Facile Synthesis of Dabigatran Etexilate Mesylate, an Anticoagulant Drug, Using a Novel Synthon, N-Hexyl-4-nitrophenyl Carbonate

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ABSTRACT: Facile synthesis for Dabigatran etexilate mesylate (1), an anticoagulant drug, is reported using a novel synthon, n-hexyl-4-nitrophenyl carbonate (32), which substantially eliminates the formation of potential impurities 20–27, which were generated due to the use of n-hexyl chloroformate in previously reported methods. Pinner reaction to prepare a key and critical intermediate, amidine 8, was optimized using design of experiment software to establish critical process parameters to achieve 8 in 97% yield. Nucleophilic substitution of 8 with novel synthon n-hexyl-4-nitrophenyl carbonate (32) furnished the dabigatran base 9, which was then converted to its mesylate salt using methane sulfonic acid to provide 1 with an overall yield of 66% over three steps.

INTRODUCTION

Dabigatran etexilate mesylate (1), chemically known as β-Alanine, N-[2-[[4-[[[[6-(hexyloxy)carbonyl]amino]-iminomethyl][phenyl]amino][methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl]-N-2-pyridinylethyl ester, methanesulfonate, is a direct thrombin inhibitor used to reduce the risk of stroke and blood clots in people who have a medical condition called atrial fibrillation.1 Dabigatran etexilate mesylate (1), which is the double prodrug of the active substance, dabigatran (29, Figure 1), was developed by Boehringer Ingelheim and was approved by the USFDA in 20102 and the EMA in 20083 under the trade name Pradaxa.

Patients with atrial fibrillation are at an increased risk of forming a blood clot in the heart, which can travel to the brain or other parts of the body and cause a stroke. Dabigatran lowers the chance of having a stroke by helping prevent clots from forming. It is also used to treat blood clots in the veins of legs (deep vein thrombosis) or lungs (pulmonary embolism) and to forming a blood clot in the heart, which can travel to the brain and cause a stroke. Dabigatran lowers the chance of having a stroke by helping prevent clots from forming. It is also used to treat blood clots in the veins of legs (deep vein thrombosis) or lungs (pulmonary embolism) and to cause a stroke.

The first reported synthesis of dabigatran etexilate (9) involves N-acylation of pyridine amino propanoate (3) with 4-methy lamino-3-nitro benzoyl chloride (2) to furnish nitro amino propanoate (4), which was then reduced to amino amide 5 under catalytic hydrogenation conditions. Coupling of amino amide 5 with acid 6 in acetic acid in the presence of CDI provided nitrile 7 (Scheme 1).5

A Pinner reaction of nitrile 7 using approximately 83 volumes of saturated ethanolic HCl under ambient temperature for 12–15 h provided imino ester 7a (Figure 2), which then reacted in situ with ammonium carbonate in ethanol to furnish amidine 8. Purification of 8 by column chromatography and subsequent reaction with n-hexyl chloroformate in tetrahydrofuran (THF) provided dabigatran etxilate 9, which required purification by column chromatography. The reported process (Scheme 1) is onerous from the manufacturing point of view as the intrinsic fragility of nitrile 7, under highly acidic conditions employed with the Pinner reaction, leads to the formation of unacceptable levels of impurities 28 and 29 (Figure 2), which further react with n-hexyl chloroformate in subsequent reactions to generate impurities 33 and 34, respectively (Figure 2). Apart from this, a set of eight impurities, 20–27 (Table 1), identified in various concentrations in product 9, was attributed to the reaction of 8 with analogous impurities (12–19, Table 1), which are usually present in n-hexyl chloroformate.6 The use of column chromatography purifications at multiple stages of the synthesis, tedious workup procedures, formation of several impurities (28, 29, 33, 34, and 20–27), and the control, management, and generation of huge amounts of effluent make this process inefficient, costly, and difficult to scale.

