(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
2 April 2015 (02.04.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/044965 A1

(51) International Patent Classification:
C07D 277/40 (2006.01)

(21) International Application Number:
PCT/IN2014/000637

(22) International Filing Date:
30 September 2014 (30.09.2014)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
3116/MUM/2013 30 September 2013 (30.09.2013) IN
826/MUM/2014 12 March 2014 (12.03.2014) IN

(71) Applicant: **MEGAFINE PHARMA (P) LTD.** [IN/IN]; 4th Floor, Sethna, 55, Maharshi Karve Road, Marine lines, Mumbai - 400 002, Maharashtra (IN).

(72) Inventors: **MATHAD, Vijayavitthal Thippannachar**; Flat no. 05, Nirman Classic, Behind HDFC Bank, Thatte, nagar, Gangapur Road, Nashik - 422007, Maharashtra, (IN). **DESHMUKH, Dattatray Gulabrao**; A/p- Dahigaon Bolka, Tal-Kopargaon, Dist-Ahmednagar, Pin code: 423603, Maharashtra (IN). **VARPE, Sagar Popat**; Plot No 24, Renuka Nagar, Kedgaon devi, Ahmednagar, Pin code - 414005, Maharashtra (IN). **NAVALE, Pravin Mahadu**; -A/p - Kanhur Pathar, Tal - Parner, Dist- Ahmednagar, Pin code: 414303 Maharashtra (IN).

(74) Agent: **Shilpa Gharve**; of LEGA SOLV, Unit No. 1309, 13th Floor, Ghanshyam Enclave, Next to Lalji Pada Police Chowki, Link Road, Kandivali (West), Mumbai - 400 067, Maharashtra (IN).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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

— *of inventorship (Rule 4.17(iv))*

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

(54) **Title**: A PROCESS FOR PREPARATION OF MIRABEGRON AND ALPHA CRYSTALLINE FORM THEREOF

(57) **Abstract**: An improved process for the preparation of Mirabegron of formula (I) where 4- nitrophenylethylamine of formula (III) or its acid addition salt of formula (IIIa) reacted with compound of formula (XII) in a solvent, optionally in presence of base and/or catalyst to obtain *(R)*-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII) followed by reducing *(R)*-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII) in a solvent to obtain *(R)*-2-[2'-(4-nitrophenyl)ethyl]amino]-l-phenylethanol of formula (XIV), optionally converting it into its acid addition salt of formula (XlVa); reducing *(R)*-2-[2'-(4- nitrophenyl)ethyl]amino]-l -phenylethanol of formula (XIV) or its acid addition salt of formula (XlVa) further in solvent to obtain *(R)*-2-[[2-(4-aminophenyl)ethyl]-amino]-l -phenylethanol of formula (XV) or its acid addition salt of formula (XVa) respectively; and reacting compound *(R)*- 2-[[2-(4-aminophenyl)ethyl]-amino]-l-phenylethanol of formula (XV) or its acid addition salt of compound of formula (XVa) with compound of formula (VII) in solvent, optionally in the presence of acid, and/or a catalyst to obtain Mirabegron of formula (I) which is further isolated as its a- crystalline form. The compound of formula (XIV) used in the foregoing process can also be prepared by reacting with a compound of formula (III) or acid addition salt of compound of formula (IIIa) in presence of a solvent, a catalyst and optionally in presence of a base to obtain compound of formula (XIV) optionally converting it into its acid addition salt of formula (XlVa); and the same is used in the above-referred process. The compound of formula (XV) used in the foregoing process can also be prepared by reacting a compound of formula (III) or its acid addition salt of formula (IIIa) with a compound of formula (XVI) in a solvent, optionally in presence of a base, optionally in presence of a catalyst to obtain compound of formula (XVII); and optionally isolate the compound of formula (XVII) followed by reducing the compound of formula (XVII) using reducing agent, in a solvent, optionally in presence of a base, optionally in presence of a catalyst to obtain compound of formula (XV) which is further used in the above- referred process for the preparation of Mirabegron of formula (I) and its a-crystalline form. Another additional single-pot process for preparation of Mirabegron of formula (I) is disclosed, wherein compound of formula (XV) or its acid addition salt of formula (XVa) reacted with compound of formula (XVIII) in presence of a solvent and oxidizing agent, optionally in presence of base, optionally in presence of a catalyst to obtain Mirabegron of formula (I).

WO 2015/044965 A1

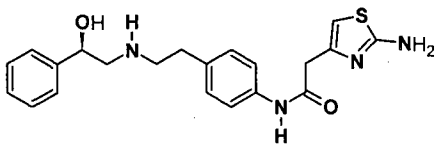
TITLE OF THE INVENTION

A PROCESS FOR PREPARATION OF MIRABEGRON AND ALPHA CRYSTALLINE FORM THEREOF

This application claims priority from Indian Patent Application No. 3116/MUM/2013 and 826/MUM/2014 filed on 30th September 2013 and 12th March 2014 respectively.

FIELD OF THE INVENTION

The present invention relates to an improved processes for the preparation of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl) amino] ethyl] acetanilide, Mirabegron of formula (I);



FORMULA (I)

and its alpha (α) crystalline form.

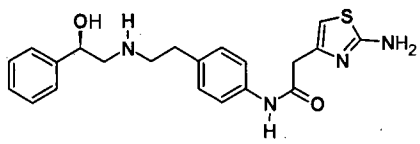
The present invention also relates to a novel processes for the preparation of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl) amino] ethyl] acetanilide, Mirabegron of formula (I).

The present invention also relates to a novel and efficient process for the preparation of alpha (α) crystalline form of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl) amino] ethyl] acetanilide, Mirabegron of formula (I).

The process of the present invention is commercially viable and industrially advantageous for the preparation of Mirabegron and α-crystalline form thereof wherein, the said process substantially eliminates the impurities formed during the preparation of Mirabegron and α-crystalline form thereof.

BACKGROUND OF THE INVENTION

(R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethyl)amino]ethyl] acetanilide (henceforth "Mirabegron") also known as MYRBETRIQ™, has a CAS number of 223673-61-8, a molecular formula of $C_{21}H_{24}N_4O_2S$ and the following structure:

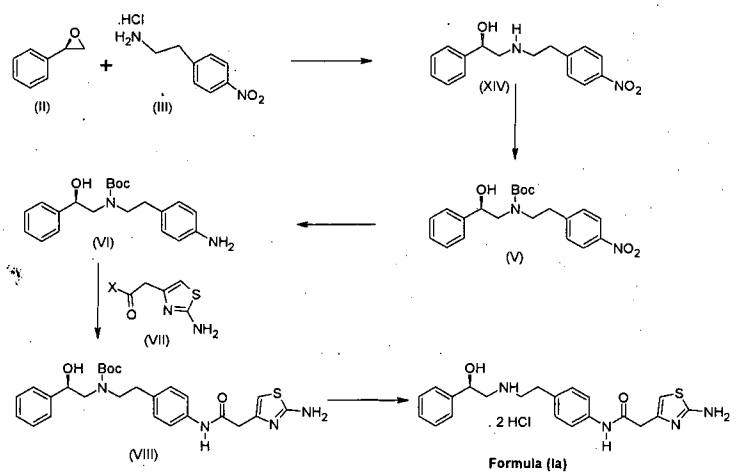


FORMULA (I)

Mirabegron, an orally active beta-3 adrenergic receptor agonist is used for the treatment of urinary frequency, urinary incontinence, or urgency associated with overactive bladder.

U.S. Patent No. 6,346,532 (henceforth US'532) discloses Mirabegron of formula (I) or salt and its derivatives and process for the preparation of the same.

Example 41 of US'532 describes preparation of Mirabegron dihydrochloride of formula (Ia), wherein 4-nitrophenylethylamine hydrochloride of formula (III) is reacted with R-styrene oxide of formula (II) to provide (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol of formula (XIV) (Reference example 1). Subsequently amino group of compound of formula (XIV) is protected by the amino protecting groups like tert-butoxycarbonyl to obtain compound of formula (V) (Reference example 2). Nitro group of compound (V) is reduced to amino group to obtain compound of formula (VI) using Palladium-carbon (Reference example 3). The compound of formula (VI) is coupled with compound of formula of (VII) to form amide of formula (VIII). Amino protecting group i.e. tert-butoxycarbonyl, is removed by using hydrogen chloride in ethyl acetate to form dihydrochloride salt of Mirabegron of formula (Ia) as represented in Scheme I.

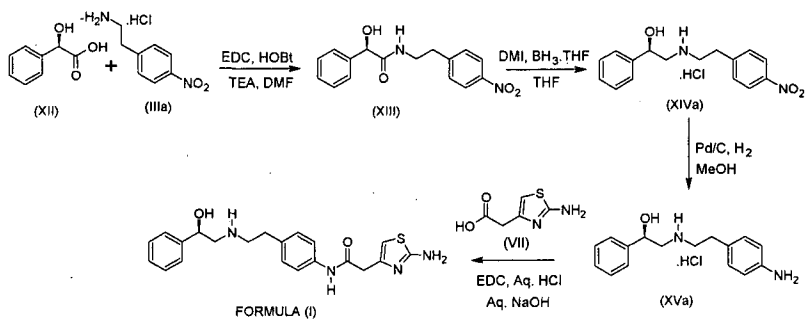


SCHEME - I

Thus, example 41 of US'532 does not discuss or exemplify the process for preparation of Mirabegron free base. Some of the limitations of the above synthetic routes are;

i. The protection and deprotection steps makes the synthesis lengthy and contributes to poor atom economy;
ii. The yields of styrene oxide ring opening are low (20-30 %);
iii. R-styrene oxide employed in the process is expensive and thereby adds to the economics of the process; and
iv. Use of column chromatography for the purification of final compound is not feasible at industrial scale.

US 7,342,117 (henceforth US'117) discloses two crystalline forms namely, α- and beta (β)-crystalline forms of Mirabegron and the process for its preparation. The process for making Mirabegron as per US'117 involves reaction of (*R*)-mandelic acid of formula (XII) with 4-nitrophenylethylamine hydrochloride of Formula (IIIa) in presence of triethylamine, EDC and HOBt to yield compound of formula (XIII), which is further reacted with borane-tetrahydrofuran solution,1, 3-dimethyl-2-imidazolidinone in tetrahydrofuran, to obtain compound of formula (XIVa). Compound of formula (XIVa) was reduced in presence of palladium-carbon under hydrogen atmosphere in methanol to obtain compound of formula (XVa). The compound of formula (XVa) was then reacted with 2-aminothiazole-4-yl-acetic acid (VII) in presence of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) in acidic medium to obtain Mirabegron of formula (I) as a clear solution (Scheme II). The acidic reaction mass was basified with sodium hydroxide solution to obtain the crystals of Mirabegron of Formula (I), which were filtered and dried. The process according to above always provides β-crystalline form.



SCHEME - II

The methods of making the α-crystalline form always uses β-crystalline form as a starting material wherein the process comprises dissolving the β-crystals in water and ethanol mixture at 80°C, seeding the solution with α-crystals, filtering and drying to obtain the α-crystalline form of Mirabegron of Formula (I).

Subsequently, patent application WO2012156998 discloses some more processes for making the α-crystalline form by dissolving the Mirabegron solid in a solvent or solvent mixture at elevated temperature, cooling the solution or adding an anti solvent to obtain the Mirabegron of Formula (I).

Some of the limitations of US'117 are as follows:

i. Process is not user-friendly, as there is difficulty in handling and storing of highly flammable and moisture sensitive reagents such as borane-tetrahydrofuran complex;
ii. The disclosed process involves use of 1-ethyl-3-(3-dimethylaminoprpyl) carbodiimide HCl (EDC.HCl) and hydroxybenzotriazole (HOBt) in step-1 which are expensive;
iii. Process is not cost-efficient as it employs addition of expensive borane-tetrahydrofuran complex and 1,3-dimethyl-2-imidazolidinone reagents in step-2, and catalyst like palladium for nitro reduction in step-3; and
iv. Preparation of α-crystalline form always involve reprocessing of β-crystalline form in separate step, use of seed material, reproducibility, use of limited solvents, which does not result in an industrially feasible process for making the α-crystalline form.

Hence, there is a need for a solution that overcomes the above stated limitations by developing process for preparation of Mirabegron and its α-crystalline form which is simple, reproducible, economic and industrially feasible.

