Asian Journal of Chemistry; Vol. 29, No. 6 (2017), 1253-1257

ASIAN JOURNAL OF CHEMISTRY

https://doi.org/10.14233/ajchem.2017.20448

# An Improved Process for Preparation of Dabigatran Etexilate Mesylate

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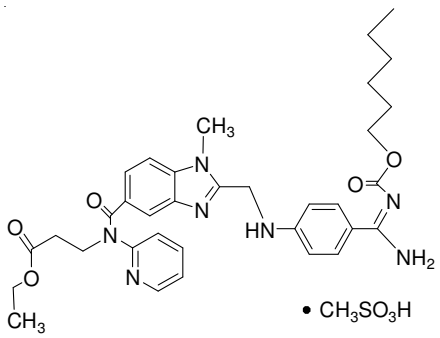
*Received*: 14 December 2016; *Accepted*: 1 February 2017; *Published online*: 10 April 2017; AJC-18335

An improved process for the preparation of dabigatran etexilate mesylate, wherein the process is substantially free to eliminates the potential impurities. The impurities are formed due to presence of contaminated starting ingredients that is present in commercially available *n*-hexyl chloro formate. The present invention is to control impurities by using pure *n*-hexanol in place of *n*-hexyl chloro formate. Over all yields is good and process can't requires expensive catalysts. Dabigtran is used to prevent strokes in those with arterial fibrillation due to heart valve causes, as well as deep venous thrombosis (DVT). Moreover, the present invention is providing simple, industrial scalable and cost-effective process, which affords good quality and yield.

**Keywords: Deep venous thrombosis, Arterial fibrillation, Contaminated, Substantially.**

## INTRODUCTION

Dabigartran etexilate mesylate is an oral anticoagulant which acts as direct thrombin inhibitor (factor II a) [1]. The drug is available in different countries such as in Australia, Europe, USA, Japan and Canada as Pradaxa [2,3]. Dabigatran helps in the prevention of heart strokes in patients accompanying atrial fibrillation [4]. The drug is more advantageous compared to warafin which also acts as one of the anticoagulant. Dabigatran is more efficient in preventing is chemic strokes and also plays a vital role in controlling the clinically significant bleeds [5,6]. The chemical name for dabigatran etexilate mesylate is β-alanine, N-[[2-[[[4-[[[(hexyloxy)-carbonyl]amino]iminomethyl]-phenyl]amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-ethylester, methanesulfonate. The empirical formula is $C_{34}H_{41}N_7O_5.CH_3SO_3H$ and the molecular weight is 723.86 g/mol. The drug structurally represented as below:




The drug is recently has been used for the treatment of coronary artery disease, hypertensive heart disease and venous thromboembolism. It is available in the market in tablet dosage form [7]. It acts as reversible and competitive direct thrombin inhibitor. The mode of action of the drug is very specific and it inactivates the active sites formed during the last step of blood coagulation. The action of dabigatran was proved to be more effective compared to other indirect thrombin inhibitors such as heparin [5]. The adverse effects of dabigatran are limited when compared to other anticoagulants, generally mild stomach pain, heartburn and nausea. Some of the severe side effects of the drug are unusual bruising or bleeding, pale urination, bleeding from gums, vomiting and frequent nose bleeds [8].

Dabigatran is firstly reported in WO 98/37075, in which the process for the preparation of dabigatran etexilate is disclosed as 1-methyl-2[N-(4-(amidino phenyl)aminomethyl]-benzimidazol-5yl carboxylic acid-N(2-pyridyl)N-(2-ethoxy-carbonylethyl)amide hydrochloride with hexyl chloro formate in the presence of potassium carbonate in tetrahydrofuran/water provides dabigatran etexilate and further converstion to mesylate salt is not disclosed [9]. The key step of the disclosed process is the conversion of the nitrile of the formula (V) into the amidine hydrochloride of formula (VI) by Pinner reaction. The low yields of the pinner reaction can be derived from the water sensibility of the reaction on the one hand while the realization of the reaction is rendered more difficult on the other by the fact that the ester as well as amide, function of the molecule is susceptible to hydrolysis [9]. According to example 58b of said patent in an analogous manner to example 25d

