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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 October 2015 (29.10.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/162536 A1

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

(21) International Application Number:
PCT/IB2015/052839

(22) International Filing Date:
18 April 2015 (18.04.2015)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
1433/MUM/2014 22 April 2014 (22.04.2014) IN

(71) Applicant: **CALYX CHEMICALS AND PHARMACEUTICALS LTD.** [IN/IN]; Unit No. 110, Marwah's Complex, Krishanlal Marwah Marg, Off. Saki-Vihar Road, Andheri (East), Mumbai-400072, Mumbai 400072 (IN).

(72) Inventors; and
(71) Applicants : **LAL, Bansi** [IN/IN]; 1005, Marathon Galaxy-II, L.B.S. Marg, Mulund (West), Mumbai-400080, Mumbai 400080 (IN). **SHENOY, Gopalkrishna** [IN/IN]; L/T26/31, Vijay Nagar, Marol, Andheri (East), Mumbai-400059, Mumbai 400059 (IN). **DAVE, Rajesh** [IN/IN]; 6B,2503, Sapphire Heights, Akurli Road, Lokhandwala Township, Kandivali (East), Mumbai-400101, Mumbai 400101 (IN). **NAMAGE, Subhash** [IN/IN]; At Post : Vanaval, Tal.- Shirpur, Dist-Dhule, Maharashtra-425405, Dhule 425405 (IN). **JANNI, Ravi** [IN/IN]; H.NO:4-3A, Gowda peta, Cherukumilli (post), Akividu (Mandalam), West Godavari (District), Andhra Pradesh - 534235, Akividu 534235 (IN). **BODKHE, Prashant** [IN/IN]; At Post : Loni (SM). Tal.- Risod, Dist.-Washim, Maharashtra - 444506, Risod 444506 (IN).

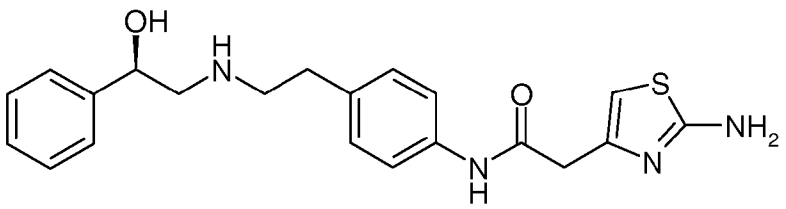
(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, 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).

Published:

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

(54) **Title**: NOVEL PROCESS FOR PREPARATION OF MIRABEGRON AND IT'S INTERMEDIATE



Formula I

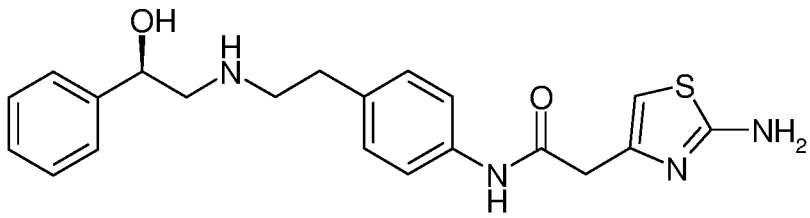
(57) **Abstract**: The present invention related to a novel process for preparation of Mirabegron of formula (I) and its intermediate. I

WO 2015/162536 A1

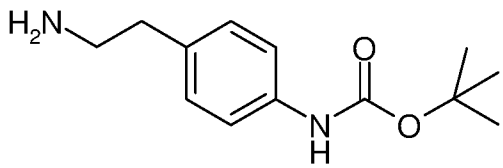
Novel process for preparation of Mirabegron and it's intermediate.

FIELD OF INVENTION

The present invention relates to an improved process for the preparation of Mirabegron of Formula I. which can be prepared from 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine of Formula II, a key starting material in the preparation of Mirabegron.



Formula I



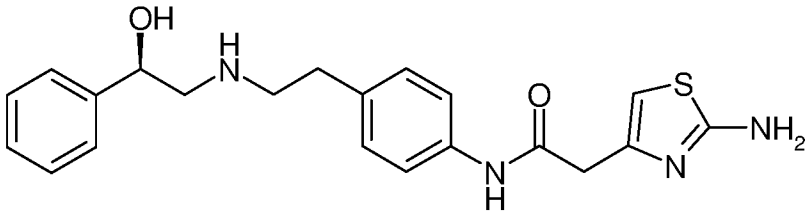
Formula II

BACKGROUND OF INVENTION

Prior art methods [a) Journal of Organic Chemistry, 2013, 78(21) 10931-10937; b) 2) Synthesis, 2009 (2) 283-289] reported for the preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula II suffers from one or more drawbacks such as low product purity and yield due to lengthy reaction sequence involving protection and deprotection of amino group or lack of efficient product isolation method in pure form from regioselective protection of aromatic amino group.

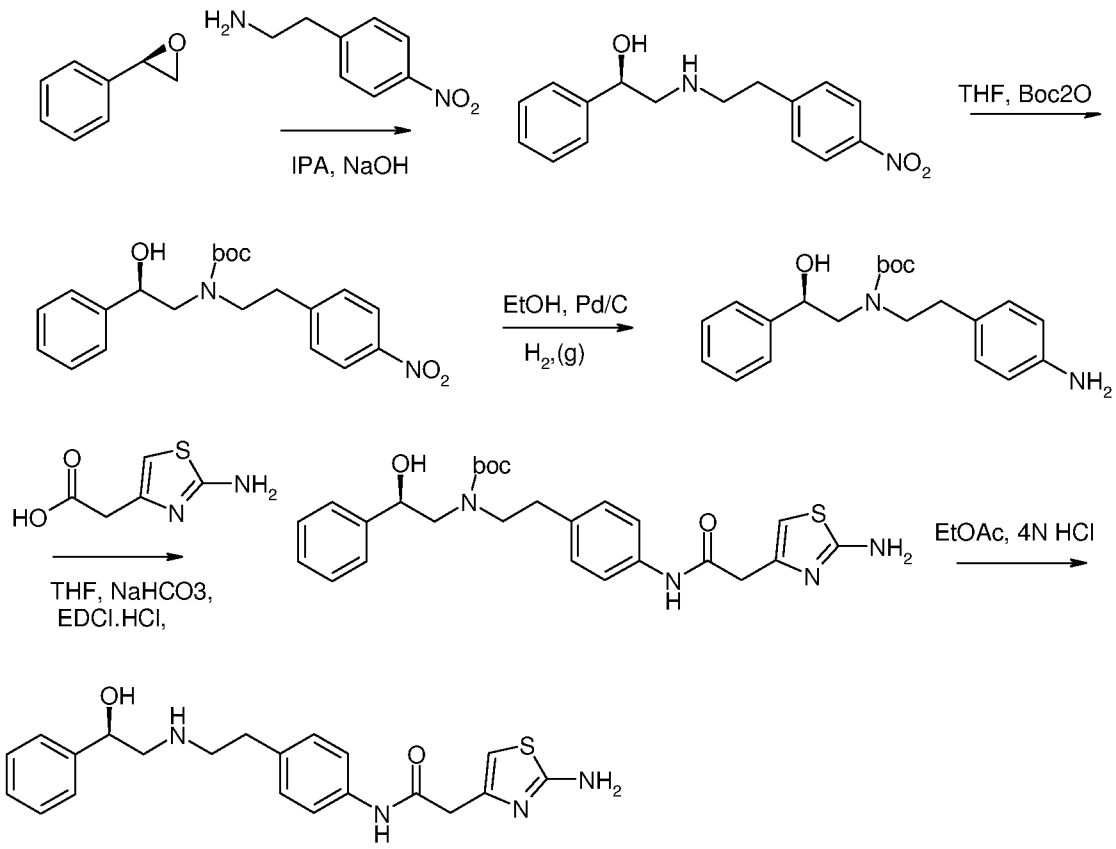
Thus, there is a need for a simple and cost effective industrially viable process for the preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine.

