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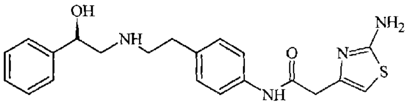
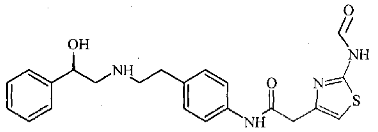
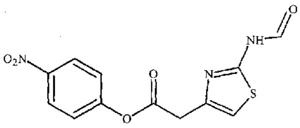
(54) **Title**: A PROCESS FOR THE PREPARATION OF MIRABEGRON AND ITS INTERMEDIATES



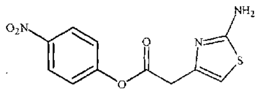
Formula (I)



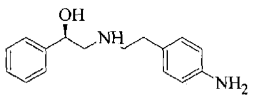
Formula (II)



Formula (IIIa)



Formula (IIIb)



Formula (IV)

(57) **Abstract**: The present invention relates to a novel process for preparation of Mirabegron of Formula (I) using intermediates of Formula (II), (IIIa), (IIIb) and (IV).

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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).

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

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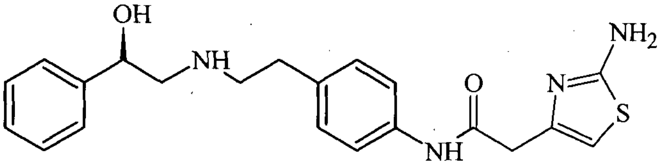
Related Applications

This is cognate complete specification for Indian patent application no. 2534/MUM/2014 filed on 07/08/2014 and 4142/MUM/2014 filed on 24/12/2014.

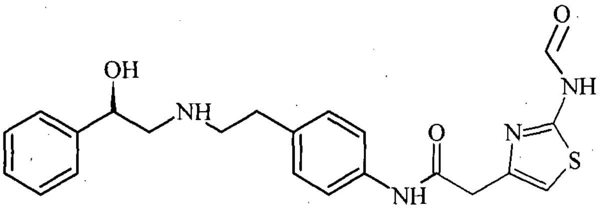
Technical field of the invention:

The present invention relates to a process for preparation of Mirabegron of Formula (I).

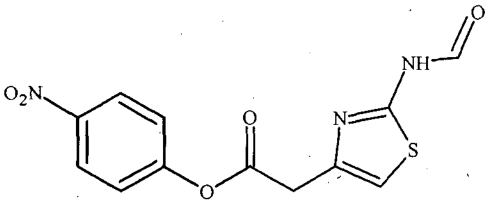


Formula (I)

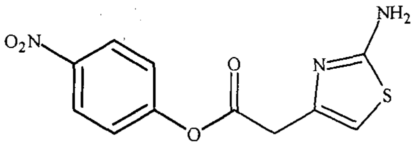
The present invention further relates to the preparation of Mirabegron of Formula (I) by using compounds of Formula (II), (IIIa), (IIIb) and (IV)



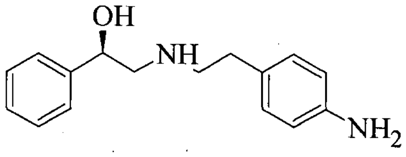
Formula (II)



Formula (IIIa)



Formula (IIIb)



Formula (IV)

Furthermore, the present invention relates to process for preparation of compound of Formula (II), (IIIa), (IIIb) and (IV).

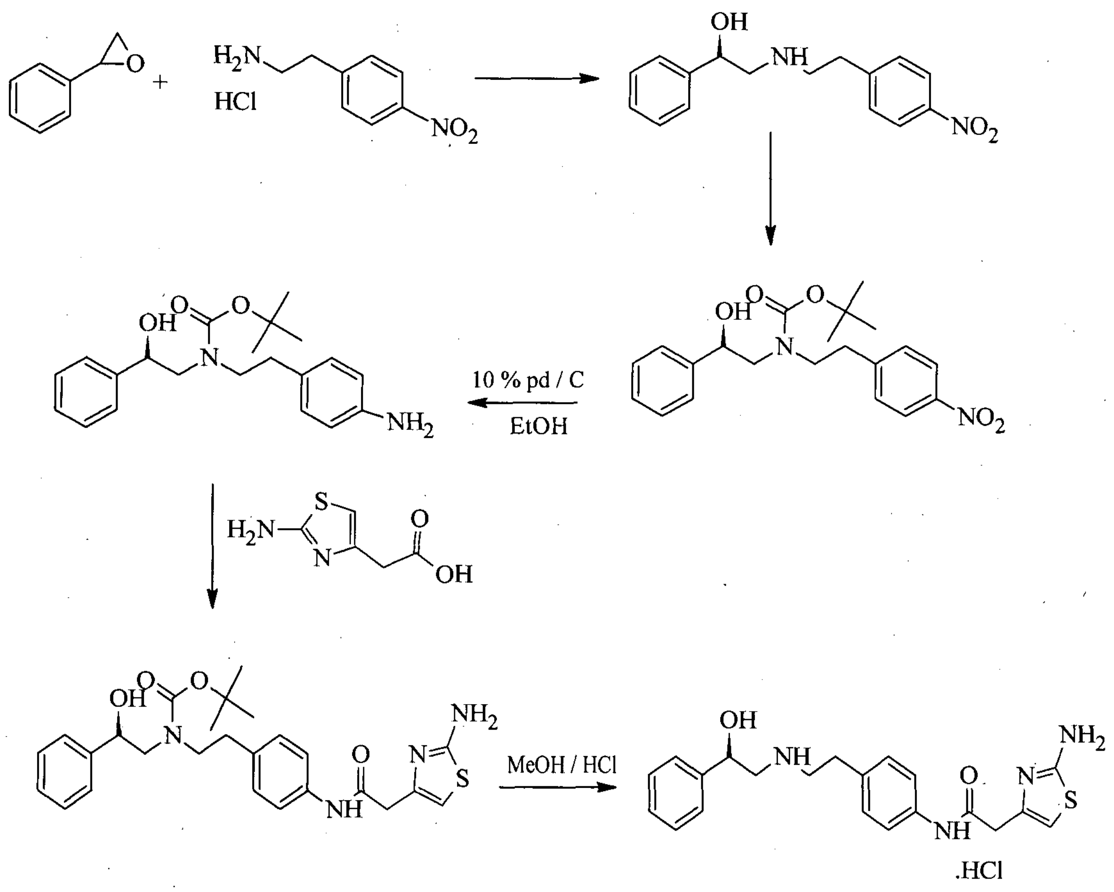
Background of the invention:

Mirabegron is chemically known as 2-amino-N-[4-[2-[[(2R)-2-hydroxy-2-phenylethyl]amino]ethyl]phenyl]-4-thiazoleactamide and is marketed under trade name Myrbetiq.

Mirabegron is a drug used for treatment of overactive bladder. It was first disclosed in US 6,346,532, wherein (R)-Styrene oxide is reacted with 4-nitrophenyl ethyl amine hydrochloride to obtain (R)-1- phenyl-2-[[2-(4-nitrophenyl)ethyl]amino]ethanol, the later is then protected with BOC anhydride and subjected to reduction in the presence of Pd/C to yield N-[2-(4-Aminophenyl)ethyl]-N-[(2R)-2-hydroxy-2-phenylethyl]carbamic acid tert-butyl ester. Thus formed compound was then coupled with (2-amino-1,3-thiazol-4yl) acetic acid to obtain BOC protected Mirabegron which is de-protected to give Mirabegron hydrochloride.

The synthetic route proposed in US 6,346,532 is presented in Scheme-I.

