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Synthesis and Characterization of Chiral Impurities of Edoxaban Tosylate Monohydrate, Used As an Anticoagulant Drug

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Abstract
The present invention relates to identified and prepared chiral impurities in Edoxaban Tosylate monohydrate (1). This 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). During the process development of Edoxaban Tosylate monohydrate (1) several unknown peaks were detected by high performance liquid column chromatography (HPLC) using chiral column. Edoxaban Tosylate monohydrate is the Tosylate salt form of edoxaban with binding one water molecule, an orally active inhibitor of coagulation factor Xa (activated factor X) with anticoagulant activity. Edoxaban having three chiral centers and has total of eight isomers, out of them only (SRS)-Edoxaban presents pharmacological activity being other seven are Edoxaban impurities. During the process development of edoxaban, the control of chiral impurities is challenging, and this is critical to remove from drug substance. Enantiomer of compound is led to form its starting material, and it tread on the heels of mechanism path up to final active pharmaceutical ingredients (API). This work helps to improve the efficacy and quality of the drug substance; therefore, concentration of these impurities must be controlled to the acceptable level.

Keywords: *Chiral; Characterization; Edoxaban; Anticoagulant; Drug; API.*

1. Introduction
Edoxaban having therapeutic category anticoagulant and is a member of the drug in a class of factor Xa inhibitors. Edoxaban was developed by Daiichi Sankyo and approved in July 2011 in Japan for prevention of venous thromboembolisms (VTE) following lower-limb orthopaedic surgery[1-2]. It was also approved by the US FDA in January 2015 for the prevention of stroke and blood clots in patients with a certain heart rhythm problem (nonvalvular atrial fibrillation). Edoxaban is also used to treat deep venous thrombosis, a condition in which harmful blood clots form in the blood vessels of the legs. These blood clots can travel to the lungs and can become lodged in the blood vessels of the lungs, causing a condition called pulmonary embolism [1-3]. It is marketed under the trade name Savaysa & Lixiana in the form of tablets for oral administration containing 15, 30 and 60 mg of Edoxaban base [1]. Chemically Edoxaban Tosylate monohydrate is known as N-(5-Chloro-2-pyridinyl)-N'-[(1S,2R,4S)-4-(dimethylcarbamoyl)-2-{[(5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo [5,4-c]pyridin-2-yl)carbonyl] amino}cyclohexyl] ethane diamide p-toluene sulfonate monohydrate (API) in the form of Tosylate monohydrate, its molecular weight is 738.27 g/mol, and Edoxaban free base 548.06 g/mol and molecular formula is C31H40ClN7O8S. It is white to pale yellowish-white crystalline powder having CAS. No. 1229194-11-9. It is available in the form of Edoxaban Tosylate monohydrate having polymorphic form-I [1-2]. Chirality is now a top-class subject for academic research as well as for pharmaceutical development. Chirality is tremendous efficient in medicine, when a Molecule cannot be superimposed

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on its mirror image, this molecule and its image are called chiral the origin of the word chiral is Greek chair, which means 'handedness'. Many naturally occurring molecule is chiral, and biologically active molecules are chiral, Chirality is a fundamental dimension of molecular structures and plays an important role in living processes, in the transfer of biological intra- and inter-species information, and in the activity and properties of exogenous compounds as drugs, agrochemical, Flavors and food additives. [4-5]. 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, 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 synthesize the chiral impurity in pharmaceutical industry to define its limit as per ICH guideline to control the unwanted isomer from the drug substance.[4-6].

2. Method

Edoxaban Tosylate monohydrate (1) has a combination of three different structurally distinct units: thiazolo carboxylic acid, chiral cyclohexane cis-diamine, and oxalate chloropyridine derivative [11]. In cis diamine cyclohexane ring has three carbons 14, 15 and 18 are chiral centres it leads to eight stereoisomers. During the process development of (1) multiple potential impurities were identified, these are well 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. Figure 6 shows For synthesis of chiral impurity 5 of Edoxaban intermediate i.e., N-[(1S,2R,4R)-4-(dimethylcarbamoyl)-2-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridin-2-yl) carbonyl] amino} cyclohexyl] oxalamic acid ethyl ester. This chromatography method consists of stationary solid phase and separates the impurities of 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 disadvantages like it take more time to separate the compound, low separation power, higher quantity of solvents are used which include hazard solvent also last but not list it is expensive. [7-10].

