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Carbonyldiimidazole (CDI) mediated synthesis of Rivaroxaban related impurities with ambient conditions

Rajesh Akkineni, Pradeep Pothana, Dr. Venkateswararao Battula, Narsimlu Mailaram and Sivarama Krishna Myla

Abstract
Rivaroxaban has the chemical name (S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl] oxazolidin-5-yl]methyl}thiophene-2-carboxamide,is oral anticoagul-ant and direct factor Xa inhibitor which is used in the prevention of stroke and venous embolism in patients with chronic atrial fibrillation, as well as treatment and prevention of deep venous thrombosis and pulmonary embolism. European pharmacopeia related substances A, B, D, G and J, and others impurities have been obtained during its synthesis. The present work describes the detection, origin, synthesis of D and J impurities with Carbonyldiimidazole (CDI) as a reagent with good yield, which may improve the commercial process.

Keywords: Rivaroxaban, anticoagulant, impurities, Carbonyldiimidazole (CDI)

Introduction
The safety of a drug is dependent on the toxicological properties of the active drug substance as well as the impurities formed during various chemical transformations [1]. According to the general guidelines for impurities in drug substances recommended by the International Conference on Harmonization, for drugs with a maximum daily dose equal to or less than 2 g, any impurities present in the drug substance greater than a level of 0.10% should be identified and characterized [2, 3]. Therefore, identification, quantification, and control of impurities in the drug substance and drug product are important parts of drug development for regulatory approval. In these impurities, synthesis of Impurity D and J is difficult and very less yield, present work our team was developed new synthetic route for both impurities with Carbonyldiimidazole (CDI) as a reagent with good yields.

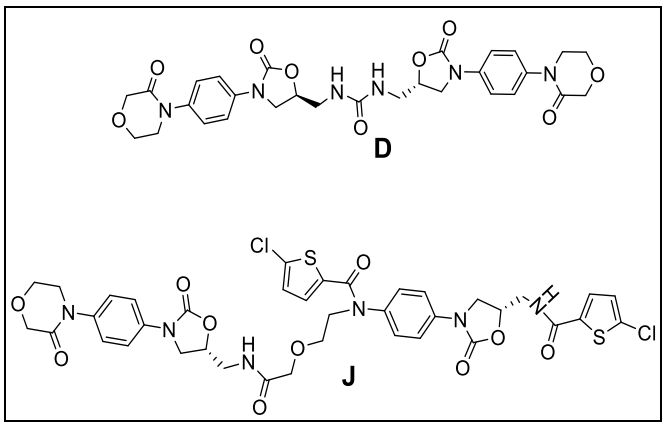

Fig 1: Impurities D and J

Rivaroxaban (1, Fig. 1) is an anticoagulant and the first orally active direct factor Xa inhibitor [4, 5]. The drug was developed and manufactured by Bayer and was marketed in the USA by Janssen Pharmaceuticals, a unit of Johnson & Johnson [6]. It is used for prophylaxis and treatment of thromboembolic disease [7]. Rivaroxaban is safe and highly effective compared with heparin anticoagulant drugs. Sales of rivaroxaban have increased rapidly year after year sales reached 8596.39 million US dollars in 2022.

Material and Methods

Because of its unique therapeutic efficiency and promising market prospect, several synthetic methods were reported for the preparation of rivaroxaban (1) [9-12]. Tian and coworkers reported an improved route of 1 and clarified impurities in the relevant synthetic process [12]. Our team also developed an efficient and expedient method to prepare rivaroxaban on a large scale in an overall yield of 85%, as outlined previously [13].

The synthesis of rivaroxaban involves the oxirin ring open of (S)-2-(oxiran-2-ylmethyl)isoindoline-1,3-dione(3) with 4-(4-aminophenyl)morpholin-3-onein(2)aqueous methanol to afford the (4) followed by cyclization with Carbonyld-iimidazole (CDI) to give (5) which is Hydrazinolysis in the presence of mono methylamine yields (S)-4-4-(5-amino-methyl)-2-oxooxazolidin-3-yl)phenylmorpho-lin-3-one (6) Which undergoes N-acylation with 5-chlorot hiophene-2-carbonyl chloride (7) to give rivaroxaban (1). In this process in Stage II. We used CDI as a reagent for carbonyl cyclization instead of triphosgene or phosgene with excellent yield, the process can be depicted by following reaction scheme.

