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Synthesis and Characterization of Chiral Impurities of Mirabegron, Used as an Overactive Bladder Drug

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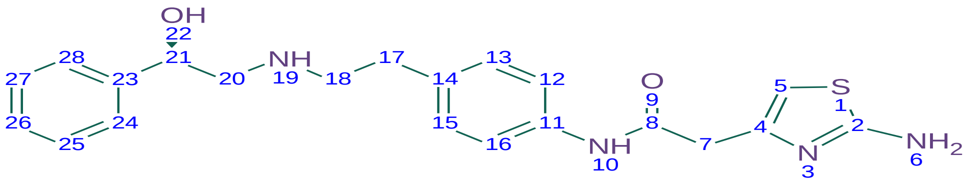
Abstract

Mirabegron is used to treat overactive bladder that drug substance is the first β3-adrenoreceptor (AR) agonist. The mechanism of action of Mirabegron is as an adrenergic beta-3-Agonist and cytochrome P450 3A inhibitor, and p-Glycoprotein inhibitor. This molecule is optical active and having one chiral center and only (R)-Mirabegron presents pharmacological activity being (S)-Mirabegron an impurity which critical to control. During the process development of Mirabegron, the chiral impurity of drug substance is challenging and also challenging to all pharmaceutical industries too, the opposite isomeric impurity is introduced form its key starting material and it follows the same reaction mechanism path up to final drug substance, present work describe the synthesis of chiral impurities of each intermediate, including key starting material and its drug substance and their characterization by spectral data (MS,1H-NMR and 13C-NMR). This work will help quality control (QC) to identify and control these impurities in the Mirabegron drug substance as per ICH guideline.

Keywords: *Critical, Chiral Impurity, Synthesis, And Characterization, Mirabegron, An Overactive Bladder.*

1. Introduction

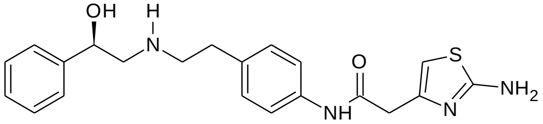
Chirality is an object cannot be superimposed with its mirror image structure; this is a geometric characteristic property of molecule [1]. There are only two chiral structures are possible for one chiral center molecule called as enantiomers or enantiomorphs, and the enantiomorphs are usually labeled as “S-isomer” or “R-isomer”, the S-isomer sinister in Latin (means Left) and R-isomer means rectus in Latin (means Right), molecules that pauses the property to rotate the plane polarized light to left is said as S-isomer similarly molecules that rotate the plane polarized light to right said as R-isomer[2]. Today, chirality is considered as an important property of material. In pharmaceutical sector about more than half of the drug substance are optical active i.e., having chiral compounds and near 90% of the last ones are marketed as racemate mixture consisting of an equimolar mixture [3], of two enantiomers, however, they have the same chemical structure, most isomers of chiral drugs exhibit marked difference in biological activities such as pharmacology, toxicology, pharmacokinetics, metabolism etc. hence, it is important to isolate or synthesized the chiral impurity in pharmaceutical industry for to define its limit as per ICH guideline to control the unwanted isomer from the drug substance [4]. Mirabegron is a drug for the treatment of overactive bladder (OAB) with symptoms of urgency, urgency incontinence and urinary frequency [5]. It was developed by Astellas Pharma. Mirabegron activates the adrenergic receptor in the detrusor muscle in the bladder. This leads to muscle relaxation and an increase in bladder capacity [6]. It is marked under the trade name Myrbetriq ™ in the form of tablets for the oral administration 25 mg and 50 mg [7]. The general information of mirabegron is tabulated below. Mirabegron is pharmacopeial drug substance, in European pharmacopeia the limit of opposite isomer of Mirabegron is NMT0.2%, which is very titan as per the route of synthesis of Mirabegron shown in Figure 2, the chirality is start from D-Mandelic acid up to API. So it is very difficult to controlled the chiral isomer in API at the level of 0.2% for that we need to understand it purge ability of each steps, so that we can develop the process control for the chiral impurity, the cost of chiral impurities are very expensive for mg level also separation technique are difficult and expensive, to overcomes these problem we decided to synthesis of chiral impurities at lab and characterized it by spectral data (MS,1H-NMR and 13C-NMR). The isolated impurities help to understand its purgability at different stage along it will be help for quality-control department for availability of impurities of each stage for control in the specification. Table 1 shows General Information.



