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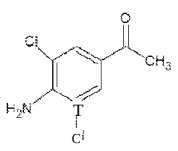
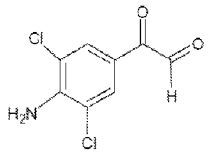


Formula II



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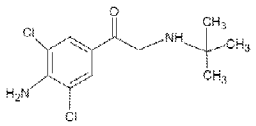

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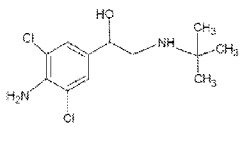


Formula I

(57) Abstract: Disclosed is a process for preparing β-agonist, l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol, of Formula I. The process comprises refluxing l-(4-amino-3, 5-dichlorophenyl) ethanone of Formula II and selenium dioxide in the presence of 1, 4-dioxane to form compound of Formula III. Further, compound of Formula III is heated at a temperature below 30 °C in the presence of t-butyl amine to form compound of Formula IV. The compound of Formula IV is treated with sodium borohydride to form compound of Formula I.

A Process for Preparing β Agonist

FIELD OF THE INVENTION

The invention relates to a process for preparing β agonist and more particularly, to a process for preparation of Clenbuterol and salts thereof.

BACKGROUND OF THE INVENTION

β-agonists are a class of sympathomimetic agents which act upon the β adrenoceptors that relax muscles of the airways and results in easier breathing.

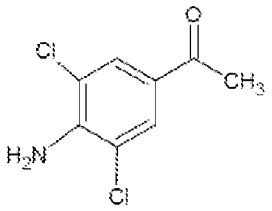
Clenbuterol (CL) is an extremely potent β-agonist with preferential affinity for β2 -adrenoceptor of the bronchial and uterine smooth muscle. Clinical trials have however revealed that the selectivity of CL for bronchodilation is not absolute and even at "therapeutic doses" this β -agonist can activate βï -adrenoceptors in the myocardium (causing palpitation) as well as β2-adrenoceptors in the central nervous system (causing tremors and headaches). (Can Vet J Volume 35, August 1994, 474, http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1686713/pdf/canveti00357-0012 .pdf). The drug is used in the form of oral tablets, granules and dry syrup for the treatment of bronchial asthma in humans in many countries. CL HC1 preparations are being used in children as well as adults. Majorly, the drug is being used for veterinary asthma.

US 3,536,712 describes the synthesis of Clenbuterol HC1 from 1-(4'amino-phenyl) -2-(t- butyl-amino)-ethanol, hydrogen chloride and chlorine. Other methods use nitro acetophenone or tertiary butyl phenyl ethanol as starting material. In the first method, reduction of nitro group to amino group and chlorination at 3 and 5 positions on the phenyl ring is needed. Also, for addition of the tertiary butyl amino group, a bromination step is needed earlier. In the second method, amino group cannot be added directly onto the phenyl ring, nitro group needs to be added, which is then reduced to amino group. Moreover, the process uses phosgene, which is a poisonous gas.

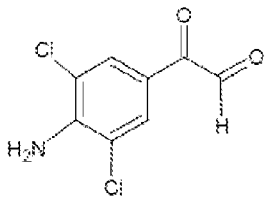
Therefore, there is a need for a process that avoids the use of poisonous materials in the synthesis steps of β-agonists.

SUMMARY OF THE INVENTION

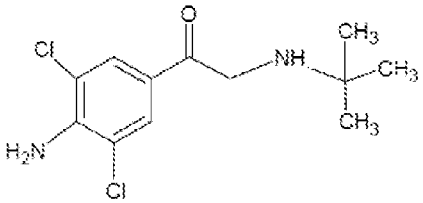
The present invention teaches a process for preparing β-agonist, l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol, of Formula I. The process comprises refluxing l-(4-amino-3, 5-dichlorophenyl) ethanone of Formula II and selenium dioxide in the presence of 1, 4-dioxane to form compound of Formula III. Further, compound of Formula III is heated at a temperature below 30 °C in the presence of t-butyl amine to form compound of Formula IV. The compound of Formula IV is treated with sodium borohydride at a predefined temperature to form compound of Formula I. The predefined temperature is in a range of 25 °C-30 °C.