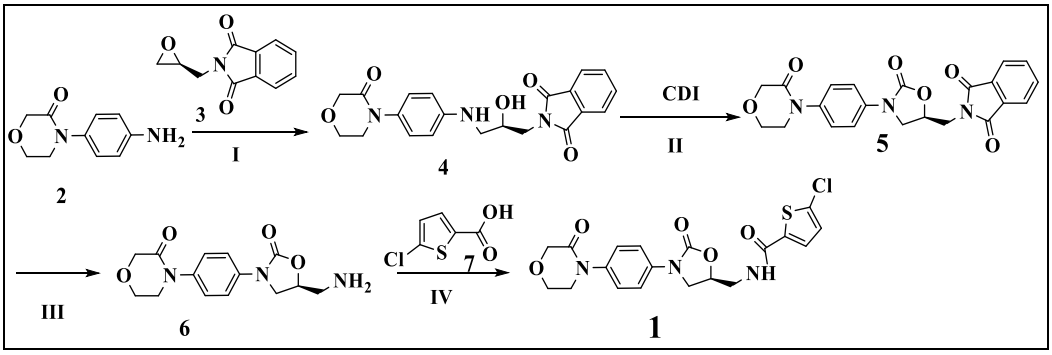

Fig 2: Synthetic route of Rivaroxaban (1): Conditions: (i) aq. MeOH, reflux 82%; (ii) CDI, DCM, rt, yield, 94%; (iii) mono methylamine (40% solution in water), Methanol, HCl, reflux, yield 81%; (iv) TEA, DCM, 0-5 °C, yield 82%

Results and Discussion

In this article we have disclosed our work regarding the synthesis and characterization of the various potential impurity of Rivaroxaban. Here we successful synthesized the potential impurities D and J with CDI as a reagent. We inspire from stage II of rivaroxaban synthesis and applied the same reagent in the synthesis of D and J impurities.

Structure of impurities

During the process development of rivaroxaban, several unreported process-related impurities were found, and the molecular weights of the impurities were identified through mass spectrometry (MS). All of the impurities were characterized by HPLC. Based on the spectral data, these impurities were identified as the compounds. All impurities could be effectively removed by recrystallization in a mixture of Acetone and water.

Source of impurities

During the deprotection reaction in the synthetic process of rivaroxaban, intermediate 5 was treated with excess hydrazine hydrate at 90 °C to give the amino intermediate 6. Impurities D and J could be generated in step iv.

Preparation of Impurity D: (N, N′-bis [[(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]-1,3-oxazolidin-5-yl] methyl] urea

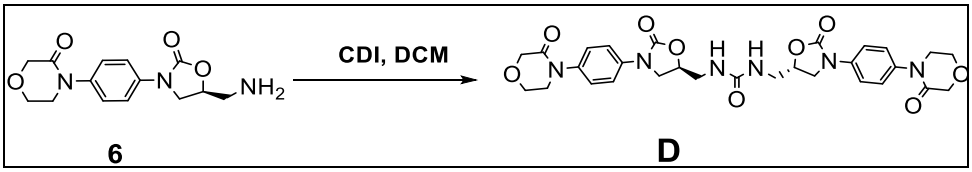

Fig 3: Synthetic route of Impurity D, Condition: DMF, CDI, RT, 16h

This impurity is formed by the (S)-4-4-(5-amino-methyl)-2-oxooxazolidin-3-yl) phenylmorpho-lin-3-one (6) treated with CDI in DCM for 2 hours at room temperature, again (S)-4,4-(5-amino-methyl)-2-oxooxazolidin-3-yl)phenylmorpholin-3-one (6) was added slowly in DCM and stirred for 12hours at room temperature, quenched by water to provide the solid impurity D. The mass spectrum showed protonated molecular ion peak at m/z 610.2(M+1). IR spectrum showed the presence of N-H Stretching (3418 Cm-1), aliphatic =C-H stretching (2926 Cm^{-1}) and -C-H stretching (2874 Cm^{-1}). It also showed the -C=O stretching (1729, 1748 and 1433, 1412 Cm^{-1}) corresponding the amide group. In 1H-NMR (solvent DMSO) the δ 3.7 and 4.4 indicates the –CH2 protons attached with urea bond of two molecules of compound, the 13CNMR 158.4 indicates the formation of urea bond between the two molecules.

Preparation of Impurity J: 5-chloro-N-(4-((S)-5-((5-chlorothiophene-2-carboxamido)methyl)-2-oxooxazolidin-3-yl)phenyl)-N-(2-(2-oxo-2-((((R)-2-oxo-3-(4-(3-oxomorpho-lino)phenyl)oxazolidin-5-yl)methyl)amino)ethoxy)ethyl)-thiophene-2-carboxamide

The synthesized rivaroxaban under the present conditions contained impurity J at a level of 0.03–0.08%. The synthesis of compound J was the most challenging [15]. Several conditions were attempted, and only a trace amount was detected. According to our efforts, synthesized the Impurity J in three steps from Rivaroxaban and CDI as a reagent.