1.2 g of l-methyl-2-[N-(4-cyanophenyl)aminomethyl]-5-benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxy-carbonylethyl]amide (V) is reacted with ethanol saturated with hydrochloric acid in large dilution. The evaporated crude product is then converted to hydrochloric acid salt of l-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5-benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonyl)-ethyl]-amide compound of formula(VI) using ethanol and ammonium carbonate. The disclosed process was not suitable for large scale production because of tedious workup procedures, less yield, low purity, separation by column chromatography, which in turn results in excessive production time and costlier process and less eco-friendly. The substance requires complex purifying operations, such as chromatography for the production of high-quality API. Further the chromatographic purification is expensive and difficult to implement in large scale. The impurity in the dabigatran single prodrug and dabigatran etexilate affects the purity of the final product dabigatran etexilate mesylate [1,10]. Hence, there is a necessity to maintain the purity level of every intermediate involved in the preparation of dabigatran etexilate mesylate.

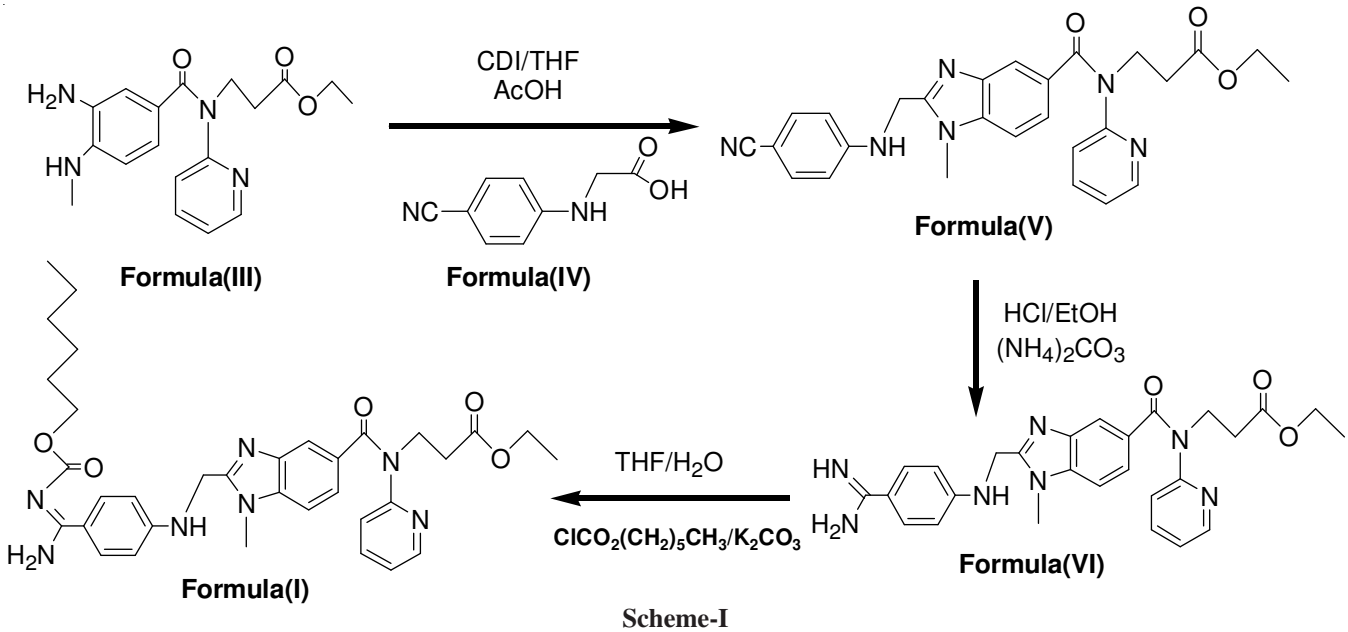
Further, other improved processes were reported for synthesis of dabigtran etexilae mesylate [10,11] in the literature. However, all procedures suffer due to use of expensive and moisture sensitive catalysts, high temperature and longer reaction times. The impurities are formed due to *n*-hexyl chloro formate used in step-3. Furthermore, the procedures' involving these reagents requires harsh and inert conditions [7]. Herein, we reported an improved synthetic process for synthesis of dabigtran etexilate mesylate in **Scheme-I**, in step-3 replace the *n*-hexyl chloro formate by pure *n*-hexanol in order to avoid the formation of impurities as reported in step-3. The improved process has a number of industrial advantages.

