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Synthesis and Characterization of Chiral Impurities of Rivaroxaban, Used as an Anticoagulant Drug

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Abstract

The mechanism of action of the anticoagulant medication rivaroxaban is the direct and specific suppression of activated coagulation factor X (FXa). With just (S)-Rivaroxaban exhibiting pharmacological activity and (R)-Rivaroxaban being an impurity that must be controlled, this molecule only has one chiral centre. The present work describes the synthesis of chiral impurities of each intermediate, including KSM and its drug substance, and their characterization by spectral data (IR, MS, 1H-NMR, and 13C-NMR). The chiral impurity of drug substance is challenging during the process development of Rivaroxaban, and it is challenging for all pharmaceutical industries as well. The opposite isomeric impurity is introduced form its key starting material and it follows the same reaction mechanism path up to final drug substance. This work will help quality control (QC) to identify and control these impurities in the Rivaroxban drug substance as per ICH guideline.

Keywords: *Critical, Chiral Impurity, Synthesis and Characterization, Rivaroxaban, An Anticoagulant Drug.*

1. Introduction

A basic feature of molecular structures, chirality is crucial to biological processes, the exchange of biological information within and across species, and the actions and characteristics of exogenous substances like medications, agrochemicals, flavors, and food additives. [1-3] Though they have the same chemical structure, nearly 90% of the last type of drug substance in the pharmaceutical industry is marketed as a racemate mixture, which consists of an equimolar mixture of two enantiomers. Most isomers of chiral drugs show notable differences 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] Column chromatography is a conventional process used to separate and purify both liquid and solid materials in order to isolate or separate the contaminants. With the use of a liquid mobile phase, this chromatography technique uses a stationary solid phase to separate the impurities and impure chemicals that pass through it. Chemical properties allow substances to be isolated and separated. In order to separate different or the same group of compounds in extracts, optimizing the method is a crucial and difficult task. This method has some drawbacks, including a longer reaction time, a lower power of separation, the use of more solvents—including hazardous solvents—and, last but not least, a higher cost. [5-9] Chemically known as 5-chlro-N-([(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl], rivaroxaban (Figure 1)The United States Food and Drug Administration (USFDA) has approved -1,3 oxazolidin-5-ylmethyk)thiophene-2-carboxamide, an orally active direct factor Xa (FXa) inhibitor medication produced by Bayer. Xarlto, also known as rivaroxaban (Figure 1), was first prescribed

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in July 2001 for the treatment and prevention of a number of thromboembolic conditions, such as cerebral stroke, angina pectoris, deep vein thrombosis, myocardial infarction, pulmonary embolism, recurrence and restenosis after angioplasty or aortocoronary bypass, and transient ischemic attacks. [11-15]

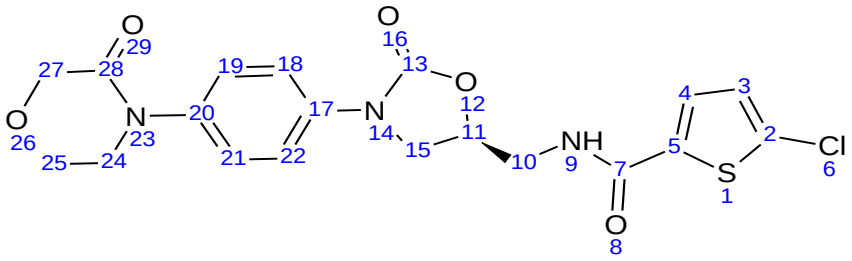

Figure 1 Rivaroxaban

2. Method

The chemical structure of Rivaroxaban (Figure 1.), the carbon 11 having chiral center, which is S -isomer of Rivaroxaban[14], during the process development of Rivaroxaban (Figure 1.) for large scale there were five chiral impurities observed, for isolation of these impurities column chromatography method is not workable or difficult to separate the chiral molecules and in column chromatography (Figure 2) large amount of expensive solvent are used which are environmentally hazardous, and hence, decided to go with green approach and cost effective methodology is used, these impurities are identified and targeted for the synthesis and characterization .[14-16]