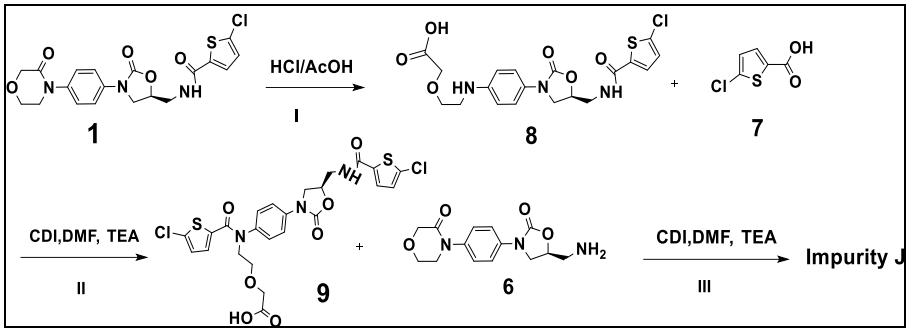

Fig 4: Synthetic route of Impurity J, Condition: (i) HCl/AcOH, reflux, 12h, (ii) CDI, Et3N, DMF, rt, 8h (iii) CDI, Et3N, DCM, rt, 6h

The impurity is formed from rivaroxaban (1) in three steps, in 1st step Rivaroxaban was treated with HCl and acetic acid, the morpholine ring was opened to form carboxylic acid (8), the obtained crude (8) was treated with 5-Chlorothio-phene-2-carboxylic acid (Compound 7) in presence of CDI to produce the crude 9, which was further treated with compound 6 in presence of CDI to provide the Impurity J, the obtained crude was further purified by silica column chromatography to obtained the impurity J as off white solid. The MS of compound J showed a molecular ion peak at m/z 892.8 (M + Na) (Calc. mass: 893.1209) in positive ion mode, and the predicted molecular formula was C38H36N6O10S2Cl2Na. The 1H NMR signals at 7.98 and 8.92 ppm indicated the amide N─H protons of group's ─OCH2CONH─ and thiophene ─CONH─, respectively. The two groups of multiplets at 4.75 and 4.86 ppm corresponded to C─H protons of the two oxazolid-inones and the additional 12 proton signals at 6.53–7.68 ppm corresponded to aromatic protons. The 13C NMR spectrum revealed 32 carbon signals (six overlapped), and distortion less enhancement by polarization transfer revealed nine secondary carbon signals (one overlapped). Based on the spectral data (HRMS, 1H NMR, and 13C NMR), the structure of compound B was confirmed.

Experimental

Materials and instruments

All solvents and reagents were purchased from the suppliers and used without purification. 1H and 13CNMR spectra of the compound were recorded on 400 MHz Bruker's NMR spectrometer (av400). The chemical shifts were recorded in parts per million (δ) relative to TMS. FT-IR (Perkin Elmer) spectrometer was used to record the IR spectrum of the compound. KBr pellet of the compound was prepared by the standard method and the spectrum was recorded at resolution from 400 cm-1-4000 cm-1. Mass spectra of the compound were recorded on Mass spectrometer (Waters).

Impurity D: **N, N′-bis [[(5S)-2-oxo-3-[4-(3-oxo morpholin-4-yl) phenyl]-1, 3-oxazolidin-5-yl] methyl] urea**

The free base of Compound **6** (5.0g, 17.18mmol) in DCM (25 ml) added the Carbonyldiimidazole (CDI) (3.48g, 21.47mmol) stirred at RT for 2h, again 5.0g of Compound-6 (free base) in 25 ml DCM was added slowly and stirred for 12h. at RT, the reaction mass was distilled off to remove the solvent, added the cold water (100 ml) and stirred 1hour, the obtained solid was filtered and washed with water and dried under vacuo to get the 7.0g (yield 67%) of Impurity-D. MP: 242.3-244.1 °C, IR(KBr, cm-1). 3418.45, 2926.33, 1729.57, 1748.06, 1651.58, 1606.54 1433.40, 1412.84, 1230.33,1122.80. 1H-NMR (solvent DMSO-d6), δ:7.56 (d, 4H, J=8.90), 7.40 (d, 4H,J=8.87Hz), 6.45 (t, 2H), 4.64 (m, 2H), 4.17 (s, 4H), 4.08 (t, 2H), 3.95 (t, 4H), 3.77 (t, 2H), 3.69 (t, 4H), 3.36 (s, 4H). 13C-NMR (solvent DMSO-d6), δ: 42.20, 47.08, 49.02, 63.48, 67.73, 72.20, 118.28, 125.99, 136.55, 136.99, 154.22, 158.41, 166.03.

