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(71) Applicant: COUNCIL OF SCIENTIFIC & INDUSTRIAL RESEARCH [IN/IN]; Anusandhan Bhawan, Rafi Marg, New Delhi 110001 (IN).

(72) Inventors: MUTHUKRISHNAN, Murugan; National Chemical Laboratory, Dr. Homi Bhabha Road, Maharashtra 411008 (IN). RAMADOSS, Velayudham; National Chemical Laboratory, Dr. Homi Bhabha Road, Maharashtra 411008 (IN). NALLA, Viswanadh; National Chemical Laboratory, Dr. Homi Bhabha Road, Maharashtra 411008 (IN).

(74) Agents: RAE, Konpal et al.; Lakshmikumaran & Sridharan, B-6/10, Safdarjung Enclave, New Delhi 110 029 (IN).

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(54) Title: A PROCESS FOR THE PREPARATION OF 8-CHLORO-1-METHYL-2,3,4,5-TETRAHYDRO-1H-BENZO[D]AZEPINE ITS ENANTIOMERS

(57) Abstract: The present invention discloses a process for synthesis of Lorcaserin and its analogues using epoxide/chiral epoxide.



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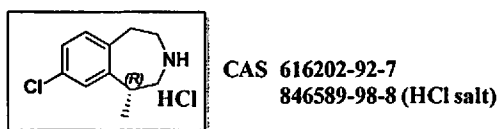
A PROCESS FOR THE PREPARATION OF 8-CHLORO-1-METHYL-2,3,4,5-TETRAHYDRO-1H-BENZO[D]AZEPINE ITS ENANTIOMERS

FIELD OF THE INVENTION

[0001] The present invention relates to a process for the synthesis of Lorcaserin and its enantiomers.

BACKGROUND AND PRIOR ART OF THE INVENTION

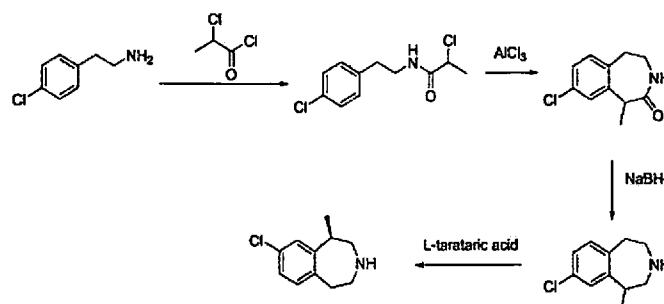
[0002] Lorcaserin is (*R*)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (lorcaserin hydrochloride) and represented by the following structure. It is a highly selective 5-HT_{2C} receptor agonist developed for the treatment of obesity.



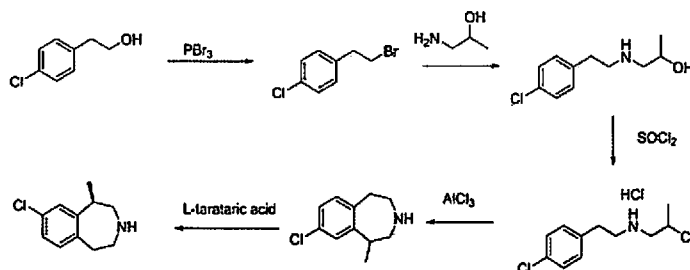
[0003] The FDA has approved this molecule for obesity treatment and its current market value in US alone is \$1 billion.

[0004] WO2005003096 relates to synthesis of lorcaserin using chlorophenethylamine as a starting material, the reaction with 2-chloropropionyl chloride, then by Friedel-Crafts alkylation, reductive splitting give chloro card color forest, although only four steps of the route, but the starting material for less chlorine phenylethylamine market demand for non-conventional chemical raw materials, and therefore expensive.