The second-generation synthesis reported (Scheme 2)7 for 9 exploited an alternative route wherein amino amide 5 was condensed with acid 10 in the presence of a coupling agent to give oxadiazole 11, which was hydrogenated in the presence of palladium catalyst to provide amidine 8, which was subsequently reacted with n-hexyl chloroformate to provide dabigatran etexilate (9). Although this process avoids the cumbersome Pinner reaction, it fails to address the control...
strategy for the formation of impurities \(20\)–\(27\) (Table 1) due to the use of \(n\)-hexyl chloroformate. Several other processes reported with minor modifications to the original process also failed to address the above-mentioned issues related to the control of impurities. Dabigatran etexilate mesylate (1) exhibits polymorphism, and the processes reported for preparing the polymorphs have also failed to address the issues discussed above. Thus, we set out to design a facile and alternate synthetic strategy for 1, which eliminates the number of impurities generated in the previously reported process.

Proficient synthesis of 1 is achieved by (1) establishing the robust process for a Pinner reaction for the synthesis of 8 by thorough optimization of the reaction using design of experiment (DoE) to establish the critical process parameters (CPPs) responsible for providing the desired yield and minimized level of impurities \(28\)–\(29\), and (2) the identification, synthesis, and use of active ester, \(n\)-hexyl-4-nitrophenyl carbonate (32), as a novel synthon for the preparation of 9, which circumvents the formation of impurities \(20\)–\(27\).

With the implementation of these two strategies (Scheme 3), the dabigatran etexilate mesylate (1) obtained is substantially free from potential impurities and meets the regulatory norms in terms of quality. We believe that the developed process provides a notable advantage over the reported processes in the literature in terms of scope and as a more practical alternative for a scalable synthesis of 1.

## RESULTS AND DISCUSSION

Process optimization using one-factor-at-a-time is often deficient in providing a coefficient contribution for the individual parameters on the outcome of the process, especially when many variables are involved and their empirical relationships need to be evaluated. Under such circumstances, a large number of experiments are required, which may also lead to the drawing of inaccurate conclusions many a times. Hence, statistical design of experiment (DoE) tool was employed for the process optimization of the Pinner reaction to prepare amidine 8. DoE software used for the optimization study was a free trial version of STAVEX, with version 5.2.

**Process Development of 8 Using DoE.** The process development work started with nitrile compound 7 (Scheme 3) as the syntheses of amidine 8 and dabigatran etexilate (9) were the most critical and cost-contributing steps in the entire process. Preliminary screening was performed for the synthesis of 8 by selecting different input variables such as strength of ethanolic HCl (25–36\% w/w), reaction time (2–10 h), reaction temperature (25–65 °C), and volume of ethanolic HCl (5–40 volumes with respect to 7).

On the basis of the outcome of the initial screening experiments, we identified that an HCl strength of less than 33\% (w/w) required prolonged reaction times and led to the hydrolysis of 7a into 7b and 7c, which in turn resulted in the formation of impurities \(28\) and \(29\) (Figure 2). Thus, reaction temperature and volume of ethanolic HCl were determined to be critical to the Pinner reaction and hence were considered for further optimization using DoE wherein strength of HCl and reaction time were fixed (Table 2).

Accordingly, a two-factor definitive screening factorial DoE with one center point was performed to optimize the ideal quantity of ethanolic HCl and reaction temperature with
respect to the response variables, such as formation of the impurities \textit{28}–\textit{29} and the yield of \textit{8}. Low and high range limits (Table 3) for these two parameters were selected based on the results of the previous set of optimization experiments.

The experiments were performed as per the design, and the results are captured in Table 4. On the basis of the experimental results, it is evident that the reaction temperature of around 41 °C with just 5 volumes of ethanolic HCl is optimum to maximize the conversion of \textit{7}–\textit{8} while minimizing impurity formation. The best condition provided 2.1% of impurity \textit{28} and around 1.3% of impurity \textit{29} and maximum yield of \textit{8} in around 97% in the set of nine experiments (entry 3, Table 4).

