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(54) Title: PROCESS FOR PREPARING REVEFENACIN AND INTERMEDIATES THEREOF

(57) Abstract: The present invention relates to processes and intermediates for the synthesis of Revefenacin or pharmaceutically acceptable salts thereof.



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“PROCESS FOR PREPARING REVEFENACIN AND INTERMEDIATES THEREOF”

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority to Indian Application No. **202021038419**, filed **5th September, 2020** and entitled “**PROCESS FOR PREPARING REVEFENACIN AND INTERMEDIATES THEREOF**” which is incorporated herein in its entirety.

FIELD OF INVENTION:

The present invention relates to an improved process for the preparation of intermediates useful in the synthesis of Revefenacin or pharmaceutically acceptable salts thereof.

BACKGROUND OF THE INVENTION:

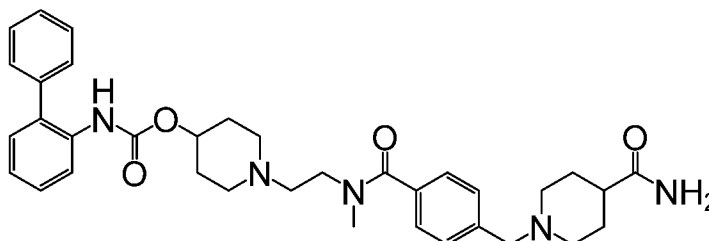
Pulmonary or respiratory disorders, such as chronic obstructive pulmonary disease (COPD) and asthma, afflict many millions of people worldwide and such disorders are a leading cause of morbidity and mortality.

Muscarinic receptor antagonists are known to provide bronchoprotective effects and therefore, such compounds are useful for treating respiratory disorders, such as COPD and asthma.

Revefenacin is a novel biphenyl carbamate tertiary amine agent that belongs to the family of the long-acting muscarinic antagonists (LAMA).

YUPELRI a sterile, clear, colorless, aqueous solution of Revefenacin, is an anticholinergic indicated for the maintenance treatment of patients with chronic obstructive pulmonary disease (COPD).

The chemical name for Revefenacin is 1-(2-{4[(4-carbamoylpiperidin-1-yl)methyl]-N-methylbenzamido}ethyl)piperidin-4-yl N-({1,1'-biphenyl}-2-yl)carbamate; its structural formula (I) is:

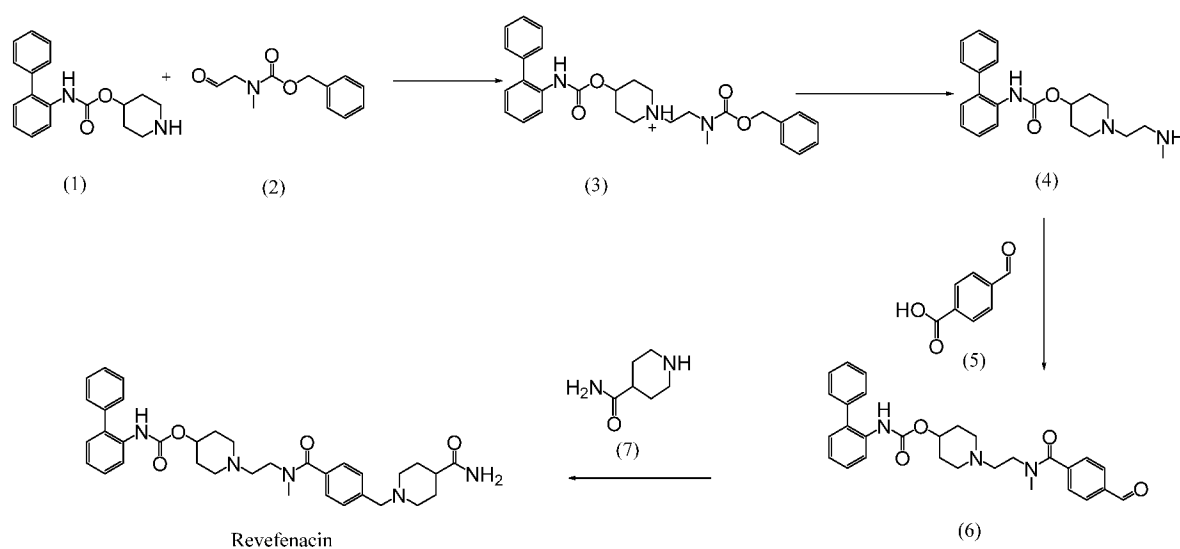


Revefenacin

US patent numbers US 7,288,657 B2 and US 7,585,879 B2 disclose novel biphenyl compounds having muscarinic receptor antagonist or anticholinergic activity to treat pulmonary disorders. In particular, Revefenacin and its process of preparation was first time specifically disclosed in these patents.

The process include oxidation of 2-(benzylmethylamino)ethanol to the aldehyde intermediate (2) followed by reductive amination with biphenyl-2-yl-carbamic acid piperidin-4-yl ester (1) and debenzylization, as depicted in reaction scheme 1 below:

Scheme 1



However, this process is not suitable on the industrial scale due to instable aldehyde intermediate (2) and low yield.

A refinement of the process is disclosed in the US 9,035,061 B2.

The process comprising the steps of:

- (a) reductive amination of a compound of formula (1): and a compound of formula (2) in the presence of a reducing agent, to yield the compound of formula (3);
- (b) debenzylation of the compound of formula (3) to yield the compound of formula (4);

wherein step (a) and step (b) are conducted in the same reaction mixture without isolation of the intermediate from step (a);

- (c) coupling a compound of formula (4) in the presence of a coupling reagent with a compound of formula (5) to yield the compound of formula (6);
- (d) reductive amination of the compound of formula (6) and a compound of formula (7) in the presence of a reducing agent to yield the compound of formula I;

wherein azeotropic distillation of water is conducted at an elevated temperature prior to the addition of the reducing agent, and reductive amination is conducted at room temperature; and

wherein step (c) and step (d) are conducted in the same reaction mixture without isolation of the intermediate reaction product from step (c).

Thus, there exists a continuous need for an efficient process of preparing Revefenacin and intermediates with high chemical purity and good overall yield, which is suitable for industrial scale up.

The present invention provides an improved process for synthesis of Revefenacin which avoids all the disadvantages associated with the prior art processes.

OBJECTS OF THE INVENTION:

One object of the present invention is to provide an improved process for preparing Revefenacin or pharmaceutically acceptable salts thereof.

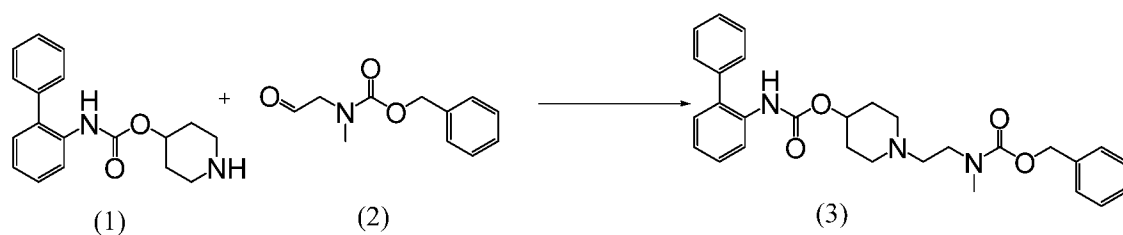
Another object of the present invention is to provide novel intermediates that are useful in the synthesis of Revefenacin or pharmaceutically acceptable salts thereof.

Another object of the present invention is to provide a purification method to obtain substantially pure Revefenacin or pharmaceutically acceptable salts thereof.

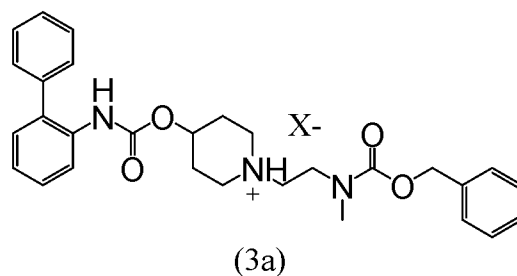
Yet another object of the present invention is to provide a process for preparing Revefenacin or pharmaceutically acceptable salts thereof which is simple, economical and suitable for industrial scale up.

SUMMARY OF THE INVENTION :

According to a first aspect of the present invention, there is provided a process for preparing compound of formula (3) or salt thereof comprising reductive amination of compound of formula (1) with compound of formula (2) in the presence of a reducing agent using suitable non polar solvent or mixtures thereof at 20-30°C and optionally converting compound of formula (3) to salt thereof.

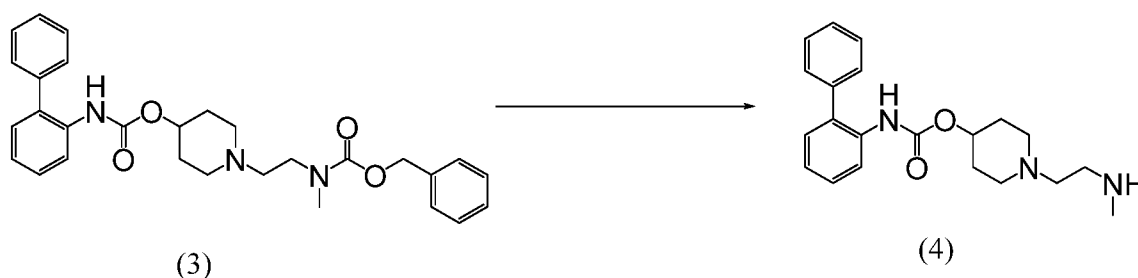


In an embodiment, the compound (3) is converted into an acid addition salt of the formula (3a) in the presence of an acid HX

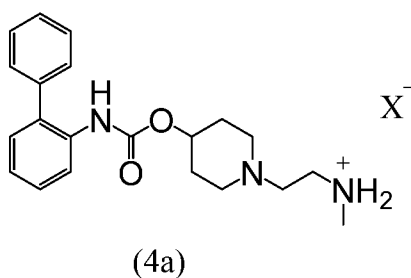


wherein X^- is an anion. The acid may be an inorganic acid or organic acid.