Mirabegron 1

Figure 1 Mirabegron

Table 1 General Information

IUPAC Name	2-(2-Amino-l,3-thiazol-4-yl)-N-[4-(2-{[(2R)-2-hydroxy-2- phenyl ethyl] amino}ethyl)phenyl] acetamide
CAS No.	223673-61-8
Structure	
Molecular Formula	C21H24N402S
Molecular Weight	396.51 g/mol
Description	White to off white crystalline powder
Solubility Profile	Practically insoluble in water. Higher solubility observed in acidic. solution, or buffered solutions with pH ~ 7.5.
Product patent Number	US 6,346,532 Bl
Product patent expiry	Oct. 15,2018.
Brand name	Myrbetriq ™
Innovator	Astellas Pharma
Dosage and Strength	25 mg and 50 mg; Tablets
Stereochemistry	Exhibits chiral centers
Therap. Cat	Treatment of overactive bladder (OAB)
Approval date	In U.S. approved in July 2012
Polymorphism	Exhibit polymorphism

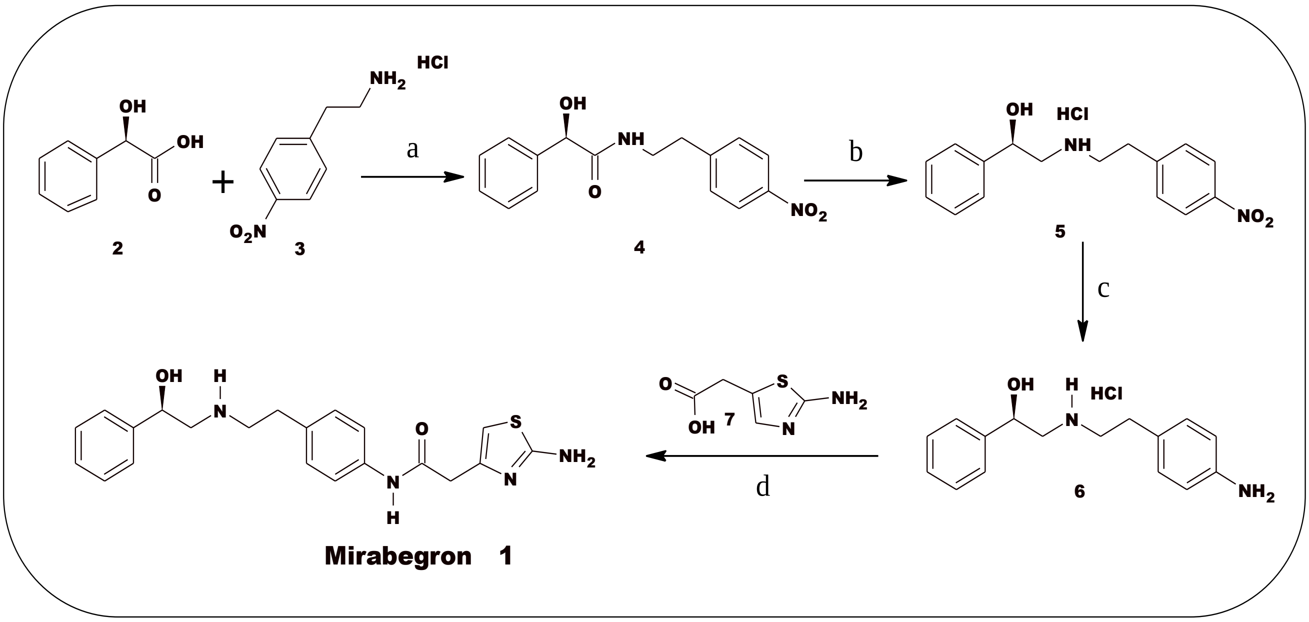


Figure 2 Route of Synthesis of Mirabegron
Whereas, a= acetonitrile, trimethyl borate b= NaBH4, THF, iodine, workup c= Methanol, Raney Ni d= con,HCl, EDC.HCL, n-Butanol, IPA, Toluene.

