Novel intermediates of the formula [IIA] and [ΓΧΑ].

Amorphous form of Indacaterol Maleate.

Declarations under Rule 4.17:
— as to the identity of the inventor (Rule 4.17(i))
— 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))
— of inventorship (Rule 4.17(iv))

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Title of the Invention

A novel process for the preparation of \((R)-5\-[2-[(5, 6\text{-diethyl-2, 3-dihydro-1H-}
\text{inden-2-yl)}\text{ amino}]\text{-1-hydroxyethyl}]\text{-8-hydroxy quinolin-2(1H)}\text{-one}

Cross reference to related application:

5 [0001] This application claims priority from the provisional specification No. 890/CHE/2012 filed on 09.03. 2012.

Field of the Invention

[0002] The present invention relates to a novel process for the preparation of Indacaterol Maleate employing novel intermediate.

Background of the Invention

[0003] Indacaterol chemically known as \((R)-5\-[2-[(5, 6\text{-Diethyl-2, 3-dihydro-1H-}
\text{inden-2-yl)}\text{ amino}]\text{-1-hydroxy ethyl}]\text{-8-hydroxyquinolin-2(1H)}\text{-one}}, is an ultra long acting beta-adrenoceptor agonist developed by Novartis and has the following structural formula:

[0004] Indacaterol maleate is a long acting inhaled \(\beta2\)- agonist. Indacaterol maleate is marketed under the trade name Arcapta Neohaler in US and Onbrez in Europe.

[0005] Indacaterol maleate was disclosed in US6878721 by Novartis. The process for Indacaterol is depicted below.
[0006] In the above process for preparing Indacaterol maleate involves the step of reacting 8 substituted oxy-5-(R)-oxiranyl-(IH)-quinolin-2-one (III) with 2-amino-(5,6-diethyl)-indan (IV) to form a intermediate 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-substituted oxy-(IH)-quinolin-2-one (V). This epoxide ring opening is not region specific thereby along with 5-[(R)-2-(5,6-
diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-substituted oxy-(IH)-quinolin-2-one, below mentioned products are being produced as impurities.

[0007] The above reaction mixture contains only about 60% of desired compound i.e. 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-substituted oxy-(IH)-quinolin-2-one. The purification of this intermediate is done using silica gel chromatography which is tedious and requires large amounts of solvents, not suitable for industrial synthesis.

[0008] To overcome the above drawbacks of the process for preparing Indacaterol, the patent US7534890 discloses a process that avoids the column purification by the formation of acid addition salts of intermediate (formula - IV). Therefore, there exists a need to develop a novel process for the preparation of indacaterol maleate.

**Summary of the Invention**

[0009] The main objective of the present invention is to provide a novel process for the preparation of Indacaterol or its pharmaceutical acceptable salts.

[0010] In one object of the present invention involves a process for the preparation of Indacaterol or its pharmaceutically acceptable salts comprising the steps of:

i) treating the compound of formula IA or its acid addition salts,
wherein R is hydrogen or hydroxy protecting group; L is a leaving group; preferable leaving groups include bromo, iodo, tosylate and mesylate; other leaving groups known in the state of art may be used; with the compound of formula II A or its acid addition salts

in an organic solvent, optionally in the presence of a base to obtain a compound of formula IIIA or its acid addition salts,

ii) treating the compound of formula IIIA or its acid addition salts with reducing agent to obtain the compound of formula IVA or its acid addition salts,
iii) optionally, deprotecting the compound of formula IVA or its acid addition salts to obtain a compound of formula VA or its acid addition salts,

![Formula IVA](image1)

iv) optionally treating the compound of formula VA with an acid in presence of solvent to obtain the compound of formula VIA,

![Formula VIA](image2)

wherein acid herein is any pharmaceutically suitable acid.