Thus the present invention provides an improved as well as novel process for preparation of Mirabegron and α-crystalline form thereof; which is economic, efficient, eco-friendly, and eliminate extensive laborious work-up as well as other stated limitations.

OBJECTS OF THE PRESENT INVENTION

The primary object of the present invention is to provide economic, efficient, eco-friendly and production friendly processes for preparation of Mirabegron of formula (I) and α-crystalline form thereof.

Another object of the present invention is to eliminate handling and storage of highly flammable and expensive borane-tetrahydrofuran complex.

Yet another object of the present invention is to provide processes for preparation of Mirabegron of formula (I) and α-crystalline form thereof, wherein the obtained Mirabegron is substantially free from impurities thereby eliminating the subsequent purification steps.

Yet, another object of the present invention is to provide a simple, efficient and production friendly process for preparation of stable α-crystalline form of Mirabegron of formula (I) which is substantially free from impurities.

BRIEF DESCRIPTION OF DRAWINGS

Figure 1 of the present invention illustrates X-ray powder diffraction (XRD) pattern of α-crystalline form of Mirabegron of formula (I), prepared according to any of the examples 1 to 9.

Figure 2 of the present invention illustrates Infrared spectrum (IR) of α-crystalline form of Mirabegron of formula (I), prepared according to any of the examples 1 to 9.

DETAILED DESCRIPTION OF THE INVENTION

Before the present invention is described, it is to be understood that this invention is not limited to particular methodologies and materials described, as these may vary as per the person skilled in the art. It is also to be understood that the terminology used in the description is for the

purpose of describing the particular embodiments only, and is not intended to limit the scope of the present invention.

Before the present invention is described, it is to be understood that unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Further, it is to be understood that the present invention is not limited to the methodologies and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described, as these may vary within the specification indicated. Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims. Further the terms disclosed embodiments are merely exemplary methods of the invention, which may be embodied in various forms.

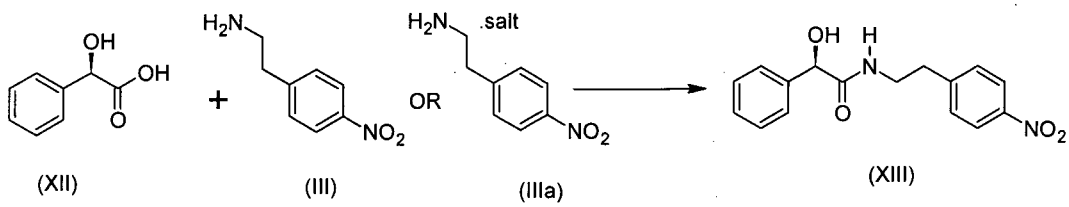
A term herein "reflux temperature" means the temperature at which the solvent or the solvent system refluxes or boils at atmospheric pressure.

The term "substantially free of" in reference to a composition, as used herein, means that an absent substance cannot be detected in the composition by methods known to those skilled in the art at the time of the filing of this application.

In one of the embodiments of the invention, there is provided an improved process for the preparation of α-crystalline form of Mirabegron of formula (I),

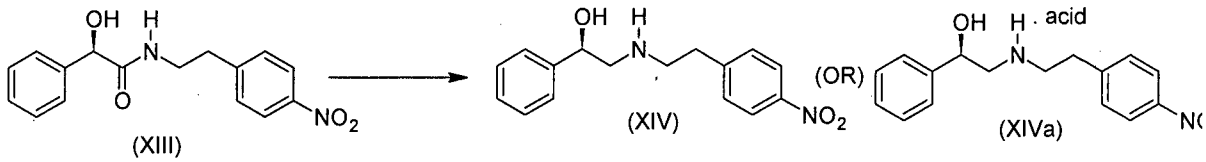
said process comprising;

a) reacting 4-nitrophenylethylamine of formula (III) or its acid addition salt of formula (IIIa) with compound of formula (XII) in presence of a solvent and reagent, optionally in presence of base, and/or catalyst to obtain (*R*)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII);

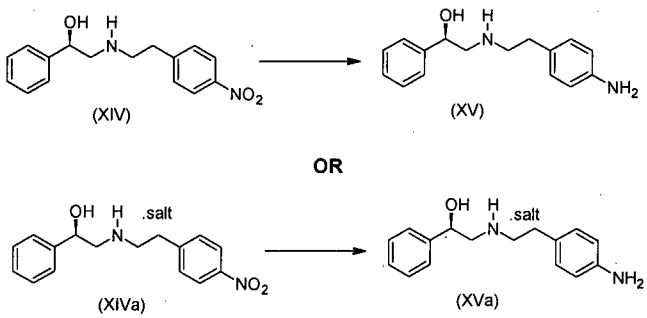


(XII) (III) (IIIa) (XIII)

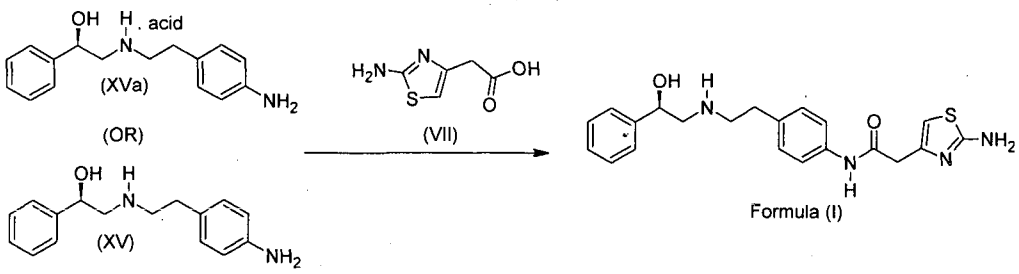
b) reducing (*R*)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII) in presence of reducing agent and a solvent to obtain (*R*)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol of formula (XIV), optionally converting it into its acid addition salt of formula (XIVa);



c) reducing (*R*)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol of formula (XIV) or its acid addition salt of formula (XIVa) in solvent to obtain (*R*)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol of formula (XV) or its acid addition salt of formula (XVa) respectively;



d) reacting compound (*R*)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol of formula (XV) or its acid addition salt of formula (XVa) obtained in the step (c) with compound of formula (VII) in the presence of solvent, acid and a condensing agent, optionally in the presence of a catalyst to obtain Mirabegron of formula (I);



and

e) Isolating α-crystalline form of Mirabegron of formula (I) obtained in step (d) and optionally purifying by solvent crystallization.

The reagent used in steps (a) are selected from but not limited to borane reagents such as boric acid, phenyl boronic acid, trimethyl borate and the like; carbodiimide reagents such as N,N'-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminoprpyl)carbodiimide (EDC) or its salt; or imidazole reagents such as 1,1'-carbonyldiimidazole (CDI) and the like.

The solvent used in step (a) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The base used in step (a) of the present invention may be organic or inorganic base; organic bases selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but

not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like;

The catalyst used in step (a) of the present invention is selected from organic or inorganic catalyst or phase transfer catalyst.

The step (a) further comprises isolation of compound of formula (XIII);
the said process comprises the steps of:

i. treating the reaction mass of step (a) with water;
ii. extracting the aqueous layer of step (i) with first solvent;
iii. separating the organic layer of step (ii) followed by washing it with acid, base and brine;
iv. concentrating the organic layer of step (iii); and
v. adding second solvent to the step (iv) to obtain compound of formula (XIII).

The first solvent used in step (ii) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

The second solvent used in step (v) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as toluene, xylene and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane and the like; alcohols

such as methanol, ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; or mixtures thereof.

Optionally the compound of formula (XIII) as obtained can be further purified by conventional methods.

The reducing agent used in step (b) is selected from lithium aluminium hydride, sodium borohydride in presence of Iodine; or sodium borohydride in presence of acids, wherein acids are selected from but not limited sulfuric acid, acetic acid, trifluoroacetic acid, zinc chloride ($ZnCl_2$), cobalt chloride ($CoCl_2$); sodium borohydride and BF_3etherate; sodium borohydride and R_2SeX_2, where R is any alkyl and X is halide group; diborane solutions like BH_3:THF, BH_3:SMe_2, BH_3:NR_3 and the like.

The solvent used in step (b) is selected from C_2 to C_8 straight chain, branched chain or cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; nitriles such as acetonitrile and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; hexamethylphosphoroustriamide (HMPT); hexamethylphosphoramide (HMPA); or mixture thereof.

The step (b) further comprises isolation of the compound of formula (XIV) or its acid addition salt of compound of formula (XIVa);
said process comprises the steps of:

A. quenching the reaction mass of step (b) with alcoholic solvent and aqueous acid solution followed by addition of water;
B. concentrating the reaction mass, adding organic solvent followed by basifying the reaction mass;
C. separating the organic layer and washing the organic layer with aqueous solution of base;
D. acidifying the organic layer of step (C) to provide acid addition salt of compound of formula (XIVa) as a solid; and

E. filtering the solid and washing it with organic solvent followed by drying it to obtain pure compound of formula (XIVa) and optionally purifying the compound of (XIVa).

Optionally, concentrating the organic layer of step (C) and adding anti solvent to the concentrated organic layer to obtain free base compound of formula (XIV) and optionally purifying the compound of (XIV).

The alcoholic solvent used in step (A) is selected from methanol, ethanol, isopropanol and the like.

The aqueous acid solution used for quenching in step (A) is selected from hydrochloric acid, sulfuric acid and the like.

The organic solvent used in step (B) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptanes and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

The base used in step (B and C) for basification is organic or inorganic base. The base used in step (B and C) for basification is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

The acid used in step (D) for acidification is selected from organic or inorganic acids like hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, oxalic acid, isopropyl alcohol hydrochloride solution, ethyl acetate hydrochloride solution and the like.

The organic solvent used in step (E) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, and the like; or mixture thereof;

Purification of compound of formula (XIV) or (XIVa) comprise solvent mediated crystallization; the crystallization process involve providing the solution of compound of formula (XIV) or (XIVa) in an alcoholic solvent and adding an anti-solvents to provide the pure compound of formula (XIV) or (XIVa).

The alcoholic solvent used for purification of compound of formula (XIV) or (XIVa) is selected from methanol, ethanol, isopropanol and the like.

The anti-solvent used in purification of compound of formula (XIV) or (XIVa) is selected from aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The reduction step (c) can be carried out either by catalytic reduction, metallic reduction, or chemical reduction.

The catalytic reduction of step (c) is carried out in presence of catalyst selected from but not limited to palladium-carbon, palladium hydroxide-carbon, platinum oxide, rhodium on carbon, raney nickel and the like and in presence of hydrogen gas or hydrogen generating source such as but not limited to ammonium formate, hydrazine hydrate and the like.

The metallic reduction in the step (c) can be carried out by using metals such as but not limited to iron, zinc, tin, and the like in presence of acid and/or solvent.

The solvent used in the step (c) is selected from C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; C_2 to C_8 straight chain or cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl-tert-butyl and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The acid used in the metallic reduction of step (c) is selected from but not limited formic acid, acetic acid, hydrochloric acid and the like.
The chemical reduction in the step (c) can be carried out using but not limited to sodium dithionate.

The step (c) further comprises isolation of the compound of formula (XV) or its acid salts of compound of formula (XVa);
the said process comprises the steps of;

I. recovering the catalyst by filtering the reaction mass of step (c) and concentrating the organic layer;
II. adding solvent to the concentrated layer to obtain the solid; and
III. filtering and washing the solid to obtain compound of formula (XV) or (XVa).

The solvent used in step (II) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic

hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

Optionally, compound of formula (XV) or (XVa) obtained in step (III) can be purified with a solvent or solvent mixture; optionally by heating it at a temperature between room temperature to reflux temperature of the solvent.

Solvent or solvent mixtures used for the purification of compound of formula (XV) or (XVa) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The solvent used in step (d) is selected from water, alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; or a mixture thereof.

The acid used in step (d) is selected from hydrochloric acid, hydrobromic acid, sulfuric acid and the like.

The condensing agent used in the step (d) is selected from but not limited to N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or its acid addition salts, 1,1'-carbonyldiimidazole (CDI) and the like.

The catalyst used in step (d) is selected from organic catalyst, inorganic catalyst, or phase transfer catalyst.

Optionally, the catalyst used along with condensing agents is selected from hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), 4-dimethylaminopyridine (DMAP) and the like.