Scheme-I



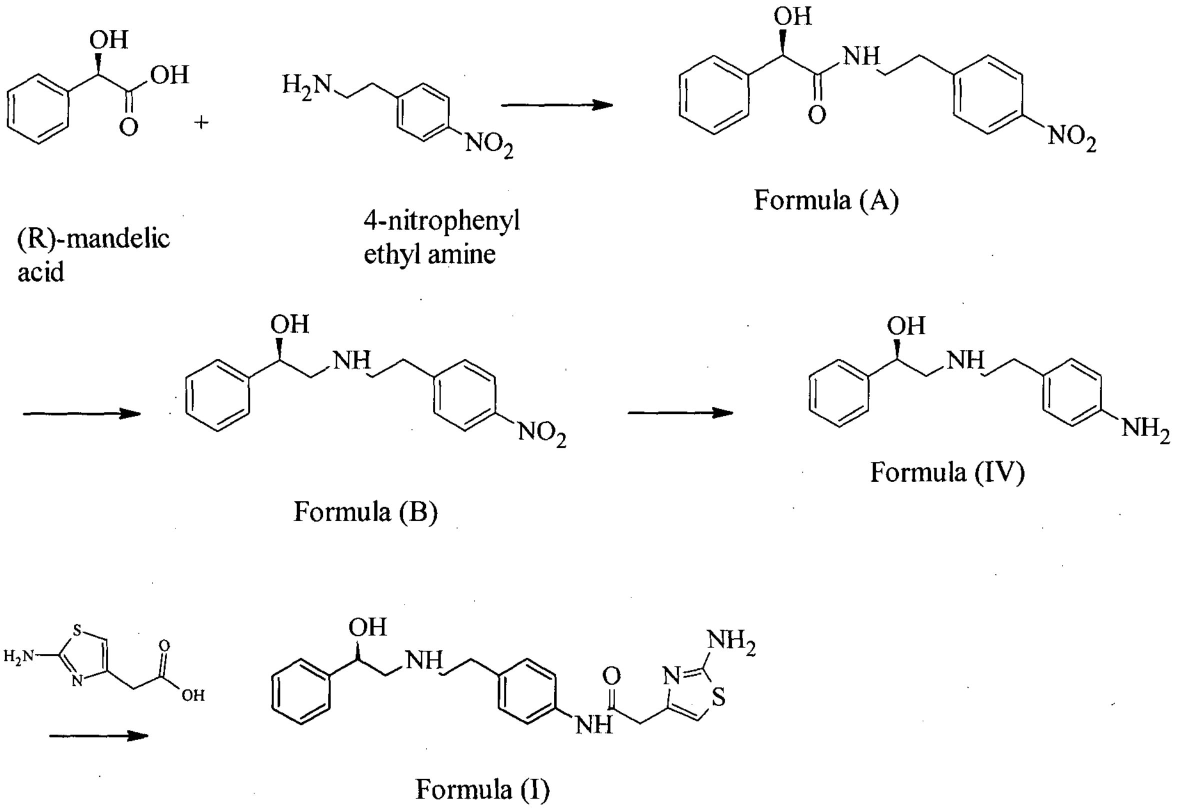
Formula I

The major draw-backs of the presented synthetic scheme are as follows:

1. Less atomic efficiency
2. Low yield and extensive impurities formations
3. Use of expensive and sensitive protecting agents
4. Column chromatographic techniques for purifications of intermediates.

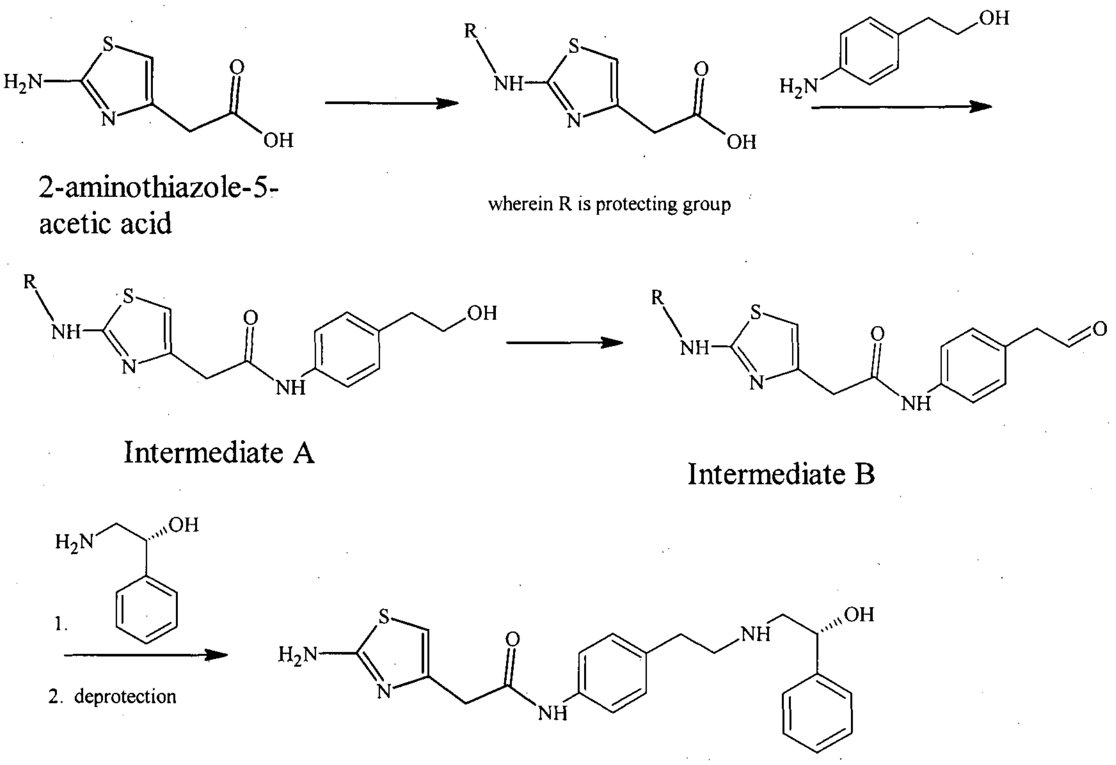
One more synthetic route for the preparation of Mirabegron have been proposed in US 6,346,532, however it is not exemplified.

US 7,342,117 disclose a process for preparation of Mirabegron. The process involves the step of condensation of 4-nitrophenyl ethylamine and (R)- mandelic acid in presence of triethylamine, hydroxybentriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide in N,N-dimethylformamide to obtain compound of Formula (A). The second step involves conversion of compound of Formula (A) to compound of Formula (B) in presence of 1,3-dimethyl-2-imidazolidone and borontetrahydro fluoride in tetrahydrofuran. In third step, compound of Formula (B) is subjected to reduction using 10% palladium-carbon in methanol to afford (R)-2-[[2'-(4-aminophenyl)-ethyl amino]-1-phenylethanol (Formula IV), which was further condensed with 2-aminothiazol-4-yl acetic acid in presence of 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide and hydrochloric acid in water to obtain Mirabegron of Formula (I). The schematic representation is as Scheme-II



Scheme-II

Another patent application CN103193730, discloses a novel process for preparation of Mirabegron wherein the amino group of 2-aminothiazole-5-acetic acid is protected with a protecting group and is condensed with 4-amino phenyl ethanol to obtain an intermediate (A); which on further oxidation yields intermediate (B). The intermediate B is subjected to reductive amination with (R)-2-amino-1-phenyl ethanol and deprotection, simultaneously to yield Mirabegron. The schematic representation is as Scheme-III.



Scheme-III

Other references wherein process for preparation of Mirabegron are disclosed in CN103387500 and CN103232352.

Most of the prior art reported for preparation of Mirabegron uses expensive and sensitive protecting agents thereby making process less feasible on industrial scale. Furthermore, the yield and purity of Mirabegron obtained by the processes known in art is not satisfactory. It is well known fact that pharmaceutical products like Mirabegron should have high purity due to the therapeutic advantages and also due to the stringent requirements of regulatory agencies. The purity requirements can be fulfilled either by avoiding the formation of by-products during the process or by purifying the end product of the process. The inventors of present invention have skillfully developed the process to provide Mirabegron with unachieved level of purity. Furthermore, the process of present invention is simple, industrially viable, and economic and avoids unfavorable reaction conditions.

Object of Invention:

1. The main object of the present invention is to provide a compound of Formula (II), (IIIa),(IIIb) and (IV), and the processes for preparation of the same.

2. Another object of the present invention is to provide a novel process for preparation of Mirabegron of Formula (I) by using compounds of Formula (II), (IIIa) , (IIIb) and (IV).

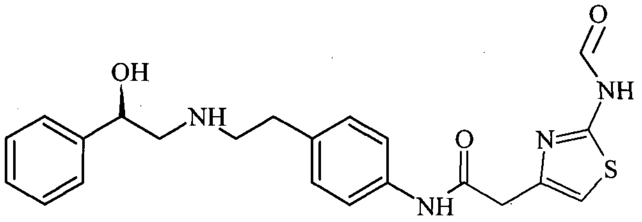
3. Another object of the invention is to provide a novel process for preparation of Mirabegron of Formula (I).

4. Another object of present invention is to provide simple, economically viable and a better yielding process for preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) or its hydrochloride/dihydrochloride salt, with a high purity.

5. Yet another object of the present invention is to provide simple, economic and industrially scalable process for the preparation of Mirabegron of Formula (I).

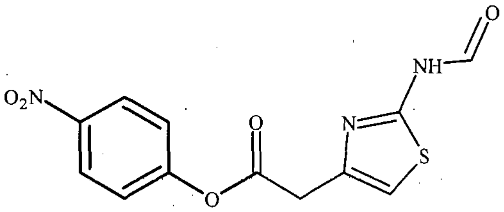
Summary of the invention

According to first aspect of present invention, there is provided a novel compound of Formula (II).



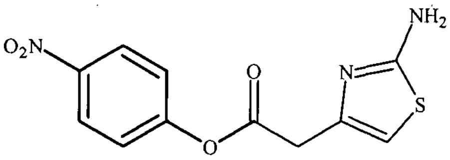
Formula (II)

According to second aspect of present invention, there is provided a novel compound of Formula (IIIa).



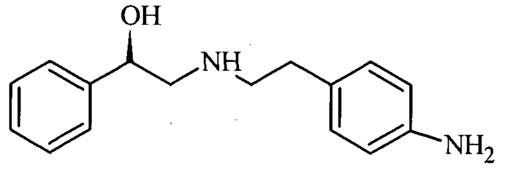
Formula (IIIa)

According to third aspect of present invention, there is provided a novel compound of Formula (IIIb) or its acid addition salt.