The route of synthesis of Mirabegron compound 1 is start from D-Mandelic acid i.e., compound 2, the condensation reaction is carried out with compound 2 and compound 3 to give compound 4, the amide reduction is done with the help of sodium borohydride , tetrahydrofuran and iodine to afford the compound 5, compound 6 is isolated form reduction reaction using Raney nickel, further this isolated intermediate get coupled with compound 7 in presence of EDC.HCl and con. HCL, final pure material is isolated in isopropyl alcohol and toluene to give Mirabegron 1 [8], this process is described in patent WO2015044965A1, form this route of synthesis there are five chiral impurities are possible including D-mandelic acid, and these chiral impurities are very importance for quality prospective and designing of process too. To isolate or to separate the impurities the traditional method like column chromatography is used, in column chromatography both solid and liquid samples can be separated and purified. This chromatography method consists of stationary solid phase and separates the impurities the impure compounds passing through it with the help of a liquid mobile phase. Based on their chemical nature compounds get separated and isolated. Optimization of the method is an important and challenging task in the separation of different or same group of compounds in extracts, this method has some disadvantage like it take more time to separate the compound, low separation power, higher quantity of solvents is used which include hazard solvent also last but not list it is expensive [9-13]. We are targeting to synthesis four chiral impurities as shown in Figure 4 form the L-mandelic acid i.e., compound 2a which is itself a chiral impurity.

2. Method

The chemical structure of Mirabegron (Figure 1), the carbon 21 having chiral center, which is R -isomer of Mirabegron[14], during the process development of Mirabegron (Figure 1) for large scale there were four chiral impurities observed, for isolation of these impurities column chromatography method is not workable also a preparative system (HPLC or SFC) is used to separate the impurity but these methods are so expensive and hence, decided to go with green approach and cost effective methodology is used, the targeted four impurities are synthesis form (L)-mandelic acid/ S-mandelic acid i.e., compound 2a, which is inexpensive and easily available, these impurities are identified and characterized, Shown in Figure 3.[14-16]