[0011] Another object of the present invention provides a novel process for the preparation of Indacaterol or its pharmaceutical acceptable salts comprising the steps of:

i) treating the compound of formula IA or its acid addition salts,

![Formula IA](image3)

where in R is hydrogen or hydroxy protecting group; L is a leaving group; preferable leaving groups are bromo, iodo, tosylate and mesylate; other leaving
groups known in the state of art may be used, with compound of formula VIIIA or
its acid addition salts,

\[ \text{VIII A} \]

wherein R1 is N-protected group, in an organic solvent, optionally in the presence
of a base to obtain a compound of formula IXA or its acid addition salts,

\[ \text{IX A} \]

ii) treating the compound of formula IXA or its acid addition salt in the presence
of a reducing agent to obtain a compound of formula XA or its acid addition salts,

\[ \text{X A} \]

iii) treating the compound of formula XA or acid or its addition salt with
palladium catalyst to obtain the compound of formula VA or its acid addition
salts,
iv) optionally treating the compound of formula VA with acid in a solvent to obtain compound of formula VIA,

wherein acid herein is any pharmaceutically suitable acid.

Brief description of the Drawings

[0012] Figure 1: Amorphous form of Indacaterol Maleate

Detailed Description of the Invention

[0013] The present invention involves a novel process for the preparation of indacaterol or its pharmaceutically acceptable salts thereof employing novel intermediates thereof.

[0014] In one embodiment of the present invention involves a process for the preparation of Indacaterol or its pharmaceutically acceptable salts comprising the steps of:

i) treating the compound of formula IA or its acid addition salts,
where in $R$ is a hydrogen or hydroxy protecting group;

$L$ is a leaving group; preferable leaving groups are bromo, iodo, tosylate and mesylate; other leaving groups known in the state of art may be used, with the compound of formula IIA or its acid addition salts,

in an organic solvent optionally in presence of a base to obtain a compound of formula IIIA or its acid addition salts,

ii) treating the compound of formula IIIA or its acid addition salts with reducing agent to obtain the compound of formula IVA or its acid addition salts,

iii) optionally, deprotecting the compound of formula IVA or its acid addition salts to obtain a compound of formula VA or its acid addition salts,
iv) optionally treating the compound of formula VA with an acid in presence of solvent to obtain the compound of formula VIA,

wherein acid is any pharmaceutically suitable acid.

[0015] The hydroxy protecting group employed in step i) of the above process is selected from the group included but not limited to silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and benzyl.

[0016] The base employed in the step i) of the above process is selected from the group of organic base or inorganic base, wherein the organic base is selected from the C1 to C6 cyclic or acyclic amines included but not limited to isopropyl amine, diisopropyl amine, diisopropyl ethyl-amine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine. Inorganic base may be selected from the group consisting of alkali metals such as sodium, potassium, lithium or alkali metal carbonates like sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate or alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate, lithium
bicarbonate, cesium bicarbonate or alkali metal hydroxides like sodium hydroxide, calcium hydroxide, potassium hydroxide, metal alkoxides like alkoxides of sodium, lithium or potassium, sodium tert-butoxide and sodium hydride, including the combination of above organic and inorganic bases in any ratio.

[0017] The organic solvent employed in step i) of the above process is selected from the group but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, isobutyl alcohol, tertiary-butyl alcohol and the like; halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform and the like; ketones such as acetone, methyl isobutyl ketone and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, tetrahydrofuran, methyl tertiary-butyl ether and the like; esters such as ethyl acetate, h-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; hydrocarbons such as hexane, benzene, xylene, toluene and the like and aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide and the like, any solvent or mixture of solvents or their combination with water or any of the solvents from the classes mentioned above is acceptable.