## EXPERIMENTAL

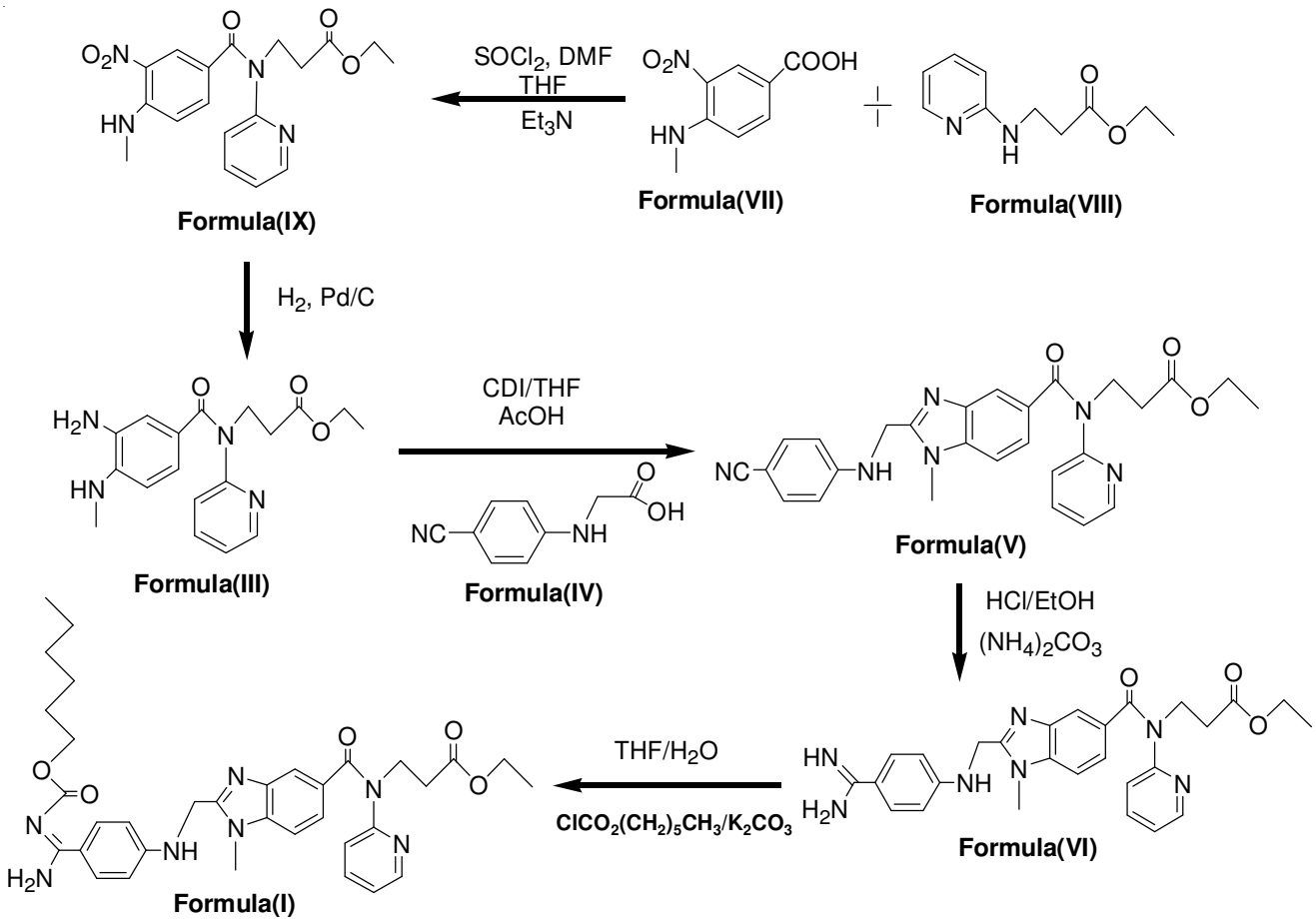
All starting materials and other reagents were purchased from commercial suppliers and were used without further purification. Nuclear magnetic resonance (NMR) spectra were recorded on bruker instrument operating at 500 MHz and $^1$H NMR spectra are obtained with TMS as internal standard in $CDCl_3$ solvent. $^{13}$C NMR spectra are also obtained in $CDCl_3$ instrument operating at 125 MHz IR and mass spectra were recorded. The reactions were assayed by thin-layer chromatography (TLC) and terminated as judged by the consumption of starting material. When peak multiplicities are reported. Intermediates are sensitive towards methanol. So don't wash equipments with these solvents, use only acetone for cleaning of equipments.