Optionally, the condensing agent used in step (d) can also selected from borane reagents selected from but not limited to phenyl boronic acid, boric acid, trimethyl borate and the like.

The isolation of α-crystals of Mirabegron of compound of Formula (I) of step (e) comprises;

ia. adding first solvent to the reaction mass of step (d);

iia. basifying the solution of step (ia) and optionally heating the reaction mixture;

iiia. separating the organic layer;

iva. extracting the aqueous layer with solvent, and combining the obtained organic layer with organic layer of step (iiia);

va. washing the combined organic layer with aqueous base followed by water, separating the organic layer and optionally distilling the organic layer; and

via. adding second solvent to organic layer of step (va) to obtain α-crystalline form of Mirabegron of compound of Formula (I).

Alternatively, the organic layer obtained in step (va) is cooled, filtered and dried to obtain α-crystalline form of Mirabegron of formula (I).

The first solvent used in step (ia) for extraction and solvent used in step (iva) for extraction is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; halogenated hydrocarbons such as dichloromethane, and the like; esters such as ethyl

acetate, methyl acetate, isopropyl acetate and the like; alcohols such as n-butanol and the like; ketones such as methyl isobutyl ketone (MIBK) and the like; ethers such as di-ethyl ether, di-isopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; cyclic ether such as 2-methyl tetrahydrofuran and the like; or mixtures thereof.

The base used step (iia) for basification and the base used in step (va) for washing is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

The second solvent used in step (via) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water or a mixture thereof.

The α-crystalline form of Mirabegron of formula (I) or its acid salt can be purified by the process known in the art like recrystallization, salt making and salt breaking process or by any other conventional purification process.

Mirabegron of formula (I) can be purified by providing solution in alcohols such as 2-propanol, n-butanol and the like; hydrocarbons such as hexane, n-heptane, toluene, xylene and the like; or mixture thereof; cooling the solution; filtering and drying the solid to obtain pure α-crystalline form of Mirabegron of formula (I).

The α-crystalline form of Mirabegron prepared by foregoing process has purity more than 99%; preferably more than 99.5% when determined by HPLC.

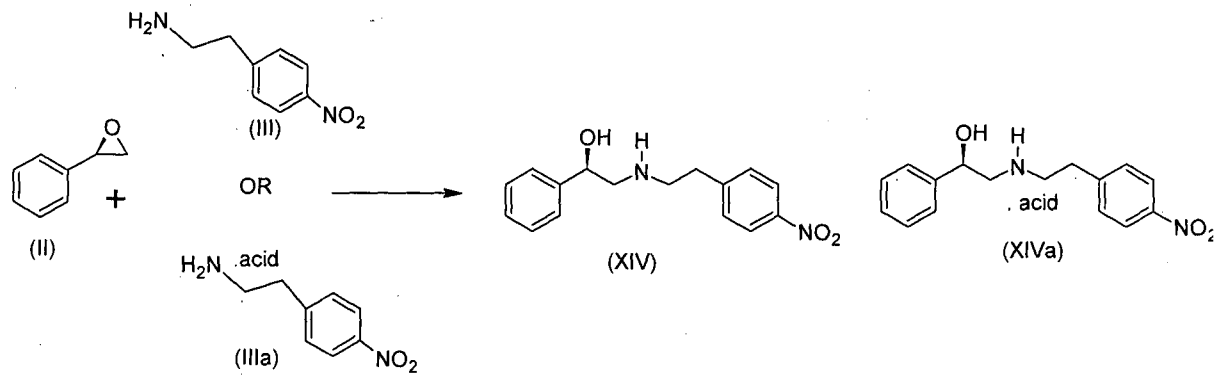
Optionally, Compound of formula (XIV), (XV) and Mirabegron of formula (I) can be converted to their corresponding acid addition salt of formula (XIVa), (XVa) and (Ia); wherein the acid addition salt may be mono, di- or tri- acid salt. The salts includes such as but not limited to acetate, hydrochloride, sulfate, oxalate, bromide, succinate, trifluoroacetate, lactate, malonate, glutarate, glutamate, citrate, ascorbate, camphor sulfonate, pamoate, pyruvate, maleate, tosylate, formate, tartarate, mesylate, oxalate, fumarate, phosphate, dimesylate, and the like.

The reduction reaction steps (b) and (c) can be optionally carried out in a single pot.

Compound of formula (XIV), (XV) and Mirabegron of formula (I) may be converted to their hydrates.

According to the present invention, the compound of formula (XIV) and (XIVa) used in the step (c) can be optionally obtained by;

(f) reacting a compound of formula (II) with a compound of formula (III) or its acid addition salt of compound of formula (IIIa) in presence of a solvent; optionally in presence of a base and/or catalyst to obtain compound of formula (XIV); and optionally converting it into its acid addition salt of formula (XIVa).



The solvent used in step (f) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water; ionic liquids; or a mixture thereof.

The base used in step (f) of the present invention may be organic or inorganic base; the organic bases such as but not limited 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like, pyrimidine, N,N-dimethylethyl amine and the like; tetra alkyl ammonium and phosphonium hydroxides; metal alkoxides and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.
The catalyst used in step (f) of the present invention is selected from organic, inorganic catalyst, or phase transfer catalyst optionally in the presence of acids like Lewis acid.

The phase transfer catalyst may be selected from tertiary alkyl ammonium halide such as tetra-butyl ammonium bromide (TBAB) and the like.

The step (f) further comprises isolation of the compound of formula (XIV) or its acid addition salt of compound of formula (XIVa);

the said process comprises the steps of:

ic. treating the reaction mass of step (f) with water;

iic. extracting the aqueous layer of step (ic) with an organic solvent;

iiic. separating the organic layer of step (iic) followed by washing it with base and brine;

ivc. concentrating the organic layer of step (iiic) to obtain the compound of formula (XIV); and

vc. optionally acidifying the organic layer obtained in step (ivc) to precipitate the acid addition salt of compound of formula (XIVa), filtering the precipitate, and washing it with organic solvent followed by drying it to obtain compound of formula (XIVa).

The organic solvent used in step (iic) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptanes and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as di-ethyl ether, di-isopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyl tetrahydrofuran and the like; or mixtures thereof.

The base used step (iiic) for washing is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

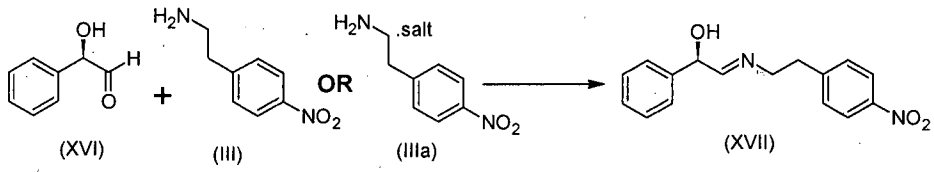
The acid used in step (vc) for acidification is selected from organic or inorganic acids like hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, oxalic acid, isopropyl alcohol hydrochloride solution, ethyl acetate hydrochloride solution and the like.

The organic solvent for washing used in step (vc) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptanes and the like; aromatic hydrocarbons such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as di-methyl ether, di-ethyl ether, di-isopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, 1,4-dioxane and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; chloroform; or mixture thereof

The compound of formula (XIV) or acid addition salt of compound of formula (XIVa) can be further purified by the methods known in the art like recrystallization, saltification, solvent purification and the like.

According to the present invention, the compound of formula (XV) and (XVa) used in the step (d) can be optionally obtained by;

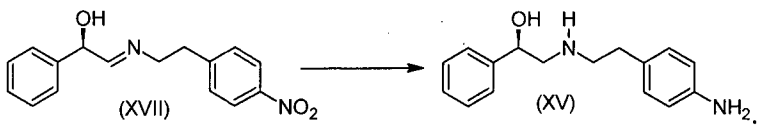
j) reacting a compound of formula (III) or its acid addition salt of formula (IIIa) with a compound of formula (XVI) in solvent, optionally in presence of a base, optionally in presence of a catalyst to obtain compound of formula (XVII); and optionally isolate the compound of formula (XVII);



(XVI) (III) (IIIa) (XVII)

and

k) reducing the compound of formula (XVII) or its acid addition salt in a solvent to obtain compound of formula (XV);



(XVII) (XV)

Step (j) can be carried out in presence of dehydrating agents or under azeotropic conditions.

The solvent used in step (j) is selected from C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; dimethylsulfoxide; nitriles such as acetonitrile; esters; C_2 to C_8 straight or substituted cyclic ethers such as tetrahydrofuran, 2-Methyl tetrahydrofuran and the like; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; chlorinated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; halogenated hydrocarbons; C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol, diols and triols and the like; water; or mixture thereof.

The base used in step (j) of the present invention may be organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like; pyrimidine; N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal Alkoxides; and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

The catalyst used in step (j) of the present invention is selected from organic, inorganic catalyst, or phase transfer catalyst. Organic or inorganic catalyst includes acid catalyst.

The compound of formula (XVII) can be isolated and optionally purified as per the techniques known in the art like recrystallization, re-saltification, solvent purification and the like.

The reduction step (k) can be carried out either by catalytic reduction, metallic reduction, or chemical reduction. The reduction step (k) can be alternatively done in two steps; imine reduction and nitro group reduction.

The catalytic reduction step (k) can be carried out in presence of a catalyst selected from but not limited to palladium-carbon, palladium hydroxide-carbon, platinum oxide, rhodium on carbon, raney nickel, charcoal and the like and in presence of hydrogen gas or hydrogen generating source such as but not limited to ammonium formate, hydrazine hydrate and the like.

The metallic reduction in step (k) can be carried out by using metals such as but not limited to iron, zinc, tin, and the like and in presence of acid such as formic acid, acetic acid, hydrochloric acid and the like and/or solvent.

The solvent used in step (k) is selected from C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol and the like; C_2 to C_8 straight or substituted cyclic ethers; ionic liquids; hexamethylphosphoroustriamide; hexamethylphosphoramide; water; ethylene glycol; esters; acid as a solvent; or mixture thereof.

The chemical reduction in step (k) can be carried out using but not limited to sodium dithionate.

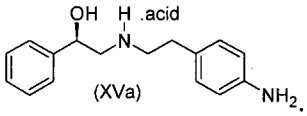
The step (k) further comprises isolation and purification of the compound of formula (XV); wherein the said process for isolation and purification comprises the steps of:

ig. filtering the reaction mass of step (k) followed by concentrating the organic layer obtained, adding a solvent to the concentrated layer, cooling, filtering the solid obtained, and washing with solvent to obtain compound of formula (XV);

iig. Optionally treating the compound of formula (XV) or its acid addition salt of formula (XVa) obtained in step (ig) in a solvent, adding an another solvent to it; and

iiig. followed by cooling, filtering the precipitate, washing the precipitate with solvent and drying it to obtain pure compound of formula (XV) or its acid addition salt of compound of formula (XVa).

The compound of formula (XV) can be converted to its acid addition salt of formula (XVa);



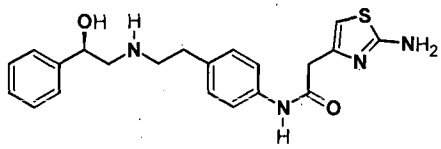
(XVa)

The solvent used in step (ig) for isolation of compound of formula (XV) or its acid addition salt of compound of formula (XVa) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like, sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The solvent, another solvent used in step (iig) and solvent used for washing in (iiig) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

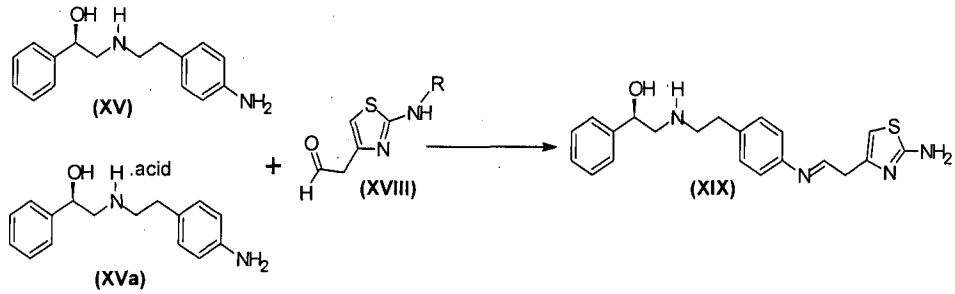
The compound of formula (XV) or its acid addition salt of formula (XVa) may be further purified by the process known in the art like recrystallization, re-saltification or by solvent purification.