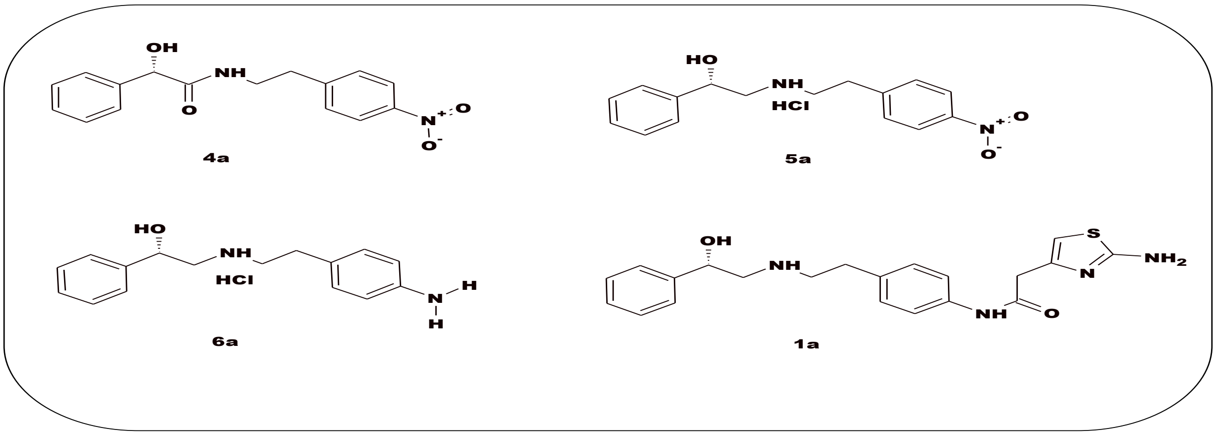


Figure 3 For Four Chiral Impurities of Mirabegro

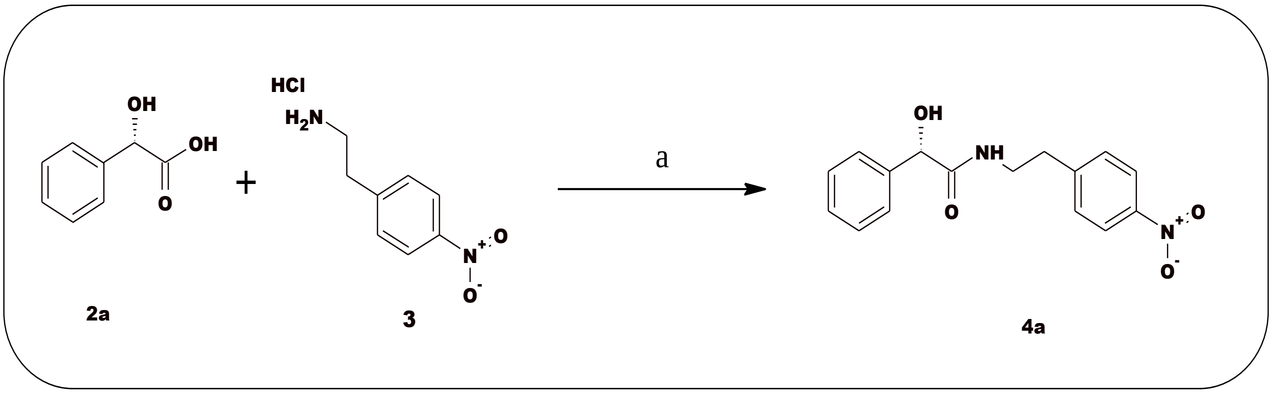


Figure 4 Synthesis Scheme of Chiral Impurity Compound 4a, Mirabegron Intermediate I.E., S-2-Hydroxy-N - [2-(4-Nitrophenyl) Ethyl]-2-Phenyl Acetamide

Reaction condition a: methanol, trimethyl borate, triethyl amine, reflux 12 hrs., ethyl acetate, dil HCl and water. The synthesis of chiral impurity 4a (Figure 2), start from (S) mandelic acid compound 2a, S-Mandelic acid coupled with compound 3 in presence of trimethyl borate and triethyl amine (TEA) in methanol as a solvent. Upon completion of reaction, gets recovered by distillation, dil HCl and water, distillation of ethyl acetate, up to slurry to furnish evaporative recrystallization, precipitated solid was filtered, dried to obtain compound 4a Figure 4 shows Synthesis scheme of chiral impurity compound 4a,

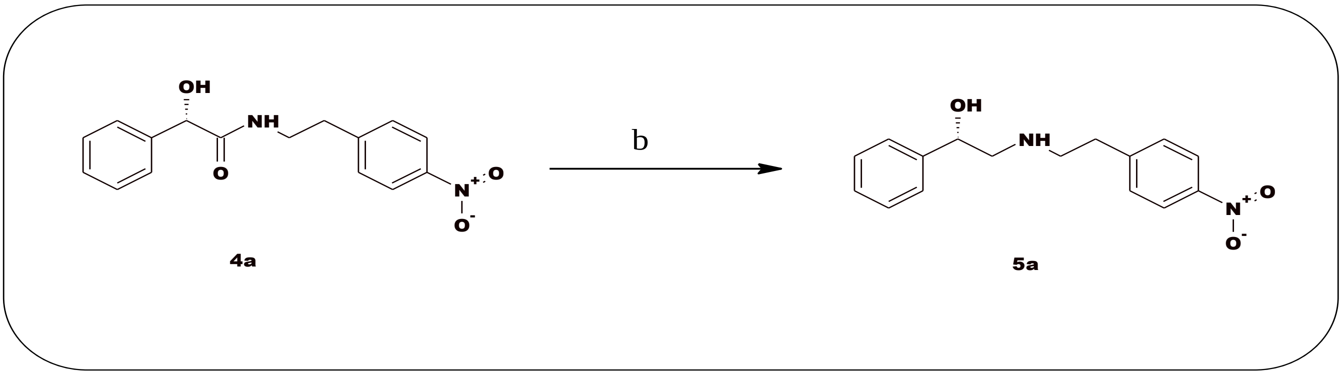


Figure 5 Synthesis Scheme of Chiral Impurity Compound 5a, Mirabegron Intermediate I.E., (S)-2-[2-(4-Nitro-Phenyl)-Ethylamine]-1-Phenyl-Ethanol Hydrochloride

Reaction condition b: THF, NaBH4, iodine, methanol, reflux 5 hrs. con. HCL. The synthesis of chiral impurity 5a (Figure 5), start from compound 4a, the amide group of compounds 4a was reduced using sodium borohydride in presence of iodine and THF as solvent, reaction is done at reflux temperature. Upon completion of compound 4a to 5a to desired extent, THF was distilled, slurred in methanol, and adjusted pH 2 using con, HCl, solid get filtered and dried to get compound 5a.