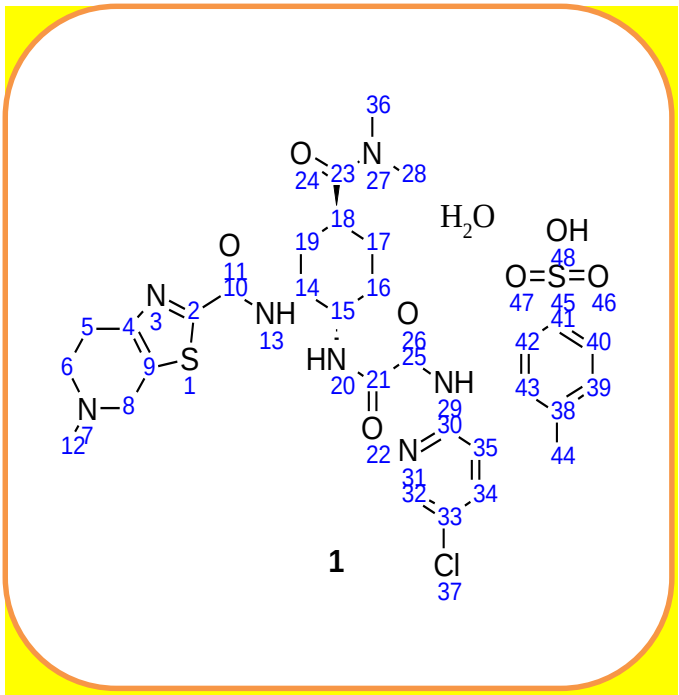

Figure 1 Edoxaban Tosylate monohydrate

Separated in reverse phase HPLC and characterized by spectroscopic technique[12]. Figure 7 shows For synthesis of Chiral impurity 6 of Edoxaban i.e., N-(5-Chloro-2-pyridinyl)-N'-[(1S,2R,4R)-4-(dimethyl carbamoyl)-2- {[(5-methyl-4,5,6,7-tetrahydro [1,3] thiazolo [5,4- c] pyridin-2-yl) carbonyl] amino} cyclohexyl] ethanediamide. But other than, 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 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 [13-15]. Figure 1 shows Edoxaban Tosylate monohydrate.

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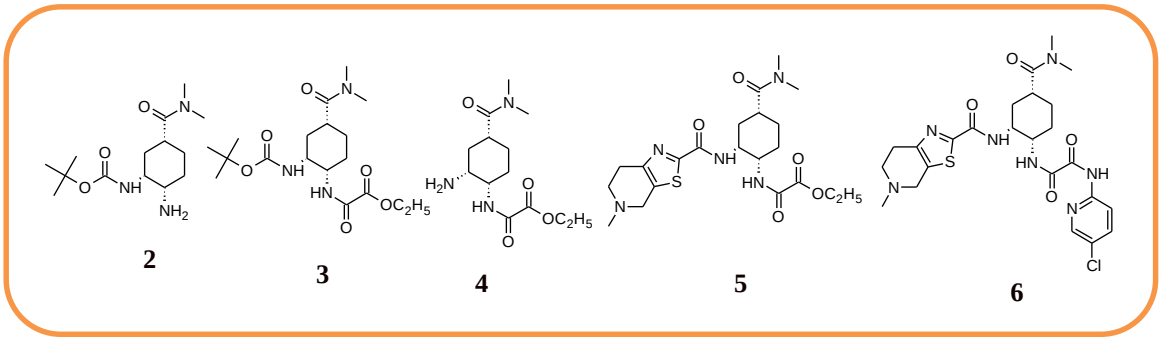