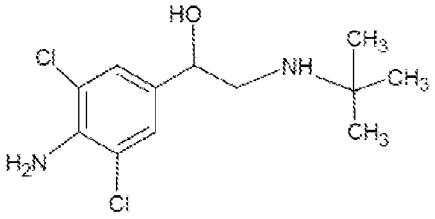
Formula II



Formula III



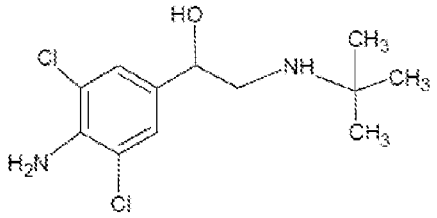
Formula IV



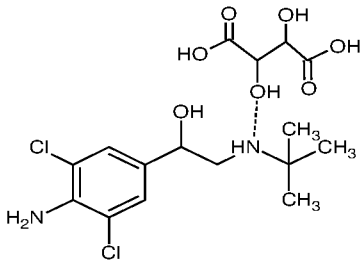
Formula I

In another embodiment the present invention provides a process for preparing β-agonist, (1RS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol, of Formula VI. The process comprises reacting compound of Formula I with an alcohol in the presence of an activated carbon and tartaric acid to form Clenbuterol tartarate salt of Formula V. The temperature of the

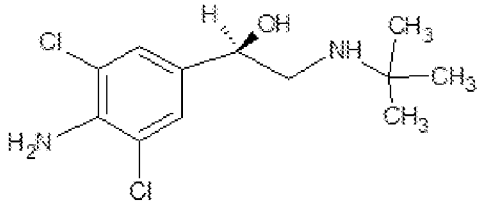
reaction is maintained in a range of 25 °C-70 °C. Further, compound of Formula V is treated with ammonia solution at a predefined temperature and at a predefined pH to obtain compound of Formula VI. The predefined pH is in a range of 10-12. The predefined temperature is below 30 °C.



Formula I

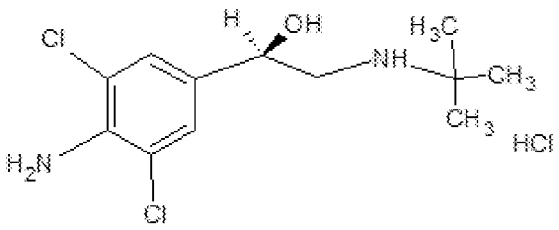


Formula V



Formula VI

In a preferred embodiment the present invention provides a process for preparing β-agonist, (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino) ethanol hydrochloride, of Formula VII. The process comprises treating compound of Formula VI with hydrochloride gas at a predefined temperature and at a predefined pH in the presence of a solvent and activated carbon to form compound of Formula VII. The predefined temperature is in a range of 60°-70° C. The predefined pH is in a range of 6-6.5. The solvent is selected from isopropyl alcohol and toluene. Preferably, the solvent is isopropyl alcohol.



