 1-[(4-Chloro phenyl) phenyl methyl] piperazine is reacted with methyl (2-chloroethoxy) acetate to give methyl-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetate in a yield 27.8%. This methyl ester is then subjected to hydrolysis with an inorganic base (sodium or potassium hydroxide) to give the sodium or potassium salt, which is easily converted into the free acid, and then into cetirizine dihydrochloride

The major disadvantage of this synthesis is that the overall yield of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid dihydrochloride is only 10.6%, based on the amount of 1-[(4-Chloro phenyl) phenyl methyl] piperazine.

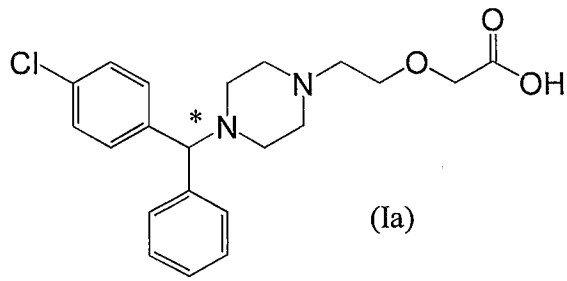
British Patent No. 2,225,321describes a process for the preparation of the enantiomers of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid dihydrochloride. This process is based on the use of levorotatory or dextrorotatory 1-[(4-Chloro phenyl) phenyl methyl] piperazine which is obtained by the chemical resolution of

racemic form, using conventional methods, in particular, by salt formation with a suitably selected optical isomer of tartaric acid.

The disadvantages of this process are, on one hand, the yield of the resolution step of the racemic 1-[(4-Chloro phenyl) phenyl methyl] piperazine is extremely low (only 12.7%) and on the other hand 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%.

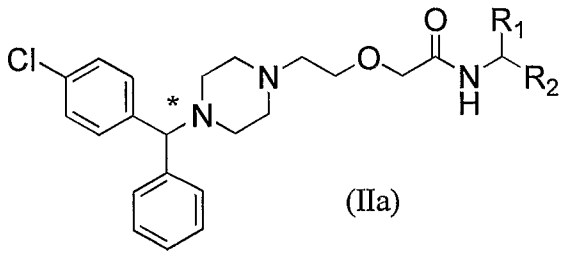
SUMMARY OF THE INVENTION

The present invention provides a process for the preparation of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, a compound of formula (Ia), which is either in the levorotatory or dextrorotatory form or a mixture thereof.



(Ia)

The process comprises converting the compound of formula (IIa),



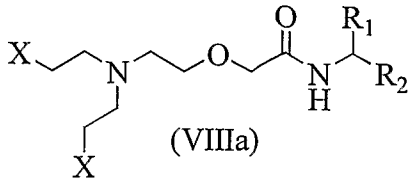
(IIa)

by treatment with acid or a base to obtain a compound of formula (Ia),

wherein R_1 = H or C_1-C_4alkyl;

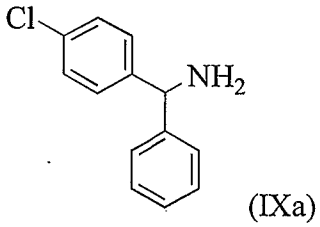
R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

In one of the embodiment, above defined compound of formula (IIa), is prepared by a process comprising condensing a compound of formula (VIIIa)



(VIIIa)

with a compound of formula (IXa),



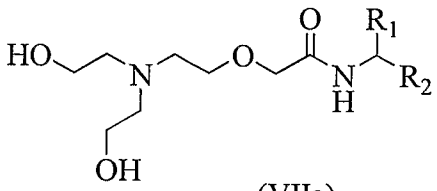
(IXa)

wherein X is a suitable leaving group consisting of, chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group;

R_1 = H or C_1-C_4alkyl;

R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

In one of the embodiment, invention relates to the process of preparing a compound of formula (VIIIa) comprising halogenation or mesylation of a compound of formula (VIIa),

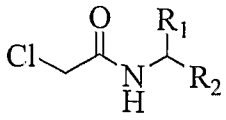


(VIIa)

wherein R_1 = H or C_1-C_4alkyl;

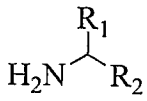
R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group, under suitable condition.

In yet another embodiment the process of preparing a compound of formula (VIIa) by the condensation of an acetamide of formula (Va)



(Va)

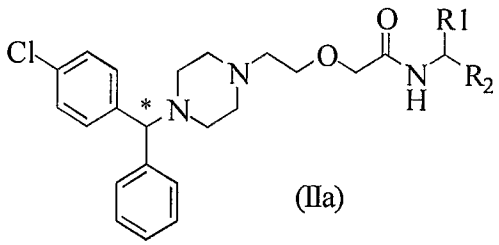
with triethanol amine VI is provided. The compound of formula (Va) can be prepared by the acylation of a requisite amine,



(IIIa)

by 2-chloroacetyl chloride. The equivalent halo derivative for example bromo, of compound of formula (Va) can be prepared by using requisite haloacetyl chloride.

In yet another embodiment invention relates to novel intermediate of formula (IIa),

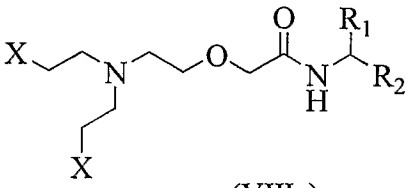


(IIa)

wherein R_1 = H or C_1-C_4alkyl;

R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

In yet another embodiment invention relates to novel intermediate of formula (VIIIa),