Impurity J: 5-chloro-N-(4-((S)-5-((5-chlorothiophe-ne-2-carboxamido)methyl)-2-oxooxazolidin-3-yl)phen-yl)-N-(2-(2-oxo-2-((((R)-2-oxo-3-(4-(3-oxomorpholino)-phenyl)oxazolidin-5-yl)methyl)amino)ethoxy)ethyl)-thiophene-2-carboxamide

Step-i: To a Stirred solution of Rivaroxaban (5.0g, 11.47 mmol) in Conc. HCl (30 ml), 8% Acetic acid in water and 15 ml of water at 60oC for 6h, the reaction was monitored by TLC, TLC indicates the absence of the rivaroxaban and formation of polar spot, then evaporated the solvents, the obtained crude was taken into isopropyl alcohol and stirred for 30 minutes at rt and filtered and dried to obtained the 3.5g of crude off white solid of Compound 8, 1H-NMR (solvent DMSO-d6, δ): 9.10 (t, 1H), 7.74 (d, 1H), 7.55 (d, 2H), 7.30 (d, 2H), 7.20 (d, 1H), 4.85 (m, 1H), 4.17 (t, 2H), 4.09 (s, 2H), 3.86 (q, 2H), 3.72 (t, 2H), 3.60 (t, 2H), 3.40 (t, 2H).

Step-ii: To a stirred solution of 5-Chlorothiophene-2-Carb--oxalic acid (Compound **7**)(6.0g, 36.39 mmol) in DMF (30 ml), added the CDI (7.08g,43.66 mmol) and triethylamine (11.02g,109.17mmol) stirred at rt for 1h, then added the compound 8 (3.30g, 7.27 mmol) in DMF (15 ml), the reaction mass quenched with ice cold water (50 ml), the obtained solids were filtered, washed with water and dried under vacuo, the obtained crude (6.0g) was used next step without further purification.

Step-iii: To a stirred solution of crude Compound 9(6.0g, 10.02 mmol) and Compound 6 (4.30g, 15.03mmol) in DMF (30 ml), added the CDI (2.43g,15.03 mmol) and triethylamine (3.03g,30.06mmol) stirred at rt for 12h, the reaction mass was quenched with ice cold water (50 ml), the obtained solids were filtered, washed with water and dried under vacuo, the obtained crude was purified by silica column to provide the 2.2 g of off white solid of Impurity J. Over all 22% yield obtained from three steps. MP: 126.3– 128.5 °C, IR (KBr, cm^{-1}). 3408.98, 2924.43, 1753.02, 1648.78, 1546.81, 1516.20 1427.77, 1313.37, 1222.27, 1127.35., 1H NMR (Solvent, DMSO-d6) δ: 3.44-3.47 (m, 2H), 3.59-3.63 (m, J = 6.0 Hz, 4H), 3.70 (t, 2H), 3.77-3.81 (m, J = 6.8 Hz, 1H), 3.87–3.96 (m, 5H), 3.94-3.97 (m, 2H), 4.10 (t, J = 8.8 Hz, 1H), 4.19–4.23 (m, 3H), 4.72–4.76(m, 1H), 4.83–4.87 (m, 1H), 6.51 (d, J = 3.2 Hz, 1H),6.93 (d, J = 3.6 Hz, 1H), 7.19 (d, J = 3.6 Hz, 1H), 7.37–7.43 (m, 4H), 7.55 (d, J = 8.4 Hz, 2H), 7.63–7.69

(m,3H), 8.07 (t, 1H), 8.99 (s, 1H); 13C NMR (solvent, DMSO-d6) δ: 41.16, 42.17, 47.31, 49.00, 49.57, 63.46, 67.44, 67.72, 69.54, 71.24, 71.49, 118.28, 118.64, 125.94, 127.06, 128.17, 128.46, 129.72, 132.03, 133.29, 133.94, 136.48, 136.58, 137.01, 138.63, 154.08, 160.21, 160.81, 165.97, 169.80.

Conclusion

These two process-related impurities of rivaroxaban were Identified, synthesized, and characterized by MS, 1HNMR and 13C NMR spectroscopy. This work proves to be valuable in complying with regulatory norms and assessing the quality of rivaroxaban.

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