Mirabegron is chemically described as 2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide and has a structure of Formula I.



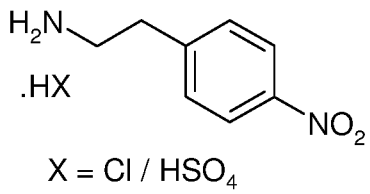
Formula I

Mirabegron (Paraguayan S, Muralidharan S, Jaya Raja Kumar K, Int. J. Res. Pharm. Sci, 4(4), 2013, 593-596) is a beta-3 adrenergic agonist, approved in USA, Europe, Canada and Japan for the treatment of overactive bladder condition by Astellas Pharma. US patent No. 6,346,532 B1 discloses mirabegron or a salt thereof and process for its preparation. Synthesis is depicted in scheme 1, which involves nucleophilic ring opening of (R)-styrene oxide with 4-nitrophenylethylamine as a key step. The major drawbacks of this approach are product synthesized is of low purity and in low yields, and there are difficulties in product isolation.

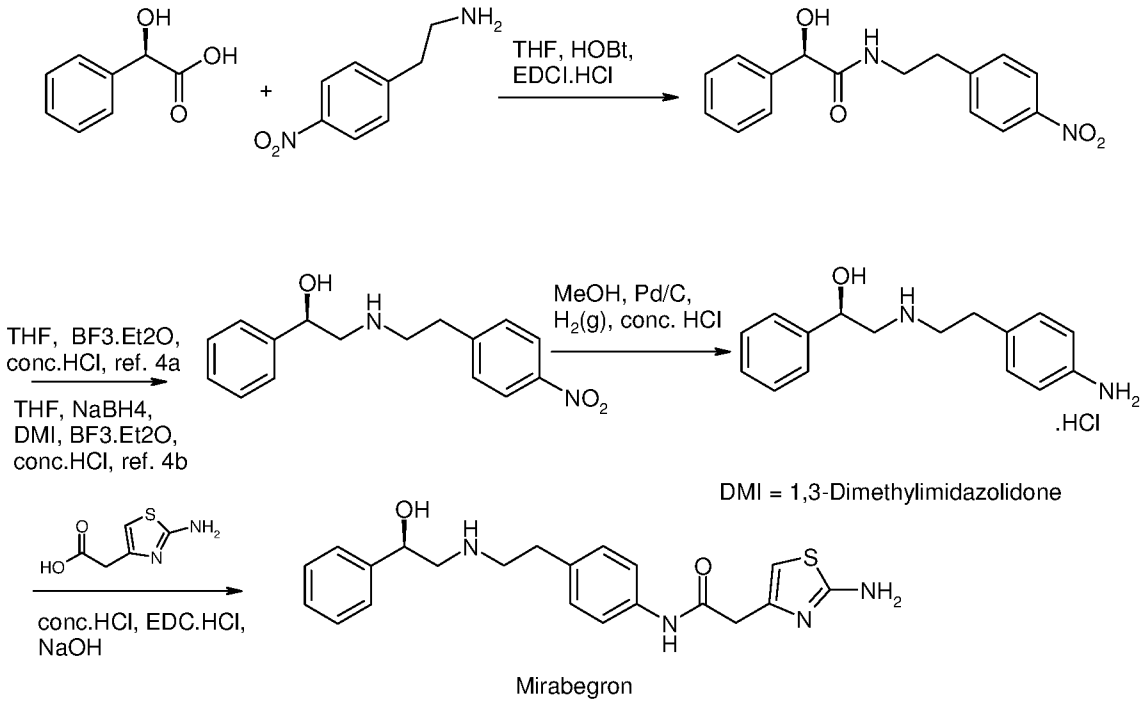


Scheme 1

US2011230530 A1 and JP2011105685 (A) discloses [a) Takasu Toshiyuki, ; Sato Shuichi, ; Ukai Masashi, ; Maruyama Tatsuya, US2011230530 A1; b) Marumo Kiyotaka, ; Sato Kiichi, ; Watanabe Takashi, ; Kurauchi Takashi, JP2011105685 (A)] the preparation of Mirabegron as shown in scheme 2, employing (R)-mandelic acid, and 2-(4-nitrophenyl)ethanamine salt of Formula III as key raw materials.