**Step-1: Ethyl 3-[2-((4-cyanophenylamino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo(d)imidazole-5-carbaxamido]propanoate:** To the solution 4-cyano phenyl glycine (15.4 g; mol) in absolute THF (25 mL). The CDI (16.1 g was in four lots over a period of 40-45 min and stirred at room temperature. Slowly charge (20 g) maintain the reaction mixture for 20-24 h at 30-35 °C, charge acetic acid (120 mL) to reaction mixture and heated to 60-65 °C and maintained 6-7 h. Cool the reaction mixture 20-30 °C and add water (120 mL) separate the organic layer distill off total solvent under vacuum and dried with sodium sulphate. Add acetone (20 mL) and methane sulphonic acid (4.2 g) heated to 50-55 °C for 45-60 min. Cooled at 2-8 °C filter the solid and wash the solid with acetone (120 mL) and cyclohexane (40 mL) dry at 55-60 °C the solid is 22-23 g molar yield is 85 %.

$^1$H NMR (500 MHz, in DMSO) δ: 8.39 (dd, 1H), 7.55 (dt, 1H), 7.47 (dd, 3H), 7.41 (d, 1H), 7.25 (t, 1H for NH), 7.17 (dd, 1H), 7.12 (dd, 1H), 6.82 (d, 2H), 6.90 (d, 1H), 4.60 (d, 2H), 4.23 (t, 2H), 3.98 (q, 2H), 3.76 (s, 3H), 2.69 (t, 2H), 1.13 (t, 3H). $^{13}$C NMR (500 MHz, in DMSO) δ: 170.9 (ethyl ester), 170.2 (amide), 109.4 (cyano), 155.9, 153.2, 151.7, 148.6, 140.8, 137.8, 137.2, 133.2, 129.3, 122.7, 122.04, 121.2, 120.3, 119.4, 112.3, 96.7, 59.9, 44.3, 39.5, 33.04, 29.8, 13.9. IR (neat, $\lambda_{max}$, $cm^{-1}$): 3271.27, 2940.47, 2215.24, 1731.11, 1639.49, 1604.77, 1581.62, 1529.55, 1435.03, 1389.31, 1328.95, 1273.01, 1243.32, 1179.35, 827.46, 777.31, 746.45. MS: *m/z* = 483.2 $[M + H]^+$, m.w.: 482.




**Scheme-I**




**Scheme-II** [Ref. 5]

**Step-2: 1-Methyl-2-(N-(4-amidinophenyl)aminomethyl)benzimidazol-5-yl-carboxylic acid-N-phenyl)-N-(2-ethoxycarbonylethyl)amide:** The solution of ethanol (132 mL) and $CaCl_2$ (g) taken in round bottom flask cooled at -15 to -5 °C purge HCl gas up to 30-35 % assay and slowly add Stage-1 (22 g) material at 0 to 5 °C. Maintained reaction mixture for 8-10 h at 20-25 °C. Expel the HCl gas with nitrogen gas under vacuum. Add ethanol (100 mL) and $NH_4CO_3$, stir the reaction mixture 30-45 min. Purge the $NH_3$ gas until the reaction mixture reached to pH 8.0. Maintain the pH 8.0 cooled the reaction mixture to 30-40 °C. Filter the solid washed with ethanol (160 mL). distilled completely at 55 °C under vacuum. Add ethanol (60 mL) at 50-60 °C. Maintained the reaction mixture for 30-45 min. Cooled at room temperature and add ethyl acetate (100 mL). Left the reaction mixture for 10-12 h, filtered the solid wash with ethyl acetate (40 mL) and dried under vacuum below 50-55 °C to obtained stage-2 is 14 g molar yield is 61.5 %.