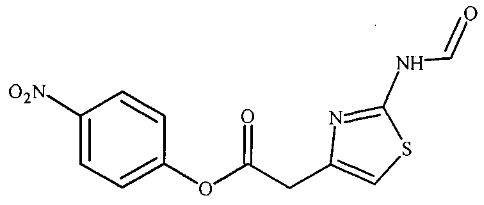


Formula (IIIb)

According to fourth aspect of present invention, there is provided a process for preparation of a novel compound of Formula (II) by coupling of compound of Formula (IV) with compound of Formula (IIIa) in presence of a base in a suitable solvent.

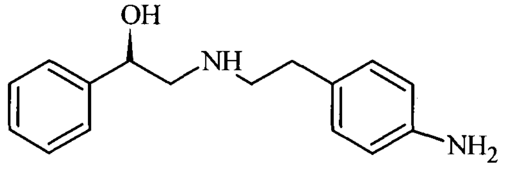


Formula (IV)

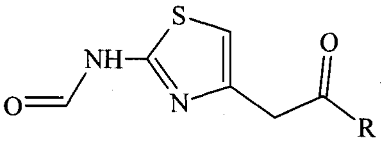


Formula (IIIa)

According to fifth aspect of present invention, there is provided an alternative process for preparation of a novel compound of Formula (II), by coupling of compound of Formula (IV), with compound of Formula (V) in the presence of a carboxyl activating agent when R is –OH, or in the presence of a base when R is –Cl, in a suitable solvent.



Formula (IV)



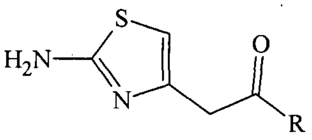
Formula (V)

Wherein R is either –OH or –Cl

According to sixth aspect of present invention there is provided a process for preparation of compound of Formula (IIIa), by esterifying compound of Formula (V) with p-nitro phenol.

According to seventh aspect of present invention there is provided a process for preparation of compound of Formula (IIIb) by esterifying compound of Formula (VI) with p-nitro phenol.

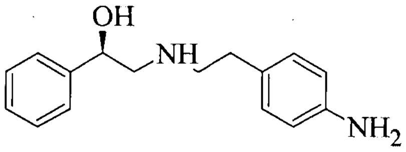
According to seventh aspect of present invention there is provided a process for preparation of compound of Formula (IIIb) by esterifying compound of Formula (VI) with p-nitro phenol.



Formula (VI)

Wherein R is either –OH or –Cl.

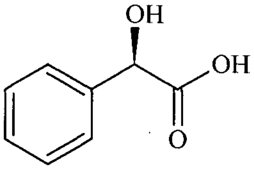
According to eighth aspect of present invention, there is provided an improved process for preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) or its hydrochloride/dihydrochloride salt;



Formula (IV)

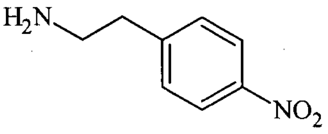
comprising steps of:

a) coupling of compound of Formula (VII) or tosyl protected compound of Formula (VII)



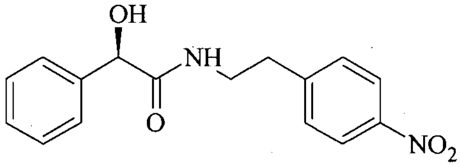
Formula (VII)

with 4-nitrophenyl ethylamine of Formula (VIII) or its hydrochloride salt



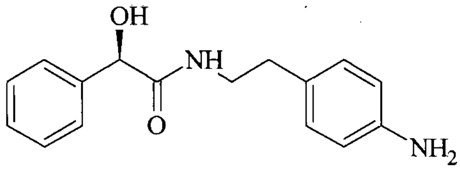
Formula (VIII)

using triethylamine in a polar aprotic solvent, optionally in presence of a coupling agent to provide (R)-2-hydroxy-N[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of Formula (IX);



Formula (IX)

b) selectively reducing the nitro group of compound of Formula (IX) to amino group using Raney nickel under hydrogen pressure in an alcoholic solvent to obtain compound of Formula (X);



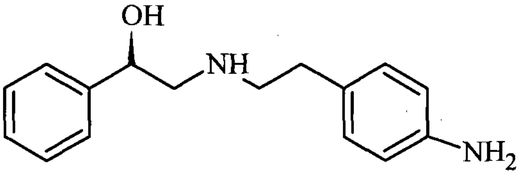
Formula (X)

c) reducing carbonyl group of compound of Formula (X) in presence of sodium borohydride in combination with borontrifluoride-ethrate in a polar aprotic solvent to obtain compound of Formula (IV);

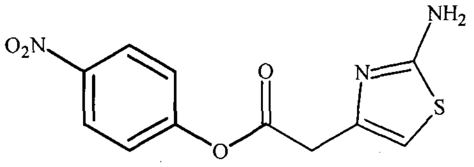
d) optionally, forming hydrochloride salt of compound of Formula (IV).

According to ninth aspect of present invention there is provided a process for preparation of Mirabegron of Formula (I) by hydrolysis of compound of Formula (II) in presence of acid or base.

According to tenth aspect of present invention there is provided a process for preparation of Mirabegron of Formula (I) by coupling of compound of Formula (IV) with compound of Formula (IIIb) in presence of a base in a suitable solvent.



Formula (IV)

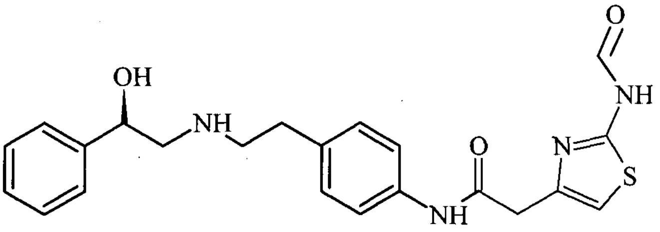


Formula (IIIb)

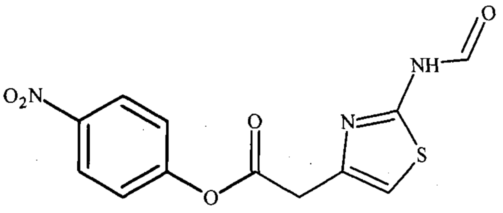
According to eleventh aspect of present invention, Mirabegron of Formula (I) is obtained in high purity and yield.

Detailed Description of the Invention

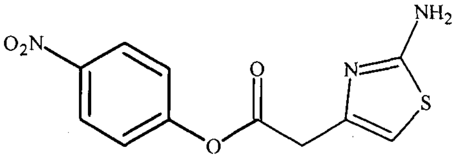
The present invention mainly relates to a novel compound of Formula (II), (IIIa) and (IIIb).



Formula (II)



Formula (IIIa)

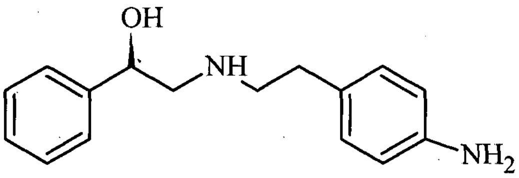


Formula (IIIb)

The compound of Formula (II), (IIIa) and (IIIb) are used in preparation of Mirabegron of Formula (I).

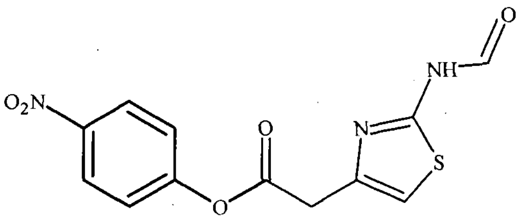
The present invention further relates to a process for preparation of compound of Formula (II), comprising:

coupling of compound of Formula (IV)



Formula (IV)

with compound of Formula (IIIa)



Formula (IIIa)

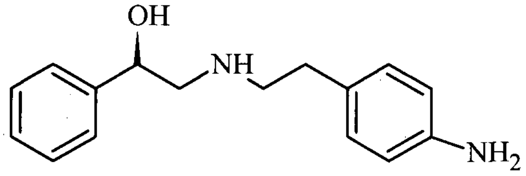
in presence of a base in a suitable solvent.

According to an embodiment the base used is selected from, but not limited to, alkali metal carbonates like sodium carbonate, potassium carbonate, lithium carbonate, alkaline earth metal carbonates like barium carbonate, calcium carbonate or alkali metal hydroxide like lithium hydroxide, sodium hydroxide and potassium hydroxide.

The suitable solvent used is selected from, but not limited to, chlorinated solvents like methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride.

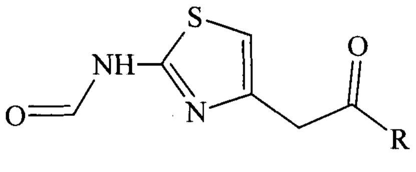
The present invention further relates to an alternate process for preparation of compound of Formula (II), comprising:

coupling of compound of Formula (IV);



Formula (IV)

with compound of Formula (V);



Formula (V)

Wherein R is –OH or –Cl,

in the presence of a carboxyl activating agent when R is –OH, or in the presence of a base when R is –Cl, in a suitable solvent.