[0006]

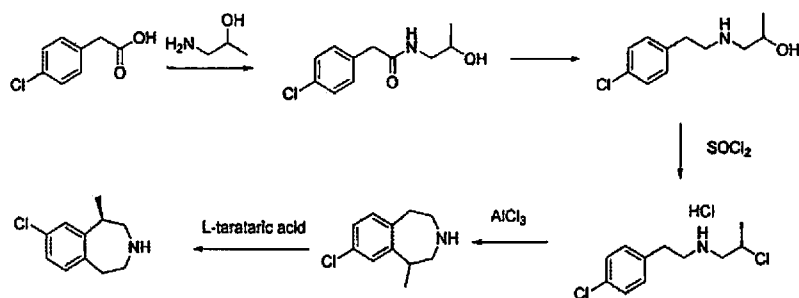


[0005] US20090143576 relates to synthesis lorcaserin using ethanol chlorobenzene as the starting material, bromide, replace, Friedel alkylation, split to obtain a product, use of this route is dangerous, big phosphorus tribromide, industrial pollution, after a large amount of hydrogen bromide treatment.



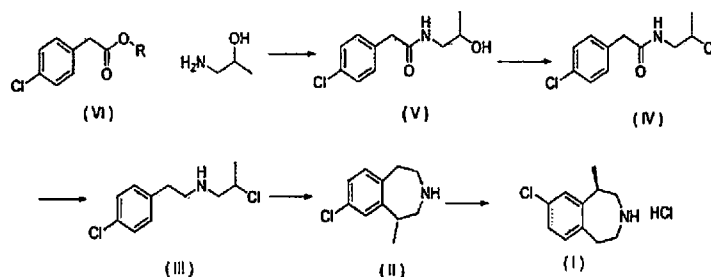
[0006] With the more readily available chlorine acid as the starting material, with isopropyl amine condensation, after reduction amide, chloro, Friedel-Crafts alkylation, split to give the product, but in the synthesis of 2- (4-chlorophenyl) -N- (2-hydroxypropyl) process acetamide formula (V), the condensation of expensive reagents, greatly increasing the production cost, or the use of a condensing agent after cheap product purification difficulties.

[0010]

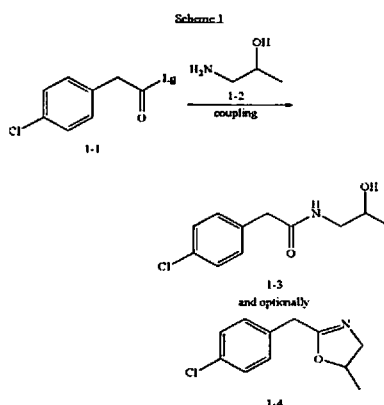


[0007] WO2008070111 relates to synthesis of lorcaserin using a condensation reaction, the use of boric acid, phenylboronic acid catalyzed condensation manner, greatly reduce the cost of the reaction, but the reaction takes a long time trap to complete, the reaction of the water requirements, long production cycle.

[0008] CN 103333111 A provides a preparation method of lorcaserin hydrochloride, namely (R) -8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride comprising the following steps: taking p- chlorophenyl acetate as raw material, performing aminolysis with isopropanol amine, then performing chlorination, reduction and Friedel-Crafts alkylation, further splitting by L-tartaric acid, and performing salt formation to get the lorcaserin hydrochloride.



[0009] US 20100305316 A1 / WO2005003096 provides processes and intermediates for the preparation of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine and salts thereof which are useful as serotonin-2C (5-HT_{2C}) receptor agonists for the treatment of, for example, obesity.



[0010] US 20130165648 A1 provides processes and intermediates for the preparation of 3-benzazepines and salts thereof which can be useful as serotonin (5-HT) receptor agonists for the treatment of, for example, central nervous system disorders such as obesity.

[0011] US 8168782 B2 provides processes, methods and intermediates for the preparation of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, salts, hydrates and crystal forms thereof which are useful as serotonin (5-HT) receptor agonists for the treatment of, for example, central nervous system disorders such as obesity.

[0012] WO 2006069363 A3 / US 20120264743 A1 provides crystalline forms of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, compositions containing the same, preparations, and uses thereof.

[0013] US 20130172322 A1 / WO2005003096 certain 1-substituted-2,3,4,5-tetrahydro-3-benzazepine derivatives of Formula (I), that are modulators of the 5HT_{2C} receptor. Accordingly, compounds of the present invention are useful for the

prophylaxis or treatment of 5HT_{2C} receptor associated diseases, conditions or disorders, such as, obesity and related disorders.

[0014] US 20110015438 A1 provides processes and intermediates useful in the preparation of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine, a serotonin (5-HT) receptor agonist that is useful in the treatment or prophylaxis of, for example, central nervous system disorders, such as obesity.