The formation of impurities \textit{28} and \textit{29} could be controlled by lowering the reaction temperature (25 °C) and increasing the volume of ethanolic HCl, but the reaction was incomplete and hence results in low yields (entries 4 and 7, Table 4). The two-dimensional contour plots generated by DoE software for the effect of the temperature range from 25 to 41 °C and the volume of ethanolic HCl over the range of 5–15 volumes for the response variable, that is, purity and yield of \textit{8}, are shown in Figures 3 and 4, respectively. The purity increases from 88 to \sim 96% while proceeding toward the pink region of the plot as the volume of ethanolic HCl is decreased from 15 to 5 at a temperature of 41 °C (Figure 4). The orange region indicates the lowest purity and yield in Figures 3 and 4, respectively, and while moving toward the green, blue, and pink regions, the purity and yield increase. Similarly, the three-dimensional surface plots for the effect of volume of ethanolic HCl and temperature of reaction for the response variable, viz., yield and purity of \textit{8}, are also shown in Figures 5 and 6, respectively.

Once the desired conversion of \textit{7} to \textit{7a} was achieved, the reaction mixture was basified with ammonia gas until a neutral pH was achieved, and \textit{7a} was subsequently reacted with ammonium carbonate at 28–32 °C to obtain \textit{8}. We were able to further control the amounts of impurities \textit{28} and \textit{29} that contaminated \textit{8} by using a mixture of ethanol and ethyl acetate in a purification process. Volumes of these solvents were optimized to achieve the desired yield and quality of \textit{8}.

**Synthesis of \textit{9} Using Novel Synthon n-Hexyl-4-nitrophenyl Carbonate (32).** To circumvent the limitations associated with the use of \textit{n}-hexyl chloroformate with respect to the formation of several analogous impurities (\textit{20}–\textit{27}), we explored the use of a novel synthon, \textit{n}-hexyl-4-nitrophenyl carbonate (32), for the synthesis of \textit{9}. \textit{N}-Hexyl-4-nitrophenyl carbonate (32) was reacted with amidine \textit{8} to provide pure \textit{9} without formation of impurities \textit{20}–\textit{27} that are associated with \textit{n}-hexyl chloroformate. However, the synthesis of \textit{n}-hexyl chloroformate using pure fractions of \textit{n}-hexanol and phosgene derivatives was not considered because the phosgene and its...
derivatives are highly hazardous to health and are highly corrosive in nature. Additionally, the conversion of 8 to 9 was incomplete even after employing the excess quantity of \( n \)-hexyl chloroformate for the reaction. Thus, we explored the safe and efficient transformation of 8 to 9 using novel synthon 32.

The synthesis of \( n \)-hexyl-4-nitrophenyl carbonate (32) was achieved by reacting commercially available bis-(4-nitrophenyl) carbonate (30) with a pure fraction of \( n \)-hexanol (31) in dichloromethane in the presence of triethylamine under ambient temperature (Scheme 3). Upon completion of the reaction, the organic layer was washed with aqueous sodium hydroxide to eliminate the byproduct \( p \)-nitro phenol and concentrated under vacuum to obtain 32 as a light-brown oil. The reaction between amidine 8 and active ester 32 occurred over 8—9 h in a mixture of acetonitrile and water in the presence of potassium carbonate at 25—30 °C (Scheme 3). As expected, series of impurities (20—27) were not detected by high-performance liquid chromatography (HPLC) analysis of
the reaction mixture. However, traces of impurities 28 and 29 found with amidine 8 were transformed into impurities 33 and 34 (Figure 2) during the reaction conditions but could be eliminated during the crystallization of 9 (acetone/water (5:4) mixture then acetonitrile), resulting in a 72% yield with 99.8% purity by HPLC. Traces of other impurities (36—40) observed at a level of ≥0.10% in crude 1 by HPLC were identified, characterized by LCMS, and synthesized. These impurities were also washed out in the crystallization process established using an acetone/water mixture followed by acetonitrile to provide the final API as per ICH guidelines.