[0018] The reducing agent employed in step ii) of the above process is selected from the group included but not limited to asymmetric reducing agents such as boranes like BH$_3$-THF, Borane DMS, Diborane with chiral catalyst Methyl CBS, phenyl CBS. The reduction also carried out using DIP chloride, Diethyl methoxy borane and sodium borohydride, lithium aluminum hydride.
[0019] The acid employed in step iv) of the above process is selected from the group of inorganic acids such as HCl, HBr, HI, H2SO4, HNO3, H3PO4 or organic acids such as C2 to C4 carbons containing organic acid like maleic acid, formic acid, oxalic acid.

[0020] The another embodiment of the present invention provides novel process for the preparation of Indacaterol or its pharmaceutical acceptable salts comprising the steps of:

i) treating the compound of formula IA or its acid addition salts,

\[
\begin{align*}
\text{IA} & \\
& \begin{array}{c}
\text{O} \\
\text{N-protected} \\
\text{group} \\
\text{in an organic solvent, optionally in the presence of a base to obtain a compound of formula IXA or its acid addition salts,}
\end{array}
\end{align*}
\]

in which R is hydrogen or hydroxy protecting group; L is a leaving group; preferable leaving groups are bromo, iodo, tosylate and mesylate; other leaving groups known in the state of art may be used, with compound of formula VIII A or its acid addition salts,

\[
\text{VIII A}
\]

wherein R is N-protected group, in an organic solvent, optionally in the presence of a base to obtain a compound of formula IX A or its acid addition salts,
ii) treating the compound of formula IXA or its acid addition salts with a reducing agent to obtain a compound of formula XA or its acid addition salts,

\[
\text{\includegraphics[width=0.5\textwidth]{formula-ixa}}
\]

iii) treating the compound of formula XA or its acid addition salts with palladium catalyst to obtain the compound of formula VA or its acid addition salts,

\[
\text{\includegraphics[width=0.5\textwidth]{formula-va}}
\]

iv) optionally treating the compound of formula V with acid in a solvent to obtain compound of formula VI

\[
\text{\includegraphics[width=0.5\textwidth]{formula-via}}
\]

wherein the acid is any pharmaceutically suitable acid.

[0021] The hydroxy protecting groups employed in step i) of the above process is from the group included but not limited to silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and hydrogen. Preferably, protecting group is silyl or benzyl.
[0022] The nitrogen protecting groups employed in step i) of the above process is selected from the group of silyl, benzyl, benzoyl, carbobenzyloxy, acetyl, tosyl.

The base employed in the step i) of the above process is selected from the group of organic base or inorganic base, wherein the organic base is selected from the C1 to C6 cyclic or acyclic amines included but not limited to isopropyl amine, diisopropyl amine, diisopropyl ethyl-amine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine. Inorganic base may be selected from the group consisting of alkali metals such as sodium, potassium, lithium or alkali metal carbonates like sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate or alkali metal bicarbonates like sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate or alkali metal hydroxides like sodium hydroxide, calcium hydroxide, potassium hydroxide, metal alkoxides such as alkoxides of sodium, lithium or potassium, sodium tert-butoxide and sodium hydride, including the combination of above organic and inorganic bases in any ratio.

[0023] The organic solvent employed in step i) of the above process is selected from the group but are not limited to: alcohols such as methanol, ethanol, isopropyl alcohol, isobutyl alcohol, tertiary-butyl alcohol and the like; halogenated hydrocarbons such as dichloromethane, ethylene dichloride, chloroform and the like; ketones such as acetone, methyl isobutyl ketone and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as dimethyl ether, diethyl ether, diisopropyl ether, tetrahydrofuran, methyl tertiary-
butyl ether and the like; esters such as ethyl acetate, n-propyl acetate, isopropyl acetate, n-butyl acetate, isobutyl acetate and the like; hydrocarbons such as hexane, benzene, xylene, toluene and the like and aprotic polar solvents such as dimethyl sulfoxide, N,N-dimethylformamide, N,N-dimethylacetamide and the like, any solvent or mixture of solvents or their combination with water or any of the solvents from the classes mentioned.