[0015] US 20120142967 A1 relates to processes and intermediates useful in the preparation of (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine (Lorcaserin), a serotonin (5-HT) receptor modulator that is useful in the treatment of, for example, central nervous system disorders, such as obesity.

[0016] US 20080009478 A1 relates to substituted-2,3,4,5-tetrahydro-3-benzazepine derivatives that are modulators of the 5HT_{2C} receptor. Accordingly, compounds of the present invention are useful for the prophylaxis or treatment of 5HT_{2C} receptor associated diseases, conditions or disorders, such as, obesity and related disorders.

[0017] All prior art processes resulted in a racemic mixture of R and S Lorcaserin, while R is the preferred enantiomer for its anti-obesity activity. No prior art process proposed a process without a final step for resolution of enantiomers.

[0018] The prior art processes suffer from several drawbacks including usage of borane which is inflammable and corrosive, processes involve many steps, poor yields and strong corrosive acids and expensive catalysts are needed.

OBJECTIVE OF THE INVENTION

[0019] Main objective of the present invention is to provide a process for the synthesis of Lorcaserin, its analogues and its enantiomers.

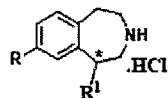
BRIEF DESCRIPTION OF THE DRAWING

[0020] Scheme 1 represents general synthetic route to racemic lorcaserin and its analogues, wherein * in the scheme represents asymmetric carbon atom.

[0021] Scheme 2 represents synthetic route for the synthesis of optically active (R)-8-chloro-1-methyl-2,3, 4, 5-tetrahydro-1H- benzazepine using S-propylene oxide in Step II.

SUMMARY OF THE INVENTION

[0022] Accordingly, present invention provides a process for synthesis of compound of Formula A



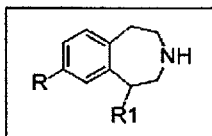
comprising the steps of:

- 5 a. adding 2-nitrobenzene sulfonylchloride to a solution of 4-chloro phenethylamine at temperature in the range of 0 to 5°C and stirred at temperature in the range of 25-30°C for period in the range of 10 to 12 hours to obtain compound (5);
- 10 b. adding compound (5) as obtained in step (a) to a solution of racemic propylene oxide to obtain a solution of compound (4);
- c. adding thionyl chloride to the solution of compound (4) as obtained in step (b) and heating at temperature in the range of 45 to 50°C for a period in the range of 10 to 12 hours to obtain compound (3);
- 15 d. reacting compound (3) of step (c) with AlCl₃ in inert atmosphere to obtain compound (2); and
- e. deprotecting nosyl group of compound 2 as obtained in step (d) by adding thiophenol to obtain racemic lorcaserin hydrochloride (1).

[0023] In an embodiment of the present invention, the chiral propylene oxide (R or S) is used in step (b) to obtain the corresponding enantiomer of Lorcaserin HCl with at least 80% ee of the enantiomer.

DETAILED DESCRIPTION OF THE INVENTION

[0024] Present invention provides a process for the synthesis of Lorcaserin, its analogues and enantiomers of Formula I,



Formula I

wherein, R is selected from H, alkyl (C1-C4), halide (Cl, Br, I and F), R1 is selected from alkyl (C1-C4), aryl, alkoxy (C1-C4), using epoxide/chiral epoxide is disclosed herein.

[0025] In an aspect, a novel process for the synthesis of compound of Formula I in its racemic form is disclosed.

[0026] The process for the synthesis of racemic Lorcaserin as is disclosed in Scheme 1, comprising the steps of:

- 5 (a) adding 2-nitrobenzene sulfonylchloride to a solution of compound 6 at 0°C and stirred at 25-30°C for 12 hours and worked up to obtain a coloured solid of compound (5);
- (b) adding compound (5) to the solution of racemic propylene oxide and worked up to obtain a solution of compound (4);
- 10 (c) adding thionyl chloride to the solution of compound (4) of step (b) and heating to 50°C for 12 hours and working up to obtain compound (3);
- (d) reacting compound (3) of step (c) with AlCl_3 in inert atmosphere to obtain compound (2) and;
- (e) deprotecting nosyl (Ns) group by adding thiophenol, potassium carbonate
- 15 (K_2CO_3) to solution of compound (2) of step (d) and working up to obtain racemic Lorcaserin hydrochloride (1).