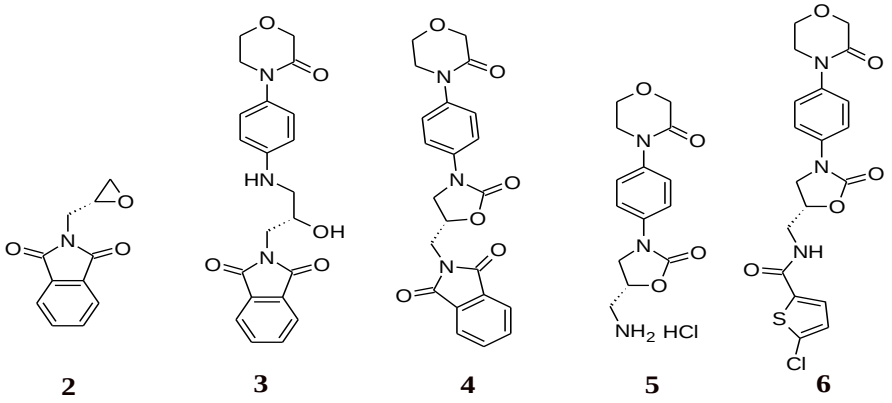

Figure 2 For Five Chiral Impurities of Rivaroxaban

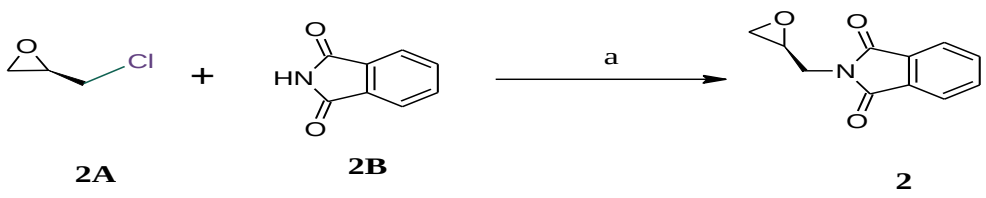

Figure 3 For Synthesis of Chiral Impurity 2 of KSM i.e., (2-[(2*R*)-Oxiran-2-ylmethyl]-1*H*-isoindole-1,3(2*H*)-dione). Reaction condition a: TBAB, methanol, water, reflux 15 hrs., toluene

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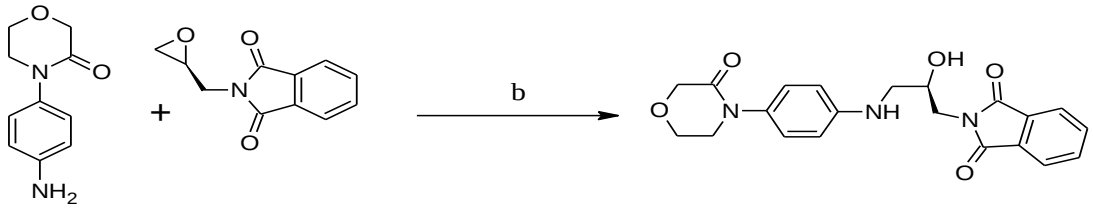
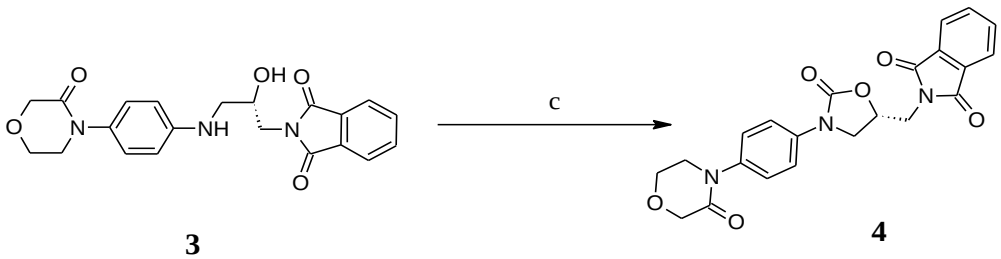


