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(54) Title: PROCESS FOR THE PREPARATION OF DABIGATRAN ETEXILATE AND INTERMEDIATES THEREOF

(57) Abstract: The present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or a salt thereof, in a purity of at least 99.0% and wherein the level of compound of formula X and XV is less than 0.15% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof, as determined by HPLC comprising: (a) subjecting a crude compound of formula I to treatment with alkyl acetate and ketone to form a mixture; (b) optionally heating the mixture; and (c) isolating the compound of formula I.
"PROCESS FOR THE PREPARATION OF DABIGATRAN ETEXILATE AND INTERMEDIATES THEREOF"

PRIORITY
5 This application claims the benefit under 35 U.S.C.§119 to Indian Provisional Application No. 2481/MUM/2012, filed on Aug 27, 2012, 3260/MUM/2012 filed on Nov 09, 2012, United States Provisional Application No. 61/711663, filed on October 9, 2012, the contents of which are incorporated by reference herein.

FIELD OF THE INVENTION
10 The present invention relates to a novel process for preparation of dabigatran etexilate and its salts. More specifically the present invention relates to preparation of dabigatran etexilate and its salts in high purity free of impurities.

BACKGROUND OF THE INVENTION
15 Dabigatran etexilate which is chemically known as 1-Methyl-2-[N-[4-(N-n-hexyloxycarbonylamidino) phenylaminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(ethoxycarbonylethyl)-amide, is represented by compound of Formula I. Dabigatran etexilate is the prodrug of dabigatran which is an anticoagulant drug having thrombin inhibitor properties.

PRADAXA®, Boehringer's dabigatran etexilate mesylate oral capsule of 75 and 150 mg, is indicated for reducing the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation.
United States Pat. No. 6087380 (US Pat. '380) discloses process for preparing dabigatran etexilate by reacting a compound of Formula VIII with n-hexyl chloroformate. The '380 patent also discloses process for preparing compound of formula VIII.

The process disclosed in the '380 patent, is time consuming, tedious and laborious. The product obtained is contaminated with many impurities which are difficult to separate and require multiple purification steps thereby reducing the yield. The process disclosed in US'380 utilizes column chromatography for isolating the compound of formula I.

Presently, we have developed a novel process wherein the compound of Formula I is isolated, without column chromatography, as a solid having a purity greater than 99% as determined by high performance liquid chromatography (HPLC). The isolated compound of formula I in purity greater than 99% can be used to prepare dabigatran etexilate mesylate compound of formula IA in high purity meeting ICH specifications, without any chromatographic techniques.

The process of the present invention is advantageous as it is high yielding, less time consuming and is industrially feasible.

**SUMMARY OF THE INVENTION**

The present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or a salt thereof.
in a purity of at least 99.0% and wherein the level of compound of formula X and XV is less than 0.15\% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof, as determined by HPLC:

\[
\text{Formula X} \quad \text{Formula XV}
\]

comprising:

(a) subjecting a crude compound of formula I to treatment with alkyl acetate and ketone to form a reaction mixture;
(b) optionally heating the reaction mixture; and
(c) isolating the compound of Formula I.

The present invention provides a compound of formula XV:

\[
\text{Formula XV}
\]

The present invention provides dabigatran etexilate mesylate wherein the level of compound of formula X and XV is less than 0.15\% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof as determined by HPLC.
DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or a salt thereof

![Formula I](image)

in a purity of at least 99.0% and wherein the levels of compound of formula X and XV are less than 0.15% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof as determined by HPLC,

![Formula X](image)  
![Formula XV](image)

comprising

(a) subjecting a crude compound of formula I to treatment with alkyl acetate and ketone to form a reaction mixture;

(b) optionally heating the reaction mixture; and

(c) isolating the compound of Formula I.

The crude compound of formula I is a compound of formula I containing impurities compound of formulae VIII, X, and XV to an extent of more than 0.5%, relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof.
When the crude compound of formula I was treated with ethyl acetate there was no substantial reduction in the impurities of compounds VIII, X, and XV. When a combination of ethyl acetate and alkanol was used to treat the crude compound of formula I there was no reduction in the amount of compound of formula XV.

Surprisingly we have found that subjecting a crude compound of formula I to treatment with alkyl acetate and ketone is able to reduce the impurities compounds of formula VIII, X, and XV to an extent of less than 0.15% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof as determined by HPLC and also the yield of the purified compound is satisfactory. More specifically the impurities compounds of formula VIII, X, and XV are reduced to less than 0.01% w/w, preferably absent.