[0027] The racemic Loracesrine hydrochloride may be resolved into respective enantiomers by processes known in the art such as HPLC separation, using chiral resolving agents such as tartaric acid, mandelic acid etc.

- 20 [0028] The above process for the preparation of racemic lorcaserin (8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine) is shown in Scheme 1.

[0029] The chiral process of the invention using chiral propylene oxide (R or S) in step (b) leads to at least 80% ee of the enantiomer of Lorcaserin hydrochloride.

- [0030] Scheme 2 represents synthetic route for the synthesis of optically active (R)-8-chloro-1-methyl-2,3, 4, 5-tetrahydro-1H- benzazepine using S-propylene oxide in Step II.
- 25

EXAMPLES

[0031] The following examples are given by way of illustration and therefore should not be construed to limit the scope of the invention.

30 EXPERIMENTAL SECTION

[0032] All reactions were carried out in oven-dried glassware under a positive pressure of argon or nitrogen unless otherwise mentioned with magnetic stirring. Air sensitive reagents and solutions were transferred via syringe or cannula and were introduced to the apparatus via rubber septa. All reagents, starting materials, and solvents were obtained from commercial suppliers and used as such without further purification. Reactions were monitored by Thin Layer Chromatography (TLC) with 0.25 mm pre-coated silica gel plates (60 F₂₅₄). Visualization was accomplished with either UV light, or by immersion in ethanol solution of phosphomolybdic acid (PMA), p-anisaldehyde, 2,4-DNP stain, KMnO₄, Ninhydrin solution, Iodine adsorbed on silica gel followed by heating on a heat gun for ~15 sec. optical rotation values were recorded on P-2000 polarimeter at 589 nm. All chemical shifts were quoted in ppm, relative to CDCl₃ and MeOD using the residual solvent peak as a reference standard. IR spectra were obtained from Perkin–Elmer Spectrum one spectrophotometer. Optical rotation values were recorded on P-2000 polarimeter at 589 nm. Enantiomeric excess was determined by chiral HPLC.

EXAMPLE 1

[0033] Synthesis of N-(4-chlorophenethyl)-2-nitrobenzenesulfonamide (5):

To a solution of 4-chloro phenethylamine (1 g, 6.5 mmol) in dry dichloromethane (10 mL) triethylamine (1.2 mL, 8.4 mmol) was added. Then, the reaction mixture was cooled to 0°C and 2-nitrobenzene sulfonylchloride (1.2 gm, 5.2 mmol) was added and the reaction mixture was stirred at room temperature (25°C) for 12 h. The reaction mixture was diluted with water (50 mL) and extracted with DCM (3 X 25 mL) and the organic layer was washed with brine, dried over Na₂SO₄. The filtrate was concentrated under reduced pressure to obtain the product 5 (2.1 gm, 96 % yield) as a pale yellow solid.

H-NMR (200 MHz, CDCl₃): δ 2.84 (t, J = 7.68 Hz, 2H), 3.42 (q, J = 5.98 Hz, 2H), 7.06 (d, J = 8.10 Hz, 2H), 7.2 (d, J = 8.10 Hz, 2H), 7.72-7.78 (m, 3H), 8.05-8.09 (m, 1H); ¹³C-NMR (400 MHz, CDCl₃): δ 35.3, 44.9, 125.3, 128.7, 130.0, 130.7, 132.6, 132.8, 133.4, 133.6, 135.9, 147.7; LCMS (ESI): 363 (M+Na)⁺

EXAMPLE 2A

[0034] Synthesis of N-(4-chlorophenethyl)-N-(2-hydroxypropyl)-2-nitrobenzenesulfonamide (4):

A solution of N-(4-chlorophenethyl)-2-nitrobenzenesulfonamide (Compound 5) (1 g, 2.9 mmol) in 10 mL dichloromethane was added drop wise to a solution of (±)-propylene oxide (1 mL, 29 mmol), amount of Lithium bromide (26 mg) in 20 mL dry dichloromethane at 0 °C under inert atmosphere. Then refluxed the reaction mixture with cold water circulation for 12 h. The reaction mixture was diluted with water (20 ml) and extracted with dichloromethane (3X20mL) and the organic layer was washed with brine, dried over Na₂SO₄. The filtrate was concentrated under reduced pressure to get the product (0.9 g, 82 % yield) as pale yellow semi solid.