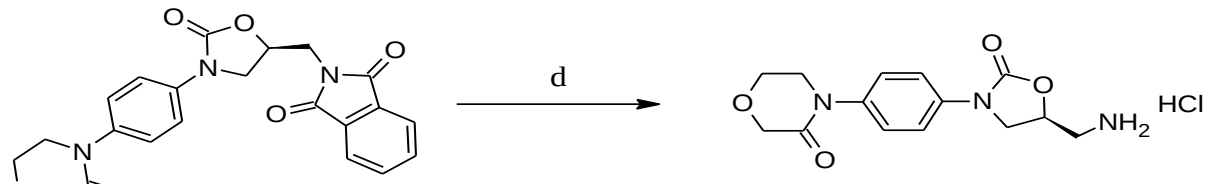
7 2 3

Figure 4 For Synthesis of Chiral Impurity 3 of rivaroxaban intermediate i.e., 2-[(2S)-2-Hydroxy-3-{[4-(3-oxomorpholin-4-yl) phenyl] amino} propyl]-1*H*-isoindole-1,3(2*H*)-dione.
Reaction condition b: Methanol, water, reflux 15 hrs



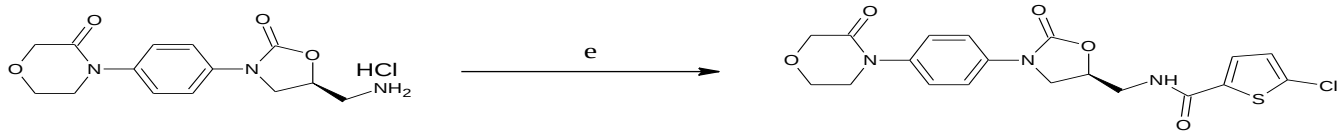
3 4

Figure 5 For Synthesis of Chiral Impurity 4 of rivaroxaban intermediate i.e., 2-({(5*R*)-2-Oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione.
Reaction condition c: CDI, toluene, methanol, water, temperature 105-110°C for 3-4 hrs



4 5

Figure 6 For Synthesis of Chiral Impurity 5 of rivaroxaban intermediate i.e., 4-{4-[(5S)-5-(Amino methyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl} morpholin-3-one hydrochloride.
Reaction condition d: Mono-methyl amine, methanol, temperature at 60–65°C for 4–6 hrs., MDC, TEA, HCl



5 6

Figure 7 For Synthesis of Chiral Impurity 6 of rivaroxaban intermediate i.e., 5-Chloro-N-({(5R)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl}methyl) thiophene-2-carboxamide.
Reaction condition e: CTC, acetonitrile, water, TEA, temperature at 10–15°C for 2–3 hrs., acetic acid.