[0024] The reducing agent employed in step ii) of the above process is selected from the group included but not limited to asymmetric reducing agents such as boranes like BH₃-THF, Borane DMS, Diborane with chiral catalyst Methyl CBS, phenyl CBS. The reduction also carried out using DIP chloride, Diethyl methoxy borane and sodium borohydride, lithium aluminum hydride.

[0025] The acid employed in step iv) of the above process is selected from the group of inorganic acids such as HCl, HBr, HI, H₂SO₄, HNO₃, H₃PO₄ or organic acids such as C₂ to C₄ carbons containing organic acidsalts such as maleic acid, formic acid, oxalic acid.

[0026] The process of the present invention provides pure Indacaterol maleate having purity not less than 98% and more than 99.5% is obtained. The process of the present invention provides Indacaterol maleate free of dimer and regioisomer. The process of the present invention provides an amorphous form of Indacaterol maleate depicted in Figure 1.

[0027] The novel intermediates or its acid addition salts of the present invention may also prepared by known methods in the state of the art. The deprotection
process of present invention may be done by the known methods in the state of the art.

[0028] The following examples are provided to enable one skilled in the art to practice the invention and merely illustrate the process of the invention. However, it is not intended in any way to limit the scope of the present invention.
**Examples**

**Example - 1 Preparation of compound of IIIA, wherein R is Benzyl**

![Chemical Reaction Diagram](image)

[0029] The compound of formula IA (25 gm) was dissolved in DMSO (75 ml) and stirred for 15 min, then compound of formula IIA (0.09 mol) was added to the reaction mixture at 25 - 30°C. The triethylamine (0.1 mol) was added to above contents slowly, following by added sodium iodide (0.03 mol) at same temperature and stirred the reaction mixture for 3 hours at same temperature. The purified water (250 ml) was added to the reaction mixture and stirred for 1.0 hour. The contents were filtered and washed with water. The wet material was dissolved in methanol (250 ml) and stirred for 30 minutes, and then water was added. The contents were stirred for 1 hour at 25 - 30°C and filtered to obtain the title compound. Yield: 76%

**Example - 2 Preparation of compound of IIIA, wherein R is Benzyl**
The compound of formula A (25 gm) was dissolved in DMSO (75 ml) and stirred for 15 min, then compound of formula IIA (0.09 mol) was added to the reaction mixture at 25 - 30°C. Potassium carbonate (0.1 mol) was added to above contents slowly, following by added sodium iodide (0.03 mol) at same temperature and stirred the reaction mixture for 3 hours at same temperature. The purified water (250 ml) was added to the reaction mixture and stirred for 1.0 hour. The contents were filtered and washed with water. The wet material was dissolved in methanol (250 ml) and stirred for 30 minutes, and then water was added. The contents were stirred for 1 hour at 25 - 30°C and filtered to obtain the title compound. Yield: 82%

Example - 3 Preparation of compound of IIIA, wherein R is Benzyl
[0031] The compound of formula IA (25 gm) was dissolved in DMSO (75 ml) and stirred for 15 min, then compound of formula IIA (0.09 mol) was added to the reaction mixture at 25 - 30°C, then Sodium iodide (0.03 mol) was added to the reaction mixture at same temperature and stirred the reaction mixture for 3 hours at same temperature. The purified water (250 ml) was added to the reaction mixture and stirred for 1.0 hour. The contents were filtered and washed with water. The wet material was dissolved in methanol (250 ml) and stirred for 30 minutes, and then water was added. The contents were stirred for 1 hour at 25 - 30°C and filtered to obtain the title compound. Yield: 84%