Control Strategy for the Impurities. The structures of all of the impurities in dabigatran etexilate identified, synthesized, and controlled in our endeavors are represented in Scheme 2. Second-Generation Syntheses Reported for Dabigatran Etexilate (9)7

Scheme 3. n-Hexyl-4-nitrophenyl Carbonate-Mediated Facile Synthesis of 1

Table 2. Parameters that Were Held Constant during DoE Optimization Based on the Outcome of Preliminary Screening

| Sr. no. | parameter       | limit       | reason for fixing the parameter |
|---------|-----------------|-------------|---------------------------------|
| 1       | strength of HCl | 34—36% (w/w)| strength ≤ 34 required prolonged hours for reaction completion, which led to the hydrolysis of 7a into 7b and 7c, which in turn resulted in the formation of impurities 28 and 29 |
| 2       | reaction time   | 6 h         | more than 6 h irrespective of ranges of any other parameters led to the hydrolysis of 7a into 7b and 7c, which in turn resulted in the formation of impurities 28 and 29 |

Table 3. Ranges of Parameters for Second-Level Optimization Using DoE

| Sr. no. | parameter       | unit        | range    |
|---------|-----------------|-------------|----------|
| 1       | reaction temperature | °C   | 25—41   |
| 2       | volume of EtOH-HCl | times (with respect to 7) | 5—15   |

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Nitro phenol (35) was an obvious byproduct formed during the synthesis of 9, and the established purification process eliminated this impurity. Impurity 36 was identified as a degradation product of either 1 or 9, mainly formed due to the hydrolysis of the amidine group when water was present. The reaction temperature and workup procedures were optimized to control this impurity. Impurity 37 proved to be a novel compound that could be formed by the reaction of trace amounts of 5 with acetic acid (Scheme 4). Hence, by using a stoichiometric quantity of acetic acid, we could control the formation of 37 during synthesis 7.

Impurity 38 was also identified as a novel compound, ethyl N-[[2-[[4-aminophenolyl]carbonyl]iminomethyl]amino]methyl]-1-methyl-1H-benimidazol-5-yl]carbonyl]-N-pyridin-2-yl-β-alaninate, which was presumably formed in the reaction between 3-methyl pentanol (39) present in trace levels in n-hexanol and 30 to furnish the active ester analogue, 3-methyl pentyl-4-nitrophenyl carbonate (40). Traces of 40, in the presence of 8, can react to form impurity 38 (Scheme 3). The established purification process, using a mixture of acetone/water followed by acetonitrile, eliminated this impurity. Impurity 36 was identified as a degradation product of either 1 or 9, mainly formed due to the hydrolysis of the amidine group when water was present. The reaction temperature and workup procedures were optimized to control this impurity. Impurity 37 proved to be a novel compound that could be formed by the reaction of trace amounts of 5 with acetic acid (Scheme 4). Hence, by using a stoichiometric quantity of acetic acid, we could control the formation of 37 during synthesis 7.

Table 4. Details of Second-Level DoE for the Pinner Reaction and Outcome of the Experiments

| exp. no. | reaction temperature (°C) | ethanolic HCl (volumes) | yield (%) | 8 | Imp. 28 | Imp. 29 | 7 |
|----------|---------------------------|------------------------|-----------|---|--------|--------|---|
| 1        | 25                        | 5                      | 84        | 89| 1      | 0.4    | 8 |
| 2        | 33                        | 5                      | 91        | 93| 1.8    | 0.9    | 3 |
| 3        | 41                        | 5                      | 97        | 96| 2.1    | 1.3    | 0 |
| 4        | 25                        | 10                     | 79        | 86| 1.3    | 0.8    | 9.5 |
| 5        | 33                        | 10                     | 88        | 89| 2.5    | 1.6    | 4 |
| 6        | 41                        | 10                     | 92        | 90| 4      | 1.9    | 0 |
| 7        | 25                        | 15                     | 81        | 83| 1.7    | 1      | 6 |
| 8        | 33                        | 15                     | 86        | 86| 3.2    | 1.8    | 5 |
| 9        | 41                        | 15                     | 91        | 88| 3.9    | 2      | 0 |