According to yet another embodiment of the present invention, there is provided a process for preparation of Mirabegron of formula (I), wherein the said process comprising:



FORMULA (I)

l) reacting a compound of formula (XV) or its acid addition salt of formula (XVa) with a compound of formula (XVIII) in a solvent, optionally in presence of base, optionally in presence of a catalyst to obtain a compound of formula (XIX); and optionally isolate the compound of formula (XIX);



(XV) (XVIII) (XIX)

(XVa)

R = H, amino protecting group

m) oxidation of the compound of formula (XIX) obtained in step (m) using oxidizing agents, in presence of a solvent, optionally in presence of base, optionally in presence of a catalyst to obtain Mirabegron of formula (I);

(XIX) FORMULA (I)

and

n) Isolating and optionally purifying Mirabegron of formula (I) obtained in step (m).

The solvent used in step (l) is selected from C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol, diols and triols and the like; C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; dimethylsulfoxide; nitriles such as acetonitrile; esters; C_2 to C_8 straight or substituted cyclic ethers such as tetrahydrofuran, 2-Methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene,

heptane, pentane, cyclohexane and the like; chlorinated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; halogenated hydrocarbons; water; or mixture thereof.

The base used in step (l) of the present invention may be organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like, pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; metal alkoxides and the like; and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides; or liquor ammonia; and the like.

The catalyst used in step (l) of the present invention is selected from organic, inorganic catalyst, or phase transfer catalyst. Organic or inorganic catalyst includes acid catalyst.

The compound of formula (XIX) can also be isolated and purified as per the techniques known in the art like recrystallization, re-saltification, solvent purification and the like.

The oxidizing agent used in step (m) is selected from hydrogen peroxide; Dess-martin periodinate; peracids including but not limited to peracetic acid, perbenzoic acid, metachloroperbenzoic acid and the like; alkyl hydroperoxides such as but not limited to tertiary butyl hydrogen peroxide; silver iodide; copper iodide; and mixture thereof.

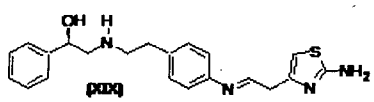
The solvent used in step (m) is selected from C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol, diols and triols and the like; C_3 to C_6 amides such as

dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; dimethylsulfoxide; nitriles such as acetonitrile; esters; C_2 to C_8 straight or substituted cyclic ethers such as tetrahydrofuran, 2-Methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; chlorinated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; halogenated hydrocarbons; water; or mixture thereof.

The base used in step (m) of the present invention may be organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, and the like; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; Metal alkoxides and the like; and inorganic bases such as but not limited to alkali metal carbonates such as potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides; or liquor ammonia; and the like.

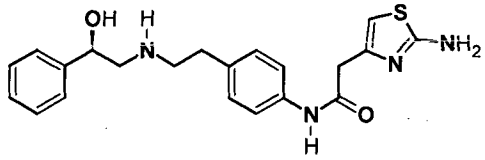
The catalyst used in step (m) of the present invention is selected from organic, inorganic catalyst, or phase transfer catalyst. Organic or inorganic catalyst includes acid catalyst.

According to additional embodiment of the present invention, there is provided a new compound of formula (XIX);



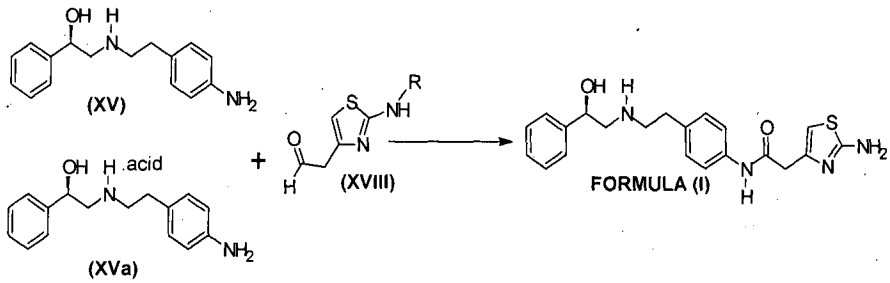
as a new intermediate for preparation of Mirabegron of formula (I).

According to another additional embodiment of the present invention, there is provided a single-pot process for preparation of Mirabegron of formula (I), wherein the said process comprising:



FORMULA (I)

o) reacting compound of formula (XV) or its acid addition salt of formula (XVa) with compound of formula (XVIII) in presence of a solvent and oxidizing agent, optionally in presence of base, optionally in presence of a catalyst to obtain Mirabegron of formula (I);



(XV) (XVa) (XVIII) FORMULA (I)

R = H, amino protecting group

Step (o) can be carried out in presence of borane reagents with or without catalyst; wherein the borane reagent is selected from but not limited to boric acid, phenyl boronic acid and trimethyl borate.

The solvent used in step (o) is selected from C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol, diols and triols and the like; C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; dimethylsulfoxide; nitriles such as acetonitrile; esters; C_2 to C_8 straight or substituted cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; chlorinated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; halogenated hydrocarbons; water; or mixture thereof.

The base used in step (o) of the present invention may be organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene;

primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like; tetraalkylammonium and phosphonium hydroxides; metal alkoxides and the like; and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides; or liquor ammonia; and the like.

The catalyst used in step (o) of the present invention is selected from organic, inorganic catalyst, or phase transfer catalyst. Organic or inorganic catalyst includes acid catalyst.

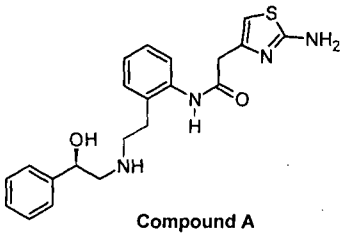
The oxidizing agent used in step (o) is selected from hydrogen peroxide; Dess-martin periodinate; peracids including but not limited to peracetic acid, perbenzoic acid, metachloroperbenzoic acid; alkyl hydroperoxides such as but not limited to tertiary butyl hydrogen peroxide; silver iodide; copper iodide; and mixture thereof.

Compound of formula (I) may be converted to its acid addition salt of formula (Ia) according to the conventional methods known in the art.

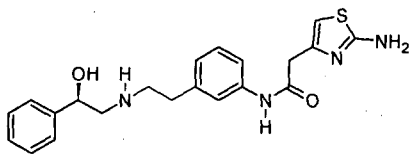
The compound of formula (I) or its acid salt of formula (Ia) obtained may be further purified by the process known in the art like recrystallization, saltification, re-saltification or by solvent purification.

According to the present invention, Mirabegron prepared according to any of the said processes having impurities comprising a compound of formula (A), compound of formula (B), compound

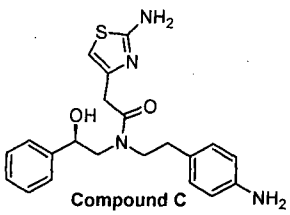
of formula (C), compound of formula (D), compound of formula (E), compound of formula (F), compound of formula (G), compound of formula (H), compound of formula (I), compound of formula (J), compound of formula (K), compound of formula (L), compound of formula (M), compound of formula (N), compound of formula (O), compound of formula (P), compound of formula (Q), compound of formula (R), compound of formula (S), compound of formula (T), compound of formula (U), compound of formula (V), compound of formula (W), compound of formula (X), and compound of formula (Y).



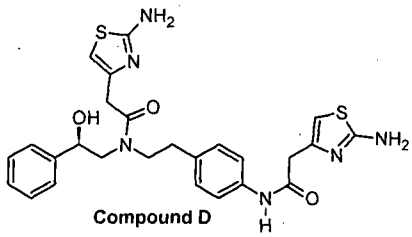
Compound A



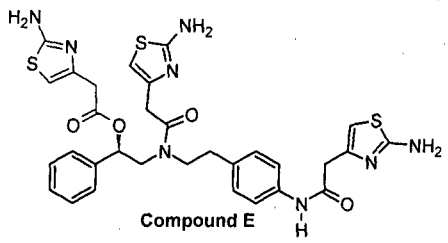
Compound B



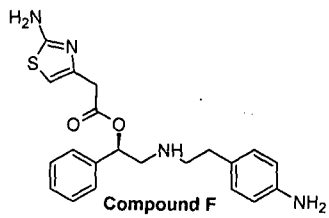
Compound C



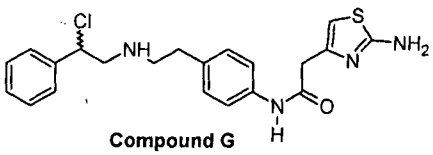
Compound D



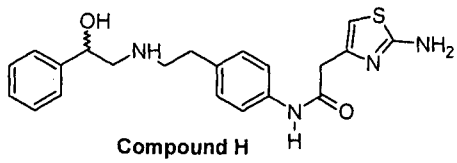
Compound E



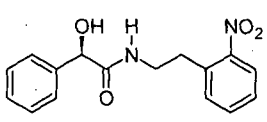
Compound F



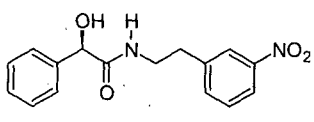
Compound G



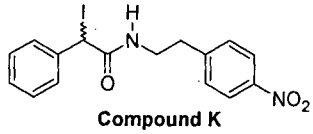
Compound H



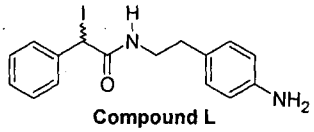
Compound I



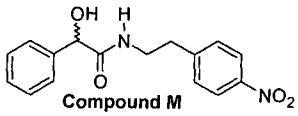
Compound J



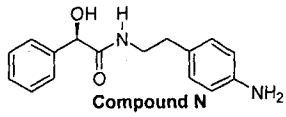
Compound K



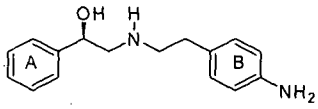
Compound L



Compound M

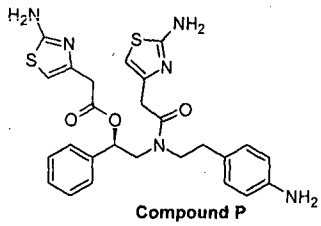


Compound N

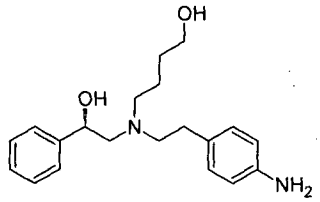


Compound O

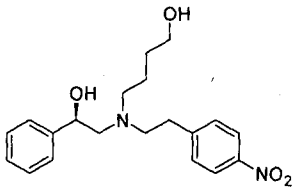
Ring A and B can be partially or completely reduced.