$^1$H NMR (500 MHz, in DMSO)δ: 8.42 (dd, 1H), 7.79 (d, 2H), 7.71 (d, 1H), 7.33 (m, 2H), 7.14 (d, 1H), 6.98 (m, 1H), 6.71 (dd, 3H), 5.23 (t, 1H $D_2O$ exchangeable), 4.51 (d, 2H), 4.43 (t, 2H), 3.73 (s, 3H), 2.81 (t, 2H), 4.12 (q, 2H), 1.21 (t, 3H). $^1$H NMR (MHz, in DMSO $D_2O$ exchange) δ: 8.43 (dd, 1H), 7.78 (d, 3H), 7.33 (m, 2H), 7.13 (d, 1H), 6.99 (dd, 1H), 6.71 (d, 3H), 4.50 (s, 2H), 4.43 (t, 2H), 3.73 (s, 3H), 2.81 (t, 2H), 4.12 (q, 2H), 1.32 (t, 3H). $^{13}$C NMR (500 MHz, in DMSO) δ: 170.9 (ethyl ester), 170.2 (amide), 164.4 (amidine), 155.9, 153.3, 153.06, 148.6, 140.8, 137.8, 137.2, 129.6, 129.4, 122.7, 122.03, 121.2, 119.4, 113.2, 111.7, 109.4, 59.9, 44.3, 39.5, 33.04, 29.9, 13.93. IR (neat, $\lambda_{max}$, $cm^{-1}$): 3414.09, 3304.06, 3148.78, 2351.22, 1735.93, 1637.56, 1605.73, 1473.61, 1430.21, 1327.98, 1286.52, 1245.04, 1186.22, 1081.14, 1029.98, 833.24, 776.34, 746.45, 628.79, 553.57. MS: *m/z* = 500.2 $[M + H]^+$, m.w.: 499.

**Step-3: (N-[[2-[[[4-(Aminoiminomethyl)phenyl]amino]-methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinyl-β-alanine):** Take the dichloromethane (40 mL) and CDI (6.8 g) in clean round bottom flask under $N_2$ atmosphere At 20-25 °C and add *n*-hexanol (10.2) g 45-60 min and maintained up to 2-3 h then add acetonitrile (15 mL) and stirred for 10-15 min. Taken the acetonitrile (42 mL) and water (20 mL) in another clean round bottom flask add stage-2 (10 g) material at 30-35 °C and add potassium carbonate (6.9 g) stirred for 10-15 min, slowly add *n*-hexonal (10.2 g) above prepared solution heated to 40-45 °C about 1-2 h filter the solid and washed with acetonitrile (2.5 mL), acetone (30 mL) and water (28 mL) and dried. Taken the dried product, dichloromethane (100 mL) and water (40 mL) in round bottom flask and is heated to 30-35 °C for 10-15 min separate organic layer and water layer. Washed the organic layer with NaCl solution and then add ethanol (1 mL) (Don't add ethanol at above 5 °C that will form impurity) cool the reaction mixture to 20-25 °C without applying external cooling and maintained up to 2-3 h. Filter the solid and washed with MTBE (2 mL) and ethyl

acetate (2 mL) and dried below the 50 °C to obtained 7.5 g of stage-3, molar yield is 60 %.