Figure 2 For Five Chiral Impurities of Edoxaban Tosylate Monohydrate

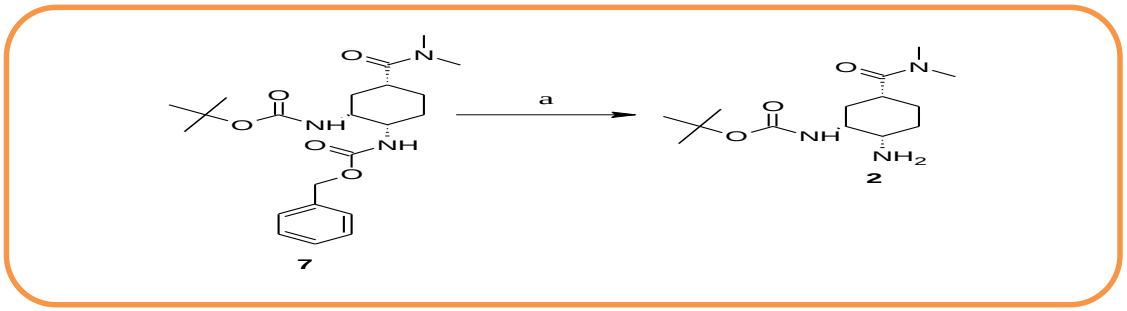

Figure 3 For Synthesis Of Chiral Impurity 2 Of KSM I.E., Tert-Butyl {(1R, 2S, 5R)-2-Amino-5-[(Dimethylamino)Carbonyl] Cyclohexyl}Carbamate

Reaction condition a: Isopropyl alcohol, n-heptane, methanol, Pd/C(H_2) at RT for 5-6 hrs.

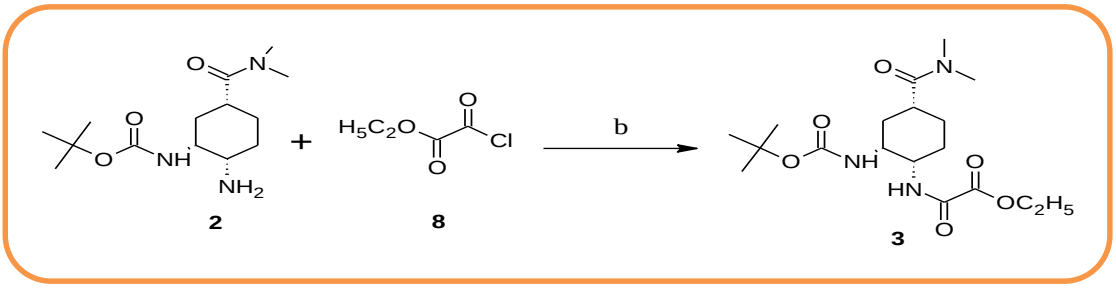

Figure 4 For synthesis of chiral impurity 3 of Edoxaban intermediate i.e., N-[(1S, 2R, 4R)-2-(tert-butoxycarbonyl)amino-4-(dimethyl carbamoyl) cyclohexyl]oxalamic acid ethyl ester

Reaction condition b: TEA, Ethyl acetate, water, RT 3 hrs., Dichloromethane.