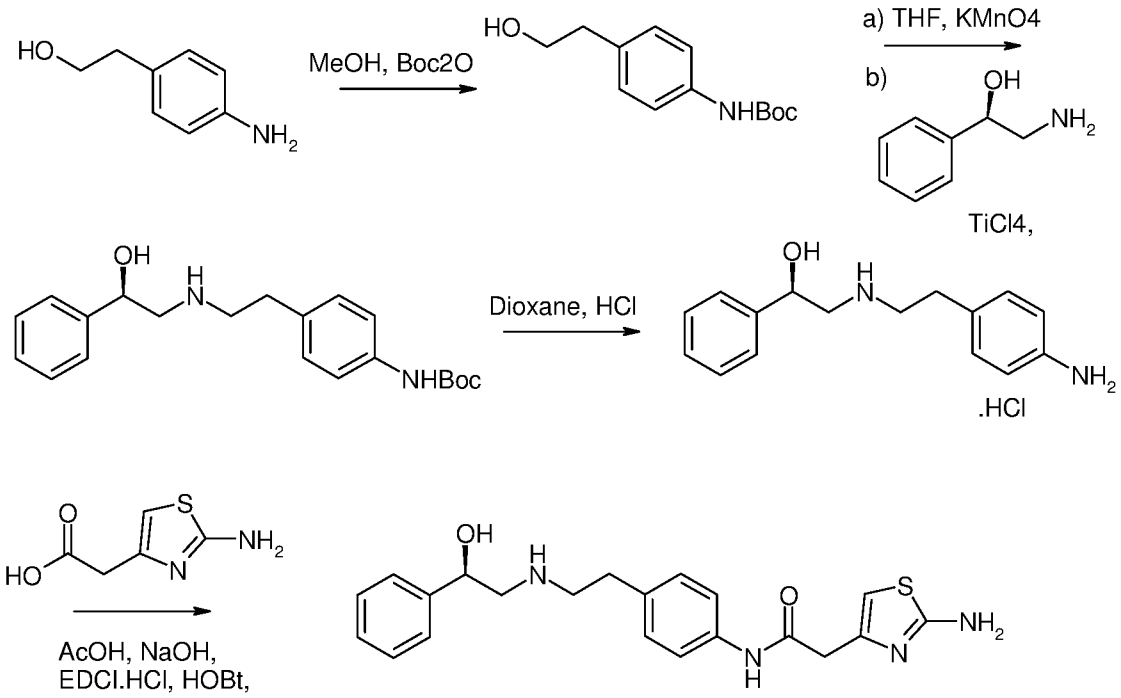
Formula III



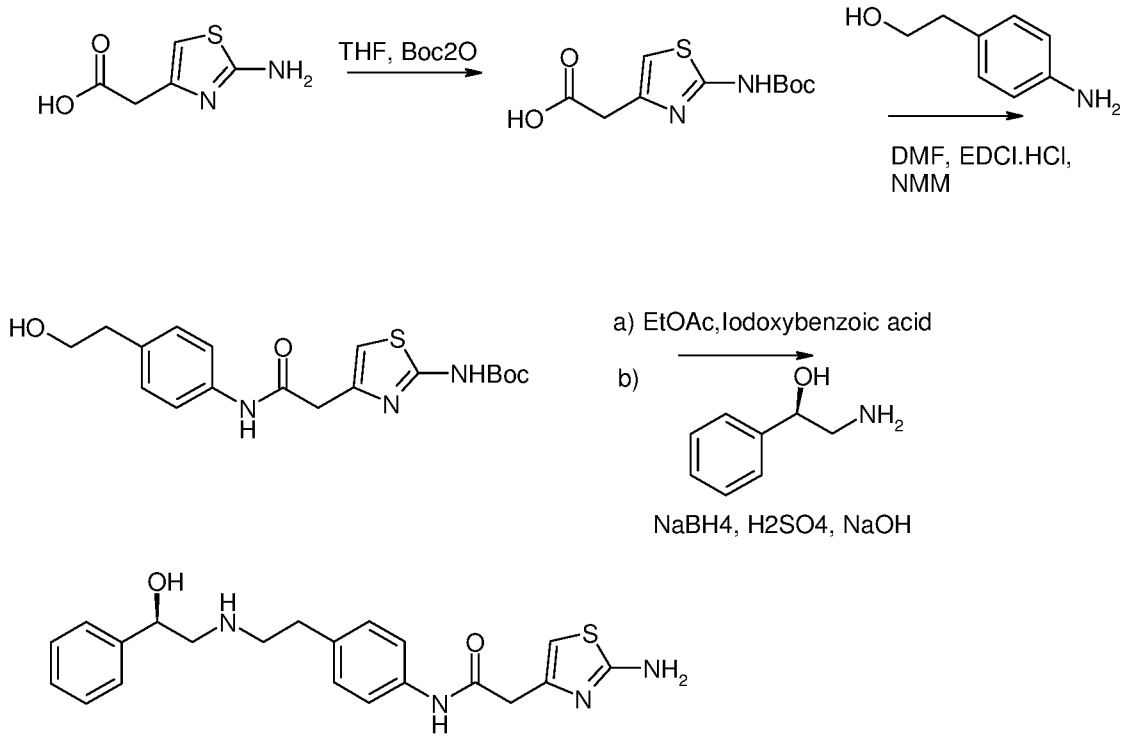
Scheme 2

The methodology entails the use of expensive 2-(4-nitrophenyl)ethanamine salt and autoclave facility for the reduction of nitro intermediate by hydrogenation.

In CN103193730, and CN103232352, Suzhou Uugene Biophrama discloses [a) Hu Fan, ; Wang Shenyong, ; Jia Xinzan, ; Wang Xiaojun, ; Hu Junkai, CN103193730 (A); b) Hu Fan, ; Wang Shenyong, ; Wang Xiaojun, ; Hu Junkai, CN103232352 (A)] (Scheme 3 & 4) another synthetic strategy for Mirabegron, in which 2-(4-aminophenyl)ethanol and (R)-2-amino-1-phenylethanol are the key starting material. Oxidation of hydroxy functionality to aldehydic group and reductive amination are the key steps in the synthesis.

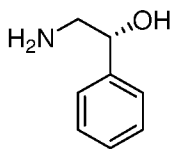

HO
NH2
MeOH, Boc2O
HO
NHBoc
a) THF, KMnO4
b)
OH
NH2
TiCl4,
OH
H
N
NHBoc
Dioxane, HCl
OH
H
N
NH2
.HCl
O
HO
S
NH2
N
AcOH, NaOH,
EDCI.HCl, HOBt,
OH
H
N
O
N
H
S
NH2
N

Scheme 3



Scheme 4

Major drawbacks of the above approaches are the formation of side products resulting due to further oxidation of aldehyde derivative to acid and impurities arising due to further reductive amination of product with aldehyde. Further, (R)-2-amino-1-phenylethanol of Formula IV is a very expensive chiral intermediate and is not available in commercial scale.



Formula IV

Hence, there is a need to provide simple, environmentally friendly, cost effective processes for the preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine and Mirabegon.

Inventors of the present invention have developed an improved process for the preparation of Mirabegron and it's intermediate, which overcome most of the disadvantages of the processes reported in the prior art.

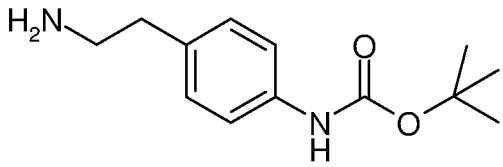
OBJECT OF INVENTION

The first aspect of the invention is to provide an improved process for the preparation of Mirabegron of Formula I.

Another aspect is to provide a simple, economical, and industrially feasible process of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine as a key raw material for the preparation of mirabegron.

SUMMARY OF INVENTION

According to first aspect of the present invention (Scheme 5), an improved process for preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine of Formula II which comprises of



Formula II

a)carrying out nitration of phenylacetonitrile (1) to provide 4-nitrophenylactonitrile (2).