According to an embodiment of the present invention, the carboxyl activating agent used is selected from 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, carbonyldiimidazole, N,N'- dicyclohexylcarbodiimide, polyphosphoric acid, Eaton's reagent, Boric acid, 2-chloro-1-methyl pyridinium iodide, benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate, O-benzotriazol-1yl-N,N,N2,N2-tetramethyluronium hexafluorophosphate, Ethyl cyano(hydroxyimino)aceto-2-tri-(1-pyrrolidinyl)phosphonium hexafluoroposphate, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), Hydroxybenzotriazole, 1-Hydroxy-7-azabenzotriazole, (Dimethylamino)(fluoro)-N,N-dimethylmethaniminium hexafluorophosphate, *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, (1- Cyano- 2- ethoxy- 2-oxoethylidenaminooxy) dimethylamino- morpholino- carbenium hexafluorophosphate, Bis(2- oxo- 3- oxazolidinyl) phosphinic chloride.

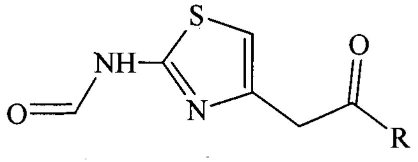
Preferably, the carboxyl activating agent used is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.

According to another embodiment of the present invention, the base used is e selected from, but not limited to, sodium carbonate, potassium carbonate, lithium carbonate, barium carbonate, calcium carbonate and lithium hydroxide, sodium hydroxide and potassium hydroxide.

According to another embodiment of present invention, the suitable solvent is selected from polar or non-polar solvent.

The polar solvent used is selected from polar protic solvent like water, n-butanol, Isopropyl alcohol, ethanol, methanol or polar aprotic solvent like dimethylformamide, dimethylsulfoxide, dioxane, dimethylacetamide, tetrahydrofuran, ethyl acetate dichloromethane, acetone, acetonitrile, hexamethylphosphorous triamide (HMPT), 1,2-dimethoxy ethane (DME), Hexamethylphosphoramide (HMPA).

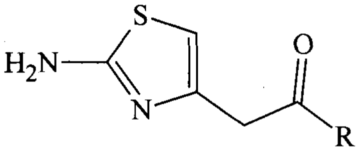
The present invention further relates to a process for preparation of compound of Formula (IIIa) by esterifying compound of Formula (V) with p-nitro phenol.



Formula (V)

Wherein R is either –OH or –Cl.

The present invention further relates to a process for preparation of compound of Formula (IIIb) by esterifying compound of Formula (VI) with p-nitro phenol.



Formula (VI)

Wherein R is either –OH or –Cl.

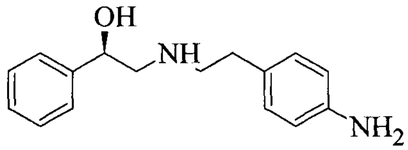
According to an embodiment of present invention, esterification of Formula (V) or (VI) is carried out in a chlorinated solvent in presence of base.

The chlorinated solvent used for esterification is selected from, but not limited to, methylene dichloride, ethylene dichloride, chloroform and carbon tetrachloride.

The weak base used for esterification is selected from, but not limited to, sodium carbonate, potassium carbonate, lithium carbonate, barium carbonate, calcium carbonate and lithium hydroxide.

Further, it is well known that a pharmaceutical product is always expected to be highly pure to reduce adverse side effects and to improve shelf life. For this purpose, it is important to produce a drug intermediate like (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) in adequate quality which in turn will provide highly pure final product i.e. Mirabegron.

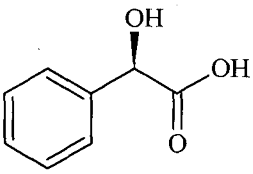
The present invention also relates to a process for the preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) or its hydrochloride/ dihydrochloride salt;



Formula (IV)

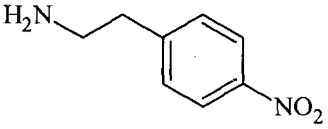
comprising steps of

a) coupling of compound of Formula (VII) or tosyl protected compound formula (VII)



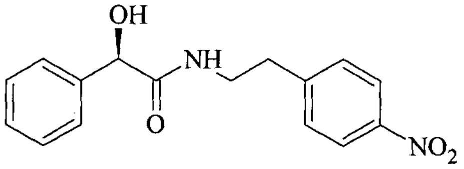
Formula (VII)

with 4-nitrophenyl ethylamine of Formula (VIII) or its hydrochloride salt



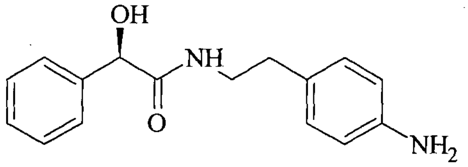
Formula (VIII)

using triethylamine in a polar aprotic solvent, optionally in presence of a coupling agent to provide (R)-2-hydroxy-N[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of Formula (IX);



Formula (IX)

b) selectively reducing the nitro group of compound of Formula (V) to amino group using Raney nickel under hydrogen pressure in an alcoholic solvent to obtain compound of Formula (X);



Formula (X)

c) reducing carbonyl group of compound of Formula (X) in presence of sodium borohydride in combination with borontrifluoride-ethrate in a polar aprotic solvent to obtain compound of Formula (IV); and

d) optionally, forming hydrochloride/dihydrochloride salt of compound of Formula (IV).

According to an embodiment of present invention, the coupling agent used in step a) is selected from N,N-carbonyldiimidazole (CDI); alkyl or aryl carbodiimides such as dicyclohexyl carbodiimide (DCC), diisopropyl carbodiimide (DIC), 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide (EDC), optionally in combination with hydroxybenzotriazole or N-hydroxysuucinamide (NHS) or N-hydroxy sulfosuccinimide (sulfo-NHS); carbonyl-di-1,2,4-triazole; alkyl and aryl haloformates such as ethyl chloroformate, phenyl chloroformate, benyl chloroformate and carbonates of Formula R1-O-CO-O-R2 wherein R1 and R2 are independently selected from branched or unbranched C1-C4 alkyl or substituted or unsubstituted phenyl group.

Preferably, the coupling agent used is combination of hydroxybentriazole with 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride.

According to another embodiment of present invention, the step a) is carried out in two steps, comprising;

a-i) protecting compound of Formula (VII) by treatment with para-toluene sulfonyl chloride in presence of triethylamine in dichloromethane; and

a-ii) coupling of protected compound of Formula (VII) with compound of Formula (VIII) or its hydrochloride salt, in presence of triethylamine in dichloromethane to obtain the compound of Formula (IX)

It was observed that protecting compound of Formula (VII) with suitable protecting group before coupling with compound of Formula (VIII) or its hydrochloride salt, offers advantages such as clean reaction profiles and high yields, these advantages concomitantly exert economical viability.

The base used in step a) is selected from inorganic base like sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide, potassium hydroxide, magnesium hydroxide, lithium hydroxide, cesium hydroxide, barium hydroxide or organic base like triethylamine, N,N-Diisopropylethylamine, pyridine, diethylamine, dimethylamine, ethylamine. Preferably, triethylamine is used.

The polar aprotic solvent used in step a) is selected from dimethylformamide, dichloromethane, tetrahydrofuran, ethylacetate, acetone, acetonitrile and dimethylsulfoxide, but preferably dimethylformamide or dichloromethane is used.

After completion of reaction, the processing of the reaction mixture of step a) typically involves partitioning the reaction mass between water and a water immiscible organic solvent, followed by separating of an organic phase and an aqueous phase, concentrating the organic phase and optionally isolating (R)-2-hydroxy-N[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of Formula (IX).

According to another embodiment of present invention, the alcoholic solvent used in step b) of the process is selected from C1-C4 alcohols like methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, iso-butanol but preferably methanol is used.

The step b) of the reaction takes place at temperature ranging from 20 to 50°C for time ranging from 3 to 9 hours with the hydrogen pressure maintained at 5-15kg/cm^2

According to yet another embodiment of present invention, the reducing agent used in step c) is selected from diborane, borane-dimethyl sulfide, borane-tetrahydrofuran complex, sodium triacetoxyborohydride, sodium cyano borohydride, sodium borohydride, sodium borohydride-boron trifluoride ethrate, lithium borohydride and lithium aluminium hydride. Preferably, sodium borohydride-boron trifluoride ethrate is used as reducing agent in step c).

It is well known in synthetic chemistry that reduction of amide derivative to respective amine is of particular importance and is commonly carried out in presence of lithium aluminium hydride and borane. In present invention in step c) such reduction is carried out i.e. compound of Formula (X) is transformed to compound of Formula (IV). However, lithium aluminium hydride and borane are highly reactive have severe limitations such as the need for anhydrous solvents and hazardous handling conditions. Based on convenience and safety, sodium borohydride was thought to be ideal reducing agent but being milder reducing agent it does not effect reduction of amide to amine. Therefore, the reactivity of sodium borohydride was enhanced and its utility was broaden by using various additives like borontrifluoride-ethrate, cerium chloride, calcium chloride, zinc chloride, copper sulfate, BH3.Me2S, sulfuric acid, catechol, trifluoroacetic acid, sulfur, zirconium chloride, Et2SeBr2, methanesulfonic acid, titanium tetrachloride, trimethylsilyl chloride, tin chloride, manganese chloride, SmCpCl2(THF)3, ErCpCl2(THF)3, Amberlyst-15(H+), aluminium oxide, (S)-lactic acid derivatives, (L)-tartaric acid, cobalt complex, (-)-N-dodecyl-N-methyl ephedrenium salt and lanthanoid complexes. On intensive studies, the inventors of present invention found that sodium borohydride in combination with borontrifluoride-ethrate gives better results as compared to other additives. Hence, being as good source of diborane, combination of boron trifluoride and borontrifluoride-ethrate is preferred for reduction of compound of Formula (X) to obtain compound of Formula (IV).