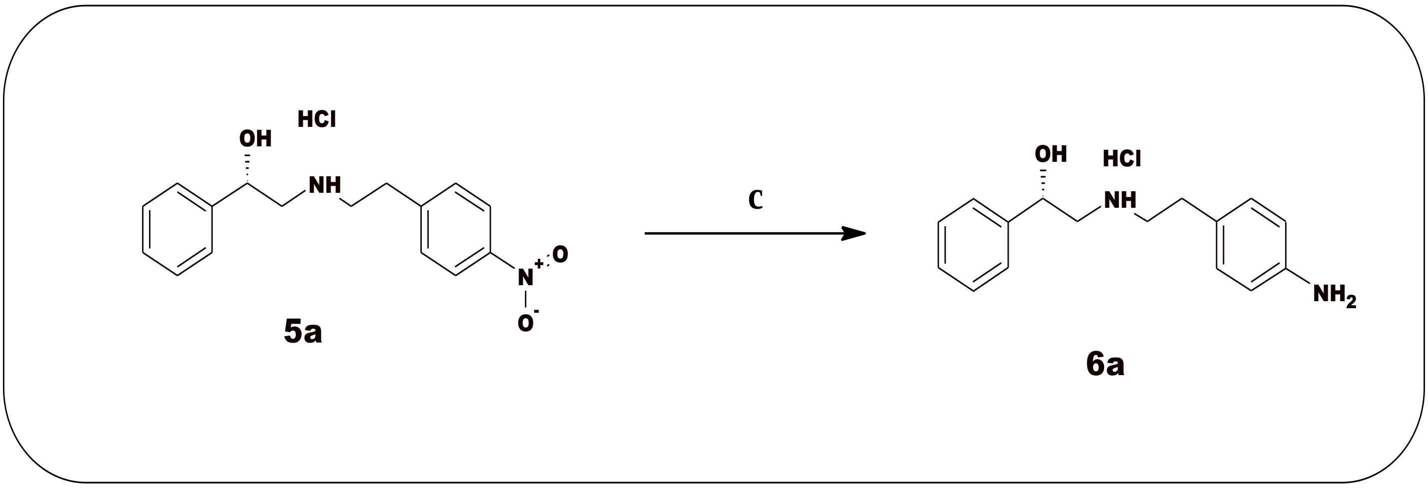


Figure 6 Synthesis Scheme of Chiral Impurity Compound 6a, Mirabegron Intermediate I.E., (*S*)-2-[2-(4-Amino-Phenyl)-Ethylamino]-1-Phenyl-Ethanol Hydrochloride

Reaction condition c: methanol, Raney Nickel, IPA and Toluene. The synthesis of chiral impurity 6a (Figure 6), the nitro group of 5a get reduced using Raney Nickel and hydrogen gas in methanol, compound 6a is isolated in IPA and toluene.