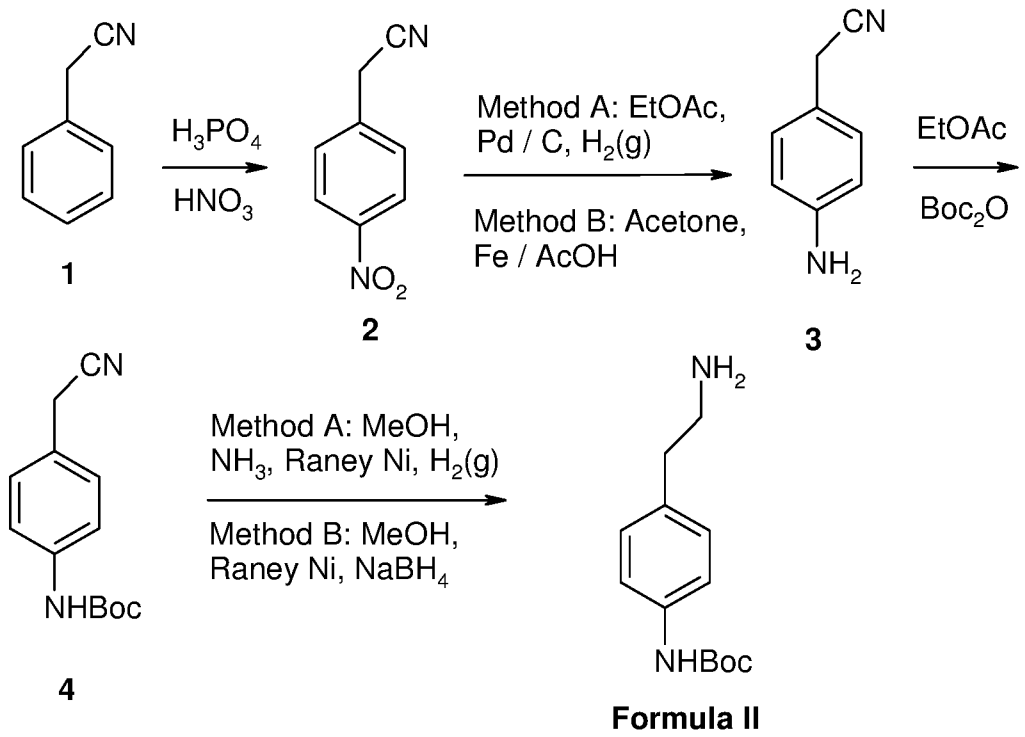
b)reducing 4-nitrophenylacetonitrile (2) to provide 4-aminophenylacetonitrile (3).

c)Protecting 4-aminophenylacetonitrile (3) with di-t-butyl dicarbonate (Boc2O) to provide N-Boc-4-aminophenylacetonitrile (4).

d)reducing N-Boc-4-aminophenylacetonitrile (4) with Raney Nickel under basic medium to provide 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II

e) purifying 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II by acid base treatment

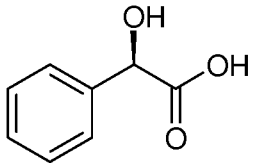
Synthetic scheme of the invention of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine



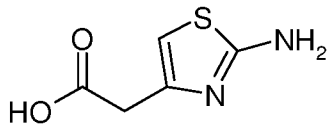
1 2 3 4 **Formula II**

Scheme 5

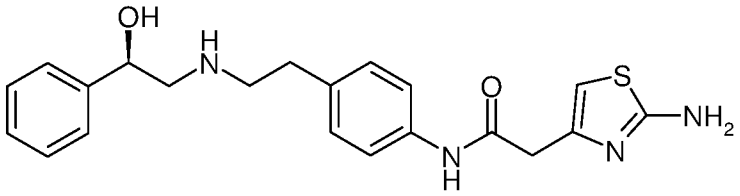
Another aspect of invention (Scheme 6) is economically viable and industrially feasible process for the preparation of Mirabegron of Formula I using (R)-Mandelic acid of Formula V, 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula II and 2-(2-aminothiazol-4-yl) acetic acid of Formula VI as the key raw materials and comprising of



Formula V

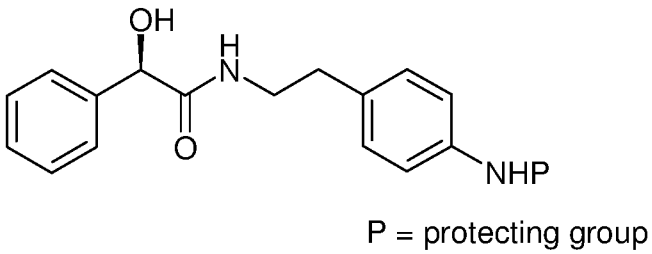


Formula VI



Formula I

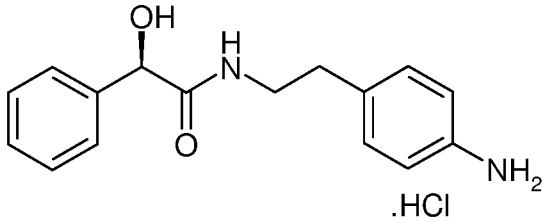
a)amide bond formation between (R)-mandelic acid of Formula V and N-protected 4-(2-aminoethyl)phenylamine of Formula II by using suitable peptide coupling reagent in organic solvent to provide N-protected (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide of Formula VII



P = protecting group

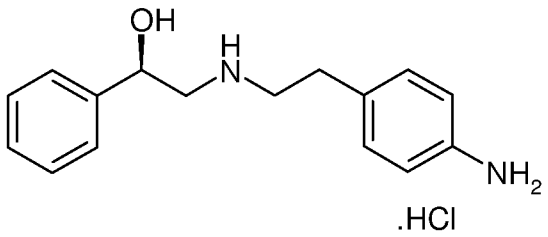
Formula VII

b)removal of protecting group of compound of Formula VII to provide (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride of Formula VIII



Formula VIII

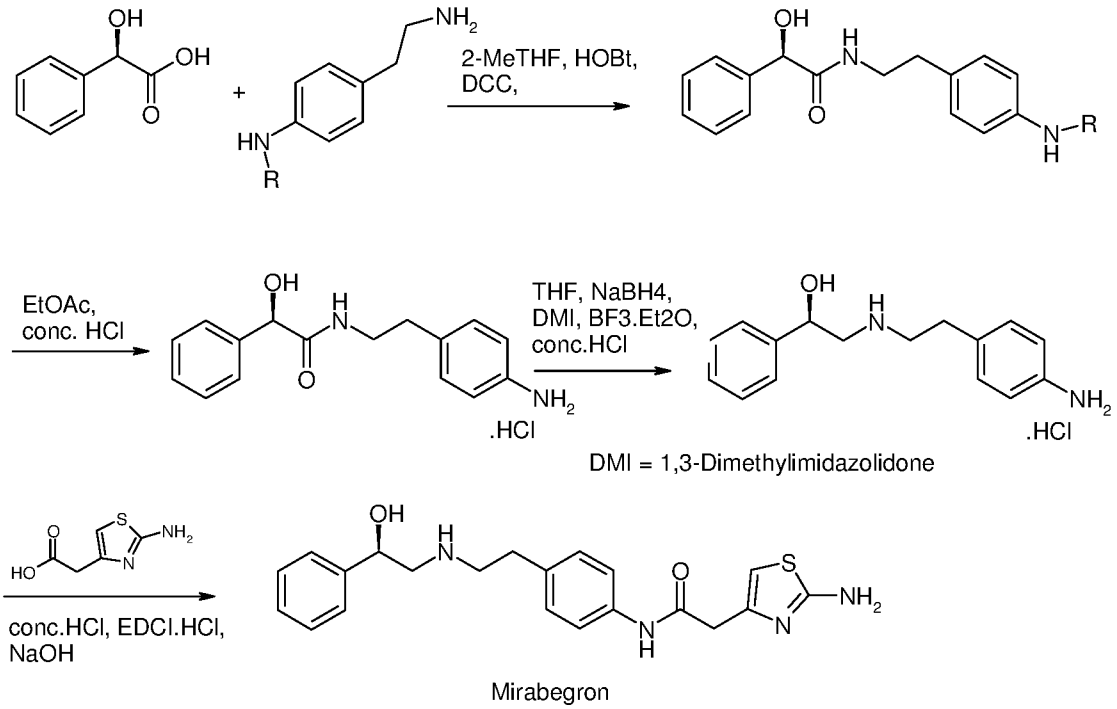
c)reduction of compound of Formula VIII to provide N-protected (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride of Formula IX



Formula IX

d)finally, coupling of compound of Formula IX with 2-(2-aminothiazol-4-yl) acetic acid of Formula VI to provide Mirabegron of Formula I

Synthetic scheme of the invention is as depicted below.