The polar aprotic solvent used in step c) is selected from dimethylformamide, dichloromethane, dioxane, tetrahydrofuran, ethylacetate, acetone, acetonitrile and dimethylsulfoxide, but preferably tetrahydrofuran is used.

The step c) of the reaction takes place at temperature ranging from 20 to 70°C for time ranging from 2 to 8 hours.

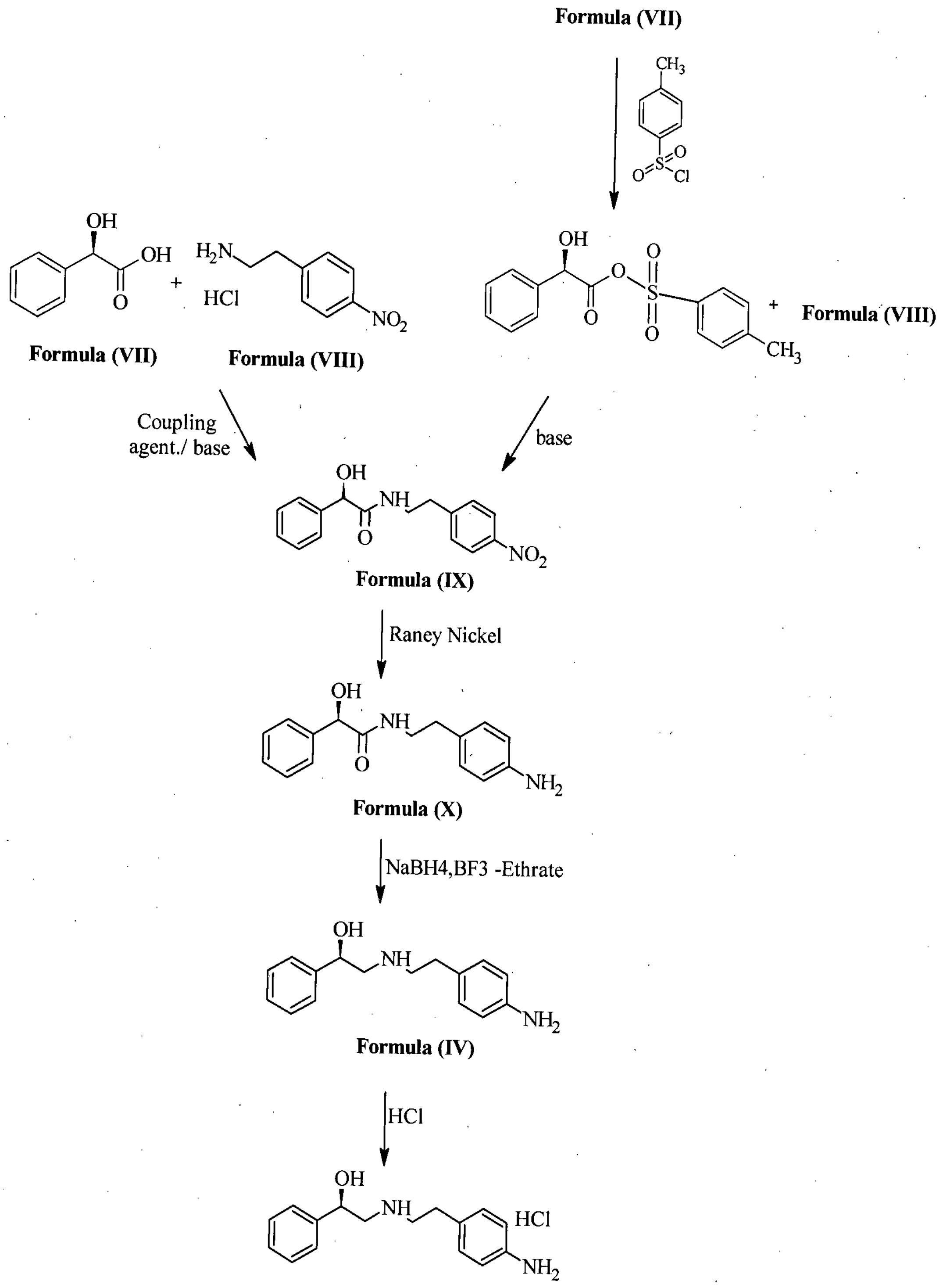
According to an embodiment of the present invention, steps a), b) and c) are carried out in-situ.

According to an another embodiment of present invention, (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) obtained in step c) is isolated directly from the reaction medium or as its dihydrochloride salt.

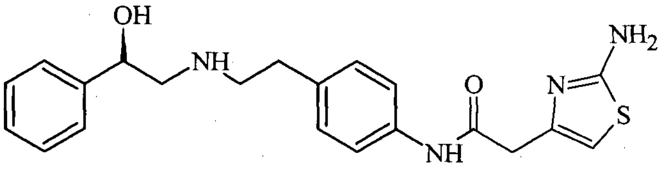
The dihydrochloride salt of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) can be prepared conventionally, for instance, by mixing a solution of the (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (I) with the hydrochloride acid in a suitable solvent system, e.g. isopropyl alcohol, and recovering the acid addition salt either as precipitate or by evaporation of the solvent from the solution.

According to present invention, the process for preparation of compound of Formula (IV), is depicted in Scheme IV

Scheme IV

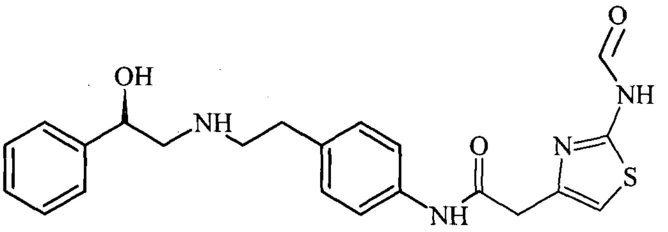

Formula (VII)
CH3
O=S=O
Cl
OH
OH
O
+
H2N
HCl
NO2
Formula (VII)
Formula (VIII)
OH
O
O
S
O
O
+
Formula (VIII)
CH3
Coupling agent./ base
base
OH
NH
O
NO2
Formula (IX)
Raney Nickel
OH
NH
O
NH2
Formula (X)
NaBH4,BF3 -Ethrate
OH
NH
NH2
Formula (IV)
HCl
OH
NH
HCl
NH2

The present invention further relates to a process for preparation of Mirabegron of Formula (I)



Formula (I)

by hydrolysis of compound of Formula (II)



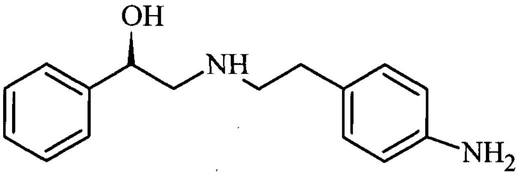
Formula (II)

The hydrolysis of the compound of Formula (II) is readily carried out using acid or base. The hydrolysis may be carried out using aqueous solution of either acid or base and then optionally heating the reaction mixture until completion of hydrolysis.

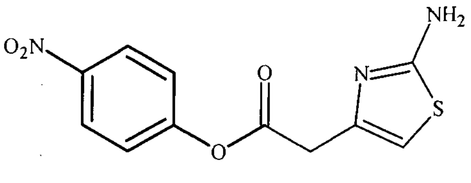
The acid used for hydrolysis is selected from mineral acid or organic acid like, but not limited to, hydrochloric acid, sulfuric acid, nitric acid, phosphoric acid acetic acid, trifluoroacetic acid and methanesulfonic acid.

The hydrolysis may also be carried out with a base selected from an alkali metal hydroxide, carbonates or bicarbonates like, but not limited to, sodium hydroxide, potassium hydroxide, barium hydroxide or calcium hydroxide.

The present invention further relates to a process for preparation of Mirabegron of Formula (I) by coupling of compound of Formula (IV) with compound of Formula (IIIb) in presence of a base in a suitable solvent.



Formula (IV)



Formula (IIIb)

According to an embodiment of present invention, coupling of compound of Formula (IV) with compound of Formula (IIIb) carried out in presence of a weak base in a chlorinated solvent.

The weak base used is selected from, but not limited to, sodium carbonate, potassium carbonate, lithium carbonate, barium carbonate, calcium carbonate and lithium hydroxide.

The chlorinated solvent used is selected from, but not limited to, methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride.