According to a second aspect of the present invention, there is provided a process for preparing compound of formula (4) or salt thereof comprising debenzoylation of compound of formula (3) or salt thereof by transfer hydrogenation under atmospheric pressure in the presence of a hydrogen donor and a hydrogenation catalyst and optionally converting compound of formula (4) to salt thereof.



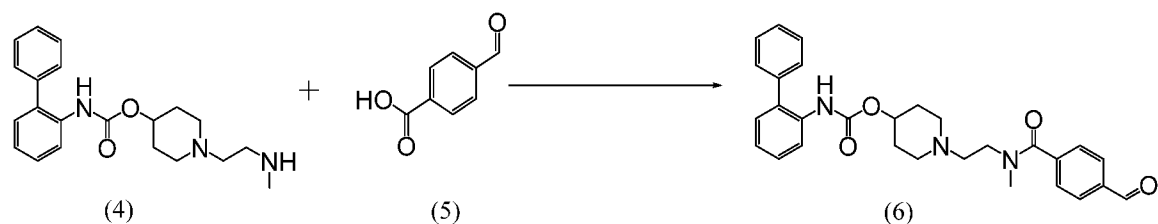
In an embodiment, the compound (4) is converted into an acid addition salt of the formula (4a) in the presence of an acid HX



wherein X^- is an anion. The acid may be an inorganic acid or organic acid.

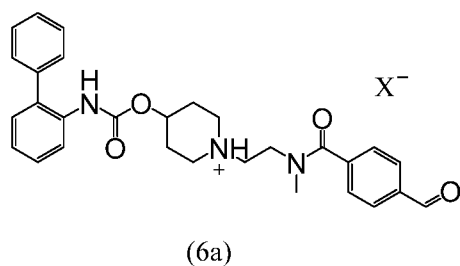
According to a third aspect of the present invention, there is provided a process for preparing compound of formula (6) or salt thereof comprising coupling of compound of formula (4) with compound of formula (5) in the presence of suitable

coupling reagent and a suitable inert ester solvent and optionally converting compound of formula (6) to salt thereof.



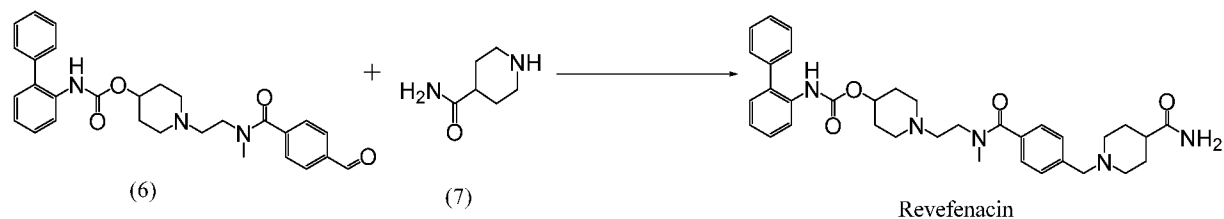
In an embodiment, the compound (6) is isolated as a solid.

In another embodiment, the compound (6) is converted into an acid addition salt of the formula (6a) in the presence of an acid HX

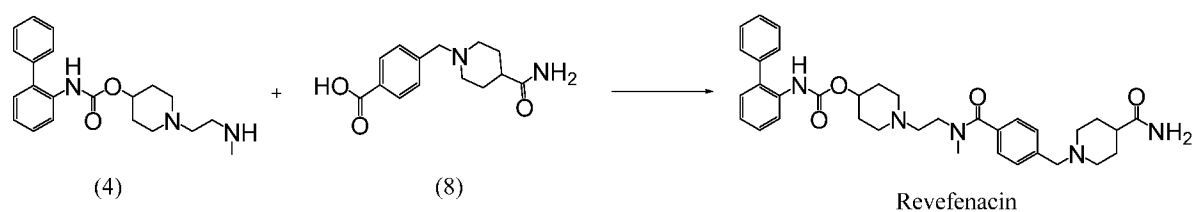


wherein X^- is an anion. The acid may be an inorganic acid or organic acid.

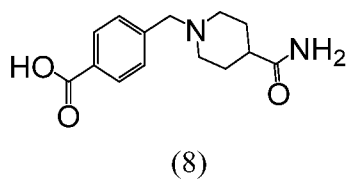
According to a fourth aspect of the present invention, there is provided a process for preparing Revefenacin of formula (I) or salt thereof comprising reductive amination of compound of formula (6) with compound of formula (7) in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures thereof and optionally converting Revefenacin of formula (I) to salt thereof.



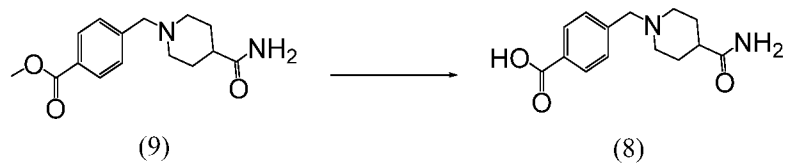
According to a fifth aspect of the present invention, there is provided a novel process for preparing Revefenacin of formula (I) or salt thereof comprising coupling of compound of formula (4) with compound of formula (8) in the presence of suitable coupling reagent and a suitable inert ester solvent and optionally converting Revefenacin of formula (I) to salt thereof.



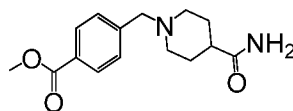
According to a sixth aspect of the present invention, there is provided a novel intermediate compound of Formula (8)



According to a seventh aspect of the present invention, there is provided a process for preparing compound of Formula (8) comprising hydrolyzing compound of formula (9) or salt thereof in the presence of a suitable base and suitable solvent/s or mixtures thereof.

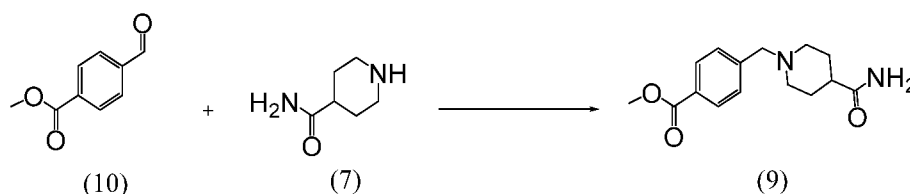


According to an eighth aspect of the present invention, there is provided a novel intermediate compound of Formula (9) or salt thereof



(9)

According to a ninth aspect of the present invention, there is provided a process for preparing compound of Formula (9) or salt thereof comprising reductive amination of compound of formula (10) with compound of formula (7) in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures thereof.



According to a tenth aspect of the present invention, there is provided a process for stabilizing Revefenacin of formula (I) or salt thereof.

The process of the present invention has certain advantages over prior art

According to another aspect of the present invention, there is provided substantially pure Revefenacin of formula (I) or salt thereof having a purity of at least 95%, preferably at least 99%, more preferably at least 99.5%.

According to another aspect of the present invention, there is provided Revefenacin of formula (I) or salt thereof prepared according to a process defined above.

According to another aspect of the present invention, there is provided the use of Revefenacin of formula (I) or salt thereof prepared according to a process defined above in medicine.

According to another aspect of the present invention, there is provided the use of Revefenacin of formula (I) or salt thereof prepared according to a process defined above in treating pulmonary disorders.

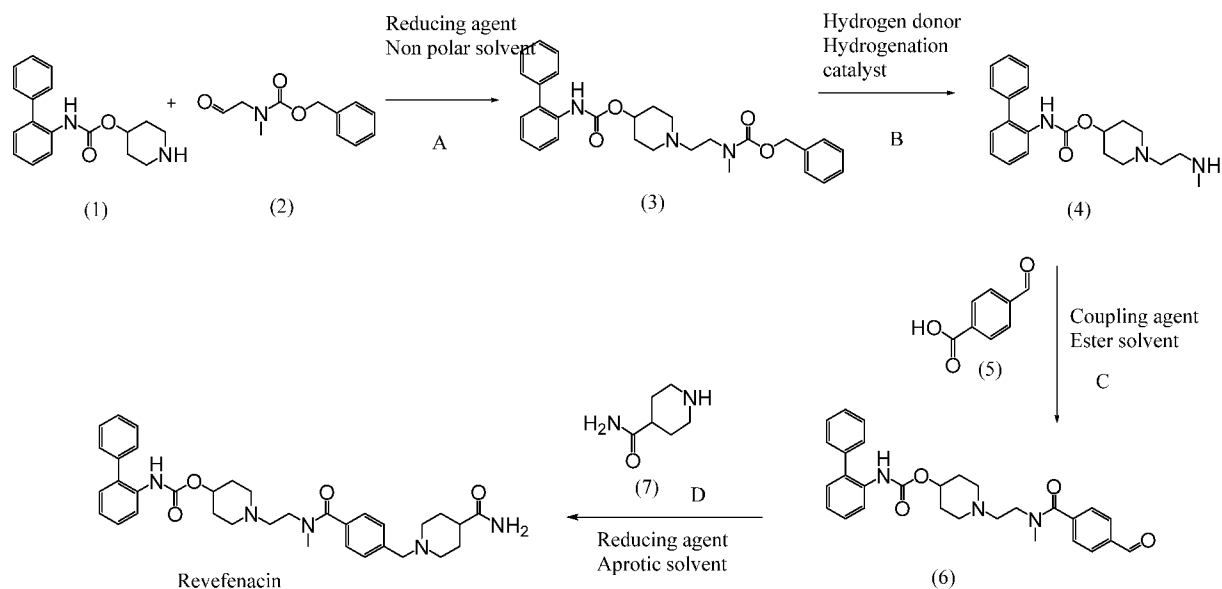
The present invention also provides a method of treating a disease state prevented, ameliorated or eliminated by the administration of a long-acting muscarinic antagonists (LAMA) in a patient in need of such treatment, which method comprises administering to the patient a therapeutically effective amount of Revefenacin of formula (I) or salt thereof prepared according to the present invention, substantially as hereinbefore described.