Example - 4 Preparation of compound of IVA, wherein R is Benzyl

[0032] The Borane-dimethyl sulfide (0.11 mol) was added at 0-5°C, followed by addition of R - (2)-Methyl CBS (0.01 mol) and stirred the contents for 10 minutes at same temperature. The compound of example-1 (20 gm) was dissolved in methylene chloride (200 ml) at same temperature and stirred the reaction mixture for 1.0 hour. The methanol was added to the reaction mixture followed by addition of 5% hydrogen peroxide (0.01 mol) at 0-5°C and stirred the contents for 15 minutes at same temperature, gradually increased the temperature to 20-
30°C. The 6.0 N sulfuric acid (10 ml) solution was added to the reaction mixture and stirred for 15 minutes. The layers were separated. The separated organic layer was washed with 2.0 N sulfuric acid solution followed by washings with water, then distilled and dissolved in ethyl acetate. The contents were stirred for 1.0 hour, filtered and dried at 60°C. Yield: 85%; E.e: >95%.

Example -5 Preparation of compound of formula VA (Indacaterol)
[0033] The compound of example-4 (10 gm) was dissolved in methanol (100 ml), followed by addition of acetic acid (50 ml) to the reaction mixture. The 5% Pd/C was added to the reaction mixture and applied hydrogen pressure 3-4 Kg/cm³ and then the contents were stirred for 4.0 hours at 25-30°C, filtered and distilled. The residue was dissolved in ethyl acetate, stirred for 10 min and distilled to obtain the compound. Yield: 79%

Example -6 Preparation of Indacaterol Maleate
[0034] To a methanolic solution of Indacaterol, maleic acid (0.9 mol) in methanol was slowly added at 25-30°C and stirred the isolated compound for 2.0 hours at same temperature. The reaction mass was cooled to 0-10°C and maintained for 2.0 hrs at same temperature. The contents were filtered, washed with methanol and dried at 60-65°C. Yield: 93%; E.e: >99%.

Example -7 Preparation of compound of formula IXA, wherein R and R¹ is benzyl
The (Bromo compound) of formula I (25 gm) was dissolved in DMF (150 ml) and stirred the contents for 1 min. The 5,6-Diethyl indane N-benzyl amine (0.9 mol) was added to the above mixture at 25 -30°C, followed by the slow addition of triethylamine, then the reaction mixture was stirred for 5.0 min. The sodium iodide (0.01 mol) was added to the reaction mixture at same temperature and stirred for 3 hours at same temperature. The purified water was added to the reaction mixture, and then the contents were filtered and washed with water. The wet compound was dissolved in methanol then water was added to the contents and stirred for 1 hour at 25 -30 °C. The contents were filtered and dried the compound at 60 °C. Yield: 70%.

**Example -8 Preparation of compound of formula XA, wherein R and R1 is benzyl**

[0036] A mixture of Borane-dimethyl sulfide (0.11 mol), R-(2)-Methyl CBS (0.01 mol) and methylene chloride was stirred for 10 minutes at 0-5 °C. The compound of example-7 (20 gm) was dissolved in methylene chloride (200 ml) and was added to the reaction mixture at same temperature. The reaction mixture was stirred for 1.0 hour. The methanol was added to the reaction mixture followed by
addition of 5% hydrogen peroxide (0.01 mol) at 0-5 °C. Stirred the contents for 15 minutes at same temperature, gradually increased the temperature to 20-30°C. The 6.0N sulfuric acid (10 ml) solution was added to the reaction mixture and stirred for 15 minutes. The layers were separated. The organic layer was washed with 2.0N sulfuric acid solution followed by washing with water. The organic layer was distilled and dissolved in ethyl acetate. Stirred the contents for 1.0 hour and filtered the compound. The compound was dried at 60°C. Yield: 80%; Purity E.e: > 95%.