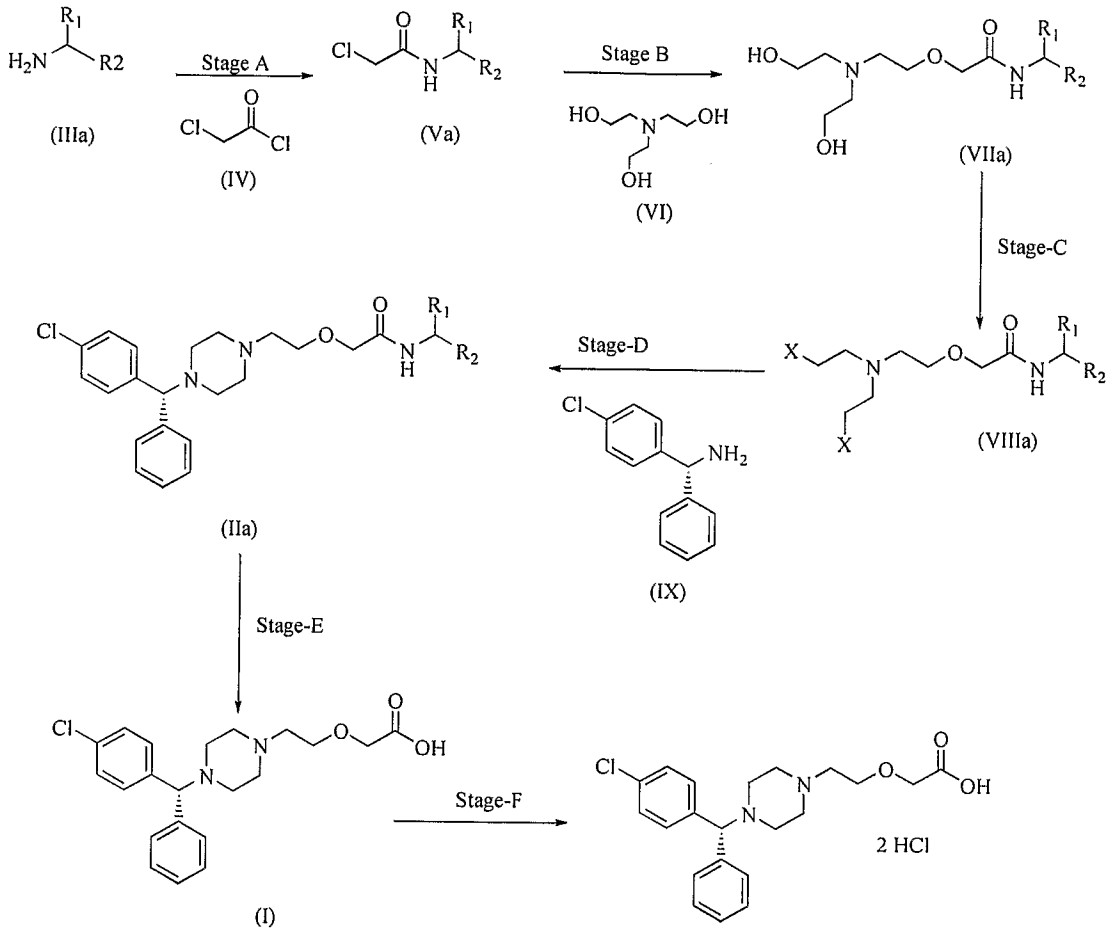


(VIIIa)

The present invention provides use of intermediate of formulae (IIa) and (VIIIa) in preparation of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid of formula (Ia) and pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION

The present invention provides a process for preparation of the levorotatory isomer, (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, a compound of formula (I), depicted schematically in scheme I below;



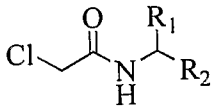
SCHEME I

wherein X is a suitable leaving group selected from the group consisting of chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group;

R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

According to the present invention, the compound of formula (Va) is prepared by any method known in the art which comprises acylation of a requisite amine (IIIa) by chloroacetylchloride,

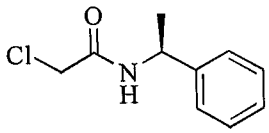


(Va)

wherein R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

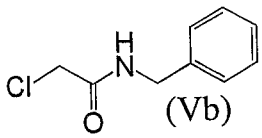
The present disclosure provides the preparation of 2-chloro-N-(1-phenyl ethyl) acetamide (V)



(V)

by acylation of 1-phenyl ethyl amine by 2-chloroacetyl chloride in the presence of an organic or inorganic base.

The present disclosure further contemplates the preparation of 2-chloro-N-benzyl acetamide (Vb)



(Vb)

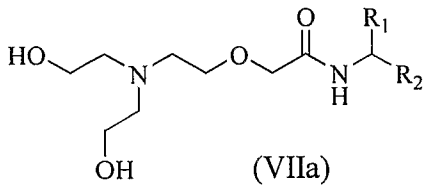
is prepared by acylation of Benzyl amine by 2-chloroacetyl chloride in the presence of an organic or inorganic base.

The solvent used in said stage-A acylation reaction may be selected from water, non-polar hydrocarbon or chlorinated hydrocarbon solvent, aprotic solvent, aromatic solvent, ether solvent. Advantageously, the aromatic solvent used in stage-A may be selected from benzene, toluene, xylene and the likes thereof, preferably toluene; the chlorinated hydrocarbons used in stage-A may be selected from dichloromethane, dichloroethane, dibromoethane, preferably dichloromethane.

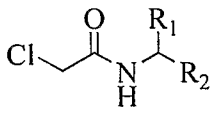
The base used in said stage-A may be selected from organic base or inorganic base. Advantageously, the inorganic base may be selected from sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, preferably sodium carbonate; organic base may be tert.butyl dimethylamine, triethylamine, diisopropylethylamine, pyridine, morpholine, p-N,N-dimethyl amino pyridine and the likes thereof, preferably triethylamine.

The acylation reaction is advantageously carried out at a temperature range of about -15°C to about +45°C, preferably about -5°C to about 35°C.

Conversion of (Va) to (VIIa) involves the reaction of an amide of formula (Va) with triethanolamine (VI),



(VIIa)

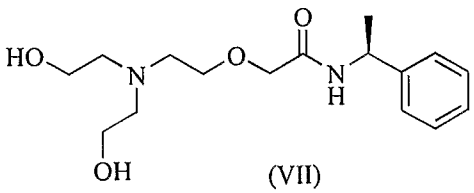


(Va)

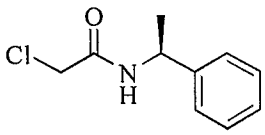
wherein R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-[N-(1-phenyl ethyl) acetamide (VII) may also be prepared by condensation of 2-chloro-N-(1-phenyl ethyl) acetamide (V) with triethanolamine (VI).

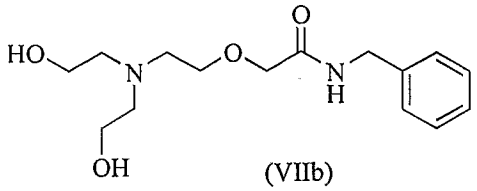


(VII)

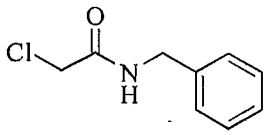


(V)

The present invention further discloses that 2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-N-benzyl acetamide (VIIb) may be prepared by condensation of 2-chloro-N-Benzyl acetamide (Vb) with triethanolamine (VI).