Still another aspect of the present invention is to provide pharmaceutical composition containing a therapeutically effective amount of Revefenacin of formula (I) or salt thereof, prepared according to the present invention, along with one or more pharmaceutically acceptable carriers, diluents and excipients. Such pharmaceutical compositions are well known to those skilled in the art and processes for preparing them are also well known.

Detailed Description of the Invention:

The present invention provides an improved process for the synthesis of Revefenacin of formula (I) or salt thereof, as depicted in reaction scheme 2 below:

Scheme 2



wherein the process is conducted with or without isolation of intermediate compounds of formula (3), (4) and (6).

In Step A, reductive amination involves combining compound of formula (1) with compound of formula (2) in the presence of a suitable reducing agent and suitable non polar solvent or solvent mixtures thereof to obtain compound of formula (3) or salt thereof

Suitable reducing agents are selected from metal hydride reagents and borane reducing agents. Exemplary metal hydride reagents include sodium triacetoxyborohydride, sodium borohydride, sodium cyanoborohydride, and the like. Exemplary borane reducing agents include borane dimethyl sulfide complex, 9-borabicyclo[3.3.1]nonane, borane 1, 2-bis(t-butylthio)ethane complex, borane t-butylamine complex, borane di(t-butyl)phosphine complex, borane-tetrahydrofuran complex, and the like.

In a preferred embodiment, the reducing agent is sodium triacetoxyborohydride.

Suitable non polar solvent is selected from halogenated solvents and hydrocarbon solvents.

Suitable halogenated solvents are selected from dichloromethane, dichloroethane, chloroform, carbon tetrachloride and the like.

Suitable hydrocarbon solvents are selected from toluene, xylene, n-hexane, n-heptane and the like.

In a preferred embodiment, the solvent is selected from dichloromethane and toluene.

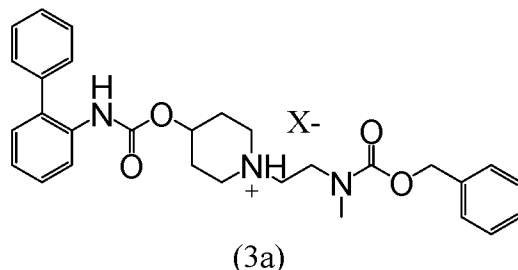
Prior art process is carried out in the MeTHF solvent, which generates more impurities. These impurities carry over to the subsequent steps for preparing Revefenacin, making it more difficult to isolate a pure product, hence the process is not viable industrially.

The use of the halogenated solvent or a mixture of halogenated solvents reduces the amount of impurities as compared to the prior art process. This forms one aspect of the present invention.

In the US '061, reductive amination is conducted at low temperature of -5°C to about 10°C . The process of present is carried out at $20-30^{\circ}\text{C}$. The reaction time is reduced drastically to 1-2 hours from few hours as reported earlier in the prior art. Thus makes the process of the present invention more suitable for industrial application. This forms second aspect of the present invention.

After completion of the reaction, compound (3) is typically isolated using conventional

procedures, such as extraction, evaporation and the like. Optionally, compound (3) base is isolated. The isolated compound (3) base may be converted to the salt. Alternatively, compound (3) base is not isolated before being converted to the salt. In an embodiment, the free base of the compound (3) may be optionally purified by converting into an acid addition salt of the formula (3a)



wherein X^- is an anion. The anion corresponds to the acid used. The acid used may be selected from inorganic acids and organic acids and the like.

Preferably, compound (3) is converted into carboxylic acid salt. Suitable carboxylic acids are selected from but not limited to fumaric acid, tartaric acid, oxalic acid, succinic acid, tartaric acid, acetic acid maleic acid, malic acid, adipic acid, formic acid, malonic acid, phthalic acid, terephthalic acid, citric acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, trifluoroacetic acid or ascorbic acid and the like.

Preferably, compound (3) is contacted with carboxylic acid in a suitable solvent at a temperature between 10-80°C by adding carboxylic acid as a solid or in aqueous solution or in an organic solution.

Preferably, 0.5 to 1.5 equivalents of carboxylic acid in relation to the starting compound (3) is used.

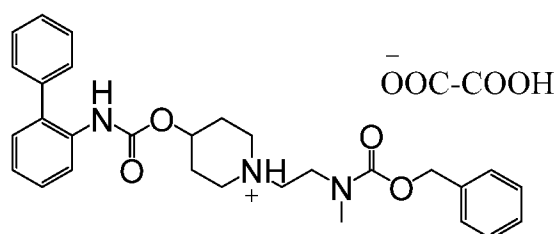
The reaction with the acid may be carried out in the presence of an organic solvent such as a ketone, ester, alcohol, aliphatic hydrocarbon or aromatic hydrocarbon, or mixtures thereof, preferably in a ketone and most preferably in acetone.

In an embodiment the compound (3) and the organic acid salt is in a molar ratio ranging from 1:0.5 to 1:1.

In a preferred embodiment, the compound (3) is converted into an oxalic acid addition salt.

In one embodiment salt is hemi oxalate salt. In another embodiment salt is mono oxalate salt.

In a preferred embodiment salt is mono oxalate of the formula (3b)



(3b)

Isolation of the intermediate compound (3) in solid form results advantages in that contributes to obtain a final product with a high purity without the need of repetitive or chromatographic purification. The handling, storage of these intermediate on larger scale and prolong time makes them suitable for industrial scale up.

Preferably, efficiency of the compound (3) increases from 84% to 95%. This forms third aspect of the present invention.

In Step B, salt compound (3a) or (3b) is first converted to compound of formula (3) and

Benzoyloxy carbonyl group is removed from compound of formula (3) under atmospheric pressure in the presence of a hydrogen donor and a hydrogenation catalyst.

Hydrogen donor is selected from not limited to of such as ammonium formate, formic acid, sodium formate, potassium formate. In a preferred embodiment, the hydrogen donor is ammonium formate.

Hydrogenation catalyst is Group VIII metal catalyst selected from palladium, platinum, Raney Ni, platinum oxide, platinum chloride and the like. In a preferred embodiment, the catalyst is palladium on Carbon.

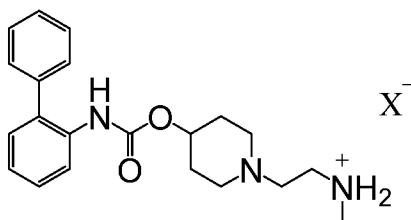
In an embodiment, the hydrogenation is carried out in the presence of an alcohol. The alcohol may be methanol or ethanol, for example denatured ethanol, isopropanol and the like.

More specifically, the hydrogenation processes in the prior arts US '789 and US '061 use hydrogen gas which is purged in either ethanol or a mixture of methanol-MeTHF, in a sealed vessel for about 3 hours. The use of atmospheric reaction conditions make the process of the present invention more suitable for industrial application. This forms one aspect of the present invention.

In an embodiment, the hydrogenation reaction takes place over a period of time ranging from about 30 minutes to about 5 hours, preferably from about 1 hour to about 1.5 hours. Most preferably, the reaction takes place over a period of time of about 1 hour. In US '789 and US '061, the reaction time is 3 hours. Thus, the use of ammonium formate reduces debenzylation time from 3 hours to 1 hour. This forms second aspect of the present invention.

After completion of the reaction, compound (4) is typically isolated using conventional procedures, such as extraction, evaporation and the like. Optionally, compound (4) base is isolated. The isolated compound (4) base may be converted to the salt. Alternatively, compound (4) base is not isolated before being converted to the salt.

In an embodiment, the free base of the compound (4) may be optionally purified by converting into an acid addition salt of the formula (4a)



(4a)

wherein X^- is an anion. The anion corresponds to the acid used. The acid used may be selected from inorganic acids and organic acids and the like.

Preferably, compound (4) is converted into carboxylic acid salt. Suitable carboxylic acids are selected from but not limited to fumaric acid, tartaric acid, oxalic acid, succinic, acetic acid, tartaric acid maleic acid, malic acid, adipic acid, formic acid, malonic acid, phthalic acid, terephthalic acid, citric acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, trifluoroacetic acid or ascorbic acid and the like.

Preferably, compound (4) is contacted with carboxylic acid in a suitable solvent at a temperature between 10-80°C by adding carboxylic acid as a solid or in aqueous solution or in an organic solution.

Preferably, 0.5 to 1.5 equivalents of carboxylic acid in relation to the starting compound (4) is used.

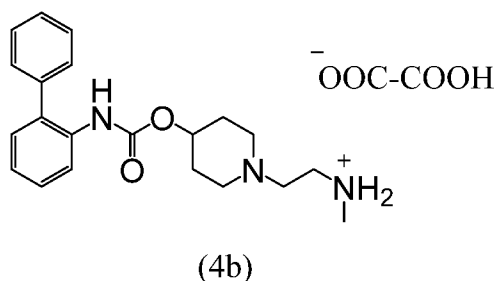
The reaction with the acid may be carried out in the presence of an organic solvent such as a ketone, ester, alcohol, aliphatic hydrocarbon or aromatic hydrocarbon, or mixtures thereof, preferably in an ester and most preferably in ethyl acetate.

In an embodiment the compound (4) and the organic acid salt is in a molar ratio ranging from 1:0.5 to 1:1.

In a preferred embodiment, the compound (4) is converted into an oxalic acid addition salt.

In one embodiment salt is hemi oxalate salt. In another embodiment salt is mono oxalate salt.

In a preferred embodiment salt is mono oxalate of the formula (4b)



Prior art teaches isolation of the compound (4) in three steps from methyl t-butyl ether and needs to be further purified in IPA to yield 65% of compound (4). Whereas by the process of the present invention, debenzylation in ammonium formate and isolation as a salt increases efficiency by 78%. This forms third aspect of the present invention.

In Step C, salt compound (4a) or (4b) is first converted to compound of formula (4) and compound of formula (4) is coupled with compound of formula (5) in the presence of suitable coupling reagent and a suitable inert ester solvent to obtain amide compound of formula (6).