Example 2B

[0035] Synthesis of optically active N-(4-chlorophenethyl)-N-(2-hydroxypropyl)-2-nitrobenzenesulfonamide (R-4) or S-4 from chiral propylene oxide S or R):

A solution of N-(4-chlorophenethyl)-2-nitrobenzenesulfonamide (5), (2 gm, 5.8 mmol) in 10 mL dichloromethane was added drop wise to a solution of (R) or (S)-propylene oxide (4 mL, 51 mmol), cat. amount of (20 mg) in 30 mL dry dichloromethane at 0 °C under inert atmosphere. Then, refluxed the reaction mixture with cold water circulation for 12 h. The reaction mixture was diluted with water (20ml) and extracted with DCM (3X25mL) and the organic layer was washed with brine dried over Na₂SO₄. The filtrate was concentrated under reduced pressure and to get the product (1.9 g, 83 % yield) as pale yellow semi solid.

¹H-NMR (200 MHz, CDCl₃): δ 1.19 (d, *J* = 7.14Hz, 3H), 2.86-2.90 (m, 2H), 3.27-3.39(m, 2H), 3.51-3.67(m, 2H), 4.0-4.05 (m, 1H), 7.08 (d, *J* = 8.47 Hz, 2H), 7.18 (d, *J* = 7.58 Hz, 2H), 7.60 -7.73(m, 3H), 7.95-7.98(dd, *J* = 7.82 Hz, 1H); ¹³C-NMR (400 MHz, CDCl₃): δ 20.4, 33.7, 49.7, 54.3, 65.6, 123.8, 128.2, 129.8, 130.4, 131.4, 132.0, 132.6, 133.3, 136.0, 147.5; LCMS (ESI): 421 (M+Na)⁺.

Example 3A

[0036] Synthesis of N-(4-chlorophenethyl)-N-(2-chloropropyl)-2-nitrobenzenesulfonamide (3):

To the stirred solution of compound 4 (0.6 g, 1.5 mmol) in dry pyridine (5 mL) was added freshly distilled thionyl chloride (0.21 ml, 3 mmol) dropwise. After completion of

the addition, the reaction mixture was heated to 50 °C for 12 h. The reaction mixture was cooled and added water (50 mL). The reaction mixture was extracted with ethyl acetate (3X20mL), and the organic phase was washed with diluted HCl (2X20 mL). The solution was dried over Na₂SO₄, concentrated, and vacuum distilled to get product as a colorless oil **3** (0.42 g, 66%).

Example 3B

[0037] Synthesis of optically active N-(4-chlorophenethyl)-N-(2-chloropropyl)-2-nitrobenzenesulfonamide (**R-3** or **S-3**):

To the stirred solution of compound **R-4** or **S-4** (1.2 g, 3 mmol) in dry pyridine (7 mL) was added freshly distilled thionyl chloride (0.42 ml, 6 mmol) dropwise. After completion of the addition, the reaction mixture was heated to 50 °C for 12 h. The reaction mixture was cooled and added water (70 mL). The reaction mixture was extracted with ethyl acetate (3X25mL), and the organic phase was washed with diluted HCl (2X20 mL). The solution was dried over Na₂SO₄, concentrated, and vacuum distilled to get product as a colorless oil **3** (0.8 g, 64%).

¹H-NMR (400 MHz, CDCl₃): δ 1.54 (d, *J* = 6.78 Hz, 3H), 2.84-2.89(m, 2H), 3.51-3.60 (m, 2H), 3.65-3.75(m, 2H), 4.17-4.25(m,1H), 7.06(d, *J* = 8.48 Hz, 2H), 7.18(d, *J* = 8.81 Hz, 2H), 7.62-7.74 (m, 3H), 7.98(d, *J* = 8.81 Hz, 1H); ¹³C-NMR (400 MHz, CDCl₃): δ 22.6, 33.9, 50.1, 55.1, 55.5, 124.4, 128.8, 130.1, 131.0, 131.8, 132.6, 133.2, 133.8, 136.2, 148.0; LCMS (ESI): 456 (M+Na)⁺