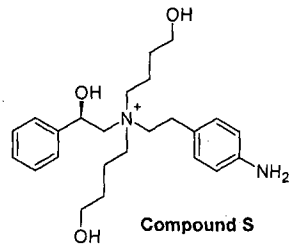
Compound P



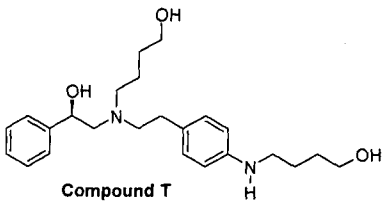
Compound Q



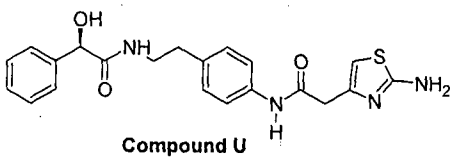
Compound R



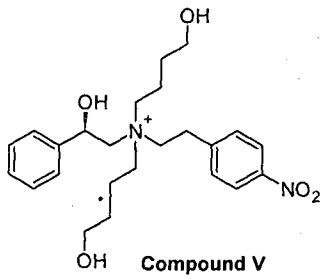
Compound S



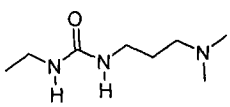
Compound T



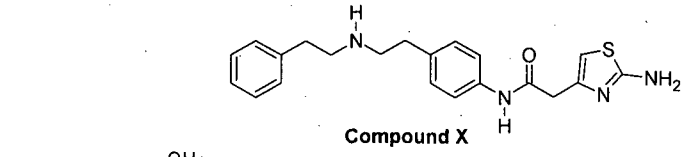
Compound U



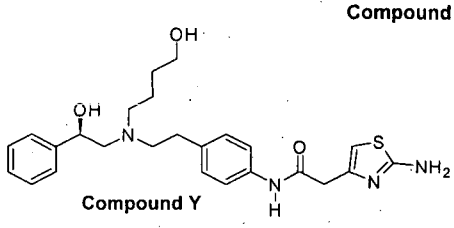
Compound V



Compound W



Compound X



Compound Y

According to the present invention, Mirabegron prepared according to any of the said processes having less than about 0.2% of compound of formula (A), less than about 0.2% of compound of formula (B), less than about 0.2% of compound of formula (C), less than about 0.2% of compound of formula (D), less than about 0.2% of compound of formula (E), less than about 0.2% of compound of formula (F), less than about 0.2% of compound of formula (G), less than about 0.2% of compound of formula (H), less than about 0.2% of compound of formula (I), less than about 0.2% of compound of formula (J), less than about 0.2% of compound of formula (K), less than about 0.2% of compound of formula (L), less than about 0.2% of compound of formula (M), less than about 0.2% of compound of formula (N), less than about 0.2% of compound of formula (O), less than about 0.2% of compound of formula (P), less than about 0.2% of compound of formula (Q), less than about 0.2% of compound of formula (R), less than about 0.2% of compound of formula (S), less than about 0.2% of compound of formula (T), less than about 0.2% of compound of formula (U),less than about 0.2% of compound of formula (V),less than about 0.2% of compound of formula (W),less than about 0.2% of compound of formula (X) and less than about 0.2% of compound of formula (Y).

BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

EXAMPLE 1

Example 1a

Step-a: Preparation of (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (XIII)

To a stirred solution of R-Mandelic acid (97.61 g) in acetonitrile (1000 mL), trimethylborate (66.66 g) was added at 28°C (±2). After addition of trimethylborate, reaction temperature was raised to 58°C (±2) and maintained for 90 minutes. To this solution, 2-(4-Nitro-phenyl)-ethylamine hydrochloride (NPA HCl) (100.0 g) was added at same temperature. To this solution, N, N-Diisopropylethyl amine (82.92 g) was added slowly and then reaction temperature was set to reflux for 12 hrs. The reaction temperature was lowered to 30°C (±2) and then diluted with ethyl acetate (1100 mL) and aqueous HCl (1M) solution (1400 mL). The separated organic layer was washed successively with 1M hydrochloric acid aqueous solution. The organic layer was washed with 5% sodium hydroxide aqueous solution and brine. The organic layer was concentrated in vacuo; the residue was recrystallized from toluene (500 mL). The solid was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain pale yellow crystals of (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide.

Yield: 125 g (84.3%); Purity by HPLC: 98.65%.

Example 1b

Step-b: Preparation of (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride (XIVa)

To a stirred solution of (100 g) (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (prepared according to example 1a) in tetrahydrofuran (400 mL), sodium borohydride (44.07 g) was added at 28°C (±2). After addition of sodium borohydride, the reaction temperature was lowered to 2°C (±2). To this chilled mass, solution of iodine (169.03 g) in tetrahydrofuran (600 mL) was added slowly. Thereafter temperature was increased to reflux and mixture was stirred for 10 hrs. The reaction mixture was cooled to 5°C (±2), to which then methanol (50 mL) was added and stirred for 30 minutes. Conc. hydrochloric acid aqueous solution (35%, 20.83 mL) was added slowly while maintaining exotherm below 10°C and the mixture was stirred for 30 minutes. The reaction mixture was allowed to warm to the 28°C (±2), water was added followed by heating the reaction mass at 68°C (±2) for 1 hr. Tetrahydrofuran and methanol were distilled under vacuo. The reaction mixture was cooled to 30°C (±2) and it was diluted with

dichloromethane (800 mL) and aqueous ammonia solution (200 mL). To the organic layer, solution of hydrochloric acid in isopropanol (17%, 100 mL) was added slowly and stirred it for 3 hrs. The solid obtained was filtered, washed with dichloromethane (100 mL) and dried under vacuo at 48°C (±2) to obtain (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride.

Yield: 94.8 g (90.5%); Purity by HPLC: 99.09%.

EXAMPLE 1b'

Step b: Preparation of (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride (XIVa)

To a stirred solution of sodium borohydride (2.5g, 4eq) in dimethoxyethane (50 ml) at 2°C (±2); sulfuric acid (3.2 g, 2 eq) was added drop wise. To this stirred mass, solution of (5 g) (R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide (prepared according to example 1a) in dimethoxyethane (50 mL) was added drop wise at 2°C (±2). After complete addition, the reaction mass was heated at 70°C (±2) till the completion of reaction. The reaction mass was cooled and quenched using methanol (2.5 mL), followed by addition of conc. hydrochloric acid aqueous (35%, 1 mL) solution. The reaction mixture was diluted with dichloromethane (40 mL) and water (35 mL) and basified it with the aqueous ammonia solution (20%, 10 mL). The organic layer was separated and washed it with ammonia solution. To the organic layer, solution of hydrochloric acid in isopropanol (17%, 5 mL) was added slowly and stirred for 3 hrs. The solid obtained was filtered, washed it with dichloromethane (100 mL) and dried under vacuo at 48°C (±2) to obtain (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride.

Yield: 3.2 g (59.6%); Purity by HPLC: 97.8 %.

Example 1c

Step c: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride (XVa)

A mixture of (100 g) (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride (prepared according to example 1b), methanol (2000 mL) and Raney Nickel (20 g, wet) was stirred under hydrogen pressure (60 psi) for 6 hrs. The reaction solution was filtered, and the filtrate was concentrated in vacuo. The residue was mixed with isopropanol (300 mL) and

reaction mixture was heated to 78°C (±2). The mixture was added to toluene (900 mL). The reaction mixture was gradually cooled to 28°C (±2) and stirred at this temperature for 3 hrs. The solid obtained was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride.

Yield: 78.1 g (86.1%); Purity by HPLC: 99.14 %.

Example 1d

Step d: Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

To a mixed solution of (100 g) (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride (prepared according to example 1c), 2-aminothiazole-4-yl-acetic acid (55.10 g), concentrated hydrochloric acid (35.61 g) and water (1500 mL); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (72.01 g) was added at 28°C (±2) and the mixture was stirred for 1 hr. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (7.2 g) was added into the mixture at 28°C (±2) and the mixture was stirred for 2 hrs. The reaction mass was washed with mixture of ethyl acetate (400 mL) and n-butanol (100 mL). To the reaction mixture, n-butanol (1000 mL) was added followed by addition of aqueous solution of ammonia (20%, 80 mL). The organic layer was separated and successively washed with aqueous ammonia (5%, 1000 mL) and then followed by water. The organic layer was partially concentrated under vacuo and the temperature was raised to 68°C (±2). To this solution, toluene (1400 mL) was added and gradually cooled to room temperature. The solid obtained was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain crystals of α form of Mirabegron having PXRD pattern shown in Fig. 1 and Infrared spectrum (IR) show in Fig 2.

Yield: 114.1 g (84.5%); Purity by HPLC: 99.80%.

Example 1e

Step e: Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

A mixture of (100 g) Mirabegron (prepared according to example 1d) and 2-propanol (600 mL) heated to the 80°C (±2) for 20 minutes. To this solution, toluene (1000 mL) was added by maintaining the same temperature. The temperature of the mixture was lowered to room

temperature and stirred the mixture at this temperature for 2 hrs. The solid obtained was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain crystals of α form of Mirabegron having PXRD pattern shown in Fig. 1 and Infrared spectrum (IR) show in Fig 2.

Yield: 89.1 g (89.1%); Purity by HPLC: 99.92%.

EXAMPLE 2

Example 2f

Step f: Preparation of (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride (XIVa)

To a stirred solution of 2-(4-Nitro-phenyl)-ethylamine hydrochloride (NPA HCl) (100.0 g) in water (600 mL); triethylamine (55.0 g) and catalytic amount of tetra-butyl ammonium bromide (TBAB) was added at 28°C (±2). To this solution, R-styrene oxide (77.05 g) was added and temperature of the solution was raised to 42°C (±2) and maintained it at this temperature for 3 hrs. The reaction mass was cooled to 28°C (±2) and diluted with dichloromethane (600 mL). The organic layer was separated and concentrated under vacuo. To the obtained residue, tetrahydrofuran (200 mL) was added and the solution cooled to 10°C. To this cooled mixture, solution of hydrochloric acid in isopropanol (17%, 100 mL) was added. The precipitated solid was stirred, filtered, washed it with tetrahydrofuran and dried it under vacuo at 40°C to obtain (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride.

Yield: 38.3 g (24.05%); Purity by HPLC: 96.5 %.

Example 2c

Step c: Preparation of (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride (XVa)

A mixture of (100 g) (R)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol monohydrochloride (prepared according to example 2f), methanol (2000 mL) and Raney Nickel (20 g, wet) was stirred under hydrogen pressure (60 psi) for 6 hrs. The reaction solution was filtered, and the filtrate was concentrated in vacuo. The residue was added into isopropanol (300 mL) and the reaction mixture was heated to 78°C (±2). To this mixture, toluene (900 mL) was added. The reaction mixture was gradually cooled to 28°C (±2) and stirred it at this temperature for 3 hrs.

The solid obtained was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride.

Yield: 78.1 g (86.1%); Purity by HPLC: 99.14 %.

Example 2d

Step d: Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

To a mixed solution of (100 g) (R)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol monohydrochloride (prepared according to example 2c), 2-aminothiazole-4-yl-acetic acid (55.10 g), concentrated hydrochloric acid (35.61 g) and water (1500 mL); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (72.01 g) was added at 28°C (±2) and the mixture was stirred for 1 hr. 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (7.2 g) was added at 28°C (±2) and the mixture was stirred for 2 hrs. The reaction mass was washed with mixture of ethyl acetate (400 mL) and n-butanol (100 mL). To the reaction mixture, n-butanol (1000 mL) was added followed by addition of aqueous solution of ammonia (20%, 80 mL). The organic layer was separated and successively it washed with aqueous ammonia (5%, 1000 mL) and then followed by water. The organic layer was partially concentrated under vacuo and the temperature was raised to 68°C (±2). To this solution, toluene (1400 mL) was added and gradually cooled to room temperature. The solid obtained was filtered, washed with toluene and dried under vacuo at 48°C (±2) to obtain crystals of α form of Mirabegron having PXRD pattern shown in Fig. 1 and Infrared spectrum (IR) show in Fig 2.

Yield: 114.1 g (84.5%); Purity by HPLC: 99.80%.

Example 2e

Step e: Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

A mixture of (100 g) Mirabegron (prepared according to example 2d) in 2-propanol (600 mL) was heated to 80°C (±2) for 20 minutes. To this solution, toluene (1000 mL) was added by maintaining same temperature. The temperature of the mixture was lowered to room temperature and it was stirred at this temperature for 2 hrs. The solid obtained was filtered, washed with

toluene and dried under vacuo at 48°C (±2) to obtain crystals of α form of Mirabegron having PXRD pattern shown in Fig. 1 and Infrared spectrum (IR) show in Fig 2.

Yield: 89.1 g (89.1%); Purity by HPLC: 99.92%

EXAMPLE 3

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

To a solution of (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-1-phenylethanol monohydrochloride (10 g), 2-aminothiazol-4-yl-acetic acid (5.67 g), water (120 mL) and concentrated hydrochloric acid (3.6 g); 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (7.20 g) was added at 28°C (±2), and the mixture was stirred for two hours. After two hours, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide monohydrochloride (EDC.HCl) (0.72 g) was added to it 28°C (±2) and the mixture was stirred for two hours. The ethyl acetate (250 mL) was added to the reaction mass, followed by drop wise addition of 6% aqueous NaOH solution to the reaction mass to attain pH in the range of 9-10. The reaction mass was heated to 58°C (±2) for 30 min. to obtain clear solution. The organic layers was separated and washed with 6% aqueous NaOH solution (100 mL), followed by washing with water and drying over sodium sulphate. The organic layer was charged into a round bottom flask, n-heptane (200 mL) was added and cooled to 28°C (±2), stirred for 3 hrs. The precipitated solid was filtered and washed with n-heptane (20 mL) and dried under vacuum at 48°C (±2) for 3 hours to obtain 11.15 g of crystals of α form of Mirabegron having PXRD pattern shown in Fig. 1 and Infrared spectrum (IR) show in Fig 2.