"The volume of HCl used is specified with respect to the amount of compound 7 used in the reaction. bYields reported for 8 are after the reaction of 7a with ammonia and ammonium carbonate and after employing the final established purification process using ethanol and ethyl acetate. cUnreacted compound 7."
these impurities to provide the final API as per the ICH
guidelines.17

■ CONCLUSIONS

In conclusion, the work described in this report provides the
synthesis of dabigatran etexilate mesylate (1) by using a novel
synthon, n-hexyl-4-nitrophenyl carbonate, which results in the
isolation of a final product, which is substantially free from the
literature-reported impurities. Our synthesis and purification
methods also allowed the removal of the impurities specific to
this new approach. Additionally, the process optimization for
the synthesis of amidine intermediate 8, using DoE, improved
the classical Pinner reaction conditions associated with the
literature-reported processes and provided a drastic improve-
ment in yield. We believe that this novel approach toward the
synthesis of 1 provides better scope and a more practical
alternative to the existing processes reported in the literature.

■ EXPERIMENTAL SECTION

All reagents, solvents, and processing aids were commercial
products and were used as received. For reactions run on pilot
scale, glass-lined reactors having variable rate agitation and a
−10 to 150 °C jacket temperature range were used.1H NMR
spectra were recorded in CDCl3 using a Varian Gemini 400
MHz FT NMR spectrometer; the chemical shifts are reported
in δ ppm relative to tetramethylsilane. Electrospray ionization
(ESI) mass spectra were performed on the Shimatsu LCMS-
2020 spectrometer. Related substance purity was monitored by
high-performance liquid chromatography (HPLC) on Agilent
Technologies 1200 series. The gas chromatography on Agilent
Technologies 7683B with headspace was used for analyzing the
residual solvents.

Preparation of Dabigatran Eteixlate Mesylate (1).
Synthesis of N-[2-[[4-(Aminoiminomethyl)phenyl]amino]-
methyl]-1-methyl-1H-benzimidazol-5-yl[carbonyl]-N-2-pyri-
dinyl-γ-alanine ethyl ester (8). Ethanolic HCl (5.0 L, 36% w/ w) was charged to the reactor and to it was added 7 in portions
(0.20 kg × 5, 2.07 mol) at temperature below 35 °C; the

Figure 6. Surface plot for purity of 8 against variable of volume of
ethanol and temperature of reaction.

Figure 7. Observed impurities in 1 as per the developed Route of Synthesis.
temperature was raised to 40–41 °C and the mixture was stirred for 6 h. After completion of reaction (by HPLC), the reaction mixture was cooled to 25–30 °C and diluted with ethanol (15.0 L). The resulting reaction mixture was cooled to 0–5 °C, and ammonia gas was purged into the reaction mixture at temperature between 0 and 15 °C until a pH ≥ 8 was achieved. To the basified reaction mixture was added ammonium carbonate (0.75 kg, 7.80 mol) at 0–10 °C; the temperature was raised to 28–32 °C and the mixture was stirred for 10 h. After completion of the reaction (by HPLC), the reaction mixture was cooled to 25–30 °C and filtered. The obtained inorganic salt was washed with ethanol (5.0 L). The combined filtrate was distilled under vacuum at temperature below 50 °C to remove ethanol and obtain a residue. To the resulting residue was added ethanol (5.0 L) and heated to 75–80 °C for 1.0 h. To the hot solution was added ethyl acetate (1.0 L). The resulting reaction mixture was cooled to 25–30 °C for 1.0 h, and the precipitated product was filtered and washed with ethyl acetate (1.0 L). The wet solid was dried for 4 h at 50–55 °C to furnish 0.99 kg (97% yield) of the title compound B. HPLC purity: 97.83%. Content of 7: not detected; content of 28: 1.93%; content of 29: not detected; total impurity: 2.17%. Chloride content: 0.6%. Ethanol content: 1628 ppm. Ethyl acetate content: 500 ppm. MS (ESI, CDCl3): [M + H]+ 551.94, 1255.94, 1219.03, 1164.89, 1109.82. 1H NMR (400 MHz, CDCl3): δ ppm 0.89–0.93 (t, J = 8.8 Hz, 3H), 1.33–1.44 (m, 6H), 1.71–1.80 (m, 2H), 4.27–4.31 (t, J = 8.8 Hz, 2H), 7.37–7.40 (d, J = 12 Hz, 2H), 8.25–8.29 (d, J = 9.6 Hz, 2H).