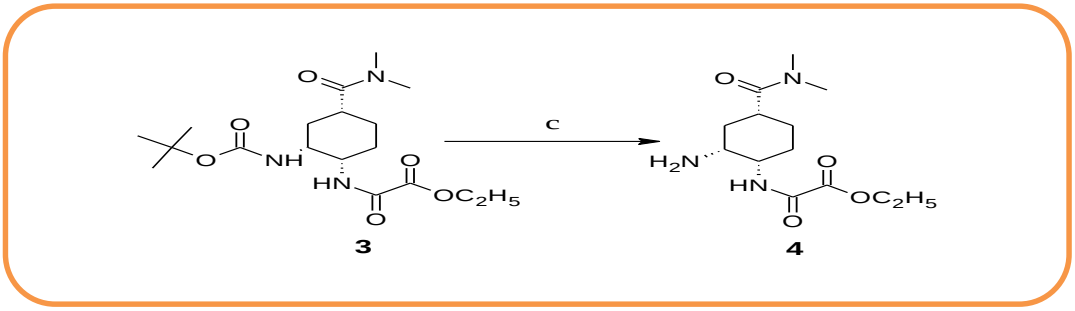

Figure 5 For synthesis of chiral impurity 4 of Edoxaban intermediate i.e., N-[(1S,2R,4R)-2-amino-4-(dimethylcarbamoyl) cyclohexyl] oxalamic acid ethyl ester

Reaction condition c: Ethyl acetate in hydrochloric acid, RT for 4-6 hrs.

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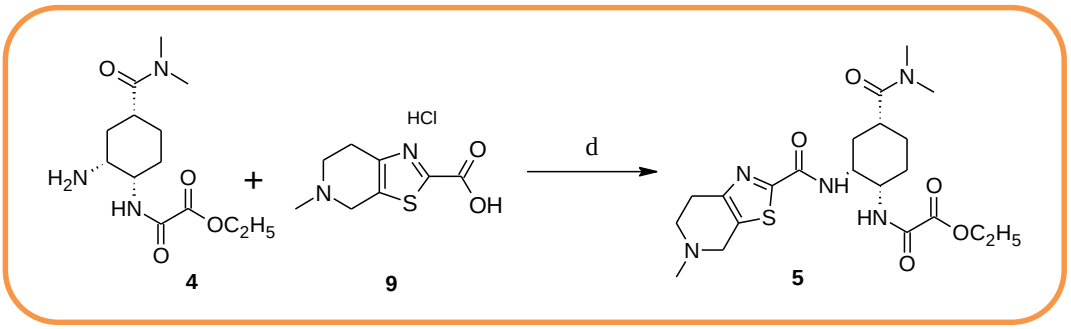

Figure 6 For synthesis of chiral impurity 5 of Edoxaban intermediate i.e., N-[(1S,2R,4R)-4-(dimethylcarbamoyl)-2-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c] pyridin-2-yl) carbonyl] amino} cyclohexyl] oxalamic acid ethyl ester

Reaction condition d: DIPEA, HOBT, CDI, Dichloromethane, DIPE, water, RT for 3-4 hrs.

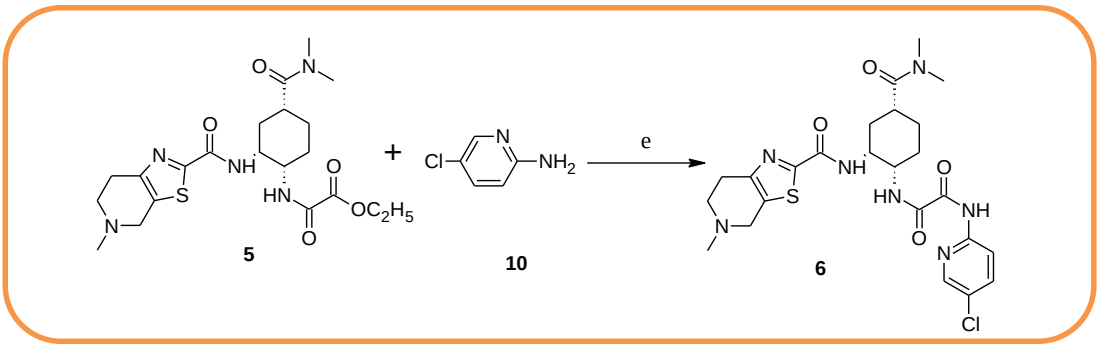

Figure 7 For synthesis of Chiral impurity 6 of Edoxaban i.e., N-(5-Chloro-2-pyridinyl)-N'-[(1S,2R,4R)-4-(dimethyl carbamoyl)-2- {[(5-methyl-4,5,6,7-tetrahydro [1,3] thiazolo [5,4- c] pyridin-2-yl) carbonyl] amino} cyclohexyl] ethanediamide

Reaction condition e: Potassium carbonate, DMF, toluene, Dichloromethane, methanol, water, temperature 108-110°C for 10-12 hrs.