**Example -9 Preparation of compound of formula VA (Indacaterol)**

[0037] The compound of example-8 (10 gm) was dissolved in methanol (100 ml), followed by addition of acetic acid (50 ml) to the reaction mixture. Then 5% Pd/C was added to the reaction mixture and applied hydrogen pressure 3-4 Kg/cm². The content was stirred for 4.0 hours at 25-30°C, filtered and the filtrate was distilled. The residue was dissolved in ethyl acetate (50 ml), stirred the contents for 10 min and distilled to obtain the compound. Yield: 80%
Claims

We Claim:

1. A process for the preparation of indacaterol or its pharmaceutical acceptable salts comprising the steps of:

5  i) treating the compound of formula IA or its acid addition salts,

\[
\text{IA}
\]

wherein R is hydrogen or hydroxy protecting group, L is a leaving group; with the compound of formula IIA or its acid addition salts,

\[
\text{IIA}
\]

10 in an organic solvent optionally in the presence of a base to obtain a compound of formula IIIA or its acid addition salts,

\[
\text{IIIA}
\]

ii) treating the compound of formula IIIA or its acid addition salt with reducing agent to obtain the compound of formula IVA or its acid addition salt,
iii) optionally, deprotecting the compound of formula IVA or its acid addition salts to obtain a compound of formula VA or its acid addition salt,

iv) optionally treating the compound of formula VA with an acid in presence of solvent to obtain the compound of formula VIA

wherein said acid is any pharmaceutically suitable acid.

2. The process according to the claim 1 wherein the hydroxy protected group is selected from the group of silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and hydrogen.

3. The process according to the claim 1 wherein the base employed is selected from the group consisting of organic base and inorganic base.
4. The process according to claim 3 wherein the organic base is selected from the group comprising of isopropyl amine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine.

5. The process according to claim 3 wherein the inorganic base is selected from the group comprising of alkali metals, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides and metal alkoxides.

6. The process according to the claim 1 wherein acid is selected from the group of inorganic acids or organic acids.

7. The process according to the claims 6 wherein the inorganic acid is selected from the group comprising of HCl, HBr, HI, H2SO4, HNO3 and H3PO4.

8. The process according to the claim 6 wherein the organic acid is selected from the group comprising of C2 to C4 carbons containing organic acids.

9. The process according to the claim 1 wherein the organic solvent is selected from the group comprising of alcohols, halogenated hydrocarbons, ketones, nitriles, ethers, esters, hydrocarbons, aprotic polar solvents or mixture of solvents and their combination with water.

10. The process according to the claim 1 wherein the reducing agent is selected from the group comprising of asymmetric reducing agents.

11. The process according to the claim 10, wherein the asymmetric reducing agents is selected from the group comprising of borane-THF, borane-DMS, diborane with chiral catalyst, methyl-CBS and phenyl-CBS.
12. A process for the preparation of compound of formula IIIA or its acid addition salt,

![Chemical structure of IIIA]

comprising the steps of:

5 i) treating the compound of formula IA or its acid addition salt,

![Chemical structure of IA]

wherein R is hydrogen or hydroxy protecting group, L is a leaving group; with the compound of formula II A or its acid addition salt,

![Chemical structure of IIA]

in an organic solvent, optionally in the presence of a base to obtain a compound of formula IIIA or its acid addition salt.

13. The process according to the claim 12 wherein the hydroxy protected group is selected from the group of silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and hydrogen.

14. The process according to the claim 12 wherein the base employed is selected from the group consisting of organic base and inorganic base.
15. The process according to claim 14 wherein the organic base is selected from the group comprising of isopropyl amine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine.

16. The process according to claim 14 wherein the inorganic base is selected from the group comprising of alkali metals, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides and metal alkoxides.

17. The process according to claim 12 wherein the organic solvent is selected from the group comprising of alcohols, halogenated hydrocarbons, ketones, nitriles, ethers, esters, hydrocarbons, aprotic polar solvents or mixture of solvents and their combination with water.