Formula VII

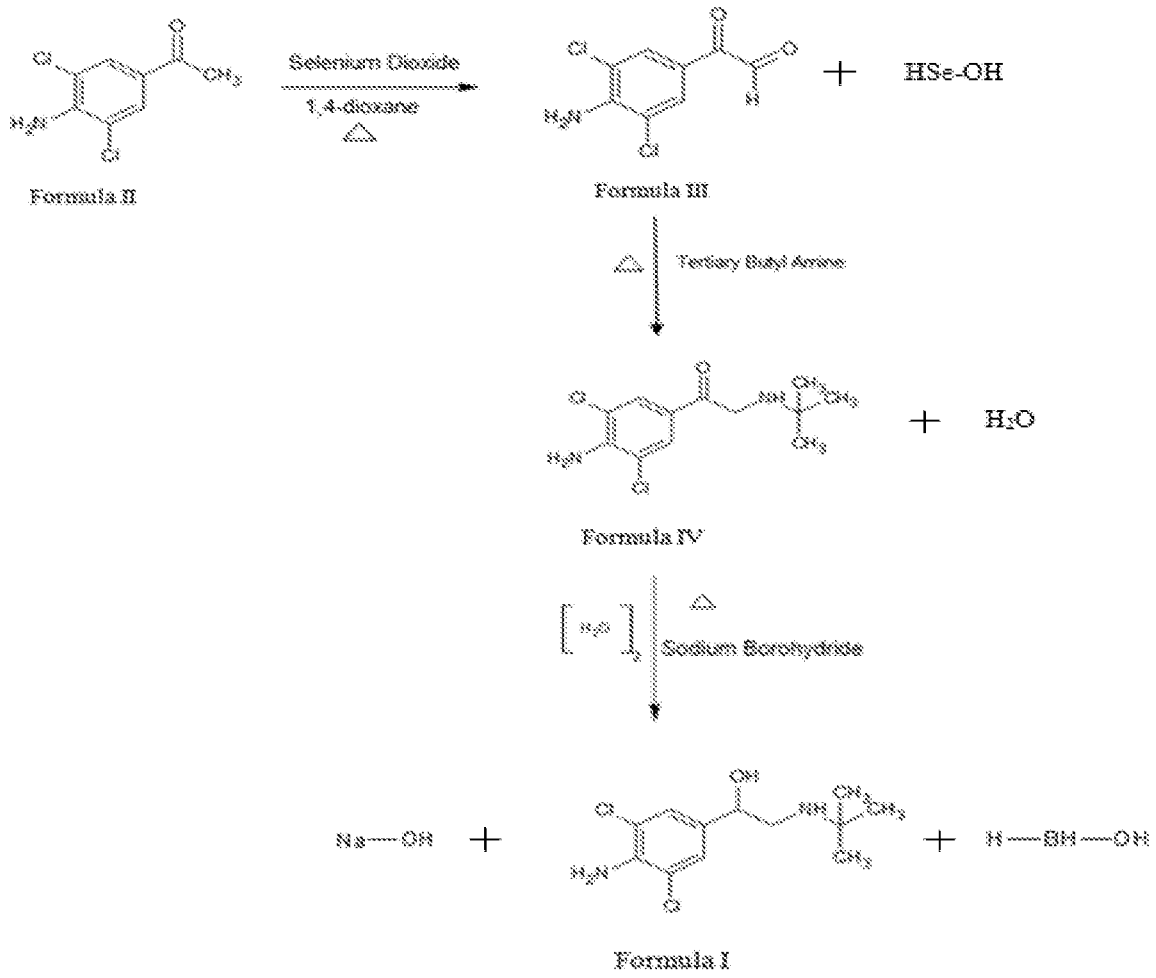
DESCRIPTION OF THE INVENTION

The foregoing objects of the present invention are accomplished and the problems and shortcomings associated with the prior art, techniques and approaches are overcome by the present invention as described below in the preferred embodiments.

An embodiment of the present invention relates to a process for preparing β-agonist, l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol, of Formula I. The process comprises refluxing l-(4-amino-3, 5-dichlorophenyl) ethanone of Formula II and selenium dioxide in the presence of 1, 4-dioxane to form compound of Formula III. In this step, selenium metal is formed as a by-product.

Further, compound of Formula III is heated at a temperature below 30 °C in the presence of t-butyl amine to form compound of Formula IV. In this step, water is formed as a by-product. The compound of Formula IV is treated with sodium borohydride in the presence of water at a predefined temperature to form compound of Formula I. The predefined temperature is in a range of 25 °C-30 °C. In this step, sodium hydroxide and boronic acid are formed as by-products.