Yield: 8.4 g (84 %); Purity by HPLC: 99.17 %

EXAMPLE 4

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (10 g) and n-Butanol (100 mL) was charged in round bottom flask at 28°C (±2). The solution was heated to 92°C (±2) to obtain clear solution, followed by addition of n-Heptane (200 mL) to obtain crystals. The obtained crystals were cooled to 28°C (±2), filtered, washed with n-

Heptane (40 mL) and dried under vacuum at 48°C (±2) for 3 hours to obtain 9.2 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2.

Yield: 8.7 g (87 %); Purity by HPLC: 99.7 %

EXAMPLE 5

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (1.5 g) and 2-methyltetrahydrofuran (45 mL) were charged in round bottom flask at 28°C (±2), and the solution was heated to 68°C (±2) for 30 min. To this solution, n-Heptane (60 mL) was added at 68°C (±2), to obtain crystals. The obtained crystals were cooled to 28°C (±2), filtered, washed with n-Heptane (6 mL) and dried the solid under vacuum at 48°C (±2) for 3 hours to obtain 1.25 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2.

Yield: 1.25 g (84.1 %); Purity by HPLC: 99.65 %

EXAMPLE 6

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (1.0 g) and 2-methyltetrahydrofuran (30 mL) were charged in round bottom flask at 28°C (±2) and the solution was heated to 68°C (±2) for 30 min. To this solution, toluene (40 mL) was added at 68°C (±2) to obtain crystals. The obtained crystals were cooled to 28°C (±2), filtered, washed with toluene (4 mL) and dried the solid under vacuum at 48°C (±2) for 3 hours to obtain 0.8 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2 and Infrared spectrum (IR) show in Fig 2.

Yield: 0.8 g (80 %); Purity by HPLC:99.7 %

EXAMPLE 7

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (10.0 g) and toluene (500 mL) were charged in round bottom flask at 28°C (±2) and the solution was heated to 88°C (±2) for 30 min. To this solution, DMF (50 mL) was added and

further heated for 30 min at 88°C (±2). To this, n-Heptane (1000 mL) was added at same temperature to obtain crystals. The obtained crystals were cooled to 28°C (±2), filtered, washed with n-heptane (40 mL) and dried under vacuum at 48°C (±2) for 3 hours to obtain 8.45 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2.

Yield: 7.0 g (70 %); Purity by HPLC: 99.6 %

EXAMPLE 8

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (1.0 g) and DMF (6 mL) were charged in round bottom flask at 28°C (±2) to obtain clear solution. To this solution, acetonitrile (100 mL) was added to obtain crystals. The obtained crystals were cooled to 28°C (±2) and further cooled to 5°C (±2). The crystals were filtered, washed with acetonitrile (6 mL) and dried under vacuum at 48°C (±2) for 3 hours to obtain 0.6 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2.

Yield: 0.6 g (60 %); Purity by HPLC: 99.85 %

EXAMPLE 9

Preparation of α-form of crystalline (R)-2-(2-aminothiazol-4-yl)-4'-[2-[(2-hydroxy-2-phenylethylamino]-ethyl]-acetanilide (Mirabegron)

Mirabegron (10 g) and 2-propanol (100 mL) were charged in round bottom flask at 28°C (±2). The solution was heated to reflux temperature to obtain clear solution. To this solution, n-Heptane (200 mL) was added at same temperature to obtain crystals. The obtained crystals were cooled to 28°C (±2). The crystals were filtered, washed with n-Heptane (40 mL) and dried under vacuum at 48°C (±2) for 3 hours to obtain 9.2 g of α form of Mirabegron having PXRD pattern shown in Fig.1 and Infrared spectrum (IR) show in Fig 2.

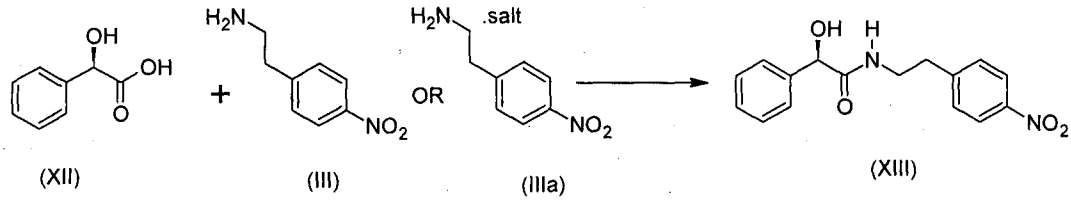
Yield: 8.5 g (85 %); Purity by HPLC: 99.65 %

We claim,

1. An improved process for the preparation of α-crystalline form of Mirabegron of formula (I),

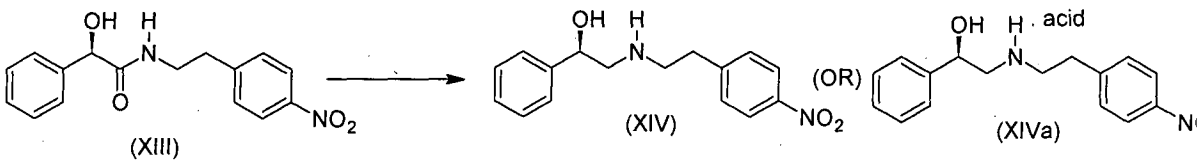
said process comprising;

a) reacting 4-nitrophenylethylamine of formula (III) or its acid addition salt of formula (IIIa) with compound of formula (XII) in presence of a solvent and reagent, optionally in presence of base, and/or catalyst to obtain (*R*)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII);



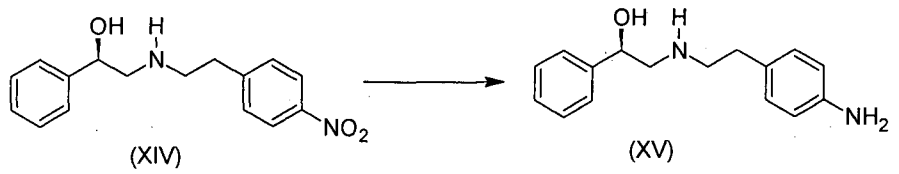
(XII) (III) (IIIa) (XIII)

b) reducing (*R*)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of formula (XIII) in presence of reducing agent and a solvent to obtain (*R*)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol of formula (XIV), optionally converting it into its acid addition salt of formula (XIVa);

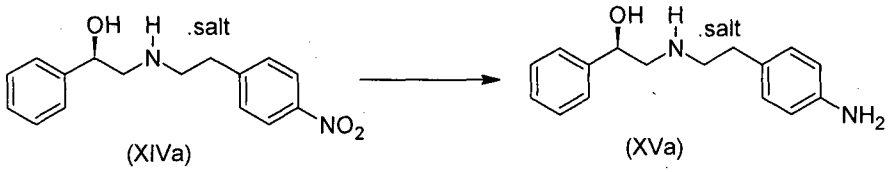


(XIII) (XIV) (XIVa)

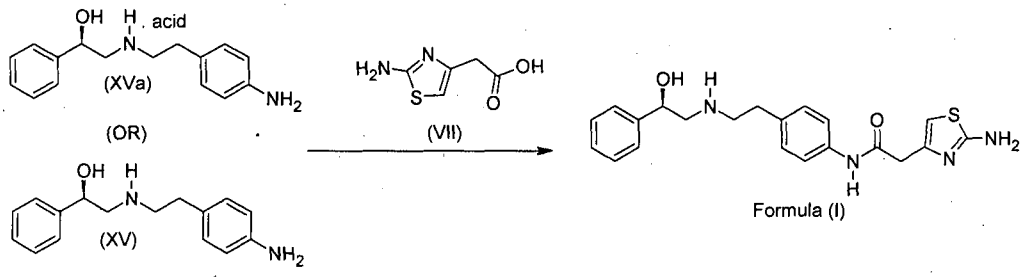
c) reducing (*R*)-2-[2'-(4-nitrophenyl)ethyl]amino]-1-phenylethanol of formula (XIV) or its acid addition salt of formula (XIVa) in solvent to obtain (*R*)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol of formula (XV) or its acid addition salt of formula (XVa) respectively;



OR



d) reacting compound (*R*)-2-[[2-(4-aminophenyl)ethyl]-amino]-1-phenylethanol of formula (XV) or its acid addition salt of formula (XVa) obtained in the step (c) with compound of formula (VII) in the presence of solvent, acid and a condensing agent, optionally in the presence of a catalyst to obtain Mirabegron of formula (I);



and

e) Isolating α-crystalline form of Mirabegron of formula (I) obtained in step (d) and optionally purifying by solvent crystallization.

2. The process as claimed in claim 1, wherein the reagent used in steps (a) are selected from but not limited to borane reagents such as boric acid, phenyl boronic acid, trimethyl borate and the like; carbodiimide reagents such as N, N'-dicyclohexylcarbodiimide (DCC) and 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide (EDC) or its salt; or imidazole reagents such as 1,1'-carbonyldiimidazole (CDI) and the like.

3. The process as claimed in claim 1, wherein the solvent used in step (a) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

4. The process as claimed in claim 1, wherein the base used in step (a) may be organic or inorganic base; organic bases selected from but not limited to 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine and the like; tertiary amines such as but not limited to triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; inorganic bases selected from alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like;

5. The process as claimed in claim 1, wherein the step (a) further comprises isolation of compound of formula (XIII);

the said process comprises the steps of :

i. treating the reaction mass of step (a) with water;

ii. extracting the aqueous layer of step (i) with first solvent;

iii. separating the organic layer of step (ii) followed by washing it with acid, base and brine;

iv. concentrating the organic layer of step (iii); and

v. adding second solvent to the step (iv) to obtain compound of formula (XIII).

6. The process as claimed in claim 5, wherein the first solvent used in step (ii) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

7. The process as claimed in claim 5, wherein the second solvent used in step (v) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as toluene, xylene and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; amides such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; or mixtures thereof.

8. The process as claimed in claim 1, wherein the reducing agent used in step (b) is selected from lithium aluminium hydride, sodium borohydride in presence of Iodine; or sodium borohydride in presence of acids, wherein acids are selected from but not limited sulfuric acid, acetic acid, trifluoroacetic acid, zinc chloride ($ZnCl_2$), cobalt chloride ($CoCl_2$); sodium borohydride and BF_3etherate; sodium borohydride and R_2SeX_2, where R is any alkyl and X is halide group; diborane solutions like BH_3:THF, BH_3:SMe_2, BH_3:NR_3 and the like.

9. The process as claimed in claim 1, wherein the solvent used in step (b) is selected from C_2 to C_8 straight chain, branched chain or cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran and the like; hydrocarbons such as toluene, xylene, heptane, pentane, cyclohexane and the like; nitriles such as acetonitrile and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane, chloroform and the like; hexamethylphosphoroustriamide (HMPT); hexamethylphosphoramide (HMPA); or mixture thereof.

10. The process as claimed in claim 1, wherein the step (b) further comprises isolation of the compound of formula (XIV) or its acid addition salt of compound of formula (XIVa);
said process comprises the steps of:
   A. quenching the reaction mass of step (b) with alcoholic solvent and aqueous acid solution followed by addition of water;
   B. concentrating the reaction mass, adding organic solvent followed by basifying the reaction mass;
   C. separating the organic layer and washing the organic layer with aqueous solution of base;
   D. acidifying the organic layer of step (C) to provide acid addition salt of compound of formula (XIVa) as a solid; and
   E. filtering the solid and washing it with organic solvent followed by drying it to obtain pure compound of formula (XIVa) and optionally purifying the compound of (XIVa).

11. The process as claimed in claim 10, wherein optionally, concentrating the organic layer of step (C) and adding anti solvent to the concentrated organic layer to obtain free base compound of formula (XIV) and optionally purifying the compound of (XIV).

12. The process as claimed in claim 10, wherein the organic solvent used in step (B) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptanes and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; carboxylic acid esters

such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

13. The process as claimed in claim 10, wherein the base used in step (B and C) for basification is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

14. The process as claimed in claim 10, wherein the acid used in step (D) for acidification is selected from organic or inorganic acids like hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, oxalic acid, isopropyl alcohol hydrochloride solution, ethyl acetate hydrochloride solution and the like.