3. Experimental

3.1 Preparation of tert-butyl {(1R, 2S, 5R)-2-amino-5-[(dimethylamino)carbonyl] cyclohexyl} carbamate (2)

To a stirred {(1S,2R,4R)-2-[(Tert-butoxycarbonyl)amino]-4-[(dimethyllamino) carbonyl] cyclohexyl} benzycarbamate (7) (10 g, 0.0023 mol) undergoes catalytic hydrogenation with 10% Pd/C in methanol (100 ml) and resulting content stirred for 5-6 hrs to furnish crude ADC which is purified in mixture of isopropyl alcohol and n-heptane to give pure compound of formula (2). [Yield = 6.5 g (95.5%); Purity (by HPLC) =96.73%].IR (KBR) :3329.32,2932.70,1713.00,1698.20,1518.35, cm^{-} ; NMR($CDCl_3$): 4.947 (s, 1H),3.762-3.783 (m, 1H), 2.926-3.042 (s,6H),2.647-2.722 (m, 1H),2.273 (m, 1H), 1.704-1.739 (d, 2H), 1.241-1.695 (s, 6H). 1.45 (s,9H); CMR 100 MHZ (CDCl3): 28.045-28.523, 35.262, 36.651, (CH3),26.687, 28.941, 31.915, (CH2), 33.372, 50.500-50.804 (CH),78.821, 156.143, 174.849 (C). MS M/Z: 286. Figure 2 shows for Five Chiral Impurities of Edoxaban Tosylate Monohydrate.

3.2 Preparation of N-[(1S,2R,4R)-2-(tert-butoxycarbonyl)amino-4-(dimethyl carbamoyl) cyclo hexyl]oxalamic acid ethyl ester (3)

To a stirred solution of tert-butyl (1R,2S,5R)-2-amino-5-(dimethylcarbamoyl)Cyclohexyl carbamate (2) (10 g, 0.0035 mol) in dichloromethane (DCM) (70 ml), was added Triethylamine (4.55 g, 0.0045 mol), followed by addition of chloroethyl oxoacetate(8)

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(5.74 g 0.0042 mol) at below 15°C. The resulting reaction mass was stirred and maintain at 20-30°C for 2-3 h. The progress of reaction was monitored by HPLC and after completion of reaction, reaction mass was diluted with purified water (70 ml), both the layers were separated, and DCM layer washed with purified water (70 ml) and concentrated under reduced pressure at below 50 °C, to obtain residue, which was further diluted with Ethyl acetate (EtoAC) (70 ml). The resultant content was heated at 50-55°C stirred & cooled at 5-10 °C, obtained solid was filtrated & dried under reduced pressure to provide white crystalline powder of compound of formula (3) [Yield = 12.4 g (91.85%); Purity (by HPLC) =99.51%].IR (KBR) :3307.39,2938.11,1724.17,1619.16,1524.73,1365.58 ,1168.27,1250.53 cm- ; NMR(CDCl3): 7.79 (bs, 2H), 4.29-4.37 (q, 2H), 4.15-4.19 (m, 1H),3.90-3.96 (m, 1H),3.05 (s, 3H),2.94 (s, 3H),2.62 (m, 1H), 2.04 (s,1H),1.93 (t, 2H),1.70-1.83 (q, 2H), 1.63-1.73 (q, 2H), 1.46 (s,9H), 1.35-1.40 (t, 3H). ; CMR 75 MHZ (CDCl3) : 13.99, 28.28, 35.70,37.10, (CH3),25.40,27.18,32.79,63.07(CH2),33.27,33.92,4 8.73,50.22-51.05,80.29(CH), 156.20,156.20,160.68,1741.25 (C). MS M/Z: 385.45. Figure 3 shows For Synthesis Of Chiral Impurity 2 Of KSM I.E., Tert-Butyl {(1R, 2S, 5R)-2-Amino-5-[(Dimethylamino)Carbonyl] Cyclohexyl}Carbamate.