**Synthesis of Ethyl 3-(((2-((4-N′-Hexyloxy carbonyl)carbamimidoyl)phenyl)aminomethyl)1-methyl-1H-benzimidazol-5-yl) Carbonyl (Pyridin-2-ylaminopropanoate (9).** Acetinone (9.0 L), amidine compound 8 (1.0 kg, 2.0 mol), water (1.5 L), and potassium carbonate (0.83 kg, 6.0 mol) were charged to the reactor. To the resulting reaction mixture, a solution of n-hexyl-4-nitrophenyl carbonate (prepared by using 0.721 kg, 2.69 mol of 32 in 0.5 L acetinone) was added at temperature 25–30 °C, and the reaction mixture was stirred for 5 h at 25–30 °C. After completion of the reaction (by HPLC), the reaction mixture was cooled to 0–5 °C and stirred for 2.0 h. The precipitated product was filtered and washed with water (1.0 L). The obtained wet solid was suspended in water (10.0 L), stirred for 1.0 h, filtered, and washed with water (2.0 L). The resulting wet solid was suspended in acetone (5.0 L) and heated to 40–45 °C for 30 min. The resulting solution was cooled to 25–30 °C and water (4.0 L) was added. The precipitated product was cooled to 25–30 °C and stirred for 1.0 h, filtered, and washed with water (1.0 L). The isolated wet solid was suspended in acetinone (8.0 L) and the resulting suspension was heated at 60–70 °C until dissolution. The solution was then cooled to 25–30 °C and stirred for 1.0 h. The precipitated product was filtered and washed with acetinone (1.0 L). The wet solid was dried for 10 h at 50–55 °C. Dry weight of 9 was 0.90 kg (72% yield). HPLC purity: 99.92%; content of 8: 0.01%; content of 28: not detected; content of 29: not detected; content of 32: not detected; content of 33: 0.02%; content of 34: 0.01%; content of 35: not detected; content of 36: 0.02; content of 37: not detected; content of 38: not detected; content of single largest unknown impurity: 0.01%; total impurity: 0.08%. FT-IR (KBr, cm−1): 3400.56, 3380.11, 2952.38, 2931.63, 1731.15, 1611.21, 1588.92, 1570.46, 1498.97, 1470.43, 1392.05, 1323.35, 1257.86, 1195.16, 1143.35, 1128.33, 1105.56, 1033.49, 1013.38, 895.98. 1H NMR (400 MHz, CDCl3): δ ppm 8.86–0.88 (t, J = 5.6 Hz, 3H), 1.18–1.21 (t, J = 6.8 Hz, 3H), 1.29 (m, 4H), 1.38 (m, 2H), 1.66–1.73 (m, 2H), 2.76–2.79 (t, J = 3.7 Hz, 2H), 3.54 (s, 3H), 4.03–4.12 (m, 4H), 4.28–4.29 (bs, 2H), 4.38–4.41 (t, J = 6.8 Hz, 2H), 5.54 (s, 1H), 6.47–6.49 (d, J = 8.4 Hz, 2H), 6.67–6.69 (d, J = 8 Hz, 1H), 6.90–6.92 (d, J = 8.4 Hz, 1H), 6.95–6.98 (t, J = 6.4 Hz, 1H), 7.12–7.14 (t, J = 6.8 Hz, 1H), 7.30–7.34 (t, J = 8 Hz, 2H), 7.61 (s, 1H), 7.61 (s, 1H), 7.65–7.67 (d, J = 8 Hz, 1H), 8.38–8.39 (d, J = 4 Hz, 1H), 9.48 (bs, 1H). 13C NMR (100 MHz, CDCl3): δ ppm is 13.85, 13.93, 22.35, 25.46, 28.69, 29.54, 31.34, 33.10, 40.39, 44.49, 60.33, 65.12, 108.64, 111.73, 119.94, 120.92, 122.22, 127.74, 123.41, 128.93, 129.58, 137.00, 137.17, 140.79, 148.71, 150.32, 152.29, 155.85, 164.90, 170.85, 171.45. MS (ESI, m/z): [M + H]+.