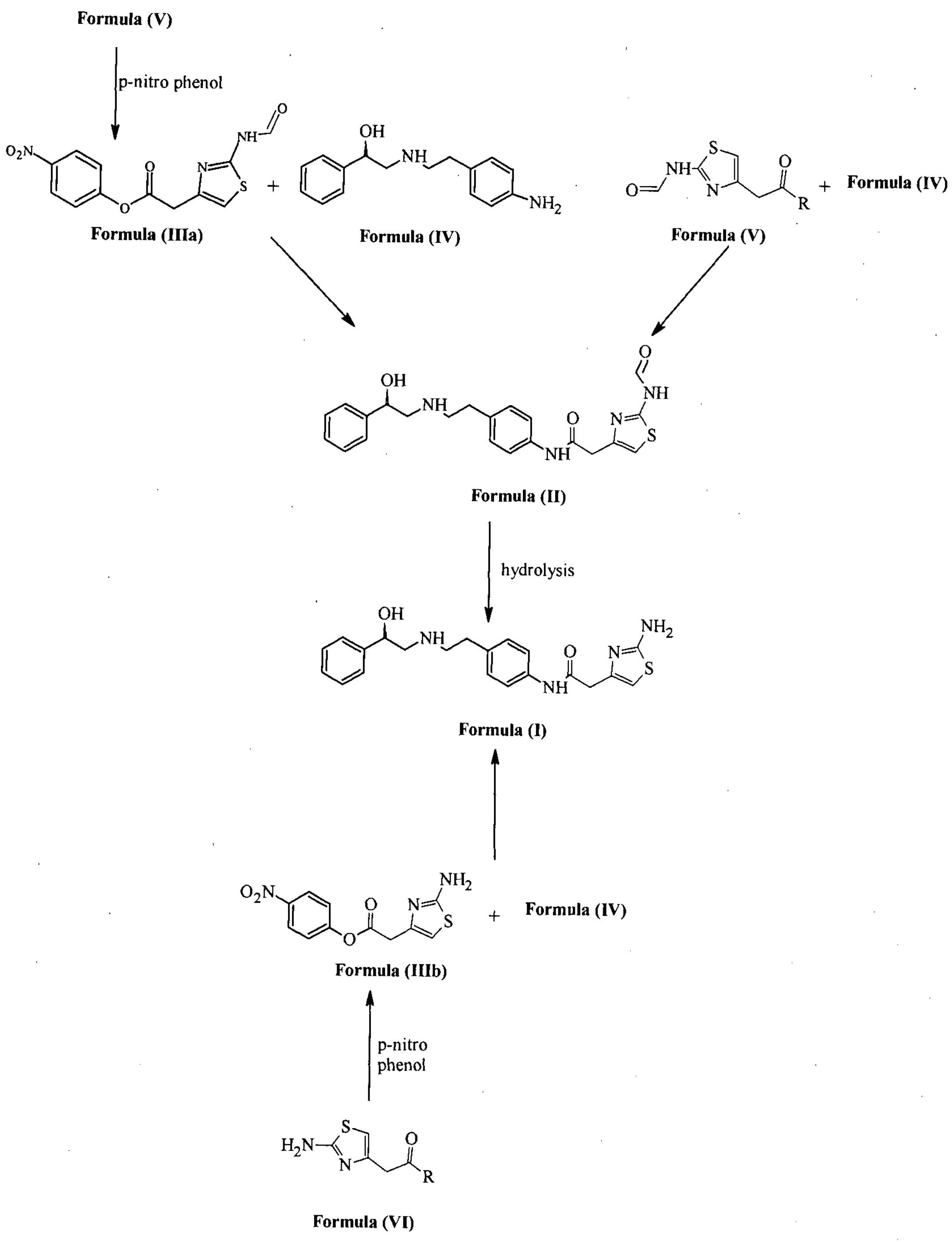
According to an embodiment of present invention, Mirabegron obtained is optionally, purified using a suitable solvent selected from polar solvent like water, n-butanol, Isopropyl alcohol, ethanol, methanol or polar aprotic solvent like dimethylformamide, dimethylsulfoxide, dioxane, dimethylacetamide, tetrahydrofuran, ethyl acetate dichloromethane, acetone, acetonitrile, hexamethylphosphorous triamide (HMPT), 1,2-dimethoxy ethane (DME), Hexamethylphosphoramide (HMPA).

According to yet another embodiment of present invention, Mirabegron of Formula (I) is obtained in high purity and yield.

Mirabegron obtained by processes known in prior art, is required to be purified and refined multiple times to meet requirements of pharmaceutical guidelines. The inventors of present invention have skillfully developed a process for preparation of Mirabegron through preparation of novel compounds of Formula (II), (IIIa) and (IIIb) which avoids formation of unwanted by-products to great extent and thereby constitutes a considerable technical advance with respect to yield and purity of final product. The said invention thus leads to an efficient and commercially acceptable synthetic process for the preparation of Mirabegron.

The schematic reaction scheme of Mirabegron according to present invention is depicted in Scheme-V.

Scheme- V


Formula (V)
p-nitro phenol
O_2N
O
NH
S
N
OH
NH
NH_2
+
Formula (IIIa)
Formula (IV)
Formula (V)
+ Formula (IV)
R
hydrolysis
Formula (II)
Formula (I)
Formula (IIIb)
+ Formula (IV)
p-nitro phenol
H_2N
Formula (VI)

Wherein R is –OH or -Cl

The detail of the invention provided in the following examples is given by the way of illustration only and should not be construed to limit the scope of the present invention.

EXAMPLES

Example 1: Preparation of [2-(formylamino)-1,3-thiazol-4-yl]acetyl chloride; Formula (V); wherein R is –Cl

20g of [2-(formylamino)-1,3-thiazol-4-yl]acetic acid was added to 250 ml of methylene dichloride and the mixture was cooled to -10°C followed by lot wise addition of 25g of phosphorous pentachloride. The mixture stirred while maintaining temperature of -10°C for 2-3 hours. After confirming completion of reaction, the product was filtered out, washed with methylene dichloride and dried to obtain 24g (Yield: 92%) of compound of Formula (V); wherein R is –Cl

Example 2: Preparation of 4-nitrophenyl-[2-(formylamino)-1,3-thiazol-4-yl]acetate; Formula (IIIa)

2g of p-nitrophenol was added to 40ml of methylene chloride and 4.963g of potassium carbonate, the mixture was cooled to 10-15°C followed by lot wise addition of 3.95g of compound of **Formula (V) of example 1**. After confirming completion of reaction, 5.87g (Yield: 99%) of compound of Formula (IIIa) was isolated. The obtained compound has been identified by;

HNMR(D_2O Exchange)
8.614 (S,1H),7.359(d,2H),8.119(d,2H),6.561(S,1H),3.765(S,2H).

Example 3: Preparation of (2-amino-1,3-thiazol-4-yl)acetyl chloride; Formula (VI); wherein R is –Cl

5g of (2-amino-1,3-thiazol-4-yl)acetic acid was added to 50 ml of methylene dichloride with few drops of dimethylformamide and 6g of oxalyl chloride at temperature ranging from 0-5°C. the mixture was maintained at 0-5°C for 4-5 hours and after completion of reaction, solid mass was filtered out, washed with methylene dichloride and dried to afford 5g (Yield: 89%) of compound of Formula (VI); wherein R is –Cl

Example 4: Preparation of 4-nitrophenyl-(2-amino-1,3-thiazol-4-yl)acetate; Formula (IIIb)

2g of p-nitrophenol was added to 40ml of methylene chloride and 4.96g of potassium carbonate, and the mixture was cooled to 10-15°C followed by lot wise addition of 3.95g of compound of **Formula (VI) prepared in example 3**. After confirming completion of reaction, 6.18g (Yield: 99%) of 4-nitrophenyl-(2-amino-1,3-thiazol-4-yl)acetate of Formula (IIIb) was isolated..

The obtained compound has been identified by

HNMR (D_2O Exchange)
7.359(d,2H),8.119(d,2H),6.425(S,1H).3.775(S,2H).

Example 5: In-situ preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol or its hydrochloride salt, of Formula (IV)

Step I – Preparation of (2R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylethanamide of Formula (IX)

(R)-2-hydroxy-2-phenylacetic acid (75g), triethylamine (50g), hydroxybenzotriazole (HOBt) (33.3g) and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride (EDC.HCl) (50g) were added to a mixture of 2-(4-nitrophenyl)ethylamine hydrochloride (100g) in N,N-dimethylformamide (375ml) at 25-30°C. The mixture was stirred for 30 minutes followed by addition of another lot of HOBt (33.3g) and EDC.HCl (50g) in reaction mixture. The reaction mixture was maintained at 25-30°C for 15 hours under stirring. After completion of reaction, water (1850ml) was added to the reaction mixture and stirred. Subsequently, ethyl acetate (1500ml) was added to the reaction mixture at 25-30°C and stirred. The organic phase was separated from aqueous phase, and was washed sequentially with 1M HCl solution, 20%aqueous potassium carbonate solution and water. The organic solvent was distilled out under reduced pressure to obtain residue comprising of (2R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylethanamide of Formula (IX)

Step II - Preparation of (2R)-2-hydroxy-N-[2-(4-aminophenyl)ethyl]-2-phenylethanamide of Formula (X)

The residue from step I, methanol (740ml) and Raney Nickel (14.8g) were charged into an autoclave vessel, 10 kg/cm2 hydrogen gas pressure was applied to the reaction mixture at 25-30°C and the mixture was maintained under stiring 6 hours. Reaction mixture filtered through hyflo bed. Distilled off the solvent completely from the filtrate under reduced pressure to obtain residue comprising (2R)-2-hydroxy-N-[2-(4-aminophenyl)ethyl]-2-phenylethanamide of Formula (X)

Step III – Preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol dihydrochloride salt, of Formula (IV)