The alkyl acetate may be selected from the group consisting of ethyl acetate, propyl acetate and butyl acetate.

The ketone may be selected from the group consisting of acetone, butanone and pentanone.

In one embodiment the crude compound of formula I is subjected to treatment with a mixture of alkyl acetate and ketone followed by heating the mixture and cooling the mixture and isolating the compound of formula I from the mixture by filtration.

In one embodiment the crude compound of formula I is subjected to treatment with alkyl acetate followed by adding ketone to precipitate the compound of formula I by solvent antisolvent method and filtering the mixture to isolate the compound of formula I.
In one embodiment, the present invention provides a process for the preparation of compound of formula I in a purity of at least 99.0% as determined by HPLC comprising isolating the compound of Formula I from a mixture of ethyl acetate and acetone.

In one embodiment, the present invention provides a process for preparing the compound of formula I in a purity of at least 99.0% and wherein the compounds of formula VIII, X, XI, XII, XIII, XIV and XV are each present to an extent of less than 0.1% as determined by HPLC, comprising isolating the compound of Formula I from a mixture of ethyl acetate and acetone.
In one embodiment, the present invention provides a process for preparing the compound of formula I in a purity of at least 99.50% and wherein the compounds of formula VIII, XI, XII, XIII, XIV and XV are each present to an extent of less than 0.1% as determined by HPLC, comprising isolating the compound of Formula I from a mixture of ethyl acetate and acetone.

In one embodiment, the present invention provides a process for preparing the compound of formula I in a purity of at least 99.50% and wherein the compounds of formula VIII, X, XI, XII, XIII, XIV and XV are each absent as determined by HPLC, comprising isolating the compound of Formula I from a mixture of ethyl acetate and acetone.

In one embodiment, the present invention provides a compound of formula X.

In one embodiment the present invention provides use of compound of formula X as reference standard for assessing the purity of compound of formula I, or IA.

In one embodiment, the present invention provides a compound of formula XV.

In one embodiment, the present invention provides a compound of formula XV with mass M+: 599.39. Mass spectra was recorded using instrument- Thermofinnigan, LCQ DECA XP MAX.
In one embodiment, the present invention provides a compound of formula XV with IHNMR (300MHz, DMSO-d6) δ : 0.86, 1.28, 1.57, 2.50, 3.76, 3.94-3.96, 4.14, 4.58, 6.74-6.84, 6.97-7.0, 7.1-7.16, 7.37-7.40, 7.47, 7.55-7.57, 7.78-7.8, 8.28. Proton NMR spectra was recorded in DMSO-d6 using NMR instrument - Varian 300 MHZ.

In one embodiment the present invention provides use of compound of formula XV as reference standard for assessing the purity of compound of formula I, or IA.

In one embodiment, the present invention provides a compound of formula XI.

![Formula XI](image)

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula X is present to an extent of less than 0.15%. Preferably less than 0.05%.

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula X is absent.

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula XI is present to an extent of less than 0.15%. Preferably less than 0.05%.

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula XI is absent.

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula X and XI are each present to an extent of less than 0.1%. Preferably less than 0.05%.

In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula X and XI are absent.
In one embodiment, the present invention provides a compound of formula I, or IA wherein the compound of formula XII, XIII, XIV XV are each present to an extent of less than 0.1%. Preferably less than 0.05%.

In one embodiment, the present invention provides a compound of formula I or IA wherein the compound of formula XII, XIII, XIV XV are absent.

In one embodiment, the present invention provides a compound of formula I or IA wherein the compound of formula X, XI, XII, XIII, XIV XV are each present to an extent of less than 0.1%. Preferably less than 0.05%.

In one embodiment, the present invention provides a compound of formula I or IA wherein the compound of formula X, XI, XII, XIII, XIV, XV are absent.

In one embodiment, the present invention provides dabigatran etexilate mesylate wherein the level of compound of formula X and XV is less than 0.15% relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof as determined by HPLC.

In one embodiment, the present invention provides a process for recrystallizing dabigatran etexilate mesylate, compound of formula IA, comprising use of ether solvents.

The ether solvent may be selected from the group consisting of diethyl ether, methyl tertiary butyl ether, tetrahydrofuran, tetrahydropyran and the