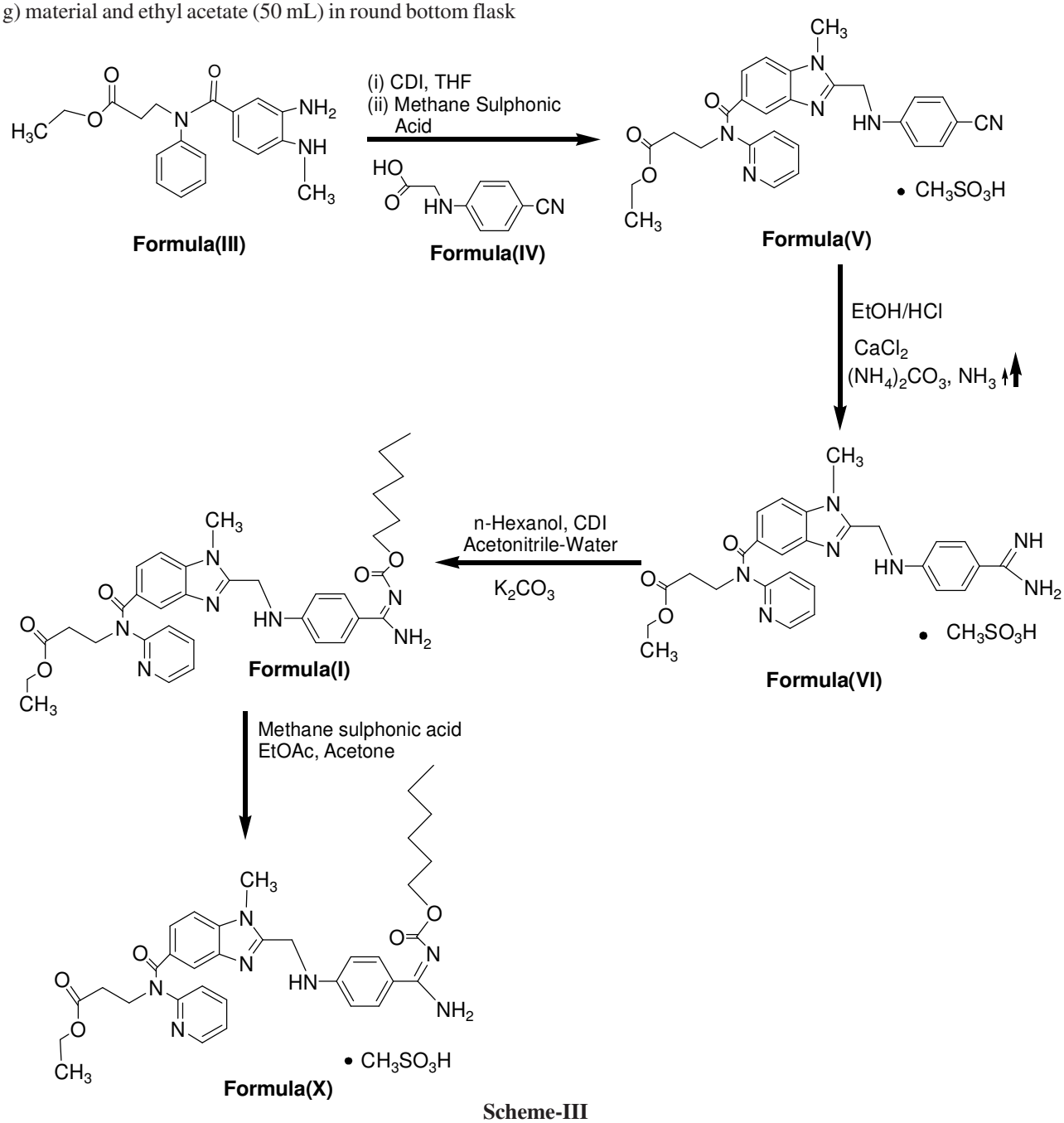
$^1$H NMR (500 MHz, in DMSO) δ: 8.39 (dd, 1H), 7.66 (d, 3H), 7.48 (d, 1H), 7.43 (d, 1H), 7.17 (dd, 1H), 7.13 (dd, 1H), 6.89 (dd, 3H), 4.70 (d, 2H), 4.24 (t, 4H), 3.98 (q, 2H), 3.79 (s, 3H), 2.69 (t, 2H), 1.68 (quintet, 2H), 1.34 (m, 2H), 1.31 (quintet, 4H), 1.13 (t, 3H), 0.88 (t, 3H), 10.01-11.88 (bs, 3H). $^{13}$C NMR (500 MHz, in DMSO) δ: 170.9 (ethyl ester), 170.3 (amide), 166.3 (amidine), 164.1 (*n*-hexyl ester), 155.9, 153.6, 151.5, 148.6, 140.8, 137.8, 137.2, 129.3, 129.1, 122.7, 122.06, 121.2, 121.06, 119.4, 111.3, 109.4, 64.08, 59.9, 44.3, 39.5, 33.03, 30.97, 29.8, 28.5, 25.1, 22.0. IR (neat, $\lambda_{max}$, cm$^{-1}$): 1733.8, 3265.3, 3052, 2932.2, 2859.1, 1646.2, 1586.4, 1533.9, 1471.7, 1371.8, 1330.2, 1205.3, 1045, 944.1, 829.8, 782.5. MS: *m/z* = 628.2 $[M + H]^+$, m.w.: 627.