Mirabegron

Scheme 6

wherein R is hydrogen or amino protecting group

DETAILED DESCRIPTION OF INVENTION

The first aspects of the invention relates to the improved and cost effective process for the preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II from easily available phenylacetonitrile (1) over 4 steps, comprising of

a)nitration of phenylacetonitrile (1) with nitrating mixture such as mixture of nitric acid with other inorganic acid like phosphoric acid, sulfuric acid etc., to give a mixture of 2-nitrophenylacetonitrile and 4-nitrophenylacetonitrile (2) in the ratio 15:85. Preferably, mixture of nitric acid and phosphoric acid is used for nitration. 4-Nitrophenylacetonitrile (2) is isolated from the mixture of compounds by crystallization from organic solvents such as ethyl acetate, dichloromethane, alcohols, etc. Preferably, methanol is the solvent of choice for crystallization.

b) reduction of 4-nitrophenylacetonitrile (2) with Fe and acid in organic solvents such as alcohols, acetone, toluene etc to give 4- aminophenylacetonitrile (3). Acid can be inorganic acid such as hydrochloric or organic acid such as acetic acid. Preferably, acid is acetic acid and organic solvent is acetone. Reduction can also be achieved by hydrogenation with hydrogen gas using Palladium on carbon as the catalyst in organic solvent such as alcohols, esters etc. Preferably, organic solvent used in the reaction is ethyl acetate or methanol.

c) protection of 4-aminophenylacetonitrile (3) with di-t-butyl dicarbonate (Boc2O) in organic solvent such as alcohols, esters of organic acids etc. to give N-Boc-4-aminophenylacetonitrile (4), preferably, in ethyl acetate and ethanol.

d)reduction of N-Boc-4-aminophenylacetonitrile (4) with Raney nickel in organic solvents in the presence of base to give 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula II. Organic solvents are alcohols, esters of

organic acid etc. and base is ammonia, organic bases, metal hydroxide etc., preferably, in methanol and base is ammonia or sodium hydroxide. Reduction of N-Boc-4-aminophenylacetonitrile (4) can also be achieved with Raney Nickel by using potassium borohydride as the source of hydrogen in organic solvents like methanol, ethanol or other hydroxy solvents. Methanol is the preferable solvent for the reduction.

e) purification of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II by converting it to salt using organic or inorganic acid, preferably hydrochloric acid. Hydrochloride salt of compound of formula II is basified with hydroxide of alkali, alkaline earth metal, to give 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II as a free base. Preferably, sodium hydroxide is used.

The second aspects of the present invention relates to the improved, simple and economic process for the preparation of Mirabegron of Formula I. Process comprises of

a)coupling reaction between (R)-mandelic acid of Formula V and N-protected 4-(2-aminoethyl)benzenamine of Formula II by using suitable peptide coupling reagent in organic solvent to give amino protected (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide of Formula VII, which on subsequent deprotection with acid give (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride of Formula VIII

The amino protecting agent is in the class of an alkoxy carbonyl amino-protecting group, acyl protecting group or a benzyl protecting group.

Further, di-t-butyl dicarbonate (Boc2O) is the preferable amino-protecting agent. It is well known that amino protection as N-BOC- & it's deprotection is simple and high yielding and also, do not generate any byproduct.

According to an embodiment of the present invention, the coupling agent or dehydrating agent is selected from dicyclohexylcarbodiimide (DCC), N,N'-

carbonyldiimidazole (CDI) can be used. Further useful coupling/dehydrating agents are trifluoroacetic anhydride, mixed anhydride, acid chlorides, 1-hydroxybenzotriazole(HOBt), 1-hydroxy-4-azabenzotriazole, 1-hydroxy-7-azabenzotriazole, N-ethyl-N'-(3-(dimethylamino)propyl)carbodimide hydro-chloride (EDCI.HCl), 3-hydroxy-3,4-dihydro-4-oxo-1,2,3-benzotriazine, O-(benzo-triazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, O-(benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate, O-(1H-benzotrizol-1-yl)-1,1,3,3-bis(tetramethylene)uranium hexafluorophophate or their combination can be employed as a coupling & dehydrating agent, preferably DCC-HOBt combination is used.

Organic solvent can be selected from halogenated, non-halogenated, polar, protic-aprotic or aromatic solvent or mixture thereof can be used. Preferably, 2-methyltetrahydrofuran is used for the reaction.

Coupling reaction can be performed at temperature ranging from 10-50°c temperature, preferably performed at 20-30°C temperature.

Deprotection of protecting group can be performed by known prior art method like in aqueous or non-aqueous acidic media in organic solvents. Preferably, aq. hydrochloric acid is used as an acid and ethyl acetate is the organic solvent. .

BOC-deprotection is observed to be very simple & gives clean reaction. It produces (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride of Formula VIII having HPLC purity more than 99%.

b) Hydrochloride salt of Formula VIII is converted into free base by using inorganic base, preferably aq. NaOH is used. Reduction of free base can be achieved by known reducing agent like, borane-THF complex, lithium aluminum hydride, Vitride reagent etc, to give (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride of Formula IX. Preferably, borane-THF complex is used as the reducing agent. It is generated in-situ in the reaction using NaBH4 and BF3.etherate.

c)Finally,coupling of (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride of Formula IX with 2-(2-aminothiazol-4-yl) acetic acid of Formula VI is carried out by using known coupling agent like DCC, CDI, and EDCl.HCl etc. under acidic condition. Preferably, EDCl.HCl is used and pH of the reaction is 1.5-3.5.