**Synthesis of Dabigatran Etxeliate Mesylate (1).** Acetinone (7.0 L) and dabigatran etexilate (9, 1.0 kg, 1.59 mol) were charged to the reactor, and the suspension was heated to 40–
45 °C until dissolution; the clear solution was filtered over a celite bed and the bed was washed with acetone (1.0 L). The combined filtrate was cooled to 25–30 °C to the resulting suspension, a solution of methane sulfonic acid (prepared by using methane sulfonic acid 0.15 kg, 1.56 mol diluted with 4.5 L acetone) was added. The precipitated salt was stirred at 25–30 °C for 1.0 h and then cooled to 17–23 °C and stirred for 1.0 h. The precipitated salt was filtered and washed with acetone (1.0 L). The resulting wet material was dried for 5 h at 40–45 °C to furnish 1.090 kg (95% yield) of title compound.

The solid was dried for 3 h at 50 °C to obtain a clear solution. The resulting solution was stirred at temperatures 25–30 °C for 1 h. After completion of the reaction (by HPLC), the reaction mixture was stirred with water (150 mL) and dichloromethane (150 mL) and stirred for 15 min. The dichloromethane layer was separated, and the pH of the aqueous layer was adjusted to 4 using acetic acid (6.0 mL). The precipitated product was filtered and washed with water (20 mL). Wet solid was dried for 3 h at 50–55 °C to furnish 1.0 g (70% yield) of title compound.

HPLC purity: 94.41%. FT-IR (KBr, cm−1): 3422.96, 3372.54, 1726.59, 1560.31, 1507.99. 1H NMR (400 MHz, DMSO-d6): δ ppm 0.88–0.89 (t, J = 6.8 Hz, 2H), 1.29–1.30 (m, 8H), 1.38–1.42 (m, 4H), 1.65–1.72 (m, 2H), 3.78 (s, 3H), 4.10–4.13 (t, J = 7.2 Hz, 2H), 4.36–4.41 (q, J = 7.2 Hz, 2H), 4.53–4.55 (d, J = 4.8 Hz, 2H), 5.34–5.36 (t, J = 4.8 Hz, 1H), 6.70–6.74 (d, J = 8.8 Hz, 2H), 7.30–7.32 (d, J = 8.4 Hz, 1H), 7.75–7.77 (d, J = 8.8 Hz, 2H), 8.43–8.44 (bs, 1H), 9.60 (bs, 1H).