3.3 Preparation of N-[(1S,2R,4R)-2-amino-4-(dimethylcarbamoyl) cyclohexyl] oxalamic acid ethyl ester (4)

To a stirred solution of N-[(1S,2R,4R)-2-(tert-butoxycarbonyl)amino-4-(dimethylcarbamoyl) cyclo hexyl]oxalamic acid ethyl ester (3) was added in equal five lots (,100 g, 0.129 mol) in ethyl acetate in hydrochloric acid 4-6% (1000 ml) at 25-30°C. The reaction mass was stirred and maintained at 20-30°C for 4-6 h. The progress of reaction was monitored by HPLC and after completion of reaction, resulting reaction mass was distilled out under reduced pressure at below 65°C to give residue. To the obtained residue was degas for 1-2hrs at below 65°C. after that solid syrup was cooled at 5-10°C and hold under nitrogen atmosphere of (4) [Yield: 100g (100%); Purity (by HPLC): 98.23%] IR (KBR) :3423.00,2941.22,1746.25,1618.53,1523.69, cm- ; NMR(CDCl3): 8.16 (bs, 3H), 4.23-4.33 (q, 2H), 3.98-4.13 (m, 1H), 3.69-3.73 (q, 1H),3.16 (s, 3H), 2.93 (s, 3H), 2.04-2.25 (q,3H),1.85-1.95 (t, 3H),1.62 (q, 1H), 1.32-1.37 (t, 3H), ; CMR 75 MHZ(CDCl3):14.0114.23,36,37.73,(CH3),22.17,24. 39,31.90,63.36(CH2),32.78,49.07,49.78,(CH),158.1 6, 160.24, 174.48(C). MS M/Z: 285.33. Figure 5 shows For synthesis of chiral impurity 4 of Edoxaban intermediate i.e., N-[(1S,2R,4R)-2-amino-4-(dimethylcarbamoyl) cyclohexyl] oxalamic acid ethyl ester.

3.4 Preparation of N-[(1S,2R,4R)-4-(dimethylcarbamoyl)-2-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2 yl)carbonyl]amino} cyclohexyl] oxalamic acid ethyl ester (5)

5-methyl-4,5,6,7-tetrahydro[1,3]thiazolo[5,4-]pyridine-2-carboxylic acid (9) (54.80g, 0.233 mol) was dissolved in Dichloromethane (DCM) (700 ml), to the solution charged 1,1 carbonyldiimidazol (CDI) (56.81 g, 0.350 mol) was added, followed by charged of 1-hydroxybenzotriazol (71.51 g, 0.467 mol) at 25-30°C. The reaction mixture was heated at 35-40°C, stirred for 30 min, followed by addition of solution of N-[(1S,2R,4R)-2-amino-4-(dimethylcarbamoyl) cyclohexyl] oxalamic acid ethyl ester (4) (75.15 g, 0.0233 mol) in methylene chloride (150 ml) at 20-30°C. The resulting reaction mass was stirred and maintained at 20-30°C for 1-3 h. The progress of reaction was monitored by HPLC, upon completion of reaction, concentrate the reaction mass and then quenched with purified water (500 ml), separated both the layers, and DCM layer was washed with purified water (500 ml), DCM layer concentrated under reduced pressure at below 45°C to obtain residue. The obtained residue was diluted with ethanol (250 ml), stirred for 30 min, obtained solid was filtered & dried under reduced pressure to provide off white crystalline powder of compound of formula (5) [Yield: 81g (80%) Purity (by HPLC): 98.1%] IR(KBR) :3300.41,2941.28,1736.34,1677.43,1520.79,1214.46 cm; NMR (CDCl3) :7.81-7.84 (d, 1H), 7.37-7.39 (d, 1H), 4.59-4.63 (q, 1H), 4.28-4.35 (q, 2H),4.05-4.13 (m, 1H), 3.72 (s, 2H), 3.05 (t,2H),2.94(s, 6H),2.79-