EXAMPLES

A)Preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula II

Step 1

4-Nitrophenylacetonitrile (2):

Nitrating mixture was prepared by adding nitric acid (966 gm, 15.34 moles) to orthophosphoric acid (457 gm, 4.66 moles) at 0-5°C. To above nitrating mixture, phenylacetonitrile (1) (400 gm, 3.41 moles) was added at 0-5°C. Mixture was warmed to 20-25°C and stirred at same temperature for two hrs. After completion of reaction, as revealed from TLC, mixture was quenched over 4 kg of ice. Precipitated solid was filtered and wet solid was crystallized from 3200 ml methanol. Solid was dried at 55-60°C for 8-10 hrs to give 305 gm of 4-nitrophenylacetonitrile (2). Filtrate was concentrated to approx. 2000 ml and cooled to 20-25°C. Precipitated 4-nitrophenylacetonitrile (2) after drying at 55-60°C for 8-10 hrs weighed 330 gm.
Dry weight of product: 330 gm (60%).
^{1}H NMR (CDCl3 and 400MHz): δ 3.47 (2H, s), 7.53 (2H, d), 8.25 (2H, d)

Step 2

4-Aminophenylacetonitrile (3):

Method A:

To a solution of (274 gm, 1.69 moles) 4-nitrophenylacetonitrile (2) in 2740 ml of ethyl acetate, wet 10% palladium on charcoal (27.4 gm) was added at 20-25°C under nitrogen atmosphere. Reaction mixture was subjected to hydrogenation at 50-60 PSI for 3-4 hrs. After completion of reaction, as revealed from TLC, reaction mixture was filtered and washed with 250 ml of ethyl acetate. Filtrate on evaporation gave 213 gm of 4-aminophenylacetonitrile (3) as orange colored solid.

Dry weight: 213 gm (96%).

^{1}H NMR(CDCl3 and 400MHZ): δ3.57 (2H, s),3.74 (2H, s), 6.63 (2H, d), 7.05 (2H, d)

Method B:

To a mixture of (25 gm, 0.154 moles) 4-nitrophenylacetonitrile and (21.52 gm, 0.384 moles) iron powder in 125 ml of acetone, acetic acid (131.12 gm, 14.16 moles) was added at 20-25°C. Reaction mixture was heated to 50-55°C for 4-5 hrs. After completion of reaction, as revealed from TLC, mixture was cooled to 20-25°C, filtered and washed with (2 X 25 ml) of acetone. Filtrate was concentrated to dryness and resulting residue was dissolved in 50 ml of ethyl acetate. Ethyl acetate solution was washed with (2 X 25 ml) of water and concentrated under vacuum to give 17.23 gm of 4-aminophenylacetonitrile (3).

Dry weight: 17.23 gm (85%)

Step 3

N-Boc-4-aminophenylacetonitrile (4):

To a solution of (208 gm, 1.57 moles) 4-aminophenylacetonitrile in 520ml of EtOAc, (429.8 gm, 1.96 moles) di-tert-butyl dicarbonate was added at 25-30°C over a period of 30-45 minutes. Reaction mixture was stirred at 25-30°C for 3-4 hrs. After completion of reaction as revealed from TLC, precipitated N-Boc-4-

aminophenylacetonitrile (4) was filtered and washed with (2 X 100vml) chilled ethanol. Solid after drying under vacuum at 50-60°C for 8-10 hrs weighed 333 gm.
Dry weight: 333 gm (92%)
^{1}H NMR (CDCl3) and 400 MHz): δ 1.51(9H, s), 3.69 (2H, s), 6.55 (1H, s), 7.25 (2H, d), 7.37 (2H, d)

Step 4

4-(2-Aminoethyl)-N-(tert-butoxycarbonyl) phenylamine (Formula II):

Method A:

To a solution of (300 gm, 1.29 moles) N-BOC-4-aminophenylacetonitrile in 3000 ml of methanol, 25% aq. ammonia solution (480 ml) and Raney nickel (45 gm) were added at 25 -30°C. Reaction mixture was subjected to hydrogenation at 50-60 PSI for 4 hrs. After completion of reaction, as indicated from TLC, reaction mixture was filtered and washed with (2 X 25 ml) methanol. Filtrate was concentrated under vacuum and resulting residue was treated with (1500 ml) 1M aq. hydrochloric acid at 25-30°C. Reaction mixture was stirred for 15 minutes and filtered to remove insoluble impurities. Filtrate was basified to pH 10-12 with 50% aq. NaOH solution below 25°C. Precipitated 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine was filtered and washed with (2 X 100 ml) water. Solid was dried under vacuum at 55-60°C for 8-10 hrs.
Dry weight: 240 gm (79%).
^{1}H NMR (CDCl3 and 400 MHz): δ 1.11 (2H, s), 1.51 (9H, s), 2.68 (2H, t), 2.93 (2H, t), 6.72 (1H, s), 7.10 (2H, d), 7.28 (2H, d)

Method B:

To a solution of (1.1 gm, 0.0047 moles) of N-BOC-4-aminophenylacetonitrile in 15ml of methanol, Raney nickel (0.6 gm) was added at 20-25°C under nitrogen atmosphere. To the reaction mixture, potassium borohydride (2.16 gm, 0.041 moles)

was added below 25°C and stirred at same temperature for 2-3 hrs. After completion of reaction as revealed from TLC, reaction mixture was concentrated under vacuum to give a residue which was purified by acid base treatment using 1M aq. Hydrochloric acid as above. 4-(2-Aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine was obtained as off-white solid after drying at 55-60°C for 8-10 hrs.
Dry weight: 0.8 gm (72%).

B)Process for preparation of Mirabegron:

Step 1 :

N-Boc-(R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide (Formula VII wherein P = tert-butoxycarbonyl):

To a mixture of (R)-mandelic acid (V) (139 gm, 0.91 moles) and 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine (Formula II) (215 gm, 0.91 moles) in 1300 ml of 2-methyltetrahydrofuran, hydroxybenzotriazole (123.4 gm, 0.91 moles) and N,N'-dicyclohexylcarbodiimide (189g, 0.91 moles) were sequentially added between 25-30°C. Reaction mixture was stirred between 25-30°C for 2 hrs. After completion of reaction, as indicated from TLC, precipitated urea, byproduct was filtered. Filtrate was washed sequentially with (200ml) 5% aq. hydrochloric acid, (200ml), 10% aq. sodium bicarbonate solution and (200ml) water. Organic layer was concentrated to approx. 600ml and cooled to 15-20°C. Precipitated urea byproduct was filtered. Filtrate was concentrated to dryness and resulting residue was dissolved in ethyl acetate (800ml) under refluxing. On cooling to 20-25°C, N-Boc-(R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide was crystallized as colorless solid, which was filtered and dried at 50-60°C for 4 hrs.
Dry Weight: 260gm (77%) and HPLC purity >99%.

1H NMR (CDCl3 and 400MHz): δ 1.51 (9H, s), 2.63-2.73 (2H, m), 3.38-3.51 (2H, m), 3.79 (1H, d), 4.93 (1H, d), 6.14 (1H, br) 6.48 (1H, s), 6.92-6.94 (2H, d), 7.21-7.26 (2H, m), 7.30-7.34 (5H, m).

Step 2:

(R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamidehydrochloride (Formula VIII):

At room temperature, N-Boc-(R)-N-(4-aminophenethyl)-2-hydroxy-2-phenyl-acetamide (245 gm, 0.66 moles) was added to a solution of conc. HCl (229 ml) in 502 ml of ethyl acetate. Mixture was stirred at room temperature for 4 hrs and precipitated (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydro-chloride was filtered and resulting solid was washed with ethyl acetate (240 ml). Hydrochloride salt was dried at 50-60°C for 5 hrs.