Preparation of 3-((2-[(4-[(Hexoxy)carbonyl]-34 benzimidazol-5-yl]carbonyl)phenyl)amino)methyl-1-methyl-1H-benzimidazol-5-yl)carbonyl(pyridin-2-yl)amino)propanoic Acid (34). Water (150 mL), ethanol (300 mL), and sodium hydroxide (2.86 g, 0.071 mol) were added to the bottom-round flask and stirred to obtain a clear solution. To the resulting solution, 9 (15 g, 0.023 mol) was added, and the reaction mixture was stirred at temperatures 25–30 °C for 1 h. After completion of the reaction (by HPLC), the reaction mixture was filtered with water (150 mL) and dichloromethane (150 mL) and stirred for 15 min. The dichloromethane layer was separated, and the pH of the aqueous layer was adjusted to 4 using acetic acid (6.0 mL). The precipitated product was filtered and washed with water (20 mL). Wet solid was dried for 3 h at 50–55 °C to furnish 1.0 g (70% yield) of title compound. HPLC purity: 94.41%. FT-IR (KBr, cm−1): 3422.96, 3372.54, 1726.59, 1560.31, 1507.99. 1H NMR (400 MHz, DMSO-d6): δ ppm 0.88–0.89 (t, J = 6.8 Hz, 2H), 1.29–1.30 (m, 8H), 1.38–1.42 (m, 4H), 1.65–1.72 (m, 2H), 3.78 (s, 3H), 4.10–4.13 (t, J = 7.2 Hz, 2H), 4.36–4.41 (q, J = 7.2 Hz, 2H), 4.53–4.55 (d, J = 4.8 Hz, 2H), 5.34–5.36 (t, J = 4.8 Hz, 1H), 6.70–6.74 (d, J = 8.8 Hz, 2H), 7.30–7.32 (d, J = 8.4 Hz, 1H), 7.75–7.77 (d, J = 8.8 Hz, 2H), 8.43–8.44 (bs, 1H), 9.60 (bs, 1H).

Preparation of 3-((2-[(4-[(Hexoxy)carbonyl]-35 benzimidazol-5-yl]carbonyl)phenyl)amino)methyl-1-methyl-1H-benzimidazol-5-yl)carbonyl(pyridin-2-yl)amino)Propa- noate (35). Dabigatran etexilate mesylate (20 g, 0.027 mol) and water (100 mL) were added to the bottom-round flask and the resulting suspension was heated for 10 h at 98–100 °C. The obtained suspension was cooled to 25–30 °C and stirred for 1 h. The precipitated product was filtered and washed with water (15 mL). The wet solid was dried for 3 h at 50–55 °C to furnish 12 g of crude 36, which was crystallized from acetonitrile to obtain 10.5 g (52% yield) of pure 36. HPLC purity: 96.24%. FT-IR (KBr, cm−1): 3347.42, 2957.14, 2934.17, 2863.03, 1853.08, 1749.45, 1689.76, 1647.73, 1588.03, 1530.60, 1485.66, 1435.54, 1247.86, 1192.98, 1136.82, 1016.18. 1H NMR (400 MHz, CDCl3): δ ppm 0.86–0.89 (t, J = 6.8 Hz, 3H), 1.18–1.22 (t, J = 7.2 Hz, 3H), 1.27–1.38 (m, 6H), 1.65–1.71 (m, 2H), 2.78–2.81 (t, J = 7.2 Hz, 2H), 3.72 (s, 3H), 4.03–4.08 (q, J = 7.1 Hz, 2H), 4.18–4.22 (t, J = 7.08 Hz, 2H), 4.40–4.43 (t, J = 7.3 Hz, 2H), 4.50–4.52 (d, J = 4.4 Hz, 2H), 5.36–5.38 (t, J = 4.4 Hz, 1H), 6.68–6.72 (d, J = 8.7 Hz, 3H), 6.96–6.99 (m, J = 6.68 Hz, 1H), 7.12–7.14 (d, J = 8.4 Hz, 1H), 7.29–7.34 (m, 2H), 7.68–7.70 (d, J = 8.7 Hz, 3H), 7.94 (s, 1H), 8.40–8.42 (dd, J = 1.2 Hz, J = 4.4 Hz, 1H).

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