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3. Experimental

3.1. Preparation of (2-[(2R)-Oxiran-2-ylmethyl]-1H-isoindole-1,3(2H)-dione) (2)

Compound 2's production as shown in Figure 3. Phthalimide 2A (100 g, 0.68 mol), Tetra butyl ammonium bromide (TBAB) (1 g), and S-epichlorohydrin 2B (150 g, 1.6 mol) were refluxed for 15 hours in a suspension containing methanol (500 mL) and water (10 mL). When the reaction was finished (as indicated by HPLC), the methanol was extracted under vacuum until a dry solid was visible. The reaction mass was then supplemented with 1000 ml of toluene, 130 g of potassium carbonate, and 15 hours of reflux. Eventually, 100 mL of toluene was washed, the precipitated inorganic solid was filtered, and the process was cooled to 25–30°C. Following two hours of chilling the reaction to 0–5°C, the solid was filtered and vacuum-dried to produce 650–700 75 g (54%).Mass/z of MS: 204 [M+1]. The 1H NMR (CDCL3, 400 MHz) values are 1.70–2.68 (m, 1H), 2.82-2.80 (t, 1H), 3.26–3.22 (m, 1H), 3.83–3.78 (dd, 1H), 3.99–3.94 (dd, 1H), 7.75–7.73 (m, 2H), and 7.88–7.86 (m, 2H). δ in 13C NMR (CDCl3, 400 MHz): 167.91, 134.07, 131.85, 123.36, 48.99, 46.06, 39.57. The chemical purity is 97.5% according to HPLC.

3.2. Preparation of 2-[(2S)-2-hydroxy-3{[4-(3 -oxomorpholin-4-yl) phenyl] amino} propyl] -1H-isoindole-1,3(2H) -dione (3)

Compound 3's production as shown in Figure 4. 4-(4-aminophenyl) morpholin-3-one (5, 100 g, 0.52 mol) and 2-[(2R)-oxiran-2-ylmethyl] were suspended inIsoindole-1,3(2H) -1H-dione (6, 116.2 g, 0.57 mol) was refluxed for 15 hours in 500 mL of methanol and 1500 mL of water. Following the conclusion of the reaction (by HPLC), the reaction mass was cooled to 25–30°C, the precipitated solid 3 was filtered, and it was then cleaned with 100 mL of methanol and dried under vacuum (650–700 mm/Hg) at 50–55°C for 6 hours to produce a solid that ranged in colour from light yellow to off white. 196.8 g (96.0%) is the yield. MS m/z: 396 [M+1]. 1.98–3.04 (m, 1H), 3.13–3.19 (m, 1H), 3.68–3.57 (m, 4H), 4.02–3.991 (m, 3H), 4.13 (s, 2H), 5.16 (d, J = 5.2 Hz, 1H), 5.65 (t, J = 6.4 Hz, 1H), 6.61 (d, J = 8.8 Hz, 2H), 7.01 (d, J = 8.8 Hz, 2H), 7.82–7.88 (m, 4H). by HPLC, the chemical purity is 97.53%.

3.3. Preparation of 2-({(5R)-2-oxo-3-[4-(3 -oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5 -yl} methyl)-1H-isoindole-1,3(2H)-dione (4)

The synthesis of Compound 4, as displayed in Figure 5. N-N-carbonyldiimidazole (CDI) (61.5 g, 0.38 mol) was combined with a suspension of three (100 g, 0.25 mol) in 700 mL of toluene at a temperature of 25–30°C. For three to four hours, or until the reaction was complete (as determined by HPLC), the reaction mixture was maintained between 105 and 110°C. At 50–55°C, add 500 millilitres of methanol to the solid. Once it cools to 25–30°C, the solid slurries. After that, four light yellow to off white particles are obtained by filtering and washing with 50 millilitres of methanol. 95.0%, or 101.1 g, were produced. The NMR spectra (DMSO-d6, 400 MHz) for MS m/z are as follows: δ 3.72–3.70 (t, 2H), 4.04–3.90 (m, 5H), 4.24–4.19 (m, 3H), 4.98–4.91 (m, 1H), 7.41–7.39 (d, 2H), 7.54–7.52 (d, 2H), and 7.93–7.85 (m, 4H). 99.66% chemical purity according to HPLC.