Example 4

[0038] Synthesis of 4-(8-chloro-1-methyl-1,2,4,5-tetrahydro-3H-benzo [d]azepin-3-yl)-3-nitro benzene sulfonic acid (**2**):

A dried two neck round bottom flask was charged with compound **3** (0.8 mL, 1.92 mmol) and AlCl₃ (1.3 g, 9.6 mmol), in chlorobenzene (6 mL) under inert atmosphere. Then, the reaction was stirred at room temperature for 12 h. The reaction mixture was quenched by addition of water (15 mL), and then neutralized with saturated aqueous NaHCO₃. The reaction mixture was filtered through a pad of celite and washed with ethyl acetate. The resulting filtrate was partitioned between ethyl acetate and water. The organic layer was dried over Na₂SO₄, concentrated under vacuum and purified by column chromatography using 30% EtOAc: Pet ether to get the product **2** (0.36 g, 48%) as a colorless solid.

¹H-NMR (200 MHz, CDCl₃): δ 1.39(d, *J* = 7.90 Hz, 3H), 2.9 -3.2 (m, 3H), 3.36-3.56 (m, 4H), 7.01 (d, *J* = 7.93 Hz, 1H), 7.06(d, *J* = 2.11 Hz, 1H), 7.12 (s, 1H), 7.57-7.70 (m,3H), 7.95-7.99 (m, 1H); LCMS (ESI): 403(M+Na)⁺

The same experimental procedures were performed also with the optically active analogues.

Example 5

[0039] Synthesis of 8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-benzo[d]azepine hydrochloride (1):

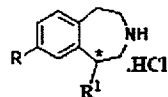
A 100 mL round bottom flask was charged with **2** (0.18 g, 0.45 mmol), K₂CO₃ (0.186 g, 1.35 mmol) dry DMF and thiophenol (0.06 mL, 0.54 mmol) and the reaction mixture was stirred for 2 h at room temperature. The reaction mixture was diluted with water (8 mL) and cold aqueous NaHCO₃. The reaction mixture was extracted with ethyl acetate (3 X10 mL). The organic layer was dried over Na₂SO₄, concentrated under vacuum. The crude residue was purified over column chromatography. The product obtained was treated with 3 mL of 5% HCl in dioxane, to get product **1** (0.064 g, 71%) as a hydrochloride salt. ¹H-NMR (400 MHz, CDCl₃): δ 1.50 (d, *J* = 5.7 Hz, 3H), 2.8 -3.05 (m, 3H), 3.5 (m, 2H), 3.6 (m, 2H), 7.09 (d, *J* = 7.8 Hz, 1H), 7.18 (d, *J* = 7.8 Hz, 1H), 7.20 (s,1H), 9.8 (br s, 1H), 10.1(br s, 1H); ¹³C-NMR (400 MHz, CDCl₃): δ 144.3, 136.8, 133.4, 131.7, 127.2, 126.5, 51.5, 45.7, 35.0, 32.1, 18; LCMS (ESI): 196(M+H)⁺ (Fig: 1 and 2).

[0040] ADVANTAGES OF THE INVENTION

- Short route of synthesis
- Can provide enantiomers as desired without need for resolution of racemic mixture
- Expensive, corrosive of inflammable reagents avoided