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2.86 (t, 2H), 2.52 (s, 3H),1.99-2.15(m 2H),1.72-1.88 (m 4H),1.52 -1.66 (m,1H),1.34-1.39 (t,3H) ; CMR 75-MHZ (CDCl3) : 13.90, 34.01, 35.71, 37.12, (CH3), 25.57, 25.72, 26.82, 27.09, 52.12, 52.54, 63.06 (CH2), 32.57, 45.11, 48.15, (CH), 133.55,150.05,156.38,159.92,160.42,160.47,173.85, (C). MS M/Z: 466. Figure 4 shows For synthesis of chiral impurity 3 of Edoxaban intermediate i.e., N-[(1S, 2R, 4R)-2-(tert-butoxycarbonyl)amino-4-(dimethyl carbamoyl)
cyclohexyl]oxalamic acid ethyl ester.

3.5 Preparation of N-(5-Chloro-2-pyridinyl)-N'-[(1S,2R,4R)-4-(dimethyl carbamoyl)-2- {[(5-methyl-4,5,6,7-tetrahydro [1,3] thiazolo [5,4-c] pyridin-2-yl) carbonyl] amino} cyclohexyl] ethanediamide (6)

To the mixture of 5-chloro-pyridin-2-ylamine (10) (2.07 g, 0. 016 mol) in toluene (50 ml) was added potassium carbonate (2.07 g, 0.015 mol) followed by addition of N-[(1S,2R,4R)-4-(dimethylcarbamoyl)-2-{[(5-methyl-4,5,6,7-tetrahydro-thiazolo[5,4-c]pyridin-2-yl)carbonyl] amino} cyclohexyl] oxalamic acid ethyl ester (5) (5.0 g,0.01 mol). The resultant reaction mass was stirred, heated at 110°C and maintained at same temperature for 24 h. The progress of reaction was monitored by HPLC after completion of reaction, reaction mass was cooled at 25-30 °C, quench with purified water (50 ml) and DCM (50 ml). Stirred the solution, separated both the layers, and DCM layer was washed with purified water (50 ml) and concentrated under reduced pressure at below 50°C to obtain residue. Diluted the residue with ethanol (50 ml), stirred for 30 min, filter and dried the obtained solid to provide off white crystalline powder of Edoxaban enantiomer (6) [Yield =4.35 g (73.97%)Purity(byHPLC)=93.2%].IR(KBR):3378.94,3313.61,2946.15,1666.96,1637.34,1497.54,1377.36 cm- ; NMR (CDCl3) :9.72 (s, 1H), 8.30 (s, 1H),8.18 -8.15(d, 1H) 8.05 -8.02 (d, 1H), 7.70-7.66 (dd, 1H),7.42-7.39 (d, 1H), 4.69-4.67 (m, 1H), 4.14-4.08 (m, 1H),3.77-6.65(q, 2H),3.05 (s, 3H), 2.95 (s, 3H),2.86-2.78(m 5H),2.52 (s 3H),2.17 -2.05 (m,3H),1.92-1.96 (d,1H), 1.86-1.72(q,1H),1.68-1.60(q,1H);CMR75MHZ(CDCl3):35.17,37.17,45.18 (CH3),25.97,26.91,27.06,32.66,52.21,52.63,(CH2),34.09,47.82,50.96,114.67,137.91,147.09(CH),127.81, 133.67,148.27,150.10,157.77,158.86,159.75,160.37, 173.72(C). MS M/Z: 548.

4. Result and Discussion

Drug substance of Edoxaban is chiral molecule and control of its opposite isomer as per developed specification is not more than 0.15% in API and need of chiral impurities will increasing step by step 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. Hence, our targeted chiral impurities are synthesized and well characterized by further analytical use.

Conclusion

We have identified and synthesized five chiral impurities related to Edoxaban tosylate monohydrate (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 Edoxaban tosylate monohydrate (1) drug substance as per ICH guideline.

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