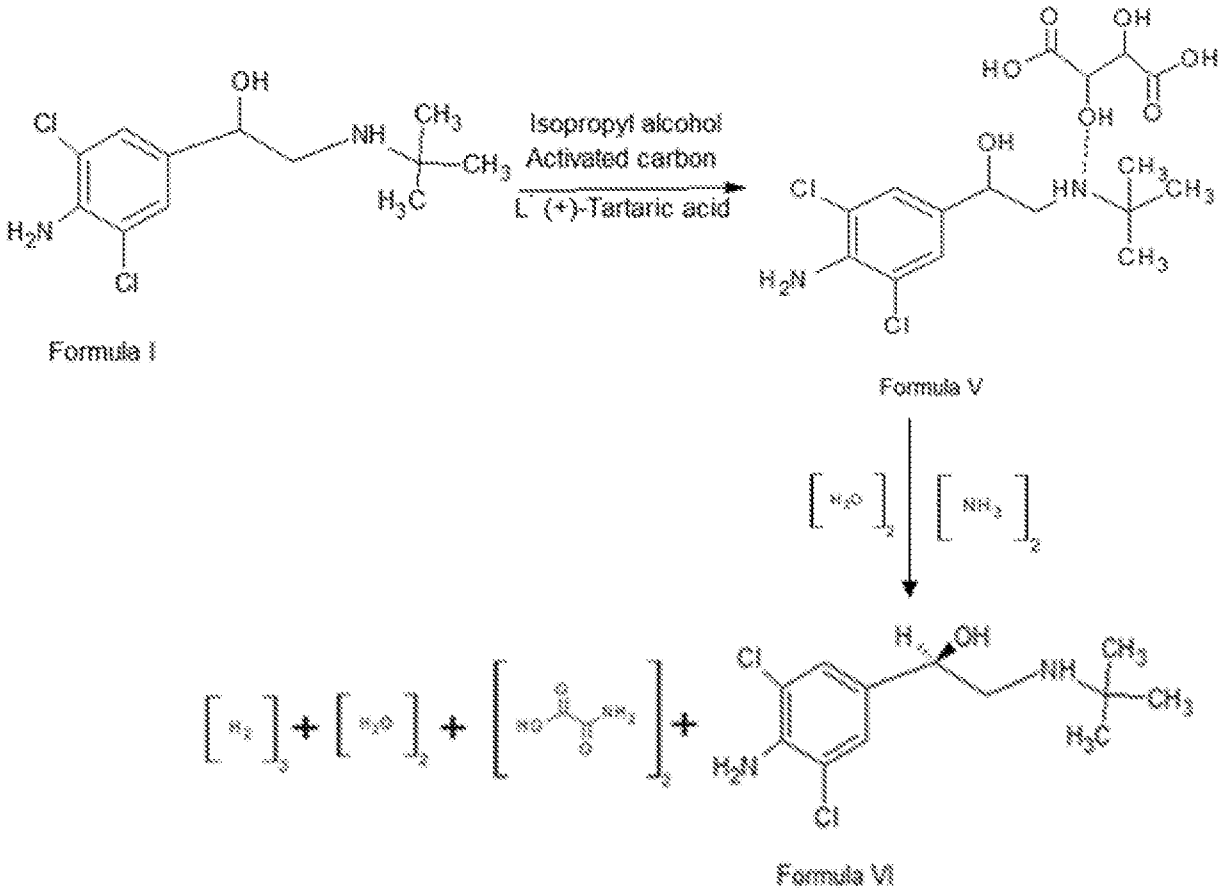
The reaction scheme of preparing compound of Formula I is represented below:



In another embodiment the present invention provides a process for preparing β-agonist, (1RS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol, of Formula VI. The process comprises reacting compound of Formula I with an alcohol in the presence of an activated carbon and tartaric acid to form Clenbuterol tartarate salt of Formula V. The temperature of the reaction is maintained in a range of 25 °C-70 °C. The alcohol used is isopropyl alcohol.