Common coupling reagents also include, but are not limited to, phosphorous oxychloride (POCl_3); Oxyma; COMU; carbodiimides such as carbonyldiimidazole (CDI); N-N'-dicyclohexylcarbodiimide (DCC), and 1-ethyl-3-(3'-dimethylaminopropyl) carbodiimide (EDCI). The carbodiimides may be used in conjunction with additives such as dimethylaminopyridine (DMAP) or 1-hydroxybenzotriazole (HOBt). Amide coupling reagents also include amininum

and phosphonium based reagents, such as N-[(dimethylamino)-1H-1,2,3-triazolo [4,5-b]pyridine-1-ylmethylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HATU), N-[(1H-benzotriazol-1-yl)(dimethylamino)methylene]-N-methylmethanaminium hexafluorophosphate N-oxide (HBTU); (2-(6-chloro-1H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU); benzotriazol-1-yloxytris(dimethylamino)phosphonium hexafluorophosphate (BOP), and benzotriazol-1-yl-N-oxytris(pyrrolidino)phosphonium hexafluorophosphate (PyBOP). The triazine-based coupling agent, include the group consisting of 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), 2-chloro-4,6-dimethoxy-1,3,5-triazine (CDMT), 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM Cl), tetrafluoroborate (DMTMM BF₄) and hexafluorophosphate (DMTMM PF₆). A preferred coupling agent is a triazine-based coupling agent. In preferred embodiments, the coupling agent is DMTMM.

Coupling conditions may include a solvent such as a (C₁-C₆)alkyl (C₁-C₆)ester, such as ethyl acetate, isopropyl acetate or isobutyl acetate or mixtures thereof. In preferred embodiments, the solvent is ethyl acetate.

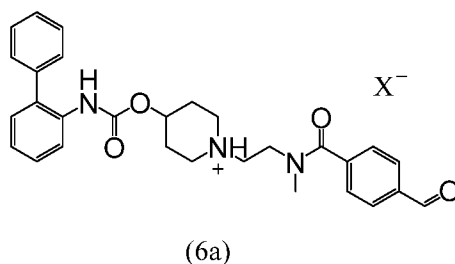
In an embodiment, the coupling reaction takes place over a period of time ranging from about 1 hour to about 10 hours, preferably from about 2 hours to about 5 hours. Most preferably, the reaction takes place over a period of time of about 2 hours to about 3 hours.

The advantage of these solvents is that, the reaction time is reduced drastically to 2 to 3 hours from overnight stirring as reported earlier in the prior art. This forms one aspect of the present invention.

After completion of the reaction, compound (6) is typically isolated using conventional procedures, such as extraction, evaporation and the like. Preferably compound (6) is isolated as a free base.

Optionally, the isolated compound (6) base may be converted to the salt. Alternatively, compound (6) base is not isolated before being converted to the salt.

In an embodiment, the free base of the compound (6) may be optionally purified by converting into an acid addition salt of the formula (6a)



wherein X^- is an anion. The anion corresponds to the acid used. The acid used may be selected from inorganic acids and organic acids and the like.

Preferably, compound (6) is converted into carboxylic acid salt. Suitable carboxylic acids are selected from but not limited to fumaric acid, tartaric acid, oxalic acid, maleic acid, malic acid, adipic acid, formic acid, malonic acid, phthalic acid, terephthalic acid, citric acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, trifluoroacetic acid or ascorbic acid and the like.

Preferably, compound (6) is contacted with carboxylic acid in a suitable solvent at a temperature between 10-80°C by adding carboxylic acid as a solid or in aqueous solution or in an organic solution.

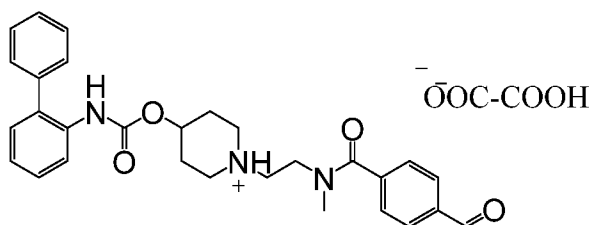
Preferably, 0.5 to 1.5 equivalents of carboxylic acid in relation to the starting compound (6) is used.

The reaction with the acid may be carried out in the presence of an organic solvent such as a ketone, ester, alcohol, aliphatic hydrocarbon or aromatic hydrocarbon, or mixtures thereof, preferably in an ester and most preferably in ethyl acetate.

In a preferred embodiment, the compound (6) is converted into an oxalic acid addition salt.

In one embodiment salt is hemi oxalate salt. In another embodiment salt is mono oxalate salt.

In a preferred embodiment salt is mono oxalate of the formula (6b)



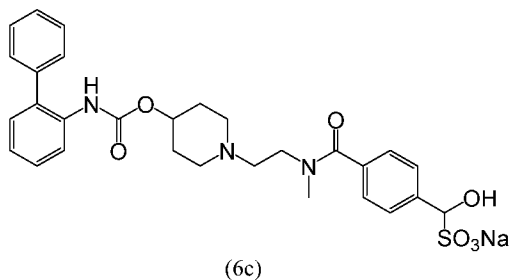
(6b)

Prior art teaches coupling reaction in MeTHF. The solvent employed not only increases reaction hours but after completion of the reaction additional solvent such as acetonitrile is added before isolation of the compound (6). Further, the resulting solution was concentrated under reduced pressure and the residue was hold at room temperature for 3 days, and then used directly for the next step. Thus prior art process is cumbersome and not suitable for the industrial scale up.

In the process of the present invention, not only the reaction hours are reduced but by

isolation of the intermediate compound (6) in the solid form results advantages in that contributes to obtain a final product with a high purity without the need of repetitive crystallization or chromatographic purification. The handling, storage of these intermediate on larger scale and prolong time makes them suitable for industrial scale up. This forms second aspect of the present invention.

Compound (6) may be optionally purified by forming aldehyde -bisulfite adduct of formula (6c).



By combining the use of a miscible organic solvent with saturated sodium bisulfite, aldehyde compound (6) can be successfully transformed into charged bisulfite adducts of formula (6c) that can then be separated from other organic components of a mixture by the introduction of an immiscible organic layer. The bisulfite addition reaction can be reversed by basification of the aqueous layer, allowing for the re-isolation of the aldehyde compound (6). The process not only improves the stability of the aldehyde, but also removes all organic impurities. This forms third aspect of the present invention.

Further, efficiency of the compound (6) increases to 75 to 77%. This forms fourth aspect of the present invention.

In Step D, reductive amination of compound of formula (6) with compound of formula (7) is carried out in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures.

Optionally, salt compound (6a) or (6b) is first converted to compound of formula (6) and then reductive amination of compound of formula (6) with compound of formula (7) is carried out in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures.

Suitable reducing agents are selected from metal hydride reagents and borane reducing agents. Exemplary metal hydride reagents include sodium triacetoxyborohydride, sodium borohydride, sodium cyanoborohydride, and the

like. Exemplary borane reducing agents include borane dimethyl sulfide complex, 9-borabicyclo[3.3.1]nonane, borane 1, 2-bis(t-butylthio)ethane complex, borane t-butylamine complex, borane di(t-butyl)phosphine complex, borane-tetrahydrofuran complex, and the like.

In a preferred embodiment, the reducing agent is sodium triacetoxyborohydride.

Suitable aprotic solvent is selected from dimethylformamide, dimethylsulfoxide, dimethyl acetamide tetrahydrofuran, acetonitrile, acetone, 2-methyl THF, MDC and the like.

In a preferred embodiment, the aprotic solvent is selected from dimethylformamide and dimethylsulfoxide.

In the prior art, reductive amination is carried out in alcoholic solvent. When low molecular weight alcoholic solvents are used, azeotropic distillation needs to carry out repetitively to remove the water prior to the addition of reducing agent. Thus making process time consuming, lengthy and tedious on the industrial scale.

The use of aprotic solvents not only reduces reaction time drastically to 1 hour from 2 hours, but also reduces the amount of impurities as compared to the prior art process. This forms one aspect of the present invention.

Further, due to the high boiling aprotic solvent, azeotropic distillation is avoided. This forms second aspect of the present invention.

The reductive reaction is preferably conducted at 20-25°C for about 1 hour.

After completion of the reaction, reaction mass is treated with an acid for example acetic acid, hydrochloric acid and the like and washed with water immiscible solvents. Solvents are capable of removing the organic impurities. The aqueous

layer is then treated with a base. Revefenacin base (I) may be isolated as a free solid by extraction, distillation, filtration and/or crystallization. The acid base purification technique removes both water miscible and immiscible impurities.

Alternatively, after completion of the reaction, reaction mass is quenched in a mixture of a saturated bicarbonate solution and non polar solvents for example MDC, EDC, ethyl acetate, toluene, xylene and the like. Revefenacin base (I) may be isolated as a solid by partition, extraction, washing, concentration/distillation, filtration and/or crystallization.

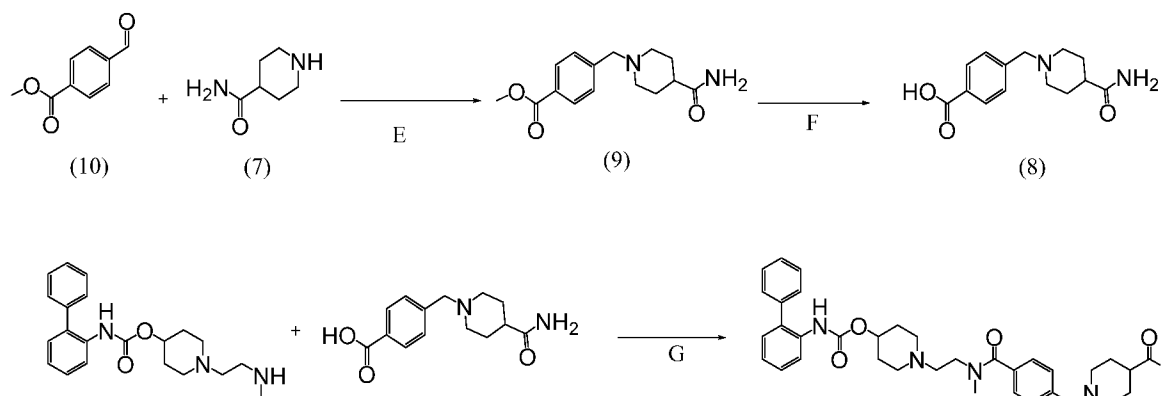
The crystalline compound can be isolated from the reaction mixture by any conventional means such as precipitation, concentration, centrifugation, drying, and the like.