18. A process for the preparation of indacaterol or its pharmaceutical acceptable salts comprising the steps of:

i) treating the compound of formula IA or its acid addition salts,

\[
\text{IA}
\]

in which \( R \) is hydrogen or hydroxy protecting group, \( L \) is a leaving group; with compound of formula VIIIA or its acid addition salt

\[
\text{VIIIA}
\]

wherein \( R_1 \) is N-protected group, in an organic solvent, optionally in the presence of a base to obtain a compound of formula IXA or its acid addition salt,
ii) treating the compound of formula IXA or its acid addition salt with a reducing agent to obtain a compound of formula XA or its acid addition salts,

iii) treating the compound of formula XA or its acid addition salt with palladium catalyst to obtain the compound of formula VA or its acid addition salt,

iv) optionally treating the compound of formula V with acid in a solvent to obtain compound of formula VI
wherein said acid is any pharmaceutically suitable acid.

19. The process according to the claim 18 wherein the hydroxy protected group is selected from the group of silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and hydrogen.

20. The process according to the claim 18 wherein the nitrogen protecting group is selected from the group comprising of silyl, benzyl, benzoyl, carbobenzyloxy, acetyl and tosyl.

21. The process according to the claim 18 wherein the base employed is selected from the group consisting of organic base and inorganic base.

22. The process according to claim 21 wherein the organic base is selected from the group comprising of isopropyl amine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine.

23. The process according to claim 21 wherein the inorganic base is selected from the group comprising of alkali metals, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides and metal alkoxides.

24. The process according to the claim 18 wherein acid is selected from the group of inorganic acids or organic acids.

25. The process according to the claim 24 wherein the inorganic acid is selected from the group comprising of HCl, HBr, HI, H2SO4, HNO3 and H3PO4.

26. The process according to the claim 24 wherein the organic acid is selected from the group comprising of C2 to C4 carbons containing organic acids.
27. The process according to the claim 18 wherein the organic solvent is selected from the group comprising of alcohols, halogenated hydrocarbons, ketones, nitriles, ethers, esters, hydrocarbons, aprotic polar solvents or mixture of solvents and their combination with water.

28. The process according to the claim 18 wherein the reducing agent is selected from the group comprising of asymmetric reducing agents.

29. The process according to the claim 28 wherein asymmetric reducing agents is selected from the group comprising of borane-THF, borane-DMS, diborane with chiral catalyst, methyl-CBS, phenyl-CBS.

30. A process for the preparation of compound of formula IXA or its acid addition salts

comprising the steps of :

i) treating the compound of formula IA or its acid addition salts

in which R is hydrogen or hydroxy protecting group, L is a leaving group; with compound of formula VIIIA or its acid addition salts
wherein R\textsubscript{1} is N-protected group, in an organic solvent, optionally in the presence of a base to obtain a compound of formula IXA or its acid addition salts.

31. The process according to the claim 30 wherein the hydroxy protected group is selected from the group of silyl, alkyl, aryl, alkoxy, alkenyl, aralkyl, haloalkyl and hydrogen.

32. The process according to the claim 30 wherein the nitrogen protecting group is selected from the group comprising of silyl, benzyl, benzyol, carbobenzoxyloxy, acetyl and tosyl.

33. The process according to the claim 30 wherein the base employed is selected from the group consisting of organic base and inorganic base.

34. The process according to claim 33 wherein the organic base is selected from the group comprising of isopropyl amine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine.

35. The process according to claim 33 wherein the inorganic base is selected from the group comprising of alkali metals, alkali metal carbonates, alkali metal bicarbonates, alkali metal hydroxides and metal alkoxides.

36. The process according to claim 30 wherein the organic solvent is selected from the group comprising of alcohols, halogenated hydrocarbons, ketones, nitriles, ethers, esters, hydrocarbons, aprotic polar solvents or mixture of solvents and their combination with water.
37. A compound of formula IIIA or its acid addition salts

wherein R is hydrogen or hydroxy protecting group.

38. A compound of formula IXA and its acid addition salts

wherein R is hydrogen or hydroxy protecting group; R1 is N-protected group.
Amorphous form of Indacaterol Maleate

Fig 1