(VIIb)



(Vb)

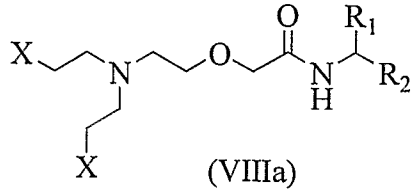
If required, a solvent may be used in said stage-B selected from water, aprotic polar solvent or aromatic solvent. Advantageously the aprotic polar solvent may be selected from N,N-dimethyl formamide, N,N-dimethyl- acetamide, dimethylsulfoxide, N-methyl-2-pyrrolidone and the likes thereof, preferably dimethylsulfoxide; the aromatic solvent may be selected from benzene, toluene, xylene and the likes thereof, preferably toluene.

The base used in said stage-B may be selected from alkali hydrides, hydroxides, carbonates or bicarbonates. Advantageously, the inorganic base may be selected from sodium hydride, lithium hydride, Butyl lithium, sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, preferably sodium hydroxide.

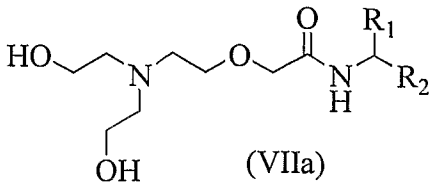
The mole equivalent ratio of triethanolamine (VI) to the acetamide (Va), may be 1:1 1:10, preferably 1:4.5. Advantageously triethanolamine can also act as a solvent, obviating the need of different solvent. The excess triethanol amine can be recovered by conventional method and recycled to increase the productivity.

The condensation reaction in stage-B may be carried out between about -15°C to about 130°C, preferably about 65°C to about 80°C.

The present disclosure further contemplates that the above obtained compound of formula (VIIa) may be further converted to compound of formula (VIIIa) by halogenation or mesylation,



(VIIIa)



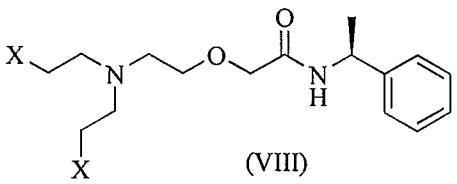
(VIIa)

wherein R_1= H or C_1-C_4 alkyl;

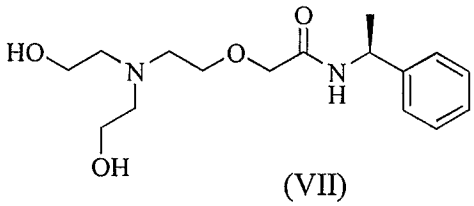
R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group;

X is a suitable leaving group selected from the group consisting of chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group.

Thus 2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-[N-(1-phenyl ethyl)] acetamide of formula (VII), further undergoes halogenation or mesylation to provide a compound of formula (VIII),



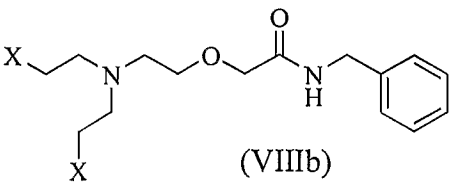
(VIII)



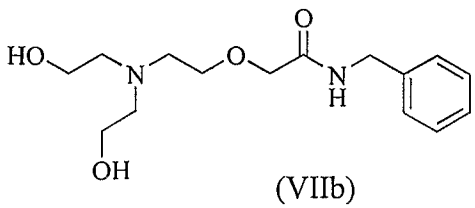
(VII)

wherein X is a suitable leaving group selected from the group consisting of chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group.

Similarly, compound of formula (VIIb) undergoes halogenation or mesylation to provide compound of formula (VIIIb),



(VIIIb)



(VIIb)

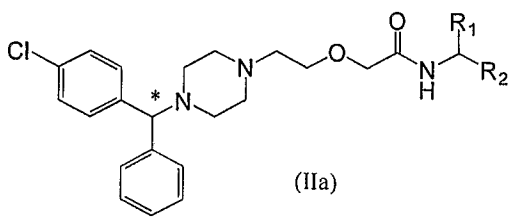
The solvent used in said stage-C may be selected from non-polar hydrocarbon, chlorinated hydrocarbon solvents, aprotic solvent, aromatic solvent, ether solvent. Advantageously, the aromatic solvent may be selected from benzene, toluene, xylene and the likes thereof, preferably toluene; the chlorinated hydrocarbons may be dichloromethane, dichloroethane, dibromoethane and the likes thereof, preferably dichloromethane.

In the work up, the excess acid can be neutralized by using a base selected from organic base or inorganic base. Advantageously, the inorganic base may be selected from sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, preferably sodium hydroxide or organic base may be triethylamine, diisopropylethylamine, pyridine, morpholine, p-N, N-dimethyl amino pyridine, preferably sodium hydroxide.

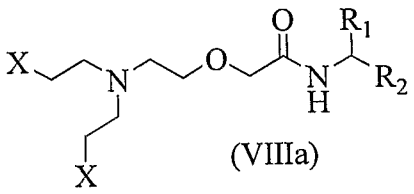
The halogenation reaction may be advantageously carried out at a temperature range of about -15°C to about +55°C, preferably about 5°C to about 30°C using halogenating agents like thionyl chloride, sulfuryl chloride, oxalyl chloride, phosphorous trichloride, phosphorous pentachloride and the likes thereof.

The mesylation reaction can be carried out using suitable agent like mesyl halide, tosyl halide at a temperature range of about -15°C to +50°C, preferably about 0°C to about 5°C.

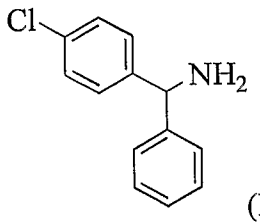
The present invention provides a novel intermediate of formula (IIa) and a process for the preparation of such novel intermediates wherein a compound of formula (VIIIa) is treated with compound of formula (IXa),



(IIa)



(VIIIa)



(IXa)

wherein R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group ;

X is a suitable leaving group selected from the group consisting of chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group or 4-bromophenyl-sulfonyloxy group, under suitable condition.