15. The process as claimed in claim 10, wherein the organic solvent used in step (E) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptane and the like; aromatic hydrocarbons such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile and the like; ethers such as diisopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, and the like; or mixture thereof;

16. The process as claimed in claim 10, wherein the purification of compound of formula (XIV) or (XIVa) comprise solvent mediated crystallization; the crystallization process involve providing the solution of compound of formula (XIV) or (XIVa) in an alcoholic

solvent and adding an anti-solvents to provide the pure compound of formula (XIV) or (XIVa).

17. The process as claimed in claim 16, wherein the alcoholic solvent used for purification of compound of formula (XIV) or (XIVa) is selected from methanol, ethanol, isopropanol and the like.

18. The process as claimed in claim 16, wherein the anti-solvent used in purification of compound of formula (XIV) or (XIVa) is selected from aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

19. The process as claimed in claim 1, wherein the reduction step (c) can be carried out either by catalytic reduction in presence of catalyst selected from but not limited to palladium-carbon, palladium hydroxide-carbon, platinum oxide, rhodium on carbon, raney nickel and the like and in presence of hydrogen gas or hydrogen generating source such as but not limited to ammonium formate, hydrazine hydrate and the like; or metallic reduction in presence of metals such as but not limited to iron, zinc, tin, and the like and in presence of acid selected from but not limited to formic acid, acetic acid, hydrochloric acid and the like and/or solvent; or chemical reduction in presence of sodium dithionate.

20. The process as claimed in claims 1 and 19, wherein the solvent used in the step (c) is selected from C_3 to C_6 amides such as dimethylformamide, dimethylacetamide and the like; N-methylpyrrolidone; C_1 to C_6 straight or branched chain alcohols such as methanol, ethanol, isopropanol and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; C_2 to C_8 straight chain or cyclic ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl-tert-butyl and the

like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

21. The process as claimed in claim 1, wherein the step (c) further comprises isolation of the compound of formula (XV) or its acid salts of compound of formula (XVa);
the said process comprises the steps of;
I. recovering the catalyst by filtering the reaction mass of step (c) and concentrating the organic layer;
II. adding solvent to the concentrated layer to obtain the solid; and
III. filtering and washing the solid to obtain compound of formula (XV) or (XVa).

22. The process as claimed in claim 21, wherein the solvent used in step (II) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

23. The process as claimed in claim 21, wherein optionally, compound of formula (XV) or (XVa) obtained in step (III) can be purified with a solvent or solvent mixture; optionally by heating it at a temperature between room temperature to reflux temperature of the solvent.

24. The process as claimed in claim 23, wherein the solvent or solvent mixtures used for the purification of compound of formula (XV) or (XVa) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the

like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

25. The process as claimed in claim 1, wherein the solvent used in step (d) is selected from water, alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ionic liquids; or a mixture thereof.

26. The process as claimed in claim 1, wherein the acid used in step (d) is selected from hydrochloric acid, hydrobromic acid, sulfuric acid and the like.

27. The process as claimed in claim 1, wherein the condensing agent used in the step (d) is selected from but not limited to N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) or its acid addition salts, 1,1'-carbonyldiimidazole (CDI) and the like; optionally borane reagents selected from but not limited to phenyl boronic acid, boric acid, trimethyl borate and the like.

28. The process as claimed in claim 1, wherein the isolation of α-crystals of Mirabegron of compound of Formula (I) of step (e) comprises;

ia. adding first solvent to the reaction mass of step (d);

iia. basifying the solution of step (ia) and optionally heating the reaction mixture;

iiia. separating the organic layer;

iva. extracting the aqueous layer with solvent, and combining the obtained organic layer with organic layer of step (iiia);

va. washing the combined organic layer with aqueous base followed by water, separating the organic layer and optionally distilling the organic layer; and

via. adding second solvent to organic layer of step (va) to obtain α-crystalline form of Mirabegron of compound of Formula (I).

29. The process as claimed in claim 28, wherein alternatively, the organic layer obtained in step (va) is cooled, filtered and dried to obtain α-crystalline form of Mirabegron of formula (I).

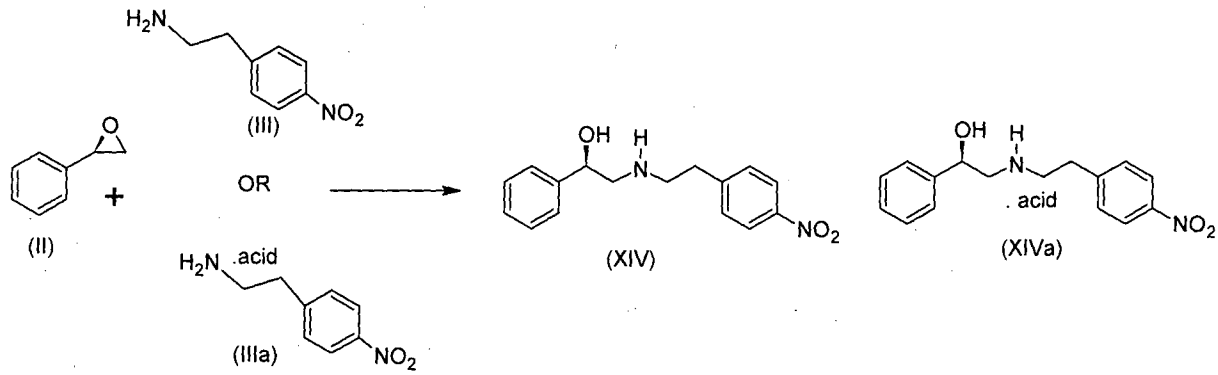
30. The process as claimed in claim 28, wherein the first solvent used in step (ia) for extraction and solvent used in step (iva) for extraction is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; halogenated hydrocarbons such as dichloromethane, and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; alcohols such as n-butanol and the like; ketones such as methyl isobutyl ketone (MIBK) and the like; ethers such as di-ethyl ether, di-isopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

31. The process as claimed in claim 28, wherein the base used step (iia) for basification and the base used in step (va) for washing is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

32. The process as claimed in claim 28, wherein the second solvent used in step (via) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water or a mixture thereof.

33. The process as claimed in any of the preceding claims, wherein the compound of formula (XIV) and (XIVa) used in the step (c) can be optionally obtained by

(f) reacting a compound of formula (II) with a compound of formula (III) or its acid addition salt of compound of formula (IIIa) in presence of a solvent; optionally in presence of a base and/or catalyst to obtain compound of formula (XIV); and optionally converting it into its acid addition salt of formula (XIVa).



34. The process as claimed in claim 33, wherein the solvent used in step (f) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the

like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water; ionic liquids; or a mixture thereof.

35. The process as claimed in claim 33, wherein the base used in step (f) may be organic or inorganic base; the organic bases such as but not limited 1,8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine and the like; pyridine or substituted pyridine such as but not limited to 2,6-lutidine, 2,4-lutidine, 3,5-lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like; tetra alkyl ammonium and phosphonium hydroxides; metal alkoxides and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide, lithium hydroxide and the like; metal hydrides; metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tert butoxide and the like; metal amides or liquor ammonia and the like.

36. The process as claimed in claim 33, wherein the catalyst used in step (f) is selected from organic, inorganic catalyst, or phase transfer catalyst, optionally in the presence of acids like Lewis acid.

37. The process as claimed in claim 33, wherein the step (f) further comprises isolation of the compound of formula (XIV) or its acid addition salt of compound of formula (XIVa);
the said process comprises the steps of:
ic. treating the reaction mass of step (f) with water;

iic. extracting the aqueous layer of step (ic) with an organic solvent;

iiic. separating the organic layer of step (iic) followed by washing it with base and brine;

ivc. concentrating the organic layer of step (iiic) to obtain the compound of formula (XIV); and

vc. optionally acidifying the organic layer obtained in step (ivc) to precipitate the acid addition salt of compound of formula (XIVa), filtering the precipitate, and washing it with organic solvent followed by drying it to obtain compound of formula (XIVa).

38. The process as claimed in claim 37, wherein the organic solvent used in step (iic) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptanes and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as di-ethyl ether, di-isopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyl tetrahydrofuran and the like; or mixtures thereof.

39. The process as claimed in claim 37, wherein the base used step (iiic) for washing is selected from inorganic bases like ammonium hydroxide; alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide and the like; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate and the like; and alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, calcium bicarbonate, ammonium bicarbonate and the like; and organic bases selected from triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N-methyl morpholine, piperidine and pyridine and their mixtures thereof.

40. The process as claimed in claim 37, wherein the acid used in step (vc) for acidification is selected from organic or inorganic acids like hydrochloric acid, hydrobromic acid, sulfuric acid, formic acid, acetic acid, oxalic acid, isopropyl alcohol hydrochloride solution, ethyl acetate hydrochloride solution and the like.

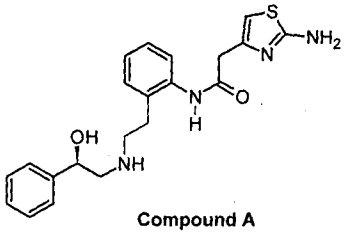
41. The process as claimed in claim 37, wherein the organic solvent for washing used in step (vc) is selected from the group comprising of aliphatic hydrocarbons such as hexane, heptanes and the like; aromatic hydrocarbons such as toluene, xylene and the like; halogenated hydrocarbons such as dichloromethane, dichloroethane and the like; ketones such as acetone, methyl ethyl ketone, methyl isobutyl ketone and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; nitriles such as acetonitrile, propionitrile and the like; ethers such as di-methyl ether, di-ethyl ether, di-isopropyl ether, methyl tertiary butyl ether and the like; cyclic ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran, 1,4-dioxane and the like; alcohols such as methanol, ethanol, isopropyl alcohol and the like; chloroform; or mixture thereof.

42. The process as claimed in any of the preceding claims, wherein the Mirabegron of formula (I) prepared by foregoing process can be purified by providing solution in alcohols such as 2-propanol, n-butanol and the like; hydrocarbons such as hexane, n-heptane, toluene, xylene and the like; or mixture thereof; cooling the solution; filtering and drying the solid to obtain pure α-crystalline form of Mirabegron of formula (I).

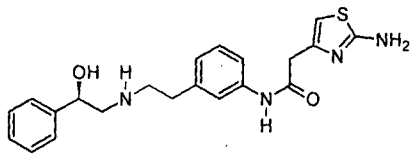
43. The process as claimed in any of the preceding claims, wherein the α-crystalline form of Mirabegron prepared by foregoing process has purity more than 99%; preferably more than 99.5% when determined by HPLC.

44. The process as claimed in any of the preceding claims, wherein optionally the compound of formula (XIV), (XV) and Mirabegron of formula (I) can be converted to their corresponding acid addition salt of formula (XIVa), (XVa) and (Ia); wherein the acid addition salt may be mono, di- or tri- acid salt. The salts includes such as but not limited to acetate, hydrochloride, sulfate, oxalate, bromide, succinate, trifluoroacetate, lactate, malonate, glutarate, glutamate, citrate, ascorbate, camphor sulfonate, pamoate, pyruvate, maleate, tosylate, formate, tartarate, mesylate, oxalate, fumarate, phosphate, dimesylate, and the like.