The advantage of the process of the present invention is :

- a. Reduces reaction hours
- b. Simplifies work up process
- c. Isolation of intermediates in the salt form increases purity and minimizes carry over impurities in the next step. Thus helps to obtain a final product with a high purity without the need of repetitive crystallization or chromatographic purification.
- d. Improves efficiency at each stage as compared to prior art process.
- e. Improves overall efficiency from 39% to 50 %.

The present invention further provides an alternative novel process for the synthesis of Revefenacin of formula (I) or salt thereof, as depicted in reaction scheme 3 below:

Scheme 3



The compound of Formula (8) and (9) are hitherto unreported intermediates useful in the process for the preparation of Revefenacin as described herein.

In Step E, reductive amination of compound of formula (10) with compound of formula (7) is carried out in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures.

The reaction conditions such as reagents, solvents and temperature shall be same as described above under reductive amination.

In Step F, compound of formula (9) is hydrolyzed in the presence of a suitable base and solvent.

The ester hydrolysis reaction may be carried out by means of various ester hydrolysis reactions known in the art.

In a preferred embodiment, hydrolysis is carried out in the aqueous solution of an organic and inorganic base.

The base is preferably selected from the group comprising of alkali metal hydroxide such as sodium hydroxide, potassium hydroxide, calcium hydroxide, strontium hydroxide, barium hydroxide or lithium hydroxide; alkali metal

carbonates such as sodium carbonate, cesium carbonate, potassium carbonate, lithium carbonate, sodium hydrogen carbonate or potassium hydrogen carbonate; alkali metal bicarbonates such as sodium bicarbonate, cesium bicarbonate or potassium bicarbonate; alkali metal alkoxides such as sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, sodium t-butoxide or potassium t-butoxide; alkali metal phosphates such as sodium hydrogen phosphate or potassium hydrogen phosphate; amine bases such as triethylamine, diisopropylamine, tripropyl amine, tributyl amine, or cyclohexyl dimethyl amine; aromatic amines such as pyridine, and lutidine; an alkali metal amides such as sodium amide, lithium diisopropylamide, sodium hexamethyldisilazide, potassium hexamethyldisilazide, lithium hexamethyldisilazide, or lithium diethylamide; an alkali metal hydrides such as sodium hydride or potassium hydride; alkyllithiums such as BuLi and N-methylpiperidine, N-methylpyrrolidine, N-methylmorpholine, or 1,8-diazabicyclo[5.4.0]undec-7-ene and the like.

A suitable inert organic solvent for use in a process according to the present invention can be selected from but are not limited to C1-C4 alcoholic solvent such as methanol, ethanol, n-propanol, isopropanol, or n-butanol, isobutanol, t-butanol and the like.

The reaction is preferably carried out at a temperature of about -5°C to about reflux temperature of the solvent used, preferably about 0°C to about 60°C, more preferably about 20°C to about 40°C; for about 30 minutes to about to about 5 hours, preferably about 1 hour to about 3 hours, most preferably about 1 hour to about 2 hours.

After completion of the reaction, reaction mass is neutralized with an acid for example hydrochloric acid, acetic acid, sulfuric acid and the like. Compound of formula (8) may be isolated as a solid by extraction, distillation and/or filtration.

In Step G, compound of formula (4) is coupled with compound of formula (8) in the presence of suitable coupling reagent and a suitable inert ester solvent to obtain Revefenacin base (I).

The reaction conditions such as reagents, solvents and temperature shall be same as described above under coupling reaction.

In an embodiment, the coupling reaction takes place over a period of time ranging from about 1 hour to about 10 hours, preferably from about 2 hours to about 5 hours. Most preferably, the reaction takes place over a period of time of about 3 hours.

After completion of the reaction, reaction mass is quenched in a saturated bicarbonate solution and Revefenacin base (I) may be isolated as a solid by extraction, seeding, distillation, or filtration.

Revefenacin base obtained by the processes of the present invention or by any prior art process may be optionally purified in a suitable solvent. Preferably, efficiency of Revefenacin base increases from 72% to 80%.

Another embodiment of the present invention relates to substantially pure Revefenacin having a purity of greater than 99.8%, wherein substantially pure Revefenacin contains the process related impurities collectively below 0.2% area percentage by HPLC and meeting the ICH guidelines.

As used herein, the term "substantially pure" refers to Revefenacin of formula (I) or salt having no greater than about 0.3% by weight of total impurities. Frequently, the Revefenacin of formula (I) or salt of the invention will have no greater than about 0.2% by weight of total impurities. The impurity contents described herein relate only to the total of Revefenacin of formula (I) or salt and related compound impurities, as determined by high performance liquid chromatography ("HPLC"), and any residual solvent impurities.

Another embodiment of the present invention related to a process for the preparation of substantially pure Revefenacin of formula (I) or salt thereof having a purity of greater than 99.8% comprising the steps of :

- a. Stirring Revefenacin of formula (I) in a suitable sterile solvent;
- b. Adjusting the pH to 6.2 to 6.4 with a buffer;
- c. Stirring for sufficient time;
- d. Isolating the solids; and
- e. Drying the solids.

A suitable sterile solvent comprises water.

Typically, pH of the reaction mass is adjusted with buffer. Typical buffers are pharmaceutically acceptable buffers. In one aspect the one or more buffer comprises acid. In one aspect the one or more acid comprises acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butanoic acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentanepropionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, Ethylenediaminetetraacetic acid (EDTA), formic acid, fumaric acid, glyceric acid, glycine, gly-gly, glycerophosphoric acid, gluco heptanoic acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalenesulfonic acid, naphthilic acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, pyruvic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosylic acid, undecylenic acid, MES, bis-tris methane, ADA, ACES, bis-tris propane, PIPES, MOPSO, cholamine chloride, MOPS, and combinations thereof, or salts thereof.

In one aspect, the buffer comprises one or more of acetate, phosphate, sulfate, carbonate, formate, propionate, butanoate, lactate, glycine, maleate, pyruvate, citrate, aconitate, isocitrate, α -ketoglutarate, succinate, fumarate, malate, oxaloacetate, aspartate, glutamate, tris(hydroxymethyl)aminomethane (tromethamine), combinations thereof, or salts thereof. In one aspect, the buffer is acetate, borate, citrate, phosphate, or succinate. In one aspect, the buffer is acetate. In one aspect, the buffer is borate. In one aspect, the buffer is citrate. In one aspect, the buffer is phosphate. In one aspect, the buffer is succinate.

In one aspect, the pH adjustment is conducted at elevated temperature. In another aspect pH adjustment is conducted at about -5°C to about 100°C . In another aspect, pH adjustment is conducted at about 0°C to about 75°C . In another aspect, pH adjustment is conducted at about 5°C to about 50°C .

The reaction mass is preferably stirred at a temperature of about -5°C to about reflux temperature of the solvent used, preferably about 0°C to about 75°C , more preferably about 5°C to about 50°C ; for about 20 minutes to about 5 hours, preferably about 30 minutes to about 3 hours, most preferably about 1 hour to about 2 hours.

Revefenacin base (I) may be isolated as a solid by filtration.

The drying may be done in a vacuum oven at a temperature of about 30°C to about 70°C . Preferably, drying is performed at a temperature of about 35°C to about 60°C , more preferably about 40°C to about 50°C . Preferably, drying is performed for about 1 hour to about 24 hours, more preferably, for about 2 to about 20 hours, most preferably about 3 hours to about 15 hours.

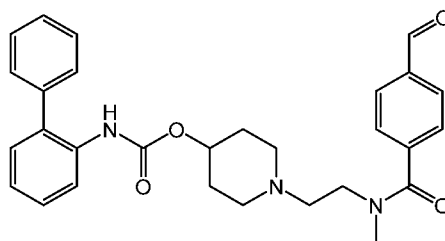
Process of the present invention is advantages over prior art process.

Revefenacin is a novel biphenyl carbamate tertiary amine. Presence of two tertiary amine groups make Revefenacin basic in nature. It has observed that during drying

of the API, level of impurity increases. Further, the isolated API was also found to be unstable even at 2°C to 8°C storage condition.

The possible impurities may be formed in the synthesis of Revefenacin are as follows:

RFC 4-formyl biphenyl carbamate, (Impurity A)



Impurity A

The decomposition of the API during storage and increase in the impurity level of RFC 4-formyl biphenyl carbamate was indicating that the product degrades at higher basic pH, whereas at highly acidic pH of < 6, API dissolves.

By treating the API with a buffer at pH between 6.2 to 6.4, the isolated API was found to be more stable as compared to API isolated without pH treatment. This forms one aspect of the invention.

There was no increase in the impurity level during drying and storage when API was stabilized at pH between 6.2 to 6.4 with an acid, preferably citric acid. This forms another aspect of the invention.

Preferably, Revefenacin of formula (I) or salt obtained by the process of the present invention contains less than about 0.15% of RFC 4-formyl biphenyl carbamate (Impurity A). More preferably, Revefenacin of formula (I) or salt obtained by the process of the present invention contains less than about 0.05% of RFC 4-formyl biphenyl carbamate (Impurity A).

Thus, Revefenacin obtained by the process of the present invention has been found to be highly stable in terms of hygroscopicity, chemical purity and good dissolution properties after ten months of storage. This forms yet another aspect of the invention.