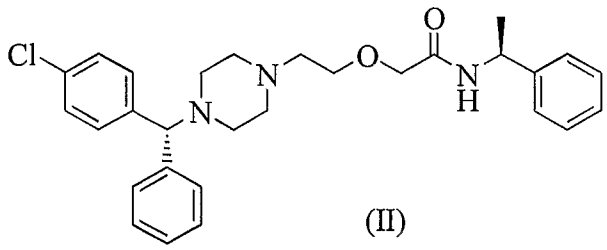
Optionally, the solvent used in said stage-D may be selected from aprotic polar solvents or hydrocarbon solvents for example, toluene, benzene, xylene, N, N-dimethyl formamide, N, N-dimethylacetamide, dimethylsulfoxide, N-methyl-2-pyrrolidone, preferably dimethylsulfoxide.

The base used in stage-D may be selected from organic base or inorganic base. Advantageously the inorganic base may be selected from sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate, preferably sodium carbonate; the organic base may be selected from triethylamine, diisopropylethylamine, pyridine, morpholine, p-N, N-dimethyl amino pyridine, preferably diisopropylethyl amine.

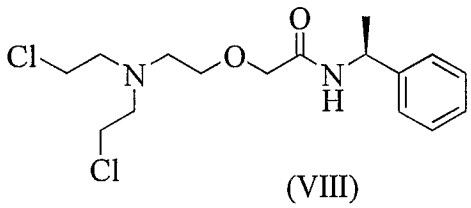
The cyclization reaction may be advantageously carried out at a temperature range of 15°C to 145°C preferably about 120°C to about 130°C.

The preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-[N-(1-phenyl ethyl)] acetamide (II) can be carried out by the cyclization of 2-[N, N-Bis (2-chloro ethyl) amino] ethoxy-1-[N-(1-phenyl ethyl)] acetamide (VIII) with (R)-4-(chlorophenyl) phenyl methyl amine (IX). Advantageously, the reaction may be carried

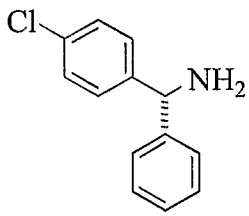
out in a solvent like toluene, benzene, xylene, N,N-dimethyl formamide, N,N-dimethylacetamide, dimethylsulfoxide, N-methyl-2-pyrrolidone in presence of a base like pyridine, TEA, potassium carbonate at about 120°C to 130°C. For example, N, N-diisopropyl amine can serve as a solvent and a base to carry out the cyclisation, obviating the need to use another solvent.



(II)

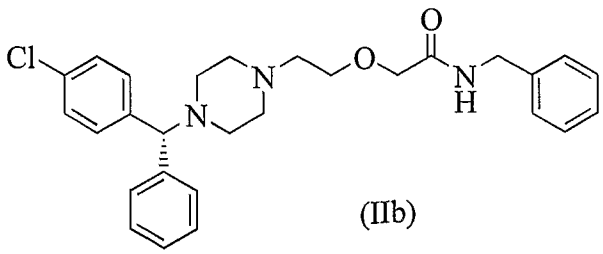


(VIII)

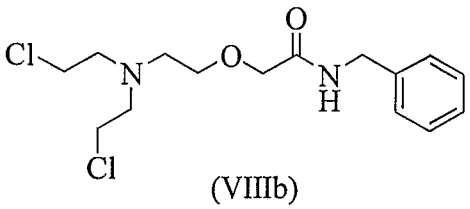


(IX)

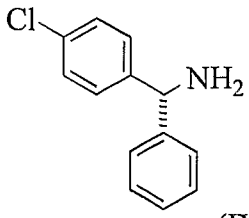
The preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-N-(1-Benzyl)] acetamide (IIb) can be carried out by the condensation of 2-[N, N-Bis (2-chloro ethyl) amino] ethoxy-1-[N-(1-Benzyl)] acetamide (VIIIb) with (R)-4-(chlorophenyl) phenyl methyl amine (IX). Advantageously, the reaction may be carried out in a solvent like toluene, benzene, xylene, N,N-dimethyl formamide, N,N-dimethylacetamide, dimethylsulfoxide, N-methyl-2-pyrrolidone in presence of a base like pyridine, TEA, potassium carbonate at about 120°C to 130°C. For example, N, N-diisopropyl amine can serve as a solvent and a base to carry out the cyclisation, obviating the need to use another solvent.



(IIb)



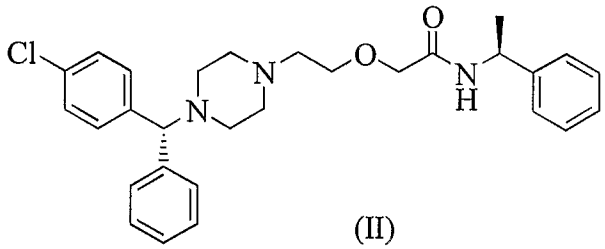
(VIIIb)



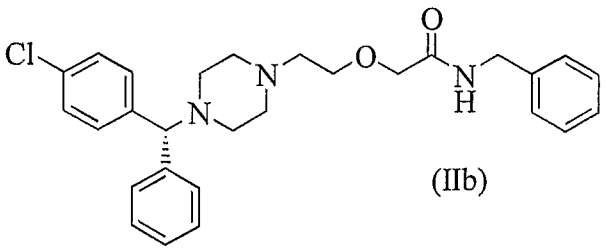
(IX)

Thus, these compounds of formula (IIa), for example (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-S-[N-(1-phenyl ethyl)] acetamide (II) or (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-N-(1-Benzyl)] acetamide (IIb) can be hydrolysed to obtain (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I). These compounds of formula (IIa) can show diastereoisomerism. The unwanted diastereomer can be removed by a simple leaching of the amide compound with suitable solvent or by solvent mixture to get substantially optically pure desired diastereomer which can be converted easily and with high yields into the substantially optically pure enantiomers of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid.

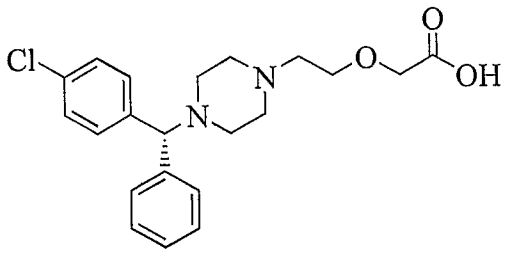
In one of the embodiments the hydrolysis of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-(S)-[N-(1-phenyl ethyl)] acetamide (II) or (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-N-benzyl acetamide (IIb) may be carried out by treatment with acid or base to obtain (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I).