**Step-4: Dabigatran etexilate mesylate:** Take stage-3 (5 g) material and ethyl acetate (50 mL) in round bottom flask under $N_2$ atmosphere heated to 50-55 °C for 15 min and then under atmosphere cooled reaction mixture to 30-35 °C and add ethanol (0.6 mL) under nitrogen atmosphere further cooled to 20-25 °C, prepared methane sulphonic acid (0.75 g) solution under nitrogen atmosphere is added to reaction mixture in 2-3 h at 25-30 °C maintained 3-4 h. Filter the solid under nitrogen atmosphere wash with ethyl acetate (5 mL). Keep the solid under nitrogen blanket. Obtained weight is (5 g). Molar yield is 90 %.

Improved synthetic route for dabigatran etexilate mesylate is described (**Scheme-III**).

## RESULTS AND DISCUSSION

The synthesized dabigatran etexilate mesylate was characterized by $^1$H NMR, IR and HPLC. $^1$H NMR was recorded in DMSO and $CDCl_3$. The chemical shifts were reported in ppm.




**Scheme-III**

The IR spectrum was recorded using as such solid on FTIR. The purity of compound can be analyzed on HPLC.

The present invention to reduce the impurities in dabigatran etexilate mesylate synthesis by replace the *n*-hexyl chloro formate in step-3 already reported synthetic route in **Schemes I** and **II** by pure *n*-hexanol to control all the impurities formed due to *n*-hexyl chloro formate in step-3. On early experimental studies suggested that the most advantageous convenient route for formula (I). The compound of ethyl 3-(3-amino-4-(methyl amino)-N-(pyridine-2-yl)benzamido)-propanoate on treatment with 4-cyano phenyl glycine in presence of CDI and methane suphonic acid to form compound formula (V) ethyl 3-(2-((4-cyano phenyl amino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo(d)imidazole-5-carbaxamido)propanoate. The formula (V) is treated with EtOH/HCl, $CaCl_2$ and $NH_4CO_3$ to afford formula(VI) 1-methyl-2-(N-(4-amidino phenyl)aminomethyl)-benzimidazol-5-yl-carboxylic acid-N-phenyl)-N-(2-ethoxy carbonyl ethyl)amide. Prepare dabigtran etexilate formula (I) by formula (VI) treated with *n*-hexanol in CDI in presence of $K_2CO_3$ in this step CDI acts as CO source. Dabigtran etexilate converted in to its salt form Formula (X) by treated with methane sulphonic acid.

## Conclusion

An improved process for synthesis of dabigtran etexilate mesylate is the replacement of *n*-hexyl chloro formate in step-3 by pure *n*-hexanol to reduce the impurities. It affords a total good yield over four steps and purity 99 %. The synthesis of compound **1** was successfully accomplished by this new process. This process will be convenient, efficient and employed for commercial production.

## ACKNOWLEDGEMENTS

The authors are thankful to Department of Chemistry, Acharya Nagarjuna University, Guntur, India for providing the facilities to carry out research work. One of the authors (SKS) gratefully acknowledges the financial support from University Grant Commission (UGC) New Delhi, India.

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