We claim

1. A process for the synthesis of compound of formula A



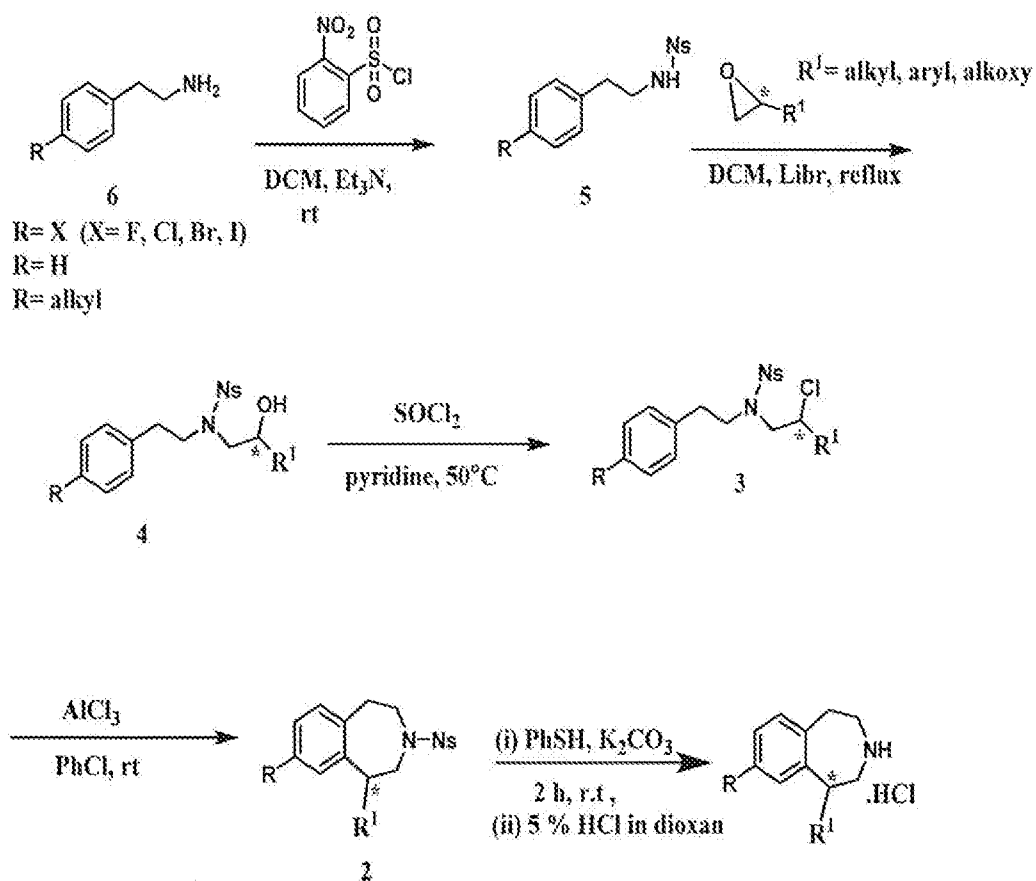
comprising the steps of:

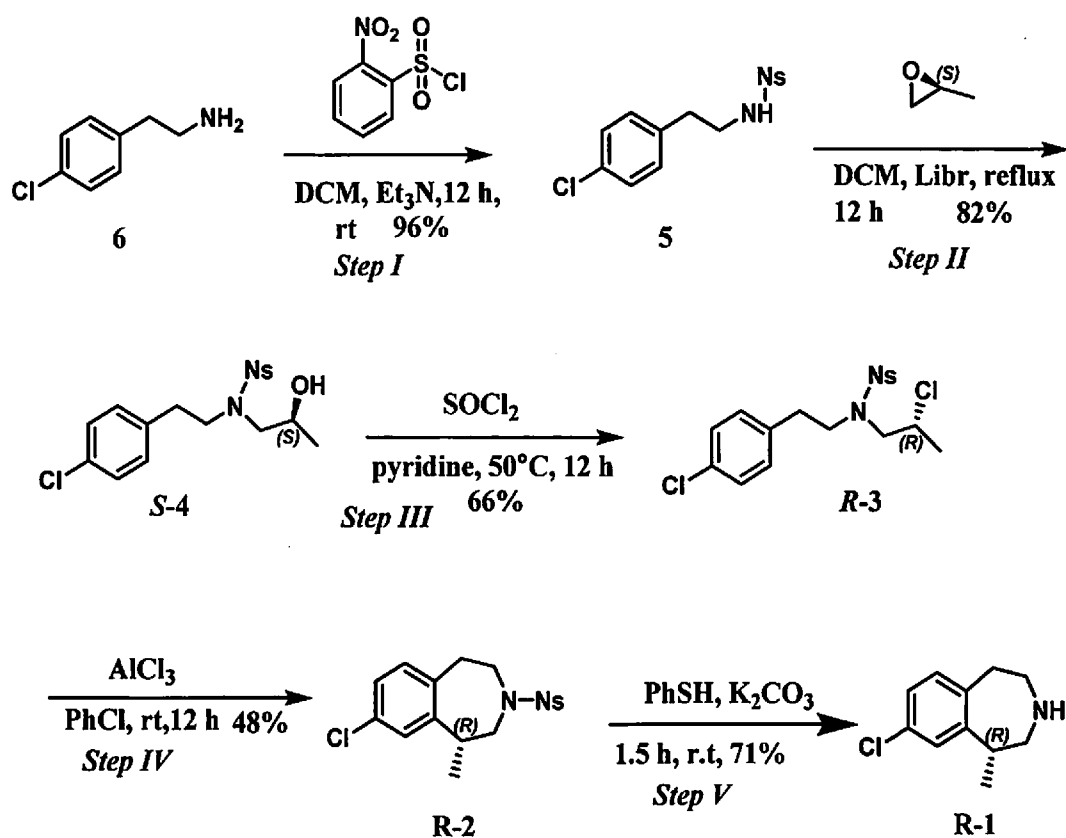
- 5 a. adding 2-nitrobenzene sulfonylchloride to a solution of 4-chloro phenethylamine at temperature in the range of 0 to 5°C and stirred at temperature in the range of 25-30°C for period in the range of 10 to 12 hours to obtain compound (5);
- 10 b. adding compound (5) as obtained in step (a) to a solution of racemic propylene oxide to obtain a solution of compound (4);
- c. adding thionyl chloride to the solution of compound (4) as obtained in step (b) and heating at temperature in the range of 45 to 50°C for a period in the range of 10 to 12 hours to obtain compound (3);
- 15 d. reacting compound (3) of step (c) with $AlCl_3$ in inert atmosphere to obtain compound (2); and
- e. deprotecting nosyl group of compound 2 as obtained in step (d) by adding thiophenol to obtain racemic lorcaserin hydrochloride (1).
2. The process according to claim 3, wherein the chiral propylene oxide (R or S) is used in step (b) to obtain the corresponding enantiomer of Lorcaserin HCl
- 20 with at least 80% ee of the enantiomer.