3.4. Preparation of 4-{4-[(5R)-5-(amino methyl)-2-oxo-1,3-oxazolidin-3-yl] phenyl}morpholin-3 -one hydrochloride (5)

Compound 5's production as shown in Figure 6. At 25–30°C, a solution of 4 (100 g, 0.23 mol) in 700 mL of methanol was added to a 40% methylamine solution (102 mL). The reaction mass was agitated for 4-6 hours at 60–65°C (HPLC was used to monitor the reaction's completion). To extract crude 5, the reaction mass was cooled to 25–30°C, its pH was adjusted to 1-2 using strong hydrochloric acid, and the precipitated solid was filtered and washed with 100 mL of methanol. To create a clear solution, the obtained crude 9 was dissolved in a combination of 800 mL of methanol and 300 mL of dichloromethane. The pH 8–9 of the process was adjusted using triethylamine at 25–30°C. Concentrated hydrochloric acid was used to acidify the reaction material to a pH of 2-3 in order to precipitate 5. The precipitated material was filtered, dried, and then washed with 150 mL of methanol. This produced pure 5, a white solid. 65.5 g (or 85.0%) of yield. 292.2 [M+1] MS m/z. At 400 MHz, 1 H NMR (D2O): δ 3.24 (d, 2H),

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3.73–3.70 (t, 2H), 3.98–3.90 (m, 3H), 4.23–4.19 (t, 3H), 4.98–4.97 (t, 1H), 7.44–7.42 (d, 2H), 7.57–7.55 (d, 2H), 8.49 (s, 3H). 99.89% chemical purity according to HPLC.

3.5. Preparation of 5-chloro-N-({(5R)-2-oxo-3-[4 (3-oxomorpholin-4-yl)phenyl]-1,3 oxazolidin -5-yl} methyl) thiophene-2 -carboxamide (6)

The synthesis of chemical 6 is shown in Figure 7. A solution of 5 (100 g, 0.30 mol), water (300 ml), triethylamine (60 g, 60 mol), and acetonitrile (500 ml) was added to 5-chlorothiophene-2-carboxylacid chloride syrup (65 g, 0.38 mol). The temperature was kept between 5 and 10°C. After the reaction mass was shaken at 10–15°C for two to three hours, water (200 mL) was added to the reaction mixture at 35–40°C (with the completion of the reaction assessed by HPLC). A temperature of 65°C was applied to the reaction mixture. At 25–30°C, the reaction mixture was cooled. After filtering and washing with 100 mL of water, the resulting solid, number 6, was obtained. After that, the wet solid, number 6, was leached off for an hour in 500 millilitres of acetic acid and 300 millilitres of water. To achieve pure number 6, the resulting solid was filtered, cleaned with 100 mL of water, and dried under vacuum (700 mm/Hg) for five hours at 50–55°C. Production: 86.0%, 114.3 g. M+1] 1 H NMR (DMSO-d6, 400 MHz): MS m/z: 436.0 δ 3.62–3.59 (t, J = 5.6 Hz, 2H); 3.72–3.69 (t, J = 5.2, 4.8 Hz, 2H); 3.87–3.83 (q, 1H); 3.98–3.95 (t, J = 4.8, 5.6 Hz, 2H); 4.21 (s, 2H); 4.16 (t, 1H); 4.85–4.82 (m, 1H); 7.18–7.19 (d, 1H); 7.41–739 (d, 2H); 7.56–7.54 (d, 2H); 7.69 (d, 1H); 8.98–8.95 (t, J = 4, 6 Hz, 1H). δ 165.97, 160.80, 154.10, 138.46, 137.05, 136.49, 133.28, 128.44, 128.15, 125.95, 118.32, 71.33, 67.73, 63.47, 49.00, 47.42, 42.20, 13C NMR (DMSO-d6, 400 MHz). Chiral purity by HPLC was 99.81%.

4. Result and Discussion

Rivaroxaban is big molecule and need of chiral impurities will be increased day by day to control of this impurity is not challenge now because from above experiments of synthesis of chiral impurities (2,3,4,5, & 6) 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.

Conclusion

We have identified and synthesized five chiral impurities related to Rivaroxaban (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 1 to provide highly pure drug substance. Thus, work will help quality control (Q.C) to identify and control these chiral impurities in the Rivaroxaban (Figure 1.) drug substance as per ICH guideline.

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