While emphasis has been placed herein on the specific steps of the preferred process, it will be appreciated that many steps can be made and that many changes can be made in the preferred steps without departing from the principles of the invention. These and other changes in the preferred steps of the invention will be apparent to those skilled in the art from the disclosure herein, whereby it is to be distinctly understood that the foregoing descriptive matter is to be interpreted merely as illustrative of the invention and not as a limitation.

The details of the invention given in the examples which are provided below are for illustration only and therefore these examples should not be construed to limit the scope of the invention.

Examples:

Example 1: Preparation of compound of formula (3) and oxalate salt (3b)

Compound (1) (100g, 0.337 moles 1.0 eq) and compound (2) (83.9 g, 0.405 moles, 1.2 eq) were charged in 1500 ml MDC at 20-25°C and stirred for 1 hour. The reaction mass was cooled to 0-5°C and sodium triacetoxyborohydride (179g, 0.845 moles 2.5 eq) was added. The temperature was raised to 20-25°C and the reaction mass was stirred further for 2 hours. Charged 5% sodium bicarbonate solution (1500 mL). The organic layer was separated, and washed with water (500 ml). The solvent was removed under reduced pressure.

The residue was stirred in acetone (1000 ml) and heated to 50-55°C. Oxalic acid (50 g, 0.393 moles 1.16 eq) was added and the reaction mass was cooled to 20-

25°C. The solids were isolated by filtration and dried at 40-45°C to yield the title compound (3b) (180 g, 95.6%).

HPLC purity >99.0%

Example 2: Preparation of compound of formula (4) and oxalate salt (4b)

Oxalate salt (3b) (100g, 0.173 moles 1.0 eq) and 5% sodium bicarbonate solution (1000 ml) were stirred in MDC (500 ml) at 20-25°C for 30 mins. The organic layer was separated, washed with water (500 ml) and concentrated under reduced pressure to yield free base of compound (3).

The compound (3) was dissolved in methanol (400 ml). Charged ammonium formate (43.72 g, 0.693 moles 4.0 eq) and 10% palladium on carbon (5g). The reaction mass heated to 32-38°C for 1 hour and cooled to 20-25°C. Charged 5% sodium bicarbonate solution (300 ml). The reaction mass was filtered and the filtrate was concentrated under reduced pressure. The residue was stirred in MDC (500ml) and water (200 ml). The organic layer was separated and washed with water (500ml). The solvent was removed under reduced pressure.

The residue was stirred in ethyl acetate (1000 ml) and heated to 75-80°C. Oxalic acid (23.2 g, 0.257 moles 1.45 eq) was added and the reaction mass was cooled to 20-25°C. The solids were isolated by filtration and dried at 40-45°C to yield the title compound (4b) (60 g, 78%).

HPLC purity > 98.0%

Example 3: Preparation of compound of formula (6) and oxalate salt (6b)

Oxalate salt (4b) (100g, 0.225 moles, 1.0 eq) and 5% sodium bicarbonate solution (1000 ml) were stirred in MDC (500 ml) at 20-25°C for 30 mins. The organic layer was separated, washed with water (500 ml) and concentrated under reduced pressure to yield free base of compound (4).

The compound (4) was dissolved in ethyl acetate (500 ml). Compound (5) (33.85g, 0.225 moles, 1.0 eq) and DMTMM (68.6 g, 0.248 moles 1.1 eq) were stirred in ethyl acetate (1000 ml) for 30 mins at 20-25°C. To this reaction mass was added solution of compound (4) in ethyl acetate. The reaction mass was stirred at 20-25°C for 3 hours and then quenched in 1000 ml 5% sodium bicarbonate solution (1000 ml) and stir at 20-25°C for 15 mins. The organic layer was separated and washed with water (500ml). The solvent was removed under reduced pressure.

The residue was stirred in ethyl acetate (1200 ml) and heated to 70-75°C. Oxalic acid (23 g, 0.255 moles, 1.14 eq) was added and the reaction mass was cooled to 20-25°C. The solids were isolated by filtration and dried at 40-45°C to yield the title compound (6b) (98 g, 76.7%).

HPLC purity > 95.0%

Example 4: Preparation of Revefenacin (1)

Oxalate salt (6b) (100g, 0.174 moles, 1.0 eq) and 5% sodium bicarbonate solution (1000 ml) were stirred in MDC (500 ml) at 20-25°C for 30 mins. The organic layer was separated, washed with water (500 ml) and concentrated under reduced pressure to yield free base of compound (6).

Compound (6) (100g, 0.205 moles, 1.0 eq) and Compound (7) (66g, 0.514 moles, 2.5 eq) were stirred in DMF (500 ml) at room temperature. To the reaction mass was added sodium triacetoxyborohydride (153 g, 0.72 moles, 3.5 eq). The reaction mass was stirred for 1 hour at 20-25°C and quenched in a mixture of 5% sodium bicarbonate solution (1000 ml) and MDC (500 ml). Stirred for 15 mins, organic layer was separated and washed with water. The solvent was removed under reduced pressure and the residue was stirred in acetonitrile (600 ml). The solution was heated to 50-55°C for 15-20 mins and then cooled to 20-25°C. The reaction mass was further stirred for 4 hours at 20-25°C. The solids were isolated by

filtration, washed with acetonitrile (200 ml) and dried under vacuum at 40-45°C to yield Revefenacin (100g, 80%). HPLC purity > 99.0%

Example 5: Preparation of Revefenacin (1)

Compound (6) (100g, 0.205 moles, 1.0 eq) and Compound (7) (66g, 0.514 moles, 2.5 eq) were stirred in DMF (500 ml) at room temperature. To the reaction mass was added sodium triacetoxy borohydride (153 g, 0.72 moles, 3.5 eq). The reaction mass was stirred for 1 hour at 20-25°C and quenched in a mixture of 5% sodium bicarbonate solution (1000 ml) and MDC (500 ml). Stirred for 15 mins, organic layer was separated and washed with water. The solvent was removed under reduced pressure and the residue was stirred in acetone (600 ml). The solution was heated to 50-55°C for 15-20 mins and then cooled to 20-25°C. The reaction mass was further stirred for 4 hours at 20-25°C. The solids were isolated by filtration, washed

with acetone (200 ml) and dried under vacuum at 40-45°C to yield Revefenacin (100g, 80%).

HPLC purity > 99.0%

Example 6: Preparation of compound of formula (9)

Compound (10) (100g, 0.609 moles, 1.0 eq) and Compound (7) (195g, 1.52 moles, 2.5 eq) were stirred in DMF (500 ml) at room temperature. To the reaction mass was added sodium triacetoxyborohydride (452 g, 1.63 moles, 2.7 eq). The reaction mass was stirred for 1 hour at 20-25°C and quenched in a mixture of 5% sodium bicarbonate solution (1000 ml) and MDC (500 ml). Stirred for 15 mins, organic layer was separated and washed with water. The solvent was removed under reduced pressure to yield the title compound (100g, 60%).

HPLC purity > 95.0%

Example 7: Preparation of compound of formula (8)

To a stirred solution of compound (9) (100g, 0.362 moles, 1.0 eq) in methanol (500 ml) was added 5% sodium hydroxide solution (200 ml). The reaction mass was stirred for 1 hour at 20-25°C and neutralized with acetic acid. The solvent was removed under reduced pressure at 25-30°C. The residue was stirred in methanol (500 ml) for 1 hour at 20-25°C. The solid were isolated by filtration and dried under vacuum at 40-45°C to yield the title compound (65g, 70%)

Example 8: Preparation of Revefenacin (1)

Oxalate salt (4b) (100g, 0.225 moles, 1.0 eq) and 5% sodium bicarbonate solution (1000 ml) were stirred in MDC (500 ml) at 20-25°C for 30 mins. The organic layer was separated, washed with water (500 ml) and concentrated under reduced pressure to yield free base of compound (4).

The compound (4) was dissolved in ethyl acetate (500 ml). Compound (9) (62.1 g, 0.225 moles, 1.0 eq) and DMTMM (68.8 g, 0.24 moles 1.1 eq) were stirred in ethyl acetate (1000 ml) for 30 mins at 20-25°C. To this reaction mass was added solution of compound (4) in ethyl acetate. The reaction mass was stirred at 20-25°C for 3 hours and then quenched in 1000 ml 5% sodium bicarbonate solution (1000 ml) and stir at 20-25°C for 15 mins. The organic layer was separated and washed with water (500ml). The solvent was removed under reduced pressure and the residue was stirred in acetonitrile (600 ml). The solution was heated to 50-55°C for 15-20 mins and then cooled to 20-25°C. The reaction mass was further stirred for 4 hours at 20-25°C. The solids were isolated by filtration, washed with acetonitrile (200 ml) and dried under vacuum at 40-45°C to yield Revefenacin (100g, 75%).

HPLC purity > 99.0%

Example 9: Preparation of compound of formula (3) and oxalate salt (3b)

Compound (1) (100g, 0.337 moles 1.0 eq) and compound (2) (83.9 g, 0.405 moles, 1.2 eq) were charged in 1000 ml Toluene at 20-25°C and stirred for 2 hours. The reaction mass was cooled to 15-20°C and sodium triacetoxyborohydride (143g, 0.674 moles 2.0 eq) was added. The temperature was raised to 20-25°C and the reaction mass was stirred further for 1 hour. Charged 5% sodium bicarbonate solution (1500 mL). The organic layer was separated and washed with water (500 ml). The solvent was removed under reduced pressure.

The residue was stirred in methanol (900 ml) and heated to 45-50°C. Oxalic acid (51.5 g, 0.393 moles 1.2 eq) was added, heated to 55-60°C to get clear solution. The reaction mass was cooled to 20-25°C and stirred for 2 hours. The solids were isolated by filtration and dried at 25-30°C to yield the title compound (3b) (180 g, 95.6%). HPLC purity > 99.0%

Compound (3b) (180 g) was stirred in methanol (1000 ml). The slurry was heated to reflux for 30 mins, cooled to 20-25°C and stirred for 2 hours. The solids were isolated by filtration and dried under reduced pressure at 40-45°C to yield the title compound (3b) (150 g, 81%).