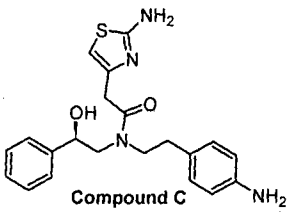
45. The process as claimed in any of the preceding claims wherein the Mirabegron and α-crystalline form thereof prepared by foregoing process, having less than about 0.2% of compound of formula (A), less than about 0.2% of compound of formula (B), less than about 0.2% of compound of formula (C), less than about 0.2% of compound of formula (D), less than about 0.2% of compound of formula (E), less than about 0.2% of compound of formula (F), less than about 0.2% of compound of formula (G), less than about 0.2% of compound of formula (H), less than about 0.2% of compound of formula (I), less than about 0.2% of compound of formula (J), less than about 0.2% of compound of formula (K), less than about 0.2% of compound of formula (L), less than about 0.2% of compound of formula (M), less than about 0.2% of compound of formula (N), less than about 0.2% of compound of formula (O), less than about 0.2% of compound of formula (P), less than about 0.2% of compound of formula (Q), less than about 0.2% of compound of formula (R), less than about 0.2% of compound of formula (S), less than about 0.2% of compound of formula (T), less than about 0.2% of compound of formula (U),less than about 0.2% of compound of formula (V),less than about 0.2% of compound of formula (W),less than about 0.2% of compound of formula (X) and less than about 0.2% of compound of formula (Y);



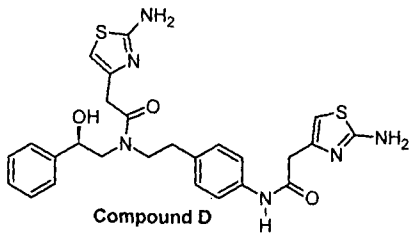
Compound A



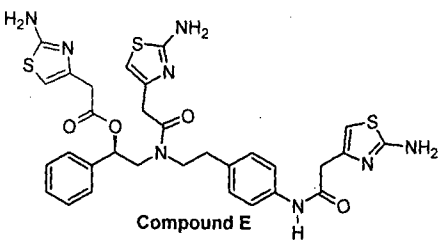
Compound B



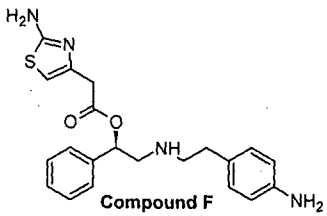
Compound C



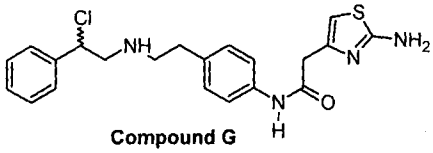
Compound D



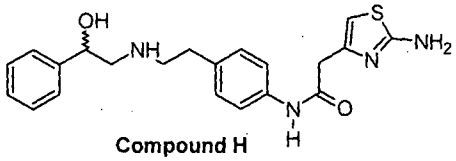
Compound E



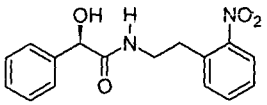
Compound F



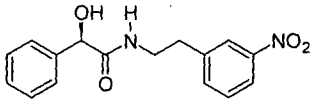
Compound G



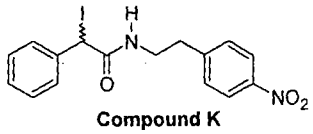
Compound H



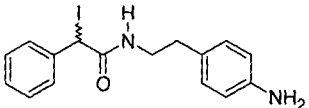
Compound I



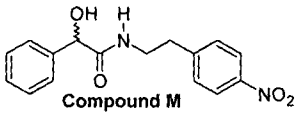
Compound J



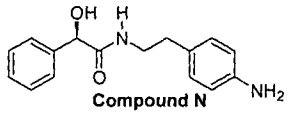
Compound K



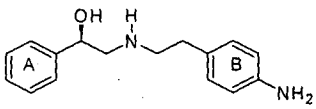
Compound L



Compound M

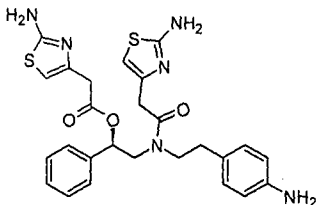


Compound N

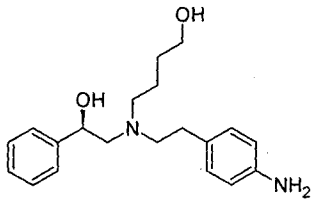


Compound O

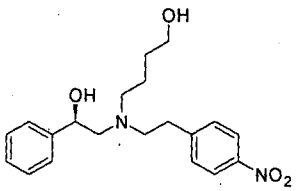
Ring A and B can be partially or completely reduced.



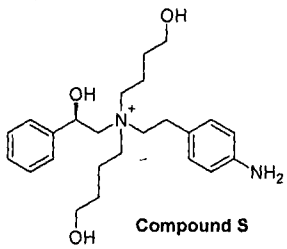
Compound P



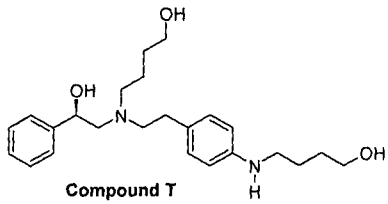
Compound Q



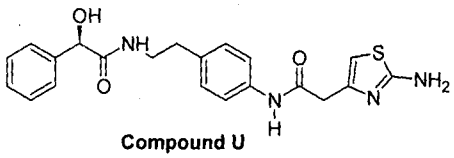
Compound R



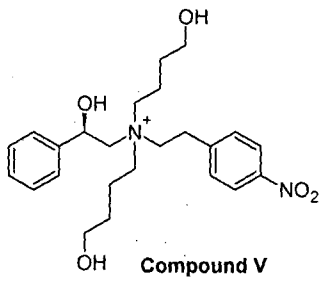
Compound S



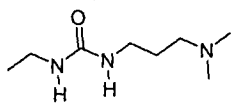
Compound T



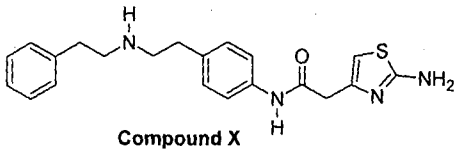
Compound U



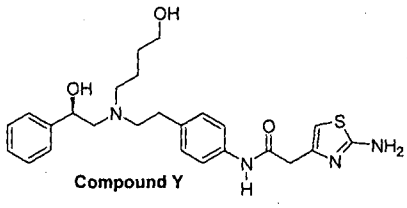
Compound V



Compound W



Compound X



Compound Y

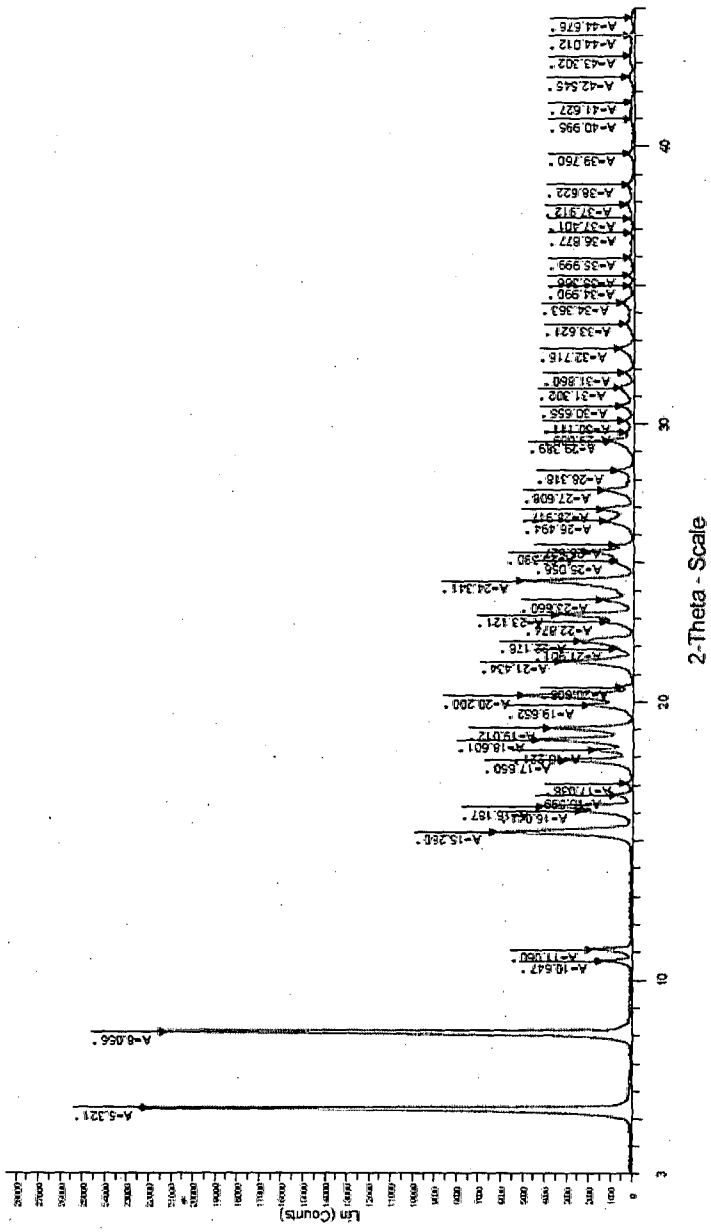


Figure 1

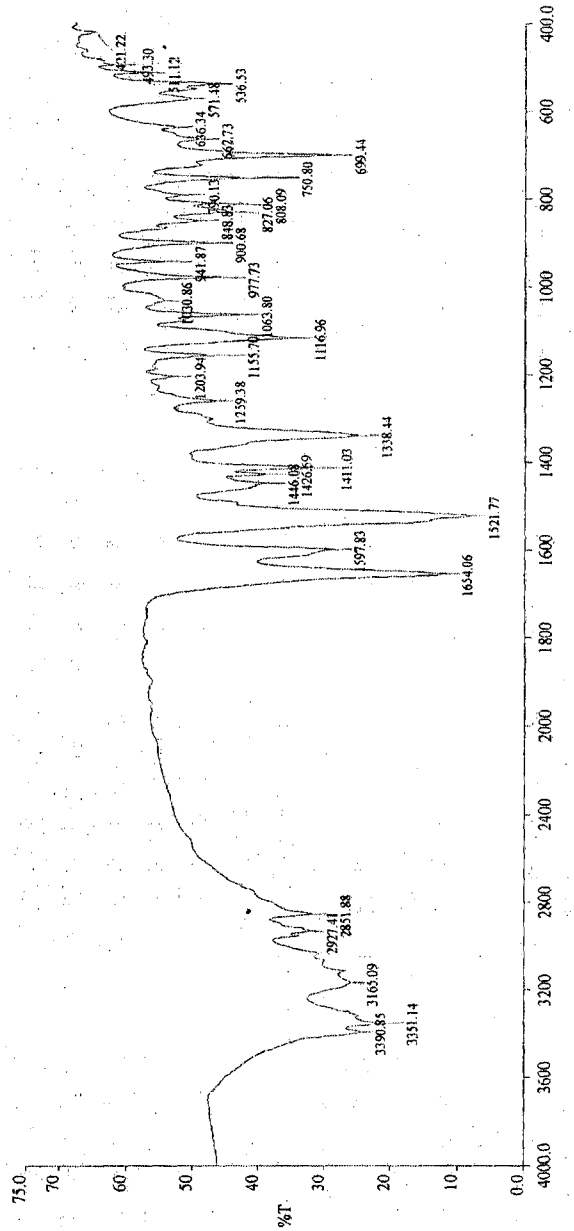

%T
75.0
70
60
50
40
30
20
10
0.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
3390.85
3351.14
3165.09
2927.41
2851.88
1654.06
1597.83
1521.77
1446.08
1426.89
1411.03
1338.44
1239.38
1203.94
1155.70
1116.96
1063.80
977.73
941.87
900.68
848.85
827.06
808.09
750.80
699.44
682.73
656.34
571.48
536.53
511.12
493.30
421.22

Figure 2

INTERNATIONAL SEARCH REPORT

International application No
PCT/IN2014/000637

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D277/40
ADD.

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

EPO-Internal, CHEM ABS Data, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 7 342 117 B2 (KAWAZOE SOUICHIROU [JP] ET AL) 11 March 2008 (2008-03-11) cited in the application referential example 1, referential example 2, referential example 3. -----	1-45

☐ 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

"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

Date of the actual completion of the international search	Date of mailing of the international search report
20 February 2015	02/03/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Bakboord, Joan

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IN2014/000637

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 7342117 B2	11-03-2008	BR 0213570 A	26-10-2004
		CA 2464068 A1	08-05-2003
		CN 1575287 A	02-02-2005
		EP 1440969 A1	28-07-2004
		EP 1932838 A2	18-06-2008
		EP 2298752 A1	23-03-2011
		ES 2404071 T3	23-05-2013
		HU 0401665 A2	29-11-2004
		JP 3800220 B2	26-07-2006
		KR 20050040837 A	03-05-2005
		MX PA04003936 A	18-06-2004
		NO 326965 B1	23-03-2009
		RU 2303033 C2	20-07-2007
		TW I322805 B	01-04-2010
		US 2005004190 A1	06-01-2005
		US 2008214633 A1	04-09-2008
		WO 03037881 A1	08-05-2003
		ZA 200403044 A	21-04-2005