(II)



(IIb)



(I)

The hydrolysis performed in said stage-E is either acid hydrolysis or alkaline hydrolysis, preferably acid hydrolysis. Advantageously, acid used for the hydrolysis is selected from a group consisting of aq. hydrochloric acid, aq. hydrobromic acid, aq. sulfuric acid, preferably aq. sulfuric acid or aq. Hydrobromic acid.

The temperature for hydrolysis in said stage-E may be between about -20°C to about 130°C, preferably about 80°C to about 85°C. The byproduct, amino compound like benzyl amine, 1-phen ethyl amine, obtained by this hydrolysis step can be recovered by conventional methods and recycled to increase the productivity.

The compound of formula (Ia) can be converted to pharmaceutically acceptable salt thereof if desired, for example hydrochloride, hydrobromide, sodium, potassium salt and the likes thereof.

The hydrochloride salt of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I) may be prepared by purging or addition of organic solvent saturated with hydrochloric acid gas or by direct purging the hydrochloric acid gas in to the reaction mass. Depending on the amount of hydrochloric acid used monohydrochloride or dihydrochloride salt can be prepared.

Advantageously, the salt formation can be carried out in suitable solvent selected from ketone solvent or alcoholic solvent optionally containing water. The ketone solvent may

be selected from acetone, methylethylketone, methyl isobutyl ketone, methyl tert. butyl ketone, preferably acetone.The alcoholic solvent may be selected from methanol, ethanol, isopropanol, t-butanol and the like.

The levorotatory and dextrorotatory enantiomers of 4-Chlorophenyl-phenyl methyl amine (IXa), used as starting materials are known compounds; they can be prepared by chemical resolution of racemic 4-Chlorophenyl-phenyl methyl amine by known methods using optically active resolving acid. For example, 4-Chlorophenyl-phenyl methyl amine can be resolved using process described by Clemo and Gardner in JMC, 1939, p-1958-1960 incorporated herein by reference.

The enantiomeric purity of levorotatory or dextrorotatory isomer of 2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (Ia) obtained by the above described process has optical purity of more than 99.5%.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention

EXAMPLES

Example-1: Preparation of 2-Chloro-N-(S-1-phenyl ethyl) acetamide (V)

A mixture of 100.0 g (0.82 mol) S-1-Phenylethyl amine, 135.0 g (1.33 mol) triethylamine and 7500.0 ml dichloromethane was cooled to 0°C -5°C and slowly a solution of 108.0 g. (0.95 mol) of chloroacetylchloride in 250.0 ml of dichloromethane was added to the reaction mass at 0°C -5°C within 2-3 hours time. The reaction mass was stirred for 3-4 hours at 5°C. 500.0 ml of water was added into the reaction mass and organic layer was separated. Organic layer was washed with 500.0 ml of brine solution. Dichloromethane was distilled out completely. 1000.0 ml of diisopropyl ether was added and the mass was stirred for 2 hours. Solid was filtered and washed with 200.0 ml of diisopropyl ether. Dry wt. =129.0 g.

NMR: 3H(d-1.35-1.38ppm); 2H(s-4.06ppm); 1H(q-4.85-4.92ppm); 5H(m-7.20-7.30ppm)
Mass: 198.35 [M+H]

Example-2: Preparation of 2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide (VII)

A mixture of 340.0 g (2.20 mol) Triethanol amine and 20.0 g (0.50 mol) sodium hydroxide and 100.0 ml toluene was heated up to 120-130°C. Water and toluene was distilled out completely. Reaction mass was cooled to 100°C. Then slowly 100.0 g (0.51 mol) 2-Chloro-N-(S-1-phenyl ethyl) acetamide (Example-1) was added in to the reaction mass. The mass temp.was maintained for 1 hr. Reaction mass was cooled to room temp. 400.0 ml of 50% v/v aq. Hydrochloric acid solution was added to the reaction mass. The solid was filtered and the mother liquor was extracted with 500.0 ml Dichloromethane at pH: 8.0. Methylene chloride was distilled out completely and oil was obtained.

NMR: 3H(dd-1.50-1.53 ppm); 6H(m-2.70-2.76 ppm); 6H(t-3.55-3.57 ppm); 2H(dt-3.91-4.03 ppm); 1H(q-5.14-5.18 ppm); 5H (m-7.24-7.33 ppm)
Mass: 311.27 [M+H]

Example-3: Preparation of 2-[N, N-Bis (2-methane sulfonyl ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide (VIIIa) (wherein X=methane sulfonyl chloride and R1=phenyl, R2= methyl)

A mixture of 50.0 g (0.16 mol) 2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide oil (Example-2), 48.8 g (0.48 mol) triethyl amine and 500.0 ml dichloro methane was cooled to 0-5°C. Methane sulfonyl chloride, 45.9 g (0.40 mol) was added in to the reaction mass slowly by maintaining the same temperature for 2 hrs. Temperature was raised to 25-30°C and stirred for 15 hrs. Methylene chloride was distilled out completely and oil was obtained.

Example-4: Preparation of 2-[N, N-Bis (2-chloro ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide (VIII)

2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide oil 10.0 g (0.03 mol) (Example-2) was dissolved in 100.0 ml dichloro methane and 0.5 ml N, N-dimethylformamide. Reaction mass was cooled to 0-5°C. Thionyl chloride 15.35 g (0.13 mol) was added dropwise in to the reaction mass slowly by maintaining the same temperature for 2 hrs. Temperature was raised to 25-30°C and stirred for 4 hrs. Reaction mass was quenched using 40.0 ml water and 10.0 ml methanol mixture. Mass was stirred for 30 mins and the aq. Layer was separated and extracted the aq. Layer with 25.0 ml of dichloro methane. Combined dichloro methane layer and washed it with 25.0 ml of water. Methylene chloride was distilled out completely and oil was obtained.