HPLC purity > 99.0%

Example 10: Preparation of compound of formula (4)

Oxalate salt (3b) (100g, 0.173 moles 1.0 eq) and 5% sodium bicarbonate solution (1000 ml) were stirred in toluene (1000 ml) at 40-45°C for 30 mins and then cooled to 20-25°C. The organic layer was separated, washed with water (500 ml) and concentrated under reduced pressure below 45°C to yield free base of compound (3).

The compound (3) was dissolved in methanol (500 ml) at 20-25°C. Charged ammonium formate (43.6 g, 0.865 moles 4.0 eq) and 10% palladium on carbon (7g). The reaction mass stirred at 20-25°C for 1 hour. The reaction mass was filtered.

Charged 5% sodium bicarbonate solution (500 ml) and MDC (1000 ml). The reaction mass was stirred for 15 mins at 20-25°C. The organic layer was separated, and aqueous layer was extracted in MDC (500 ml). Combined organic layers and washed with water (500ml). The solvent was removed under reduced pressure below 45°C. Charged ethyl acetate (400 ml), stirred and solvent was removed under reduced pressure below 45°C till 3 volumes (300 ml). The reaction mass was cooled to 20-25°C and used directly in the next step.

Example 11: Preparation of compound of formula (6)

Compound (5) (26g, 0.173 moles, 1.0 eq) and DMTMM (55.1 g, 0.199 moles, 1.15 eq) were stirred in ethyl acetate (500 ml) for 30 mins at 20-25°C under inert atmosphere. To this reaction mass was added solution of compound (4) in ethyl acetate. The reaction mass was stirred at 20-25°C for 2 hours and then quenched in 5% sodium bicarbonate solution (1000 ml) and stirred at 20-25°C for 15 mins. The organic layer was separated, and aqueous layer was extracted in ethyl acetate (300 ml). Combined organic layers and washed with water (500ml). The solvent was removed under reduced pressure below 45°C till 1 volume. Charged IPA (400ml) and the reaction mass heated to reflux for 15-20 mins to get clear solution. The solution was cooled to 20-25°C and stirred further for 2 hours. The solids were isolated by filtration, washed with IPA (100 ml) and dried under vacuum at 40-45°C to yield the title compound (6) (60 g). HPLC purity > 95.0%

Example 12: Purification of compound of formula (6)

Stirred compound (6) (60 g) in a mixture of ethyl acetate (600 ml) and methanol (300 ml) at 20-25°C to get clear solution. Charged 3.0% sodium bisulfite solution (600 ml) and stirred further for 30 mins at 20-25°C. The layers were separated. The aqueous layer was washed with ethyl acetate (2X 600 ml). Charged ethyl acetate (600 ml) and 3.5% sodium carbonate solution (60 ml) to the aqueous layer. Stirred and separated layers. The aqueous layer was extracted in ethyl acetate (60 ml).

Combined organic layers and washed with water (60ml). The solvent was removed under reduced pressure below 45°C. Charged IPA (120 ml), stirred and solvent was removed under reduced pressure below 45°C till 1 volume. Charged IPA (240 ml) and reaction mass was heated to reflux for 15-20 mins to get clear solution. The solution was cooled to 20-25°C and stirred further for 2 hours. The solids were isolated by filtration, washed with IPA (60 ml) and dried under vacuum at 40-45°C to yield the title compound (6) (50 g). HPLC purity > 99.0%

Example 13: Preparation of Revefenacin (1)

Compound (6) (100g, 0.205 moles, 1.0 eq) and Compound (7) (66g, 0.514 moles, 2.5 eq) were stirred in DMSO (600 ml) at room temperature under inert atmosphere. To the reaction mass was added sodium triacetoxymethylborohydride (153 g, 0.72 moles, 3.5 eq). The reaction mass was stirred for 2 hours at 20-25°C. After completion of the reaction, the reaction mass was cooled to 15-20°C. Charged water (1500 ml), MDC (1000 ml) and acetic acid (150 ml) and stirred for 30 minutes. Aqueous layer was separated and washed with MDC (2X 1000 ml). To the aqueous layer was added MDC (1000 ml). The pH of the reaction mass was adjusted to 8.5 to 9.0 with 25% sodium hydroxide solution (~ 250 ml solution). Stirred for 15 minutes, organic layer was separated and washed with water (2x1000 ml). The organic layer was clarified and concentrated under vacuum below 45°C. The residue was stirred in acetone (600 ml). The solution was heated to 40-45°C for 15-20 mins and then cooled to 20-25°C. The reaction mass was further stirred for 2 hours at 20-25°C. The solids were isolated by filtration, washed with acetone (2x100 ml) and dried under vacuum at 40-45°C to yield Revefenacin (85g).

HPLC purity > 99.8%

Example 14: Purification of Revefenacin (1)

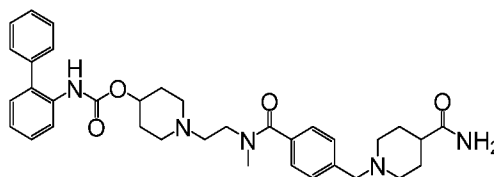
Stirred Revefenacin (85g) in 10 volumes of sterile water at 20-25°C for 15 minutes. Prepared 1% citric acid solution by dissolving citric acid (0.85 g) in 85 ml sterile

water. The pH of the reaction was adjusted to 6.2 to 6.4 with 1% aqueous citric acid solution. Stirred at 20-25°C for 15 minutes and pH rechecked. The reaction mass further stirred at 20-25°C for 1 hour. The solids were isolated by filtration, washed with 2 volumes of sterile water and dried for 24 hours under vacuum at 40-45°C to yield Revefenacin (78-80g). HPLC purity > 99.8%

The product was packed in a virgin food grade double clear LDPE bags, tightly closed or heat sealed by purging nitrogen to prevent the contact with air and moisture. The packed polythene bag was further enclosed in a black polybag and TLHB bags, hermetically sealed and placed in a fiber drum. The pack was stored at 2 to 8°C.

We Claims,

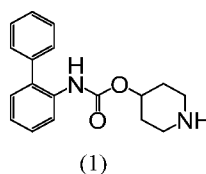
1. A process for the synthesis of Revefenacin of formula (I) or salt thereof,



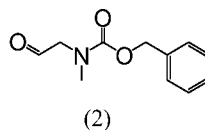
Revefenacin

the process comprising the steps of:

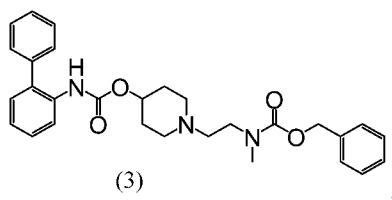
- (A) reductive amination of compound of formula (1)



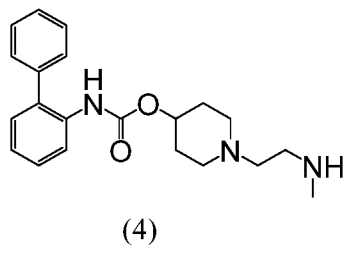
with compound of formula (2)



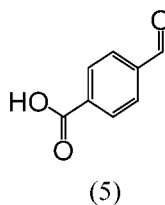
in the presence of a reducing agent and non polar solvent or solvent mixtures thereof to obtain compound of formula (3) or salt thereof



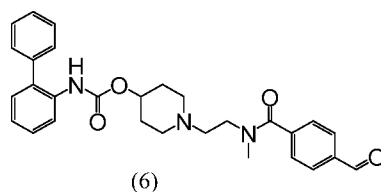
- (B) removing benzyloxy carbonyl group from compound of formula (3) under atmospheric pressure in the presence of a hydrogen donor and a hydrogenation catalyst, to obtain compound of formula (4) or salt thereof.



(C) coupling compound of formula (4) with compound of formula (5)

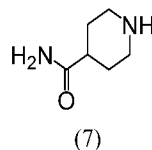


in the presence of a coupling reagent and an inert ester solvent to obtain amide compound of formula (6) or salt thereof



and ;

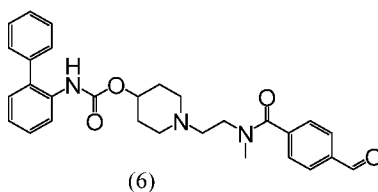
(D) reductive amination of compound of formula (6) with compound of formula (7)



in the presence of a reducing agent and aprotic solvent/s or mixtures thereof to obtain Revefenacin of formula (I) or salt thereof.

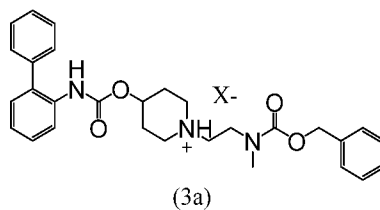
2. The process of claim 1, wherein the reducing agent in step (A) is selected from metal hydride reagents and borane reducing agents.
3. The process of claim 2, wherein the metal hydride reducing agent is sodium triacetoxo borohydride.
4. The process of claim 1, wherein non polar solvent in step (A) is selected from halogenated solvents and hydrocarbon solvents.
5. The process of claim 1, wherein step (A) is conducted at 20-30°C.

6. The process of claim 1, wherein the hydrogen donor in step (B) is selected from ammonium formate, formic acid, sodium formate, and potassium formate.
7. The process of claim 1, wherein the hydrogenation catalyst in step (B) is Group VIII metal catalyst.
8. The process of claim 1, wherein the coupling reagent in step (C) is 4-(4,6-dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride.
9. The process of claim 1, wherein the reducing agent in step (D) is selected from metal hydride reagents and borane reducing agents.
10. The process of claim 9, wherein the metal hydride reducing agent is sodium triacetoxy borohydride.
11. The process of claim 1, wherein steps (A), (B), (C) and (D) are conducted with or without isolation of intermediate compounds of formula (3), (4) and (6).
12. The process of claim 11, wherein compound of formula (6)

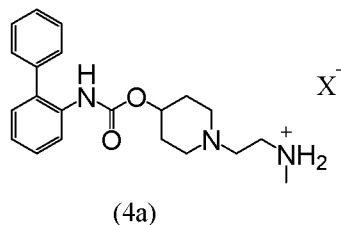


is isolated as a solid.