Dry weight: 161gm (79%) and HPLC purity >99%

Filtrate was neutralized to pH 8-9 with 50% aq. NaOH solution. Ethyl acetate layer was separated and concentrated to approx. 100ml and conc. HCl (13ml) was added at room temperature. Precipitated (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride was filtered and resulting solid was washed with ethyl acetate (50ml). Hydrochloride salt was dried at 50-60°C for 5hrs.

Dry weight: 18 gm (9%) and HPLC purity >98%.

1H NMR (DMSO-d6, 400MHz): δ 2.72-2.75 (2H, t), 3.29-3.31 (2H, t), 4.87 (1H, s), 7.23-7.35 (9H, m), 8.12 (1H, d), 10.3 (3H, s).

Step 3 :

(R)-N-(4-Aminophenethylamino)-1-phenylethanol hydrochloride (Formula IX):

To a solution of (23.5 gm, 0.0766 moles) of (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride in water (140 ml), 10% aq. NaOH solution was slowly added between 10-15°C till pH of the solution is 9-10. Reaction mixture was

extracted with ethyl acetate (3 X 50 ml) and organic layer was washed with water (2 X 50 ml). Organic layer was evaporated under vacuum and 20.5 gm of oily residue obtained was dissolved in tetrahydrofuran (55 ml).

This solution was slowly added to a mixture of sodium borohydride (4.3 gm, 0.11 moles) and 1,3-dimethylimidazolid-2-one (18.6 gm, 0.16 moles) in tetrahydrofuran (115 ml) between 5-10°C under nitrogen atmosphere. To reaction mixture, 47% solution of boron trifluoride etherate complex (32.3 gm, 0.22 moles) was cautiously added below 15°C under nitrogen atmosphere. After completion of addition, reaction mixture was heated to 65°C for 4 hrs. After completion of reaction mixture, as revealed from TLC, reaction mixture was cooled to 5-10°C and methanol (10 ml) and conc. HCl (15 ml) were cautiously added below 10°C under nitrogen atmosphere. After stirring for 30 minutes, water (40 ml) was added and reaction mixture was concentrated to remove tetrahydrofuran. Reaction mixture was cooled to 20-25°C and pH adjusted to 9-10 with 30% aq. NaOH solution. Reaction mixture was extracted with (2 X 50 ml) of ethyl acetate and organic layer was washed with water (80ml). To the organic layer, 15% solution of HCl in isopropanol (20 ml) was added at 20-25°C. Precipitated (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride was filtered and washed with ethyl acetate (20ml). Solid was dried at 50-60^{0}C for 5 hrs.

Dry weight: 20.2 gm (90%), HPLC Purity: 99.7% and Chiral purity 99.8%.

1H NMR (DMSO-d6, 400 MHz): δ 3.03-3.17 (6H, m), 5.03 (1H, d), 6.01-6.23 (1H, br), 7.36-7.38 (9H, m), 9.08 (1H, br), 9.59 (1H, br) and 10.57 (3H, br).

Step 4 :

2-(2-Amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}-ethyl)phenyl]acetamide (Formula I):

To a mixture of (7.9 gm; 0.027 moles) (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride and (4.32gm; 0.027 moles) 2-aminothiazol-4-yl acetic acid in (80ml) water, conc. HCl was added between 15 to 20°C till the pH of the

solution in the range of 1.8 -2. To the reaction mixture, (10.48 gm; 0.054moles) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride was added and mixture stirred for 1hr. After completion of reaction, as revealed from TLC, pH of the reaction mixture was adjusted to 9-10 with 5% aq. sodium hydroxide solution. Precipitated 2-(2-amino-1,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2-phenylethyl]amino}ethyl)phenyl]acetamide was filtered and filtered cake was washed with water. Wet solid was dried at 600C for 6 hrs.

Dry wt: 10.0 gm (92%) and HPLC purity 99.5%

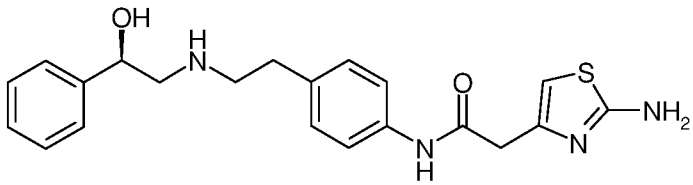
The above (10gm) dried product was crystallized from mixture of methanol and water (1:2) to give 9.0 gm of colorless solid. It was dried under at 60°C for 6 hrs

Dry weight: 9 gm; HPLC Purity 99.7% and Chiral Purity 99.8%.

1H NMR (DMSO-d6, 400MHz): δ 1.60 (1H, s), 2.59-2.66 (4H, m), 2.68-2.77 (2H, m), 3.44 (2H, s), 4.59 (1H, br), 5.23 (1H, br), 6.30 (1H, s), 6.92 (2H, s), 7.11 (2H, d), 7.19-7.23 (1H, m), 7.27-7.33 (4H, m), 7.49 (2H, d), 10.01 (1H, s).

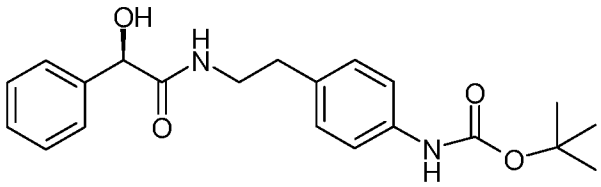
We Claim:

1. A novel process for preparation of Mirabegron of formula (I), comprising



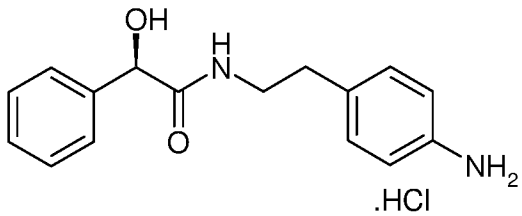
Formula I

a) Coupling of Mandelic acid of Formula (V) with 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenyl amine of Formula II in the presence of activating agent such as DCC or EDCI.HCl ot obtain compound of formula (VII)



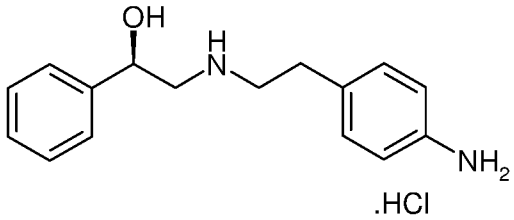
Formula VII

b) Deprotection of Compound of (VII) in presence of inorganic acid or organic acid preferably hydrochloric acid and Ethyl acetate to obtain compound of Formula (VIII)



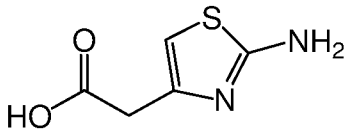
Formula VIII

c) Reduction of compound of Formula (VIII) using Sodium borohydride and BF3.etherate in the presence of N,N'-dimethylimidazolidinone and tetrahydrofuran to obtain compound of Formula (IX).