NMR: 3H(dd-1.37-1.39 ppm); 6H(m-2.72-2.87 ppm); 6H(m-3.49-3.58 ppm); 2H(s-3.89 ppm); 1H(q-4.97 ppm); 5H (m-7.28 ppm)

Mass: 347.18 [M+H]

Example-5: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-S-[N-(1-phenyl ethyl)] acetamide (II)

A mixture of 50.0 g 2-[N, N-Bis (2-methane sulfonyl ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide oil (Example-3), 35.0 g (0.16 mol) R-(4-chloro phenyl) phenyl methylamine and 500.0 ml of toluene was heated to 75°C -80°C for 7 hrs. Water 500.0 ml was added to the reaction mass and the organic layer was separated. Product was

extracted using 1000.0 ml of toluene. Distilled out toluene completely under vacuum. Residue was stripped out using 200.0 ml of diisopropyl ether. Diisopropyl ether (500.0 ml) was added to the residue and the mass was heated to reflux temperature. Reflux was maintained for half an hour and the mass was cooled to 25-30°C. The white solid thus obtained was filtered. Dry wt. = 30.0 g

NMR: 3H(dd-1.48-1.50 ppm); 2H(t-2.04 ppm); 4H(m-2.30-2.34 ppm); 4H(m-2.47-2.55 ppm); 2H(t-3.59 ppm); 2H(s-3.89 ppm); 1H(q-4.11 ppm); 14H (m-7.166-7.31 ppm)
Mass: 492.71 [M+H]

Example-6: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-S-[N-(1-phenyl ethyl)] acetamide (II)

A mixture of 50.0 g (0.144) 2-[N, N-Bis (2-chloro ethyl) amino] ethoxy-1-S-[N-(1-phenyl ethyl)] acetamide oil (Example-4), 35.0 g (0.16 mol) R-(4-chloro phenyl) phenyl methylamine and 100.0 ml of diisopropyl ethyl amine was heated to 125-130°C for 3 hrs. 500.0 ml of water added to the reaction mass and the organic layer was separated. The product was extracted by 1000.0 ml of toluene, the toluene layer washed with 10% hydrochloric acid solution. The toluene was completely distilled under vacuum. The residue was stripped out using 200.0 ml of diisopropyl ether. 500.0 ml of Diisopropyl ether was added to the residue and heated to reflux temperature and maintained the reflux for half an hour and cooled the mass to 25-30°C. The white solid was filtred. Dry wt. 60.0 g.

NMR: 3H(dd-1.48-1.50 ppm); 2H(t-2.04 ppm); 4H(m-2.30-2.34 ppm); 4H(m-2.47-2.55 ppm); 2H(t-3.59 ppm); 2H(s-3.89 ppm); 1H(q-4.11 ppm); 14H (m-7.166-7.31 ppm)
Mass: 492.71 [M+H]

Example-7: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I)

A mixture of 10.0 g (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-S-[N-(1-phenyl ethyl)] acetamide (II) (Example-5), 30.0 ml of conc. Hydrobromic acid and 50.0 ml water was heated to 90°C -95°C for 24 hrs. The reaction mass was cooled to

25°C -30°C and the reaction mass was diluted by adding 50.0 ml water. Reaction mass was extracted with 100.0 ml ethyl acetate followed by adjusting the pH=9.5-10.0 with dilute sodium hydroxide solution. This was followed by adjusting the pH to 4.5-5.0 using dilute hydrochloride solution. Product was extracted using 100.0 ml dichloro methane. Dichloromethane was distilled out to obtain oil (4.8 g).

Example-8: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I)

A mixture of 10.0 g (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-S-[N-(1-phenyl ethyl)] acetamide (II) (Example-6), 20.0 ml of conc. Sulfuric acid (98%) and 150.0 ml water was heated to 80-85°C for 48 hrs. The reaction mass was cooled to 25-30°C, filtered using hyflow bed. The pH=4.5-5.0 was adjusted by adding 40% w/v sodium hydroxide solution. It was extracted with 100.0 ml dichloro methane. Dichloromethane was distilled out to get 6.2 g oil.

Example-9: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid Dihydrochloride

Dissolved 9.0 g (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I) oil (Example-5) in 100.0 ml of acetone and cooled it to 0°C -5°C. Purged hydrogen chloride gas to get pH=1.0-2.0 constant. Stirred the reaction mass for 4 hrs at 25-30°C. Filtered the solid and washed with 20.0 ml of acetone. Dry wt. = 8.0 g

NMR: 6H(t-3.45 ppm); 4H(t-3.66 ppm); 2H(t-3.87 ppm); 2H(s-4.17 ppm); 1H(s-5.33 ppm); 9H(m-7.34-7.55 ppm)Mass: 389.84 [M+H]

Example-10: Preparation of 2-Chloro-N-benzyl acetamide (Vb)

Benzylamine (500 g) was added to a solution of sodium carbonate (370.0 g in 6000.0 ml water). Reaction mass was cooled to 0-5°C and to this chloroacetyl chloride was added over 1-2 hours time. The reaction mass was stirred for 2-3 hour. The solid was filtered and washed with water and dried. Dry wt. =550.0 g

1H NMR: 7.33 (m, 5H), 4.49 (d, 2H), 4.09 (s, 2H)

Mass: 184.13 [M+H]+

HPLC purity: 95.60%

Example-11: Preparation of 2-[N, N-Bis (2-hydroxy ethyl) amino] ethoxy-1-N-benzyl acetamide (VIIb)

A mixture of triethanol amine (185.0 ml) and sodium hydroxide powder (109.0 g) was heated to 70-75°C to get a clear solution. 2-Chloro-N-benzyl acetamide was added to this solution over a period of 2-3 hours. Reaction was maintained for 3 hours. Reaction mass was cooled to 25-30°C. The pH was adjusted to 1.0-1.5 using dil. hydrochloric acid. Again reaction mass was stirred for one hour. Solid was filtered. To the mother liquor 40% sodium hydroxide solution was added and pH was adjusted to 6.-6.5.Sodium chloride was added. Aqueous layer was extracted using methylene chloride (2x2000ml). Methylene dichloride was distilled completely and oil was obtained.