The residue of step II was added in tetrahydrofuran (665ml) and the mixture was cooled to -5 to 0°C. To this cooled mixture was then successively added sodium borohydride (56.26g) and BF3-diethyl ether (466g), and the mixture was stirred for 15 minutes. The temperature of reaction mixture was gradually increased to 50-55°C and was maintained under stirring for 5 hours. After completion of reaction, the reaction mixture was cooled to 0-5°C and 50% sodium hydroxide solution was added till pH is basic. The temperature of reaction mixture is then raised to 25-30°C followed by addition of ethyl acetate (500ml). The organic layer was separated and subjected to distillation to afford a residue. To the residue was added isopropyl alcohol (665ml) and mixture was refluxed for 30 minutes. The mixture was then allowed to cool to 40-45°C, isopropyl alcohol hydrochloride (200ml) was added till pH acidic and mixture was stirred for 2 hours to afford precipitate. The precipitate was filtered out and washed with isopropyl alcohol. The wet cake thus obtained was added to 20% aqueous sodium hydroxide solution (till pH basic) followed by addition of dichloromethane (500ml). The organic layer was separated from aqueous layer and was subjected to distillation under reduced pressure to obtain residue. The residue was taken in toluene (500ml), heated to 55-60°C for 30 minutes and cooled to 10-15°C. The precipitate obtained was filtered, washed with toluene and to the wet cake afforded was added isopropyl alcohol (665ml). The mixture was refluxed for 30 minutes and then cooled to 50-55°C. At 50-55°C slowly isopropyl alcohol hydrochloride (200ml) till pH acidic was added and mixture was stirred for 2 hours to obtain precipitate. The precipitate was filtered out, washed with isopropyl alcohol and dried to get (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol dihydrochloride salt, of Formula (IV)

Yield-70%
HPLC Purity: 98%

Example 6: Alternate method for preparation of (2R)-2-hydroxy-N-[2-(4-nitrophenyl)ethyl]-2-phenylethanamide of Formula (IX)

Step I - A mixture of (R)-2-hydroxy-2-phenylacetic acid (10g), dichloromethane (50ml) and triethylamine (24ml) was cooled to 0-5°C and slowly para-toluene sulfonyl chloride (12.53g) was added to it. The temperature of reaction mixture was raised to 25-30°C and maintained for 12 hours. After completion of reaction, water (100ml) was added to the reaction mixture and the mixture was stirred for 15 minutes. The organic phase was separated and distills out completely under reduced pressure to obtain [(R)-2-hydroxy -2-phenyl acetic tosyl ester].

Yield-56%

Step II - 2-(4-nitrophenyl)ethylamine hydrochloride (6g) was added to dichloromethane (50ml) and stirred for 30 minutes at 25-30°C. The mixture was then cooled to 0-5°C and triethylamine (13ml) was added. To say cooled mixture was then slowly added a mixture of (R)-2-hydroxy -2-phenyl acetic tosyl ester (10g) and dichloromethane (50ml). The temperature of reaction mixture was then raised to reflux temperature and maintained for 5 hours. After completion of reaction, water (50ml) was added to the reaction mixture and the mixture was stirred for 15 minutes. The organic phase was separated and distill out completely under reduced pressure to obtain (R)-2-hydroxy-N-[2-(4-nitrophenyl) ethyl]-2-phenylacetamide

Yield-70%, Purity-96%

Example 7: Preparation of compound of Formula (II) from compound of Formula (V); wherein R is -OH

1.58g of [2-(formylamino)-1,3-thiazol-4-yl]acetic acid of Formula (V) was added solution of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) in water (2g of Formula (IV) in 50ml water) followed by addition of 0.66g concentrated hydrochloric acid and 3.27g of 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride. The mixture was stirred at 25-30°C for 0.5 hours. After completion of reaction, pH was adjusted to 8-9 using aqueous saturated solution of sodium carbonate. The solid precipitated out was filtered, washed with water and dried to obtain 2.1g of compound of Formula (II). (Yield: 72%) The obtained compound has been identified by HNMR 2.502(m,4H),2.599(m,2H),3.685(S,2H),4.9(S, NH protons),7.01(m, 10H, aromatic), 8.54(S,1H), 10.0(S, -OH proton),

HNMR(D2O Exchange) 2.502(m,4H),2.60(m,2H),4.57(m,1H),7.0(m, 10H, aromatic), 8.43(S,1H)

Example 8: Preparation of compound of Formula (II) from compound of Formula (V); wherein R is –Cl

10g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) (prepared by methods known in prior art/ as given in example 5), was added to 150ml of acetonitrile with 16.17g of potassium carbonate and the mixture was cooled to 10-15°C. 18.8g of Formula (V) of example 1 was added to above mixture at 10-15°C in lot wise. After completion of reaction, the reaction mixture was concentrated under vacuum and 90ml of water was added for isolation. The product was then filtered out, washed with water and dried to obtain 72g (Yield: 70%) of compound of Formula (II).

Example 9: Preparation of compound of Formula (II) from compound of Formula (IIIa)

5.87g of compound of Formula (IIIa) was added to 40 ml of methylene dichloride with 2.36 g of potassium carbonate and 3.67g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol (Formula-IV ; prepared by methods known in prior art/ as given in example 5) . The mixture was stirred at 25-30°C for 1 hour. After completion of reaction, the reaction mixture was concentrated followed by addition of 60 ml of water to isolate 1g of compound of Formula (II).

Example 10: Insitu preparation of compound of Formula (II) without isolation of compound of Formula (IIIa)

2g of p-nitrophenol was added to 40 ml of methylene chloride with 4.963g of potassium carbonate, and the mixture was cooled to 10-15°C followed by lot wise addition of 3.95g of [2-(formylamino)-1,3-thiazol-4-yl]acetyl chloride of Formula (V) **of example 1**. After confirming complete formation of compound of Formula (IIIa), 2.36g of potassium carbonate and 3.67g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) (prepared by methods known in prior art/ as given in example 5) was added insitu, and the mixture was stirred at 25-30°C for 1 hour. After completion of reaction, the reaction mixture was concentrated followed by addition of 60 ml of water to isolate 1g of compound of Formula (II).

Example 11: Preparation of Mirabegron from compound of Formula (II)

To 2g of compound of Formula (II) was added 30ml of 10% sodium hydroxide and the mixture was stirred at 55-60°C for 3 hours. After completion of reaction, the mixture was cooled to 25-30°C and the solid obtained was filtered, washed with water and dried to yield 1.3g of Mirabegron. (Yield: 70%)

Example 12: Preparation of Mirabegron from compound of Formula (IIIb)

6.18g of 4-nitrophenyl-(2-amino-1,3-thiazol-4-yl)acetate was added to 40ml of methylene dichloride with 2.36g of potassium carbonate and 3.65g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) (prepared by methods known in prior art/ as given in example 5), and the mixture was stirred at 25-30°C for 1 hour. After completion of reaction, solid was filtered out, washed with methylene dichlrode and dried to yield 1g of Mirabegron of Formula (I).

Example 13: Insitu preparation of Mirabegron without isolation of compound of Formula (IIIb)

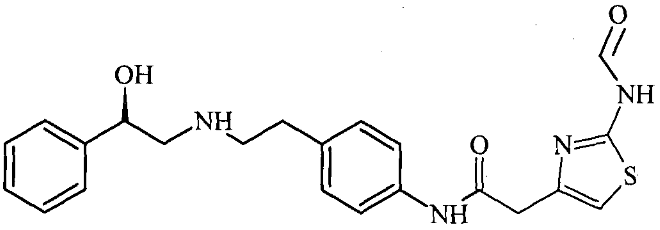
To 40ml of methylene chloride was added 2g of p-nitrophenol and 4.96g of potassium carbonate, and the mixture was cooled to 10-15°C followed by lot wise addition of 3.95g of compound of Formula (VI) prepared in example 3. After confirming complete formation of compound of Formula (IIIb), 2.36g of potassium carbonate and 3.65g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) (prepared by methods known in prior art/ as given in example 5) was added insitu, and the mixture was stirred at 25-30°C for 1 hour. After completion of reaction, After completion of reaction, solid was filtered out, washed with methylene dichlrode and dried to yield 1g of Mirabegron of Formula (I).

Example 14: Preparation of Mirabegron from compound of Formula (VI); wherein R is -Cl

To 20ml of acetone was added 2g of (1*R*)-2-{[2-(4-aminophenyl)ethyl]amino}-1-phenylethanol of Formula (IV) and 2.15g of potassium carbonate, and the mixture was cooled to 10-15°C followed by addition of (2-amino-1,3-thiazol-4-yl)acetyl chloride of Formula (VI). After completion of reaction, acetone was concentrated under vacuum and 90ml of water was added for for isolation. The product was then filtered out, washed with water and dried to obtain 2g (Yield: 70%) of Mirabegron.