13. The process of claim 11, wherein compound (3) is isolated as an acid addition salt of the formula(3a)

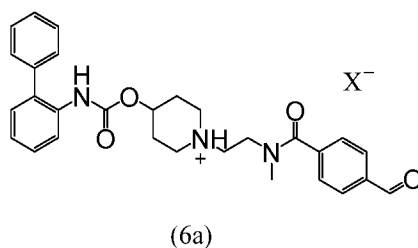


compound (4) is isolated as an acid addition salt of the formula (4a);



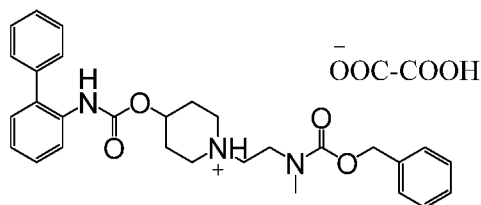
and;

compound (6) is isolated as an acid addition salt of the formula (6a)



wherein X^- is an anion;

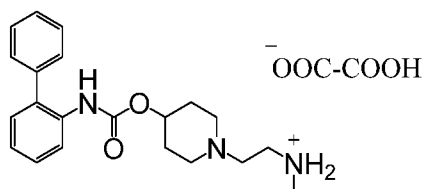
14. The acid addition salt according to claim 13, wherein anion corresponds to carboxylic acid selected from fumaric acid, tartaric acid, oxalic acid, succinic acid, tartaric acid, acetic acid maleic acid, malic acid, adipic acid, formic acid, malonic acid, phthalic acid, terephthalic acid, citric acid, methane sulfonic acid, ethane sulfonic acid, p-toluene sulfonic acid, trifluoroacetic acid or ascorbic acid and the like.
15. The acid addition salt of claim 13 or 14, wherein the acid is oxalic acid.
16. The acid addition salt of claim 15, wherein the compound (3) is compound of formula (3b)



(3b)

;

the compound (4) is compound of formula (4b)

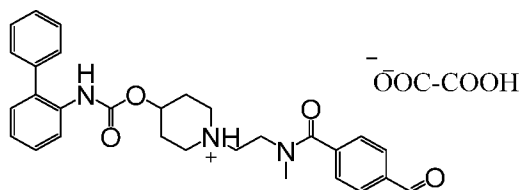


(4b)

;

and;

the compound (6) is compound of formula (6b)



(6b)

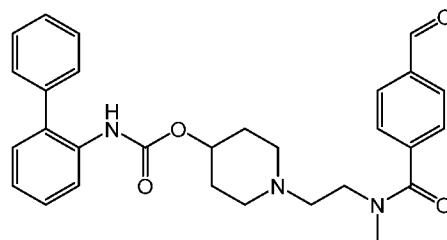
17. Substantially pure Revefenacin of formula (I) or salt thereof having a purity of greater than 99.8%.

18. A process for the preparation of substantially pure Revefenacin of formula (I) or salt thereof comprising the steps of :

- a. Stirring Revefenacin of formula (I) in a suitable sterile solvent;
- b. Adjusting the pH to 6.2 to 6.4 with a buffer;
- c. Stirring for sufficient time;
- d. Isolating the solids; and
- e. Drying the solids.

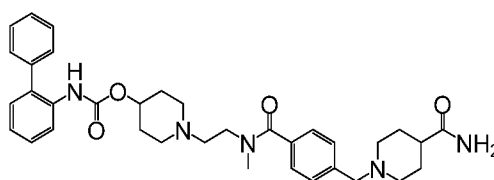
19. The process of claim 18, wherein the sterile solvent is water.

- 20.** The process of claim 18, wherein buffer comprises acid, selected from acetic acid, acetylsalicylic acid, adipic acid, alginic acid, ascorbic acid, aspartic acid, benzoic acid, benzenesulfonic acid, bisulfic acid, boric acid, butanoic acid, butyric acid, camphoric acid, camphorsulfonic acid, carbonic acid, citric acid, cyclopentanepropionic acid, digluconic acid, dodecylsulfic acid, ethanesulfonic acid, Ethylenediaminetetraacetic acid (EDTA), formic acid, fumaric acid, glyceric acid, glycine, gly-gly, glycerophosphoric acid, gluco heptanoic acid, gluconic acid, glutamic acid, glutaric acid, glycolic acid, hemisulfic acid, heptanoic acid, hexanoic acid, hippuric acid, hydrobromic acid, hydrochloric acid, hydroiodic acid, hydroxyethanesulfonic acid, lactic acid, maleic acid, malic acid, malonic acid, mandelic acid, methanesulfonic acid, mucic acid, naphthalenesulfonic acid, naphthilic acid, nicotinic acid, nitrous acid, oxalic acid, pelargonic, phosphoric acid, propionic acid, pyruvic acid, saccharin, salicylic acid, sorbic acid, succinic acid, sulfuric acid, tartaric acid, thiocyanic acid, thioglycolic acid, thiosulfuric acid, tosylic acid, undecylenic acid, MES, bis-tris methane, ADA, ACES, bis-tris propane, PIPES, MOPSO, cholamine chloride, MOPS, and combinations thereof, or salts thereof.
- 21.** The process of claim 20, wherein buffer comprises one or more of acetate, phosphate, sulfate, carbonate, formate, propionate, butanoate, lactate, glycine, maleate, pyruvate, citrate, aconitate, isocitrate, α -ketoglutarate, succinate, fumarate, malate, oxaloacetate, aspartate, glutamate, tris(hydroxymethyl)aminomethane (tromethamine), combinations thereof, or salts thereof.
- 22.** The process according to claim 18 to 21, wherein the Revefenacin of formula (I) or salt thereof contains less than about 0.05% of the RFC 4-formyl biphenyl carbamate (Impurity A)



Impurity A

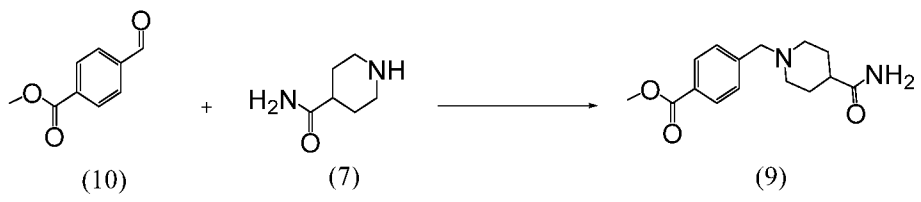
23. A process for the synthesis of Revefenacin of formula (I) or salt thereof,



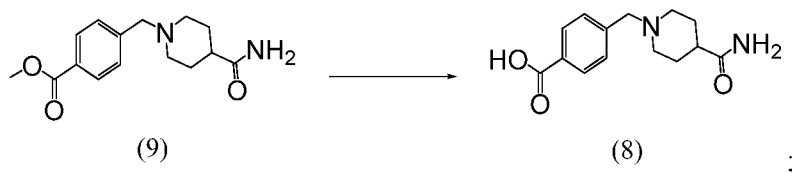
Revefenacin

the process comprising the steps of:

(E) reductive amination of compound of formula (10) with compound of formula (7) in the presence of a suitable reducing agent and suitable aprotic solvent/s or mixtures thereof to obtain compound of formula (9) or salt thereof

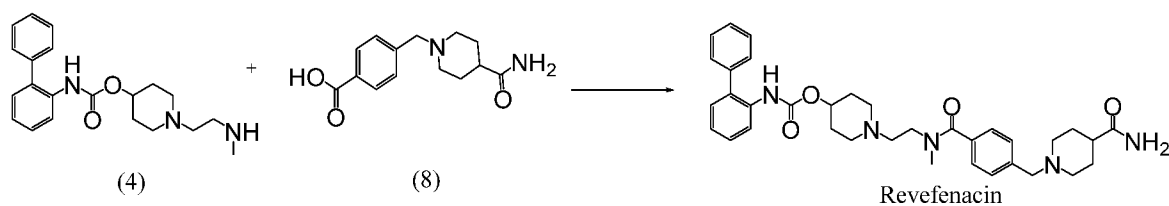


(F) hydrolyzing compound of formula (9) or salt thereof in the presence of a suitable base and suitable solvent/s or mixtures thereof to obtain compound of formula (8)



and;

(G) coupling of compound of formula (4) with compound of formula (8) in the presence of suitable coupling reagent and a suitable inert ester solvent and optionally converting Revefenacin of formula (I) to salt thereof



24. Novel intermediate compound of Formula (8).

25. Novel intermediate compound of Formula (9) or salt thereof.

26. A process substantially as herein described with reference to the examples.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IN2021/050859

A. CLASSIFICATION OF SUBJECT MATTER
C07D279/12 Version=2021.01

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)

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)

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.
Y	CN110526859A (SHANDONG BESTCOMM PHARMACEUTICAL CO LTD) 3 December 2019 (03-12-2019) whole document	1-26
Y	US20060281740A1 (THERAVANCE BIOPHARMA R&D IP LLC) 1 June 2010 (01-06-2010) whole document	1-26
Y	US20140121378A1 (THERAVANCE BIOPHARMA R&D IP LLC) 1 May 2014 (01-05-2014) whole document	1-26

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

* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "D" document cited by the applicant in the international application "E" earlier application or patent but published on or after the international filing date "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "&" document member of the same patent family
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Date of the actual completion of the international search

20-12-2021

Date of mailing of the international search report

20-12-2021

Name and mailing address of the ISA/

Indian Patent Office
Plot No.32, Sector 14, Dwarka, New Delhi-110075
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Authorized officer

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Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IN2021/050859

Citation	Pub.Date	Family	Pub.Date
US US20060281740 A1	01-06-2010	WO 2006138218 A1	28-12-2006
		EP 1893577 A1	05-03-2008
US 20140121378 A1	01-05-2014	WO 2012009166 A1	19-01-2012
		EP 2593429 A1	22-05-2013
		JP 2015127342 A	09-07-2015