Wt of oil=410.0g

1H NMR: 7.28 (m, 5 H), 5.28 (s, 2H), 4.45 (d, 2H), 4.01 (s, 2H), 3.54 (m, 6H), 2.75 (m, 6H)
Mass:297.65 [M+H]+

HPLC purity: 92.00%

Example-12: Preparation of 2-[N, N-Bis (2-chloro ethyl) amino] ethoxy-1-N-benzyl acetamide (VIIIb)

Compound (VIIb) 400.0 g was dissolved in methylene dichloride (4800.0 ml).Thionyl chloride was added over a period of one hour maintaining temp. of 25°C-30°C Reaction mass was stirred for 13 hours. Reaction mass was added to cold water (3000.0 ml) over a period of one hour. The pH of reaction mass was adjusted to 6.0-6.5 using 40% sodium hydroxide solution. Mass was stirred for 30 min and layer separated. To the organic layer activated charcoal was added. Stirred for one hour and mass filtered through hyflo. Methylene dichloride was completely distilled under vacuum. The reaction mass was degassed. Wt. of oil=400.0 g

1H NMR: 7.30 (m, 5 H), 5.28 (s, 2H), 4.47 (d, 2H), 4.01 (s, 2H), 3.55 (t, 2H), 3.40 (t, 4H), 2.83 (t, 4H), 2.76 (t, 2H)

Mass: 333.59 [M]+
HPLC purity: 95.36%

Example-13: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy-1 -N-benzyl acetamide (IIb)

A mixture of diisopropyl ethyl amine (400.0 ml), (S)-4-chlorobenzhydryl amine (200 g), compound (VIIIb) (367.5 g) was heated to 120°C-125°C for 6 hours. Reaction mass was cooled to 80°C to 90°C. To this ethylacetate layer was added 2000.0 ml water was added. Reaction mass was cooled to 25°C-30°C. Stir the reaction mass for 2 hour. Layer separated. To the organic layer 2000 ml of water was added and stirred mass for one hour. Again layer separated. To this 20% (v/v) acetic acid was added and stirred reaction mass for one hour. Again layer separated. 1000 ml of water was added to the organic layer. To the organic layer 40% sodium hydroxide solution was added and pH was adjusted to 10.0-11.0. Stirred reaction mass for one hour and layer separated. To the organic layer brine solution was added, reaction mass was stirred for one hour and layer separated. Distilled ethyl acetate layer under vacuum .Wt of oil=420.0 g

Chiral purity: 99.95%

1H NMR: 7.24 (m, 14H), 4.46 (d, 2H), 4.03 (d, 4H), 3.61 (t, 2H), 2.58 (t, 2H), 2.56 (m, 2H), 2.25 (m, 2H), 2.03 (s, 2H), 1.92 (s, 1H)

Mass: 478.41 [M]+
HPLC purity: 96.42%

Example-14: Preparation of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid (I)

A mixture of compound (IIb) 400.0 g and aq sulfuric acid was heated to 80°C-85°C for 8 hours. The reaction mass was cooled to 25°C-30°C and further cooled to 0°C-5°C. Reaction mass was stirred for one hour. Reaction mass was filtered through hyflow. The pH of the filtrate was adjusted to 4-4.5 using 40% sodium hydroxide. The temperature wasraised to 25°C-30°C and methylene dichloride was added. The reaction mass was stirred for one hour. The layers were separated. Methylene dichloride layer was distilled

completely under vacuum. Water 1000.0 ml was added and pH adjusted to 10-11 using 40% sodium hydroxide. Ethyl acetate 1000.0 ml was added to the mass and stirred for 30 min. Layer separated. To the organic layer was added 5000.0 ml of water and reaction mass was further stirred for one hour. 50% dil hydrochloric acid was added and pH adjusted to 4.0-4.5, methylene dichloride 2000.0 ml was added to the reaction mass and again reaction stirred for one hour. Layer separated. To the Aq. layer was added methylene dichloride 2000.0 ml. and mass stirred for one hour. Layer separated and the organic layers were pooled. Methylene dichloride was distilled completely under vacuum. Acetone 1600.0 ml was added to the oil. Conc hydrochloric acid 40.0 ml was added to the reaction and the reaction mass stirred for 15 hour. Solid was filtered and washed with acetone (200.0 ml). Dry wt. =100.0 g

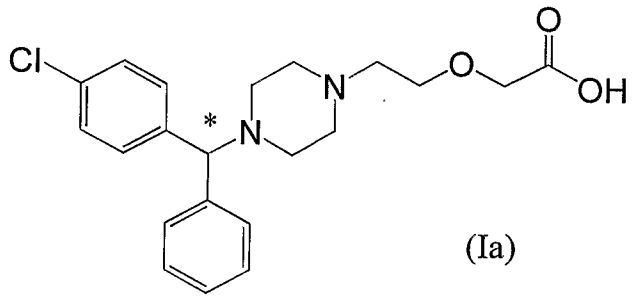
Chiral purity: 99.95%; HPLC purity: 99.82%

1H NMR: 7.47 (m, 4H), 7.38 (m, 5H), 5.23 (s, 1H), 4.11 (s, 2H), 3.81 (m, 2H), 3.58 (m, 4H), 3.42 (m, 2H), 3.35 (m, 4H)

Mass: 389.53 [M+H]+

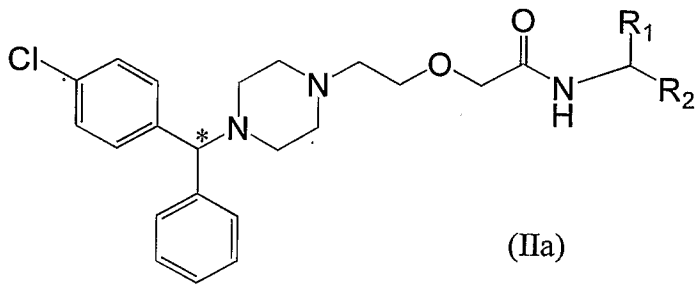
The invention is particularly represented by;

1] A process for the preparation of, 2-[2-[4-[(4-chlorophenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, a compound of formula (Ia),



(Ia)

in the form of levorotatory isomer, dextrorotatory isomer, mixture thereof or pharmaceutically acceptable salt thereof comprising converting the compound of formula (IIa),



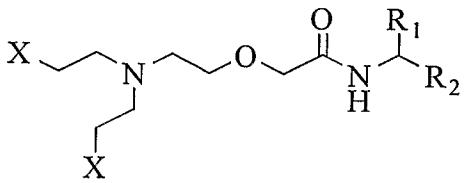
(IIa)

by treatment with acid or a base to obtain a compound of formula (Ia) wherein,

R_1 = H or C_1-C_4alkyl;

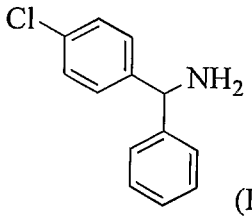
R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

2] The process as defined in claim 1, wherein the compound of formula (IIa) is prepared by a process comprising condensing a compound of formula (VIIIa),



(VIIIa)

with a compound of formula (IXa),



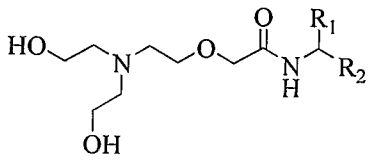
(IXa)

wherein R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group and X is a suitable leaving group.