25

30

Sheet No.: 1
Total No. of Sheet: 2





Scheme: 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000204

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D223/14
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 data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CN 103 601 645 A (SHANGHAI SHIJI BIOLOG SCIENCE & TECHNOLOGY CO LTD; HANGZHOU LEDUN TECH) 26 February 2014 (2014-02-26) paragraphs [0015], [0016], [0026], [0032], [0045], [0077] - [0087]	1,2
A	US 2013/165648 A1 (WOLGAST BEVERLY L [US] ET AL) 27 June 2013 (2013-06-27) pages 15,16 examples 1-7 ----- -/--	1,2



Further documents are listed in the continuation of Box C.



See patent family annex.

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"A" document defining the general state of the art which is not considered to be of particular relevance

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Date of the actual completion of the international search

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Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040,
Fax: (+31-70) 340-3016

Authorized officer

Samsam Bakhtiary, M

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2015/000204

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SMITH B M ET AL: "Discovery and SAR of new benzazepines as potent and selective 5-HT_{2C} receptor agonists for the treatment of obesity", BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol. 15, no. 5, 1 March 2005 (2005-03-01), pages 1467-1470, XP027801904, ISSN: 0960-894X [retrieved on 2005-03-01] page 1468; compounds 12-15 -----	1,2

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IN2015/000204

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
CN 103601645	A	26-02-2014	NONE
US 2013165648	A1	27-06-2013	
		AU 2004267016 A1	03-03-2005
		BR PI0411613 A	08-08-2006
		CA 2529401 A1	03-03-2005
		EP 1636191 A2	22-03-2006
		EP 2189448 A1	26-05-2010
		EP 2332919 A2	15-06-2011
		EP 2332921 A1	15-06-2011
		HK 1144428 A1	02-05-2014
		JP 4920409 B2	18-04-2012
		JP 5421311 B2	19-02-2014
		JP 5667593 B2	12-02-2015
		JP 2007521269 A	02-08-2007
		JP 2011116780 A	16-06-2011
		JP 2012107067 A	07-06-2012
		JP 2014133771 A	24-07-2014
		KR 20060023163 A	13-03-2006
		MX PA05013364 A	17-03-2006
		US 2008045502 A1	21-02-2008
		US 2013165648 A1	27-06-2013
		US 2013178620 A1	11-07-2013
		WO 2005019179 A2	03-03-2005