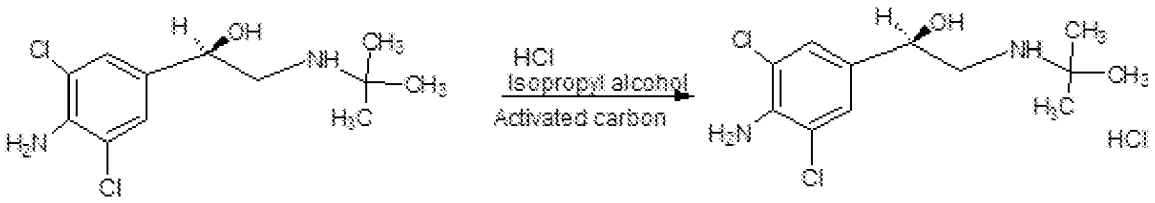
Further, compound of Formula V is treated with ammonia solution at a predefined temperature and at a predefined pH to obtain compound of Formula VI. The predefined pH is in a range of 10-12. The predefined temperature is below 30 °C. In this step, poly[amino(oxo) acetic acid, water and hydrogen are formed as by-products.

The reaction scheme of preparing compound of Formula VI is represented below:



In a preferred embodiment the present invention provides a process for preparing β-agonist, (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino) ethanol hydrochloride, of Formula VII. The process comprises treating compound of Formula VI with hydrochloride gas at a predefined temperature and at a predefined pH in the presence of a solvent and activated carbon to form compound of Formula VII. The predefined temperature is in a range of 60 °C-70 °C. The predefined pH is in a range of 6-6.5. The solvent is selected from isopropyl alcohol and toluene. Preferably, the solvent is isopropyl alcohol.

The reaction scheme of preparing compound of Formula VII is represented below:



Formula VI Formula VII

EXAMPLES

The following examples illustrate the invention, but are not limiting thereof.

Example 1

Preparation of l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol

A clean and dry reactor was charged with 1, 4-dioxane at 25-30 °C. To the reactor, 4-amino 2, 4-dichloro acetophenone was added followed by selenium dioxide with continuous stirring. The temperature was maintained at 25-30 °C at all times. The mixture was refluxed for 12 hours. Temperature was monitored and recorded every hour. After 12 hours of reflux, the reaction mass was filtered, washed with 1, 4-dioxane and the filtrate was cooled to 18-20 °C. Tertiary butyl amine was added to the cooled filtrate gradually while maintaining temperature at all times. The reaction was allowed to continue for 2 hours and temperature was monitored every 30 min. Completion of reaction was checked with TLC. If the reaction had not proceeded in the desired manner, the reaction was allowed to continue for another hour. Once the reaction was complete, the reaction mixture was cooled to 0-5 °C and then charged with sodium borohydride slowly. The further reaction was carried out at 25-30 °C for 12 hours. Temperature was monitored and recorded every hour. Completion of the reaction was checked with TLC and distilled water was added to the mixture and the precipitate thus formed was filtered through Nutch filter and dried at 50-60 °C to obtain l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol. The formed product was stored in double lined poly bag kept in a HDPE small container.

Example 2

Process for preparation of (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol

A clean and dry reactor was charged with isopropyl alcohol at 25-30 °C. To the reactor, l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol obtained in example 1 was added with continuous stirring. The mixture was refluxed for 30 min to check for dissolution. Temperature was monitored every hour up to 4 hours. After 4 hours, activated charcoal was added to the refluxing mixture, stirred for 30 min, filtered through a hypo bed in Bucker funnel and washed with isopropyl alcohol. Tartaric acid was added to the filtrate slowly within 30-40 min. at 60-70 °C. The mixture was refluxed at 50 °C for 1.5 hours and temperature was monitored every 30 min. The mixture was then filtered through Buckner funnel, washed with isopropyl alcohol and residue was air dried. Distilled water was added to the residue and pH was adjusted to 10-12 using ammonia solution. Mixture was stirred and the temperature was monitored every hour for 3 hours. The mixture was filtered through Buckner funnel and washed with distilled water till pH became neutral. The residue was air dried to obtain (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol and stored in a double lined poly bag kept in a HDPE small container.