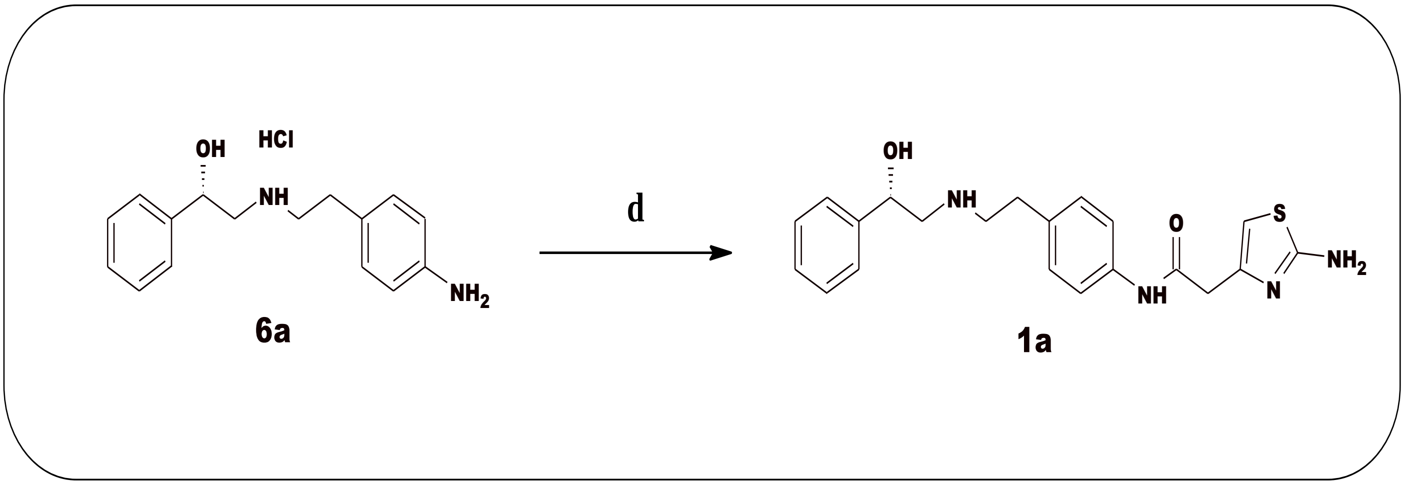


Figure 7 Synthesis Scheme of Chiral Impurity Compound 1a, Mirabegron Opposite Isomer I.E., 2-(2-Amino-1, 3-Thiazol-4-Yl)-N-[4-(2-{[(2S)-2-Hydroxy-2-Phenyl Ethyl] Amino} Ethyl) Phenyl] Acetamide

Reaction condition d: EDC.HCL, con. HCL, sodium carbonate, IPA. The synthesis of chiral impurity 1a i.e., opposite isomer of Mirabegron API (Figure 6), the compound 6a get coupled with compound 7 in presence of EDC.HCL and hydrochloric acid in water at room temperature. Upon completion of reaction, pH is adjusted 9-10 using sodium carbonate and precipitated solid get filtered and purified in IPA to get opposite isomer of Mirabegron i.e., compound 1a.

3. Experimental

3.1. Preparation of S-2-Hydroxy-N -[2-(4-nitrophenyl)ethyl]-2-phenyl acetamide (Compound 4a)

The synthesis of compound 4a as represented Figure 4.: A solution of S-Mandelic acid 2a (100 g, 0.6578 mol), in methanol (500 ml), was added trimethyl borate (70 g, 0.6730 mol), stir for 60 min to obtained clear solution, compound 3 (120 g, 0.5940 mol) and triethyl amine (70 g, 0.6930 mol) was added the reaction mass was refluxed for 12 hrs. After completion of reaction (by TLC), distil out methanol under vacuum till dry solid observed, ethyl acetate (1000 ml) was added followed by dilute HCl wash and water wash given to organic layer, ethyl acetate layer gets distil up to the slurry mass, reaction mass was cool to 5-10°C, solid get filtered and dried to get pure compound 4a as a light yellow to off white coloured solid. Purity by HPLC 99.3%. Yield: 153.6 g (86%).MS m/z: 301 [M+1]. 1H NMR (DMSO-d6, 400 MHz): δ 2.85–2.88 (t, 2H), 3.39-3.43 (m, 2H), 4.83–4.84 (d, 1H), 6.12– 6.14 (d, 1H), 7.22-7.31 (m, 5H), 7.37-7.41 (d, 2H), 8.04–8.08 (d, 2H), 8.04–8.12 (m, 1H).

3.2. Preparation of (S)-2-[2-(4-nitro-phenyl)-ethylamine]-1-phenyl-ethanol hydrochloride. (Compound 5a)

The synthesis of compound 5a as represented Figure 5.: A suspension of compound 4a (100 g, 0.3333 mol) and sodium borohydride (22.6 g 0.666 mol) in tetrahydrofuran THF (750 ml), was refluxed for 5 hrs. After completion of reaction by TLC, reaction mass was cooled to 25–30°C, THF was distilled up to solid precipitated, methanol (200 ml) was added followed by pH=2 was adjusted by con. HCL, observed solid 5a was filtered, washed with methanol (100 ml) and dried the solid under vacuum (650–700 mm/Hg) at 50–55°C for 6 h to afford 5a as off white coloured solid. Chemical purity by HPLC: 97.53%. Yield: 94.6 g (88%). MS m/z: 287 [M+ 1]. 1H NMR (DMSO-d6, 400 MHz): δ 3.04 (m, 1H), 3.14–3.25 (m, 5H), 4.98-5.01 (d, 1H), 6.23-6.24 (s, 1H), 7.30-7.39 (m, 5H), 7.40-7.55 (d, 2H), 8.20-8.22(d, 2H), 8.95 (s-br, 1H), 9.35(s-br, 1H). 13C NMR (DMSO-d6, 400 MHz): δ 146.48, 145.58, 141.75, 130.12, 128.43, 127.86, 125.92, 123.73, 68.21, 53.36, 47.17, 31.08.

3.3. Preparation of (S)-2-[2-(4-amino-phenyl)-ethylamino]-1-phenyl-ethanol hydrochloride (Compound 6a)

The synthesis of compound 6a as represented Figure 6.: A solution of compound 5a (100g, 0.3101 mol) in methanol (1000 ml) was added Raney Nickel (10g), reaction mass maintained under hydrogen pressure 5-6 kg/cm2 for 7-8 hrs. after completion of reaction by TLC, reaction mass get filtered through hyflow bed and Raney nickel get discarded in con.hcl, the cleared reaction mass was evaporated up to slurry. IPA (500ml) was added, and refluxed for 1 hr, at refluxed temperature toluene (700 ml) was added, reaction mass gets chilled to 0-5°C, precipitated solid get filtered and dried to furnish 6a as light brown to off white solid. purity by HPLC: 99.66%. Yield: 78 g (86%). MS m/z: 257 [M+1]. 1H NMR (DMSO-d6, 400 MHz): δ 2.49-2.56 (m, 2H), 2.62-2.77 (m, 4H), 4.62-4.65 (m, 1H), 4.84 (s, 2H), 5.35 (s-br, 1H), 6.46-6.48 (d, 2H), 6.82-6.84 (d, 2H), 7.20–7.23 (m, 1H), 7.24-7.33 (m, 4H). 13C NMR (DMSO-d6, 400 MHz): δ 146.66, 144.35, 128.94, 127.95, 126.82, 126.79, 125.86, 114.00, 71.04, 57.17, 50.97, 34.66.

3.4. Preparation of 2-(2-Amino-1, 3-thiazol-4-yl)-N-[4-(2-{[(2S)-2-hydroxy-2-phenyl ethyl] amino} ethyl) phenyl] acetamide (Compound 1a)

The synthesis of compound 1a as represented Figure 7.: A solution of compound 6a (70g, 0.239 mol) and compound 7 (39g, 0.2478 mol) in con.hcl (1000ml) was added EDC.HCL (56g, 0.2921 mol) lot wise in 10 min time interval, reaction mass maintained at room temperature for 3 hrs. after completion of reaction by TLC, pH was adjusted 8-10 using the sodium carbonate solution (10% solution in water), resulted precipitation of solid get filter out and wash water (280ml), wet crude solid get hot slurry in IPA (800ml) and afford the solid was dried to get compound 1a i.e., opposite isomer of Mirabegron. Purity by HPLC 99.80%. Yield: 75.9 g (80%). MS m/z: 397.0 [M+1]. 1H NMR (DMSO-d6, 400 MHz): δ 1.90 (s-br, 1H), 2.58-2.67 (m, 4H), 2.68-2.77 (m, 2H), 3.44 (s, 2H), 4.56-4.60 (m, 1H), 5.23 (s-br, 1H), 6.29 (s, 1H), 6.90 (s, 2H), 7.10-7.12 (d, 2H), 7.18–7.23 (m, 1H), 7.27–7.32 (m, 4H), 7.47-7.50 (d, 2H), 9.99 (s, 1H). 13C NMR (DMSO-d6, 400 MHz): δ 168.13, 168.31, 145.81, 141.84, 138.04,131.95, 128.86, 128.41, 127.80, 125.95, 119.32, 102.76, 68.24, 53.58, 48.14, 39.91, 30.88.

4. Result and Discussion

Mirabegron is drug substance, and control of its opposite isomer as per Ph. Eur. NMT 0.2% and need to control all chiral impurities, for that will be increased day by day to control of this impurity is not challenge now because from above experiments of synthesis of chiral impurities (4a, 5a, 6a, & 1a) having good yield and purity along with all structural data with respective impurities elucidate or confirmed the structure of targeted impurities, this indicate that these process is capable to generate the impurities for future requirement of quality control department. Hence, our targeted chiral impurities are synthesized and well characterized further analytical use and spike and purge experiment to justify the limit form D-mandelic acid.

Conclusion

We have identified and synthesized four chiral impurities related to Mirabegron (Figure 1), these synthesized chiral impurities were characterized by various spectral techniques like MS, 1HNMR, 13CNMR and chiral purity by HPLC. Present work is helpful in controlling these processes related chiral impurities in an intermediate stage and at final API i.e., Mirabegron 1 to provide highly pure drug substance. Thus, work will help quality control (Q.C) to identify and control these chiral impurities in the Mirabegron (Figure 1) drug substance as per ICH guideline.

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