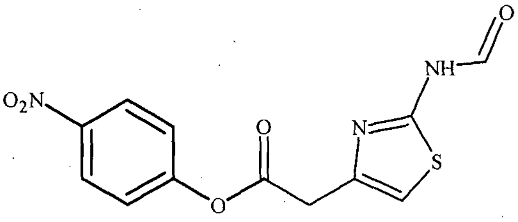
We claim:

1. A compound of Formula (II)



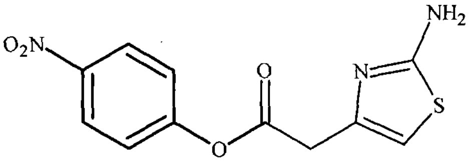
Formula (II)

2. A compound of Formula (IIIa)



Formula (IIIa)

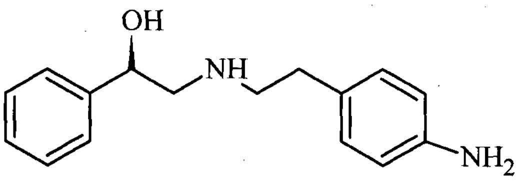
3. A compound of Formula (IIIb) or its acid addition salt



Formula (IIIb)

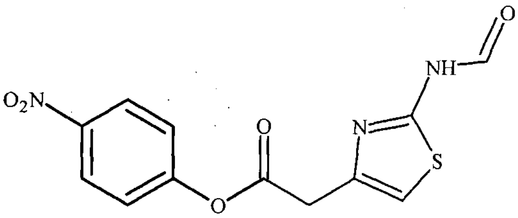
4. A process for preparation of compound of Formula (II), comprising:

coupling of compound of Formula (IV)



Formula (IV)

with compound of Formula (IIIa)



Formula (IIIa)

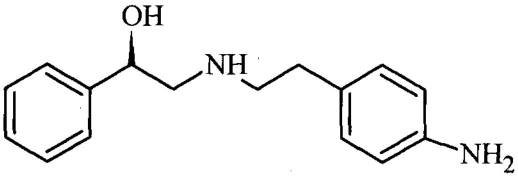
in presence of a base in a suitable solvent.

5. The process as claimed in claim 4, wherein the base used is selected from alkali metal carbonates like sodium carbonate, potassium carbonate, lithium carbonate, alkaline earth metal carbonates like barium carbonate, calcium carbonate or alkali metal hydroxide like lithium hydroxide, sodium hydroxide and potassium hydroxide.

6. The process as claimed in claim 4, wherein the solvent used is selected from chlorinated solvents like methylene dichloride, ethylene dichloride, chloroform and carbon tetrachloride.

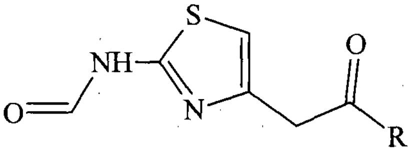
7. An alternate process for preparation of compound of Formula (II), comprising:

coupling of compound of Formula (IV);



Formula (IV)

with compound of Formula (V);



Formula (V)

Wherein R is –OH or –Cl,

in the presence of a carboxyl activating agent when R is –OH, or in the presence of a base when R is –Cl, in a suitable solvent.

8. The process as claimed in claim 7, wherein the carboxyl activating agent used is selected from 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide, carbonyldiimidazole, N,N'- dicyclohexylcarbodiimide, polyphosphoric acid, Eaton's reagent, Boric acid, 2-chloro-1-methyl pyridinium iodide, benzotriazol-1-yl-oxy-tris(dimethylamino)phosphonium hexafluorophosphate, O-benzotriazol-1yl-N,N,N2,N2-tetramethyluronium hexafluorophosphate, Ethyl cyano(hydroxyimino)aceto-2-tri-(1-pyrrolidinyl)phosphonium hexafluoroposphate, 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate), Hydroxybenzotriazole, 1-Hydroxy-7-azabenzotriazole, (Dimethylamino)(fluoro)-N,N-dimethylmethaniminium hexafluorophosphate, *N*-Ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline, (1- Cyano- 2- ethoxy- 2-

oxoethylidenaminooxy) dimethylamino- morpholino- carbenium hexafluorophosphate, Bis(2- oxo- 3- oxazolidinyl) phosphinic chloride.

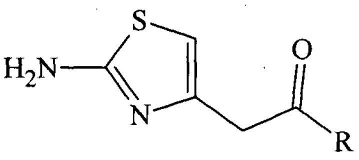
9. The process as claimed in claim 7, wherein the carboxyl activating agent used is 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide.

10. The process as claimed in claim 7, wherein the base used is selected from sodium carbonate, potassium carbonate, lithium carbonate, barium carbonate, calcium carbonate and lithium hydroxide, sodium hydroxide and potassium hydroxide.

11. The process as claimed in claim 7, wherein the solvent is selected from polar protic solvent like water, n-butanol, Isopropyl alcohol, ethanol, methanol or polar aprotic solvent like dimethylformamide, dimethylsulfoxide, dioxane, dimethylacetamide, tetrahydrofuran, ethyl acetate dichloromethane, acetone, acetonitrile, hexamethylphosphorous triamide (HMPT), 1,2-dimethoxy ethane (DME) and Hexamethylphosphoramide (HMPA).

12. A process for preparation of compound of Formula (IIIa) by esterifying compound of Formula (V) with p-nitro phenol in a chlorinated solvent in presence of base.

13. A process for preparation of compound of Formula (VI) with p-nitro phenol in a chlorinated solvent in presence of base.



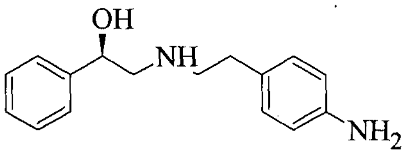
Formula (VI)

Wherein R is either –OH or –Cl.

14. The process as claimed in claim 12 or 13, wherein the chlorinated solvent used for esterification is selected from methylene dichloride, ethylene dichloride, chloroform, carbon tetrachloride.

15. The process as claimed in claim 12 or 13, wherein the base used is selected from sodium carbonate, potassium carbonate, lithium carbonate, barium carbonate, calcium carbonate and lithium hydroxide.

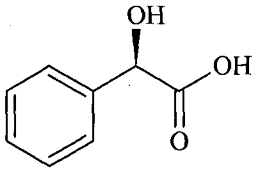
16. A process for preparation of (1R)-2-[[2-(4-aminophenyl)ethyl]amino]-1-phenylethanol of Formula (IV) or its hydrochloride/dihydrochloride salt;



Formula (IV)

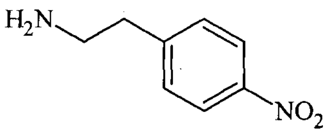
comprising steps of:

a) coupling of compound of Formula (VII) or tosyl protected compound of Formula (VII)



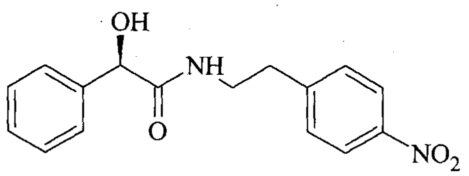
Formula (VII)

with 4-nitrophenyl ethylamine of Formula (VIII) or its hydrochloride salt



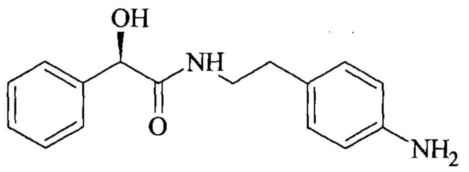
Formula (VIII)

using triethylamine in a polar aprotic solvent, optionally in presence of a coupling agent to provide (R)-2-hydroxy-N[2-(4-nitrophenyl)ethyl]-2-phenylacetamide of Formula (IX);



Formula (IX)

b) selectively reducing the nitro group of compound of Formula (IX) to amino group using Raney nickel under hydrogen pressure in an alcoholic solvent to obtain compound of Formula (X);



Formula (X)

c) reducing carbonyl group of compound of Formula (X) in presence of sodium borohydride in combination with borontrifluoride-ethrate in a polar aprotic solvent to obtain compound of Formula (IV);

d) optionally, forming hydrochloride salt of compound of Formula (IV).

17. The process as claimed in claim 16, wherein the coupling agent used in step a) is combination of hydroxybentriazole and 1-(3-dimethylaminopropyl)-3-ethyl carbodiimide hydrochloride.

18. The process as claimed in claim 16, wherein the step a) is carried out in two steps a-i) protecting compound of Formula (VII) by treatment with para-toluene sulfonyl chloride in presence of triethylamine in dichloromethane; and a-ii) coupling of protected compound of Formula (VII) with compound of Formula (VIII) or its

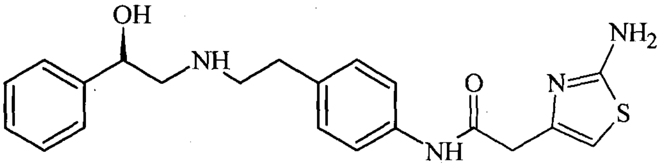
hydrochloride salt, in presence of triethylamine in dichloromethane to obtain the compound of Formula (IX).

19. The process as claimed in claim 16, wherein the polar aprotic solvent used in step a) and c) is selected from dimethylformamide, dichloromethane, tetrahydrofuran, ethylacetate, acetone, acetonitrile and dimethylsulfoxide.

20. The process as claimed in claim 16, wherein the alcoholic solvent used in step b) of the process is selected from C_1-C_4 alcohols like methanol, ethanol, n-propanol, isopropyl alcohol, n-butanol, iso-butanol but preferably methanol is used

21. The process as claimed in claim 16, wherein steps a), b) and c) are carried out in-situ

22. A process for preparation of Mirabegron of Formula (I)



Formula (I)

by hydrolysis of compound of Formula (II) in presence of acid or base.