Example 3

Process for preparation of (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino) ethanol hydrochloride

A clean and dry reactor was charged with 7.5 -10 L of toluene at 25-30 °C. To the rector, (1RS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol obtained in example 2 was added under stirring at 25-30 °C. The mixture was heated up to 60 -70 °C to dissolve (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol. Temperature was monitored every 30 min for 1.5 hours after which activated charcoal was added at 60 -70 °C and the mixture was further stirred for 1.5 hours. The mixture was filtered and washed with toluene and HC1 gas was passed through the mixture at pH 6-6.5 and at 15-20 °C. The mixture was stirred at room temperature for 3-4 hours and the temperature was monitored every 30 min. The mixture was filtered through Nutch filter and washed with toluene. The wet cake was charged with isopropyl

alcohol/toluene at room temperature, stirred for 1.5 hours, filtered and again washed with isopropyl alcohol/toluene. The final material is air dried to obtain (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino) ethanol hydrochloride and stored in double lined poly bag kept in a HDPE small container.

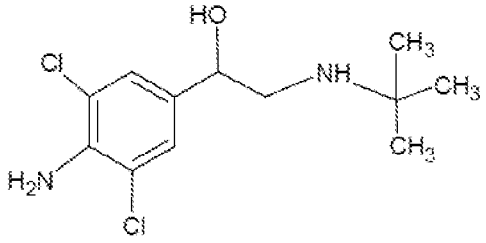
The foregoing description of specific embodiments of the present invention has been presented for purposes of illustration and description. They are not intended to be exhaustive or to limit the present invention to the precise forms disclosed, and obviously many modifications and variations are possible in light of the above teaching.

The embodiments were chosen and described in order to best explain the principles of the present invention and its practical application, to thereby enable others, skilled in the art to best utilize the present invention and various embodiments with various modifications as are suited to the particular use contemplated.

It is understood that various omission and substitutions of equivalents are contemplated as circumstance may suggest or render expedient, but such are intended to cover the application or implementation without departing from the scope of the present invention.

Claims :

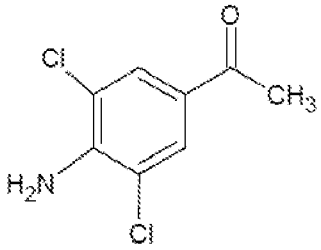
1. A process for preparing β-agonist, l-(4-amino-3, 5-dichlorophenyl)-2-(tert-butylamino) ethanol, of Formula **I**



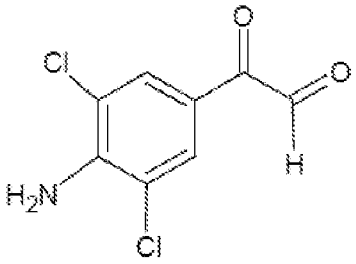
Formula **I**

comprising the steps of:

a) refluxing l-(4-amino-3, 5-dichlorophenyl) ethanone of Formula **II** and selenium dioxide in the presence of 1, 4-dioxane to form compound of Formula **III;**

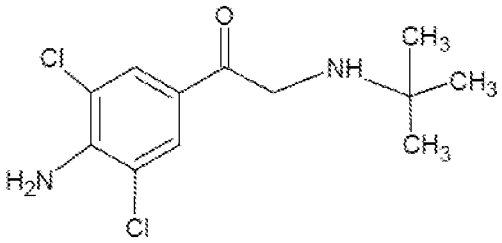


Formula **II**



Formula **III**

b) heating compound of Formula **III** at a temperature below 30 °C in the presence of t-butyl amine to form compound of Formula **IV;** and

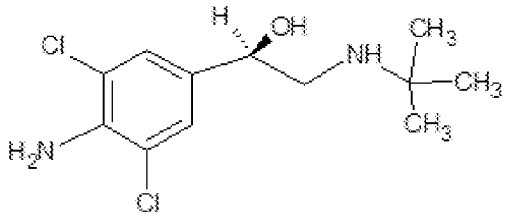


Formula **IV**

c) treating compound of Formula IV with sodium borohydride at a predefined temperature to form compound of Formula I.