Formula IX

d) Coupling of Compound of Formula (VI) & compound of formula (IX) using 3-(Ethyliminomethyleneamino)-*N*,*N*-dimethylpropan-1-amine in Hydrochloric acid and water to obtain Mirabegron of formula (I)



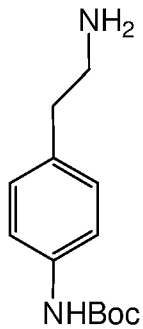
Formula VI

2. A process as claimed in claim 1(d) coupling of Compound of formula (VI) with compound of formula (IX) between pH 1.5 to 3.0.

3. A process as claimed in claim 1(d), coupling of compound of formula (VI) with compound of formula (IX) at the 1.5 to 5.0 mole equivalent

.

4. A process for preparing 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenyl amine of Formula (II) an intermediate of Mirabegron, comprising



Formula II

a) Nitration of phenyl acetonitrile (1) to obtain 4-nitrophenylacetonitrile (2)

b) Reduction of 4-nitrophenylacetonitrile (2) to obtain 4-aminophenyl-acetonitrile (3)

c) Protection of amino group of 4-aminophenylacetonitrile (3) to obtain N-Boc-4-aminophenylacetonitrile (4)

d) Reduction of nitrile group of N-Boc-4-aminophenylacetonitrile (4) to obtain 4- (2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine of Formula (II).

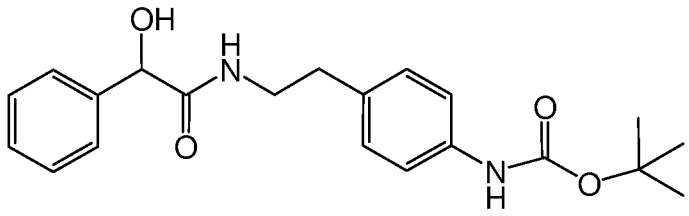
e) Treating formula (II) with other organic acid or inorganic acid preferably aqueous hydrochloric acid.

f) Basifying the filtrate with aqueous alkali preferably sodium hydroxide to obtain 4- (2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula (II) in pure form.

5. A process as claimed in claim 4, wherein solvent use in reaction step (d) is methanol, ethanol, propanol, isopropanol or higher hydroxyl or poly hydroxy alcohol.

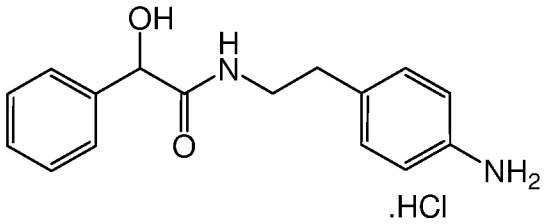
6. A process as claimed in claim 4, wherein metal catalyst in reaction step (d) is Raney nickel & source of hydrogen is hydrogen gas or metal borohydride or hydrazine hydrate.

7. A novel compound of Formula (VII) as a single enantiomer or a mixture thereof



Formula VII

8. A novel compound of Formula (VIII), as a enantiomer or a mixture thereof, or hydrochloride salt thereof



Formula VIII

9. Preparation of Mirabegron using compound of Formula (II) as a intermediate.

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/052839

A. CLASSIFICATION OF SUBJECT MATTER
C07D277/40 Version=2015.01

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

C07D277/40

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

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

PATSEER, IPO Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 2011/230530 A1, ASTELLAS PHARMA INC, 22 September,2011(22-09-2011), Whole document	1-9
Y	US 6346532 B1, ASTELLAS PHARMA INC, 12 February, 2002(12-02-2002), Whole document	1-9
Y	JP 2011/105685 A, ASTELLAS PHARMA INC, 02 June, 2011(02-06-2011), whole document	1-9

☐ 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
30-07-2015	30-07-2015

Name and mailing address of the ISA/	Authorized officer
Indian Patent Office Plot No.32, Sector 14,Dwarka,New Delhi-110075 Facsimile No.	Dr. Sunita Rani Telephone No. +91-1125300200

INTERNATIONAL SEARCH REPORT
Information on patent family members

International application No.
PCT/IB2015/052839

Citation	Pub.Date	Family	Pub.Date
US 2011/230530 A1	22-09-2011	WO 2004041276 A1	21-05-2004
		JP 3815496 B2	30-08-2006
		IN DELNP-2007-06316 A	31-08-2007
		US 2009093529 A1	09-04-2009
		IN DELNP-2005-01871 A	09-10-2009
		EP 1559427 B1	09-03-2011
		US 8835474 B2	16-09-2014
US 6346532 B1	12-02-2002	WO 9920607 A1	29-04-1999
		JP 3193706 B2	30-07-2001
		EP 1028111 B1	12-05-2004
		KR 100506568 B1	21-04-2006
		CA 2305802 C	18-11-2008
		NO 2013013 I1	29-07-2013

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB2015/052839

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:
1. Group-I: Claims 1-3 and 7-9

Claim 1 defines a novel process for the preparation of Mirabegron of Formula I using (R)-Mandelic acid of Formula V, 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)phenylamine of Formula II and 2-(2-aminothiazol-4-yl) acetic acid of Formula VI as the key raw materials and comprising of
a) amide bond formation between (R)-mandelic acid of Formula V and

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☒ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

Continuation of Observations where unity of invention is lacking(Box III)

N-protected 4-(2-aminoethyl)phenylamine of Formula II by using suitable peptide coupling reagent in organic solvent to provide N-protected (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide of Formula VII
b) removal of protecting group of compound of Formula VII to provide (R)-N-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide hydrochloride of Formula VIII
c) reduction of compound of Formula VIII to provide N-protected (R)-N-(4-aminophenethylamino)-1-phenylethanol hydrochloride of Formula IX
d) finally, coupling of compound of Formula IX with 2-(2-aminothiazol-4-yl) acetic acid of Formula VI to provide Mirabegron of Formula I
Dependent claims 2-3 defines the reaction parameters and claims 7-9 defines the intermediates and final product.

2. Group-II: Claims 4-6

Claim 4 defines the preparation of 4-(2-aminoethyl)-N-(tert-butoxycarbonyl) phenylamine of Formula II which comprises of

a) carrying out nitration of phenylacetonitrile (1) to provide 4-nitrophenylactonitrile(2).
b) reducing 4-nitrophenylacetonitrile (2) to provide 4-aminophenylacetonitrile (3).
c) Protecting 4-aminophenylacetonitrile (3) with di-t-butyl dicarbonate (Boc2O) to provide N-Boc-4-aminophenylacetonitrile (4).
d) reducing N-Boc-4-aminophenylacetonitrile (4) with Raney Nickel under basic medium to provide 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II
e) purifying 4-(2-aminoethyl)-N-(tert-butoxycarbonyl)-phenylamine of Formula II by acid base treatment

Dependent claims 5-6 defines the reaction parameters.