3] The process as defined in claim 2, wherein the suitable leaving group is selected from a group consisting of chlorine, bromine, iodine, 4-methylphenyl-sulfonyloxy, methylsulfonyloxy group and 4-bromophenyl-sulfonyloxy group.

4] The process as defined in claim 2, wherein the compound of formula (VIIIa) is prepared by a process comprising halogenation or mesylation of a compound of formula (VIIa), 2-[N, N-bis (2-hydroxy ethyl) amino] ethoxy acetamide,

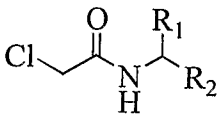


(VIIa)

wherein R_1 = H or C_1-C_4alkyl;

R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

5] The process as defined in claim 4, wherein the compound of formula (VIIa) is prepared by the condensation of 2-Chloro amide of formula (Va)

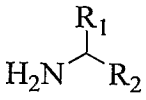


(Va)

with triethanol amine VI, wherein R_1 = H or C_1-C_4alkyl;

R_2 = aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

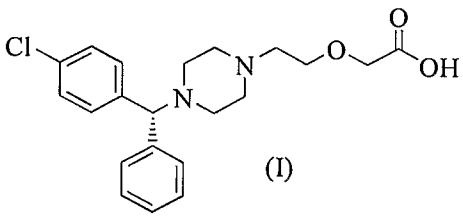
6] The process as defined in claim 5, wherein the compound of formula (Va) is prepared by the acylation of an amine compound of formula (IIIa)



(IIIa)

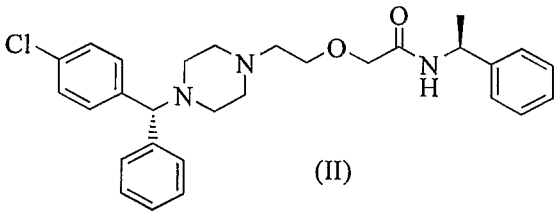
by 2-chloroacetyl chloride.

7] The process, as defined in claim 1, for the preparation of levorotatory isomer, (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, compound of formula I,



(I)

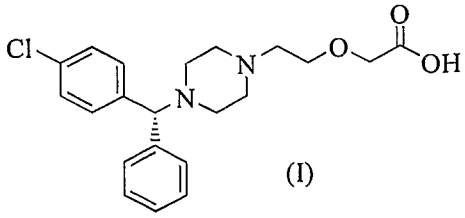
comprising the treatment of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-(S)-[N-(1-phenyl ethyl)] acetamide, compound of formula (II),



(II)

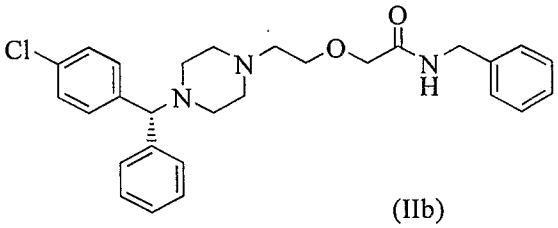
with an acid or a base.

8] The process, as defined in claim 1, for the preparation of levorotatory isomer, (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy acetic acid, compound of formula I,



(I)

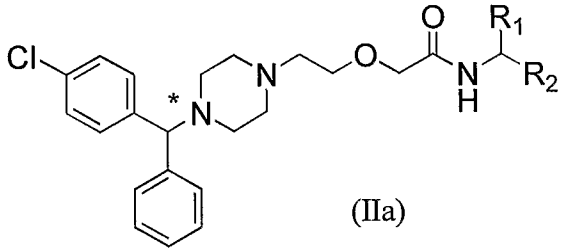
comprising the treatment of (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-N-benzyl acetamide, compound of formula (IIb),



(IIb)

with an acid or a base.

9] The compound of formula (IIa),

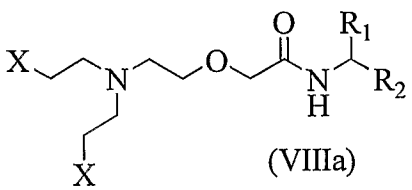


(IIa)

wherein R_1= H or C_1-C_4 alkyl;

R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group.

10] The compound of formula (VIIIa),

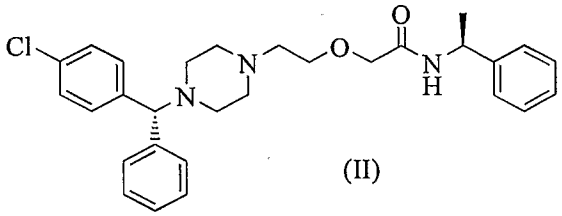


(VIIIa)

wherein R_1= H or C_1-C_4 alkyl;

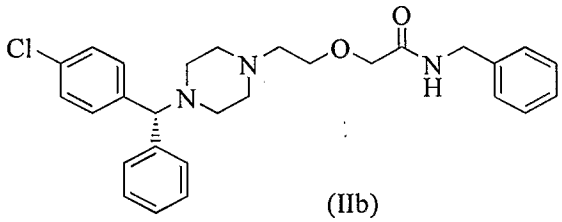
R_2= aryl or heteroaryl or R_1 and R_2 together with the carbon to which they are attached form a C_3-C_8 cycloalkyl group and X is a suitable leaving group.

11] The Compound, (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy -1-(S)-[N-(1-phenyl ethyl)] acetamide.



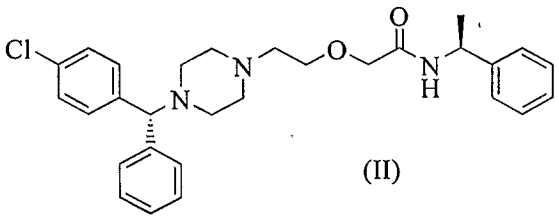
(II)

12] The Compound, (R)-2-[2-[4-[(4-chloro phenyl) phenyl methyl]-1-piperazinyl] ethoxy 1-N-benzyl acetamide.

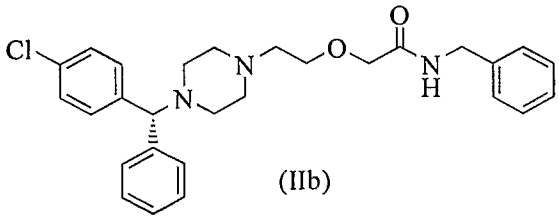


(IIb)

13] Use of compound of formula (II) or (IIb) in preparation of levocetirizine.



(II)



(IIb)