2. The process as claimed in claim 1, wherein the predefined temperature in step c) is in a range of 25 °C-30 °C.

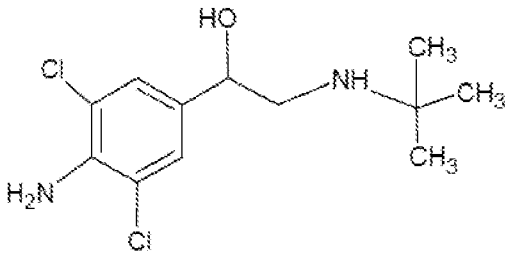
3. A process for preparing β-agonist, (lRS)-l-(4-amino-3,5-dichlorophenyl)-2-(tert-butylamino)ethanol, of Formula VI



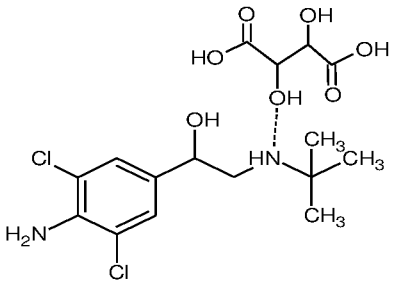
Formula VI

comprising the steps of:

a) reacting compound of Formula I with an alcohol in the presence of an activated carbon and tartaric acid at a predefined temperature to form Clenbuterol tartarate salt of Formula V; and



Formula I



Formula V

b) treating compound of Formula V with ammonia solution at a predefined temperature and at a predefined pH to form compound of Formula VI.

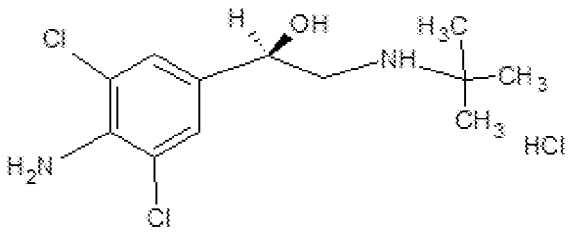
4. The process as claimed in claim 3, wherein the predefined temperature in step a) is in a range of 25 °C-70 °C.

5. The process as claimed in claim 3, wherein the alcohol used in step a) is isopropyl alcohol.

6. The process as claimed in claim 3, wherein the predefined temperature in step b) is below 30°C.

7. The process as claimed in claim 3, wherein the predefined pH in step b) is in a range of 10-12.

8. The process as claimed in claim 3 further comprising treating compound of Formula VI with hydrochloride gas at a predefined temperature and at a predefined pH in the presence of a solvent and activated carbon to form compound of Formula VII.



Formula VII

9. The process as claimed in claim 8, wherein the predefined temperature is in a range of 60 °-70° C.

10. The process as claimed in claim 8, the predefined pH is in a range of 6-6.5.

11. The process as claimed in claim 8, wherein the solvent is selected from isopropyl alcohol and toluene, preferably isopropyl alcohol.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2016/050259

A. CLASSIFICATION OF SUBJECT MATTER
C07C213/00 Version=2016 .01

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)

C07C

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)

Patseer, IPO Internal Database

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	CA 1041545 (A) (THOMAE GMBH DR K) 31 October 1978 see; Page 5-7, example A and 1, claims	1-2
A	CN 104387284 A (WUHAN TONGBIAO STANDARDS TECHNICAL SERVICES CO LTD) 4 Mar 2015 see; [abstract, para (0010, 0018)] .	1-2
A	Lijuan Wang et al "Enantioseparation of Three b-Agonists Using Di-n-butyl D-Tartrate-Boric Acid Complex as Chiral Selector by Means of MEEKC" Chromatographia (2012) 75:181-185, DOI 10.1007/s10337-011-2176-2 whole document	3-11

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

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