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Synthesis and Structural Characterization of Process Related Impurities of Mirabegron: A Beta-3 Adrenergic Agonist Drug

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In the synthesis of active pharmaceutical ingredient and the development of pharmaceutical products, the impurities profiling plays a significant role. The control of impurities is essential for producing the quality, safe and efficient drug products for therapeutic use. Few works reported for the synthesis of potential impurities and further characterized to support the synthesis route and purity of the synthesized compound. Hence in present study, five impurities of mirabegron such as impurity 3, 4, 6, 8 and 9 were synthesized and structural characterization was carried using NMR, IR and mass spectral studies. Based on the results, it was confirmed that the route of synthesis established in the study was simple, convenient and economical and can be useful for the products of potential impurities of mirabegron. By characterizing each of these impurities, the regulatory need has been met. Additionally, the analytical method development and validation studies have utilized the generated impurity standards. This effort helped with the process development's optimization stage and made it possible to identify the crucial parts of the process. The production method for mirabegron was carefully adjusted to eliminate or reduce the formation of impurities, which is helpful for the creation of safe pharmaceutical goods.

Keywords: Mirabegron, Impurities, Synthesis, Characterization, NMR studies, Mass spectral analysis.

INTRODUCTION

Mirabegron, a beta-3 agonist, has been used to treat overactive bladder. Its advantages are comparable to those of anti-muscarinic drugs like solifenacin or tolterodine [1]. In children three years of age and older, neurogenic detrusor overactivity (NDO), a bladder dysfunction linked to neurological disability, is also suggested for treatment with mirabegron [2]. By triggering the beta-3 receptors, which relax the detrusor smooth muscle during the storage phase of the urine bladder fill-void cycle and enhance the bladder's storage capacity, mirabegron reduces feelings of urgency and frequency [3]. The most frequent negative side effect associated with using mirabegron is elevated blood pressure [4].

Active pharmaceutical ingredients (APIs) or therapeutic product formulations may contain undesirable compounds called pharmaceutical contaminants. The impurities found in pharmacological compounds may develop during synthesis or may come from starting materials, intermediates, reagents, solvents, catalysts and reaction byproducts, among other sources [5]. The quality and safety of a medication product can be significantly impacted by the presence of impurities in the drug component. The acceptable level for all impurities present should be less than 0.10% or 1.0 mg per day intake (whichever is lower), as per the general recommendations on impurities in new drug substances made by the International Conference on Harmonization (ICH), for medications with a maximum daily dose equal to or less than 2 g [6,7]. The impurities present in the drug material, which are greater than the levels specified above must be located and characterized in order to comply with these standards.

The literature survey proved that there is no synthetic method reported for the synthesis and characterization of potential impurities in mirabegron. Only one synthetic method available for the synthesis of mirabegron API [8]. In literature, few methods reported for HPLC separation and quantification of impurities of mirabegron [9,10] and few methods available for the separation and characterization of stress degradation

products of mirabegron [11-13]. In view of the significance of impurity synthesis and lack of available synthesis methods for the synthesis of potential impurities of mirabegron, the present study aimed to synthesize impurity 3, 4, 6, 8 and 9 of mirabegron by using simple, easy, convenient and economical synthesis route. The molecular structure of mirabegron and its impurities synthesized in the present study are given in Fig. 1.

EXPERIMENTAL

The chemicals used in the study such as butylammonium bromide, (*R*)-2-((4-nitrophenethyl)amino)-1-phenylethanol hydrochloride, mirabegron (2-(4-nitrophenyl) ethamine, 2-hydroxy-2-phenyl acetic acid, dicyclohexyl carbo-diimide, *N*-hydroxybenzotriazole, palladium carbon, hydrazine hydrate, dichloromethane, tetrahydrofuran, triethylamine, acetyl chloride, potassium carbonate, methanol, methyl iodide, palladium carbon, hydrazine hydrate and hydrochloric acid were analytical reagent grade and purchased from Merck India and SDFCL Chemicals, India. The HPLC grade chemicals such as methanol and acetonitrile were purchased from Merck India. The Merck MilliQ water was used for the preparation of buffers in HPLC analysis. The Merck brand 0.2 µm Nylon membrane filter papers were used for the filtration of mobile phases as well as sample solutions.

Under positive nitrogen flow, all experimental procedures requiring anhydrous conditions were carried out. All of the glassware used in the study were air dried before use. Flash column chromatography was used to isolate and purify the chemicals using silica gel 60 (230-400 mesh). The analytical thin-layer chromatography (TLC) plates made of silicon gel 60 F_{254} and aluminium foil, spots were detected using UV light and/or colouring chemicals.

The ^{1}H NMR spectra were obtained in $CDCl_3$ using a 300 MHz FT NMR spectrometer (Bruker Ultrasheld 500 plush) and the chemical shifts were reported in δ ppm relative to TMS. Mass spectrum (70 eV) was recorded spectrometer (Agilent - Ultivo triple quadrupole LCMS G6465BA). The synthesized compounds were characterized by Agilent (USA) 1200 series IR spectroscopy instrument at a scan range of 4000-450 cm^{-1}. HPLC system (Agilent 1200 series) equipped with YMC Pack C18 (4.6 × 150 mm, 3 µm, 12 nm) as stationary phase, programmable UV detector and Empower software. Equitron digital sonicator (Verilux) was used for sonication of standard impurity preparations. The pH meter make thermo Scientific (Orion Versa Star Pro - no VSTAR10) was used for adjusting the pH of HPLC mobile phase.

Synthesis of impurity 3: A single step synthesis process was developed using (*R*)-2-((4-aminophenethyl)-amino)-1-phenylethanol dihydrochloride as starting material for the synthesis of impurity **3** of mirabegron. An accurately weighed 4 g of starting material was placed in a round bottom flask containing 40 mL of dichloromethane. The content was stirred for 8 h at 0-5 ºC followed by the addition of tetrabutylammonium bromide (0.85 g) and triethylamine (0.9 g) and continued to stirr for 5 min at 0-5 ºC. Then acetyl chloride (1.4 g) was added slowly while stirring the reaction mixture at room temperature for overnight (**Scheme-I**). The progress of the reaction was monitored by using TLC analysis.

Synthesis of impurity 4

Step-1: Synthesis of *N*-methyl derivative of mirabegron: Impurity **4** of mirabegron was synthesized in a three-step process using ((*R*)-2-((4-nitrophenethyl)amino)-1-phenylethanol hydrochloride as starting material. An accurately weighed 1.0 g of starting material was taken in 100 mL round bottom flask containing 20 mL of tetrahydrofuran at room temperature. The

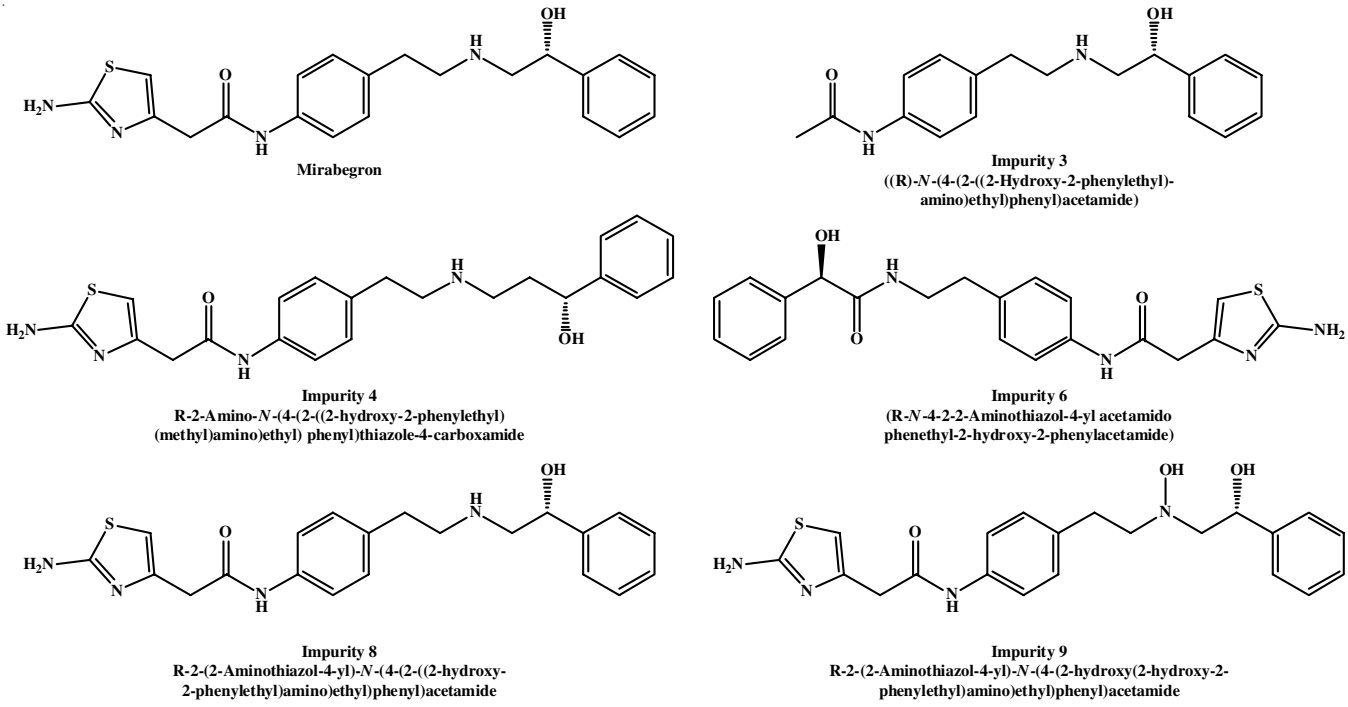
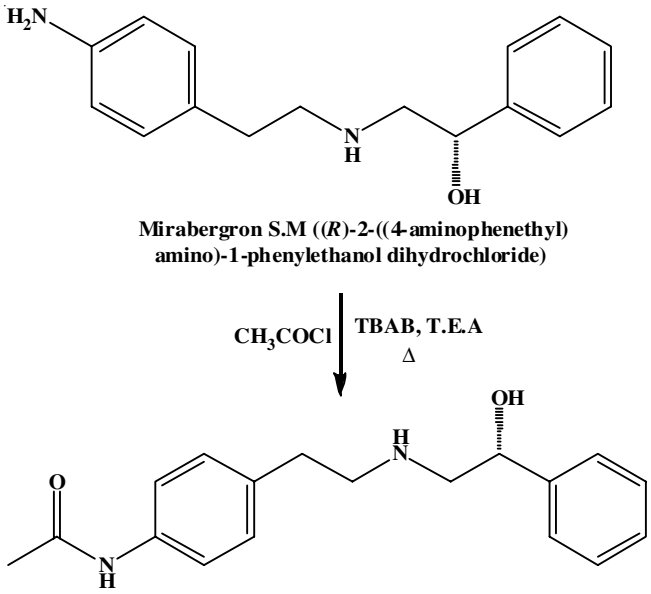


Fig. 1. Molecular structure of mirabegron and its impurities synthesized in the present study



Scheme-I: Synthetic route of impurity **3** of mirabegron drug

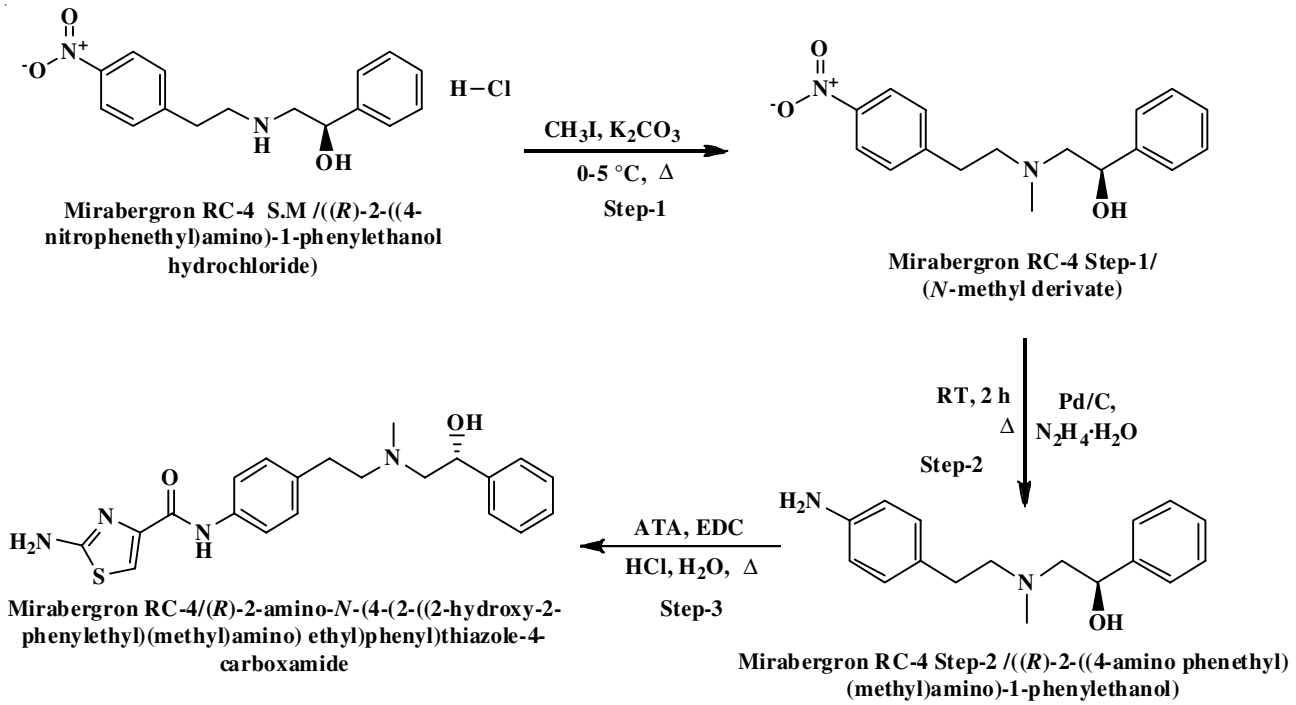
reaction mixture was cooled to 0-5 ºC and then K_2CO_3 (0.5 g) was added and stirred for 2 h. The methyl iodide (0.88 g) was then added and again stirred the reaction mixture to 2 h at 0-5 ºC. The completion of the starting material was assessed by TLC analysis and after the completion of staring material, distilled water was added in excess to separate the organic layer and then extract the aqueous layer with dichloromethane. The crude *N*-methyl derivative of mirabegron was obtained as end product which was further purified by column chromatography. A white colour crystal solid powder at a quantity of 800 mg was obtained as final product in step-1.

Step-2: The *N*-methyl derivative of mirabegron obtained in step-1 was used as staring material in step-2 for the synthesis of (*R*)-2-((4-aminophenethyl)(methyl)amino)-1-phenyl-ethanol. In a 100 mL volumetric flask, 350 mg of product obtained in step-1, methanol (20 mL) and palladium carbon (0.5 g) was mixed and stirred at room temperature followed by the addition of hydrazine hydrate (0.5 mL) and methanol (5 mL) and then stored at room temperature for 2 h by keeping the lid on to the flask. The crude end product was obtained in the reaction mixture was collected by filtration and followed by drying. The compound was further purified by preparative column chromatography and the pure compound as white colour crystal solid powder at a quantity of 360 mg was obtained.

Step-3: The final product obtained in step-2 (270 mg) was placed in a 100 mL round bottom flask containing water (6 mL) and HCl (3 g of 36.46 g/mL) and then stirred the reaction mixture for 15 min at 0-5 ºC followed by the addition of 2-(2-aminothiazole 5-yl)acetic acid (200 mg) and again stirred for 15 min at 5-10 ºC. The (1-ethyl-3-(3-dimethyl aminopropyl)-carbodiimide hydrochloride (3.28 g) was added and stirred the reaction mixture at of 5-10 ºC slowly at room temperature and again stirred the reaction overnight. The completion of the reaction was verified by TLC analysis and after completion of the reaction, 960 mL water was added and basified with 40 mL of 2 N NaOH solution. The final product was extracted using dichloromethane (200 mL) and the pure compound was collected by drying the organic layer under vacuum (**Scheme-II**). Pale yellow solid powder of impurity **4** at a quantity of 710 mg was obtained as final product.

Synthesis of impurity 6: Impurity **6** of mirabegron was synthesized in a three-step mechanism using 2-(4-nitrophenyl) ethamine as starting material.

Step-1: An accurately weighed 1.4 g of 2-(4-nitrophenyl)-ethamine and 2-hydroxy-2-phenyl acetic acid was mixed in a



Scheme-II: Synthetic route of impurity **4** of mirabegron drug

100 mL round bottom flask. To this *N*-hydroxy benzotriazole (HOBT, 0.2 g), dicyclohexyl carbodiimide (DCHC, 3.56 g), ethyl acetate (100 mL) and triethylamine (TEA, 2.0 g) were added and stirred at room temperature for 2 h. The progress of the reaction and the formation of the end product was monitored by TLC analysis. After the completion of reaction, the final product 2-(4-nitro-phenethyl)amino-1-phenyl ethanol was collected by filtration. An off white colour powder at a quantity of 1700 mg was obtained.

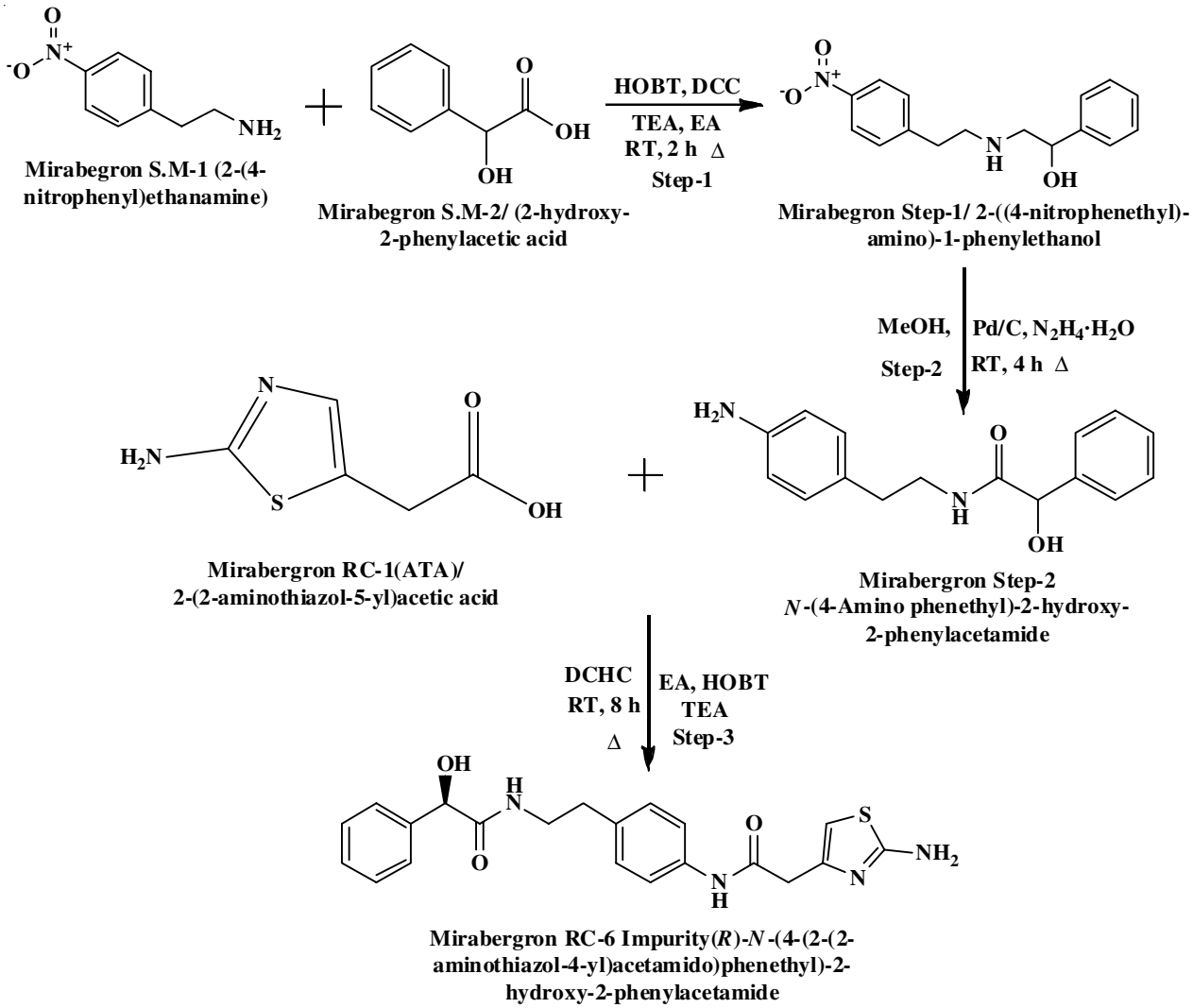
Step-2: In a 100 mL volumetric flask, the product obtained in step-1 (1.0 g), palladium carbon (0.2 g), hydrazine hydrate (2.0 g) and methanol (25 mL) was mixed and stirred for 4 h at room temperature. The completion of the reaction and the purity of the end product was assessed by TLC analysis. The solid final product of *N*-(4-aminophenethyl)-2-hydroxy -2-phenylacetamide was obtained. An off white colour powder at a quantity of 4150 mg was obtained.

Step-3: In a 100 mL round bottom flask, the final product of step-2 *i.e. N*-(4-aminophenethyl)-2-hydroxy-2-phenylacetamide (1.0 g), 2-(2-aminothiazole-5-yl)acetic acid (0.6 g), dicyclohexyl carbodiimide (2.0 g), *N*-hydroxybenzotriazole (0.1 g), ethyl acetate (50 mL) and triethylamine (3.0 g) were added and stirred at room temperature for 8 h. A yellow solid powder of impurity **6** (R-N-4-2-2-aminothiazol-4-yl acetamido phenethyl-2-hydroxy-2-phenylacetamide) was collected by filtration and the ethyl acetate layer was removed by distillation at 50 ºC in vacuum (**Scheme-III**). The obtained crude material of impurity **6** was purified by column chromatography (on 60-120 mesh silica gel) using 10% methanol in CH_2Cl_2) as eluents.

Synthesis of impurity 9

Preparation of peracetic acid solution: In a 10 mL round bottom flask, acetic acid (2.8 mL) and hydrogen peroxide (2.1 mL) were added and stirred well. Then sulfuric acid (0.1 mL) was added slowly dropwise and stirred at room temperature for 1.5 h.

The synthesis of impurity **9** of mirabegron was carried in a single step simple process using active pharmaceutical ingredient of mirabegron was used as starting material. In a 100 mL round bottom flask, ethyl acetate solution (10 mL) and acetic acid (2 mL) was added and stirred at room temperature for 15 min. Then peracetic acid solution (5.0 mL) was added and stirring continued for 2 h at room temperature. The progress



Mirabegron S.M-1 (2-(4-nitrophenyl)ethanamine)

Mirabegron S.M-2/ (2-hydroxy-2-phenylacetic acid

Mirabegron Step-1/ 2-((4-nitrophenethyl)-amino)-1-phenylethanol

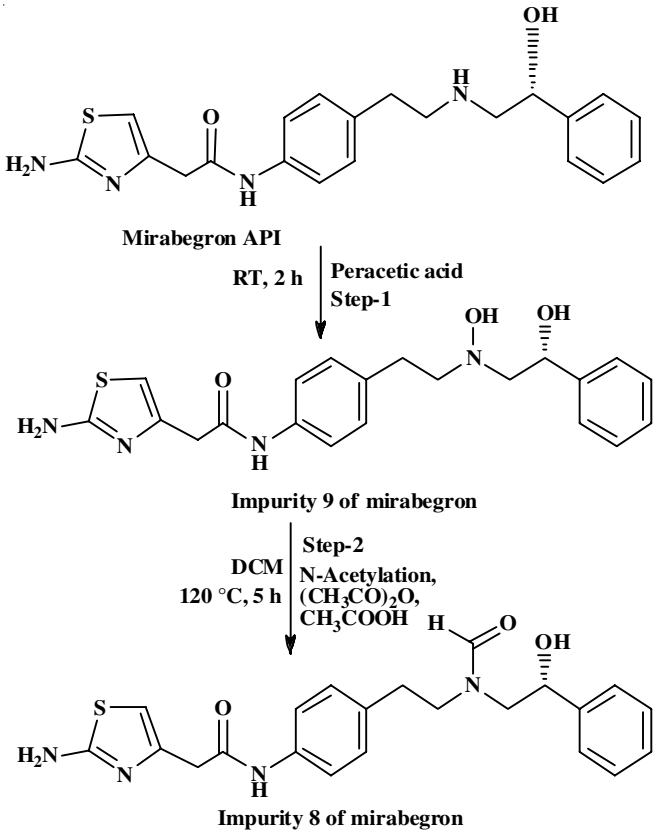
Mirabergron RC-1(ATA)/ 2-(2-aminothiazol-5-yl)acetic acid

Mirabergron Step-2 *N*-(4-Amino phenethyl)-2-hydroxy-2-phenylacetamide

Mirabergron RC-6 Impurity(*R*)-*N*-(4-(2-(2-aminothiazol-4-yl)acetamido)phenethyl)-2-hydroxy-2-phenylacetamide

Scheme-III: Synthetic route of impurity **6** of mirabegron drug

of reaction was monitored by TLC. After the completion of reaction, the reaction mass was filtered and the ethyl acetate layer was separated by distillation at 50 ºC under dry vacuum (**Scheme-IV**). The obtained crude material was further purified by column chromatography (60-120 mesh silica gel) using 10% methanol in DCM as eluents. A pale yellow solid powder mass of impurity **9** at a quantity of 1800 mg was obtained.



Scheme-IV: Synthetic route of impurities **9** and **8** of mirabegron drug

Synthesis of impurity 8: Impurity **9** of mirabegron synthesized in the study was used as starting material for the synthesis of synthesis of impurity **8**. In a 100 mL round bottom flask, impurity **9** (0.9 g), acetone solvent (10 mL) and acetic acid (10 mL) were added and stirred at 120 ºC for 5 h in reflux. The completion of reaction was identified by TLC analysis and then the reaction mass was filtered and extract the compound in water and dichloromethane. The dichloromethane layer was collected and distilled at 50 ºC under dry vacuum (**Scheme-IV**). The compound was further purified by column chromatography and the column eluents was dried using rotatory vacuum evaporator. A pale yellow powder mass of impurity **8** at a quantity of 510 mg was obtained.

Evaluation of the purity of the synthesized impurities by HPLC: The purity of the impurities synthesized in the study were evaluated using HPLC analysis. The HPLC method established for the impurity analysis was validated as per the guidelines with the parameters such as linearity, precision, accuracy, ruggedness and robustness studies. The method that produces all the validation parameters with in the acceptable levels was used for the assay of impurities synthesized in the study. The summary of the method parameters developed for the impurity analysis is tabulated in Table-1.

TABLE-1
ANALYTICAL CONDITIONS USED FOR THE QUANTIFICATION OF MIRABEGRON IMPURITIES SYNTHESIZED

Parameter	Condition		
Column description	YMC Pack C18 4.6 × 150 mm, 3 µm, 12 nm		
Column temperature	30 °C		
Sample temperature	Ambient		
Wavelength	UV 210 nm and 260 nm		
Flow rate	1.25 mL/min		
Injection volume	5 µL		
Run time	57 min		
Mobile phase	A: pH 4.0 phosphate buffer, acetonitrile 98:02 (v/v)		
	B: pH 4.0 phosphate buffer, acetonitrile 70:30 (v/v)		
Elution mode	Gradient		
Gradient program	Time	A (%)	B (%)
	0.01	93	7
	30.00	72	28
	35.00	58	42
	42.00	52	48
	45.00	50	50
	51.00	35	65
	52.00	93	7
	57.00	93	7

RESULTS AND DISCUSSION

A simple and convenient synthetic route for the synthesis of different process related impurities of mirabegron drug is reported herein.

Impurity **3** of mirabegron obtained as final product was characterized for the evaluation of the quality of the product. The FT-IR spectrum of impurity **3** shows the characteristic peaks for various functional groups present in the skeleton of the structure. The spectrum shows prominent peaks at 3302.78 cm^{-1} (OH), 3117.66 cm^{-1} and 3054.31 cm^{-1} (C-H *str.*), 2932.77 cm^{-1} (aliph. –CH group) 1738.02 cm^{-1} (-C=O), 1618.63 cm^{-1} (amide), 1529.15 cm^{-1}, 1415.75 cm^{-1} (benzene), 1368.88 cm^{-1}, 1314.60 cm^{-1} (CH_3) & (CH_2), 1229.38 cm^{-1}, 1111.39 cm^{-1}, 1025.13 cm^{-1} (amines C-N *str.*), 945.50 cm^{-1}, 829.78 cm^{-1}, 755.63 cm^{-1}, 700.14 cm^{-1} (alkenes and aromatic compounds) and the identified peaks shows good correlation with the pure impurity **3** of mirabegron. The ^1H NMR (300.13 MHz) spectrum of the synthesized impurity **3** shows signals (δ) at 0.94-1.04 (3H, methyl group), 1.25 (1H, alcohol), 1.46 (2H, methylene group), 2.18 (1H, C attached O), 2.73 (1H, C attached N), 2.93 (1H, methane group), 3.37 (2H, methylene group), 4.70 (1H, methine group), 7.34-7.44 (3H, benzene). The mass spectrum of synthesized impurity **3** shows the characteristic fragments at *m/z* of 298 and other important peaks observed at *m/z* 294.16, 298.86 (100%), 299.91. The mass spectra doesn't shows any fragment corresponds to the unwanted compound or impurity and hence proved that the compound obtained as final product in the study was pure impurity **3** of mirabegron.

Impurity 4: The FT-IR spectrum shows the various signals represents the impurity **4** of mirabegron. The signals observed at 3298.64 cm^{-1}, 3191.41 cm^{-1} (OH), 2945.13 cm^{-1} (-CH_2), 2318.59 cm^{-1} (thiazol), 1664.06 cm^{-1} (C-O), 1607.77 cm^{-1} (C-N), 1518.91 cm^{-1}, 1457.58 cm^{-1}, 1410.90 cm^{-1}, 1337.68 cm^{-1} (CH_3) & (CH_2), 1257.14 cm^{-1}, 1172.76 cm^{-1}, 1115.87 cm^{-1}, 1022.80 cm^{-1} (sulphur, alochols), 828.71 cm^{-1}, 755.20 cm^{-1}, 696.83 cm^{-1} and the similar signal bands were identified for standard compound of mirabegron. The H NMR spectra of impurity **4** shows intense peaks at δ value of 2.44-2.80 (3H, -CH_3), 3.49 (1H, -CH_2), 3.61 (1H, OH), 4.67-8.95 (7H, aromatic phenol) and the signals were correlated to pure impurity **4**. The mass spectra of impurity **4** of mirabegron show molecular ion (M^+) peaks at *m/z* 410.53. The molecular ion observed at *m/z* 446, other important peaks appeared at *m/z* other important peaks appeared at *m/z* 408.95, 411.00 (100%). The HPLC analysis of the synthesized impurity confirms that impurity **4** product obtained having high purity of 99.32%. The spectral analysis results proved that there is no detection of any additional products/ impurities or the intermediates formed during the synthesis of impurity **4**.

Impurity 6: The synthesized impurity **6** was evaluated for its structural confirmation using FT-IR, NMR and mass spectral study and the purity of the compound was evaluated using HPLC analysis. The FT-IR spectrum shows significant bands at 3262.38 cm^{-1} (OH), 3090.91 cm^{-1} (=C-H), 2930.71 cm^{-1}, 2855.43 cm^{-1} (-CH_2), 1615.08 cm^{-1}, 1516.31 cm^{-1} (C-N, C-C, NH), 1452.25 cm^{-1}, 1363.24 cm^{-1}, 1261.37 cm^{-1}, 1247.62 cm^{-1}, 1192.28 cm^{-1}, 1151.02 cm^{-1}, 1101.34 cm^{-1}, 1055.09 cm^{-1} and 1027.31 cm^{-1} (ethers, alcohols, sulphur), which are in good argument with the pure compound of impurity **6**. The H NMR spectrum shows signals at δ of 2.63-2.72 (2H, methylene), 3.28 (1H, alochol), 3.45 (2H, methylene group), 4.86 (1H, *sec*.-amide), 6.13 (2H, methine), 7.08-8.01 (11H, H is attached benzene), 10.04 (1H, aldehyde). The mass spectra of impurity **6** of mirabegron synthesized showed a molecular ion (M^+) peaks at *m/z* 410.49. The molecular ion observed at *m/z* 446, other important peaks appeared at *m/z*, Other important peaks appeared at *m/z* of 383.26, 395.88, 403.70, 409.88, 411.04 (100%), 417.07. These characteristic signals were corresponds to impurity **6** of mirabegron and the signals were in correlation with the standard compound of impurity **6**. There is no additional peaks/signals that indicate the presence of impurities or the intermediates in the reaction confirmed that compound was pure. Further the quantitative analysis of the synthesized impurity using HPLC analysis confirms that impurity **6** was high pure with a quantity of 99.72%.

Impurity 9: The FT-IR spectra shows the signals at 3390.84 cm^{-1}, 3351.82 cm^{-1}, 3163.41 cm^{-1}, 3113.64 cm^{-1}, 3032.15 cm^{-1}, 2951.56 cm^{-1}, 2927.64 cm^{-1}, 2851.60 cm^{-1} (-CH, -CH_2-, -CH_3), 2360.43 cm^{-1} (-C≡N-), 1652.97 cm^{-1}, 1597.24 cm^{-1} (C-C,C N, NH), 1489.94 cm^{-1}, 1458.28 cm^{-1}, 1445.82 cm^{-1}, 1426.32 cm^{-1}, 1410.46 cm^{-1}, 1337.99 cm^{-1} (CH_3 & CH_2), 1299.37 cm^{-1}, 1259.37 cm^{-1}, 1226.84 cm^{-1}, 1204.02 cm^{-1}, 1185.78 cm^{-1}, 1155.33 cm^{-1}, 1116.67 cm^{-1}, 1063.47 cm^{-1}, 1074.94 cm^{-1}, 1030.48 cm^{-1} (C-O-C, C-OH) and the similar type of signals were impurity **9** in $CDCl_3$ shows the signals (δ) at 2.85-2.93 (6H, CH_2), 3.61 (2H, CH_2), 4.66 (1H, CH), 5.00 (1H, *sec*.-amide), 7.11-8.94 (9H, H is attached to benzene), whereas the mass spectra shows molecular ion (M^+) peaks at *m/z* of 412. The molecular ion observed at *m/z* 412.79, other important peaks appeared at *m/z*, other important peaks appeared at *m/z* 413.10, 412.79 (100%), 415.30, 416.33, 419.67. The spectral data of the synthesized impurity **9** was in accordance with the standard and confirms the purity of the compound. Further, the quantification of the synthesized impurity was evaluated using HPLC. In HPLC analysis, the retention time of synthesized compound was same as the standard. It was observed that obtained product contain 99.12% impurity **9** confirms that the synthetic route was very efficient for the production of impurity **9**.

Impurity 8: Impurity **8** synthesized was utilized as starting material for synthesizing impurity **8** of mirabegron. A pale yellow powder mass of impurity **8** at a quantity of 510 mg was obtained. The FT-IR spectrum of the synthesized compound shows peak at 3393.19 cm^{-1} (-OH), 2926.19 cm^{-1}, 2860.12 cm^{-1} (-CH, -CH_2-, -CH_3), 2284.59 cm^{-1} (-C≡N-), 1619.80 cm^{-1}, 1516.57 cm^{-1} (C-C, C-N, NH), 1413.12 cm^{-1} and 1337.63 cm^{-1} (CH_3 & CH_2) represents various functional groups in the compound. The ^{1}H NMR spectra (300 MHz) spectrum of final product in $CDCl_3$ shows signals (δ) at 1.90 (3H, CH_3), 2.02-3.48 (8H, CH_2), 3.51 (1H, OH), 3.67 (1H, amine group), 6.35 (1H, CH), 7.01-7.47 (11H, H is attached to benzene), 9.07 (2H, amide), whereas the mass spectra of the final product in showed molecular ion (M^+) peaks at *m/z* 438.54. The molecular ion observed at *m/z* 439.03, other important peaks appeared at *m/z*, Other important peaks appeared at *m/z* 274.05, 421.03, 437.21, 439.03 (100%), 461.00, 713.58. Based on the spectral analysis, the obtained final product was confirmed as impurity **8** of mirabegron with molecular formula of $C_{22}H_{24}N_4O_3S$ and IUPAC name of *R*-2-(2-aminothiazol-4-yl)-*N*-4-2-2- hydroxy-2-phenylethylamino ethyl phenyl acetamide. Further the purity of impurity **8** was evaluated using HPLC and based on the results, it was confirmed that the obtained impurity **8** have 99.32% purity.

Conclusion

In this study, a productive, safe and commercial synthesis route was developed for the synthesis of five impurities of mirabegron such as impurity 3, 4, 6, 8 and 9. The TLC analysis was used for monitoring the progress of the reaction and the final products obtained were characterized using FT-IR, NMR and mass spectral studied. The raw materials employed in the synthetic process were inexpensive and accessible. Additionally, since all intermediate products could be employed directly as the raw material for the following step, no intermediate products between the raw materials and the finished compound needed to be chromatographed. As a result, the production efficiency significantly increased while the reaction time was significantly decreased. The synthetic technique, on the other hand, has the benefits of easily accessible raw materials, straightforward operation and mild reaction. Most importantly, the target product developed through this synthetic approach has a purity level high enough to support various types of study for the detection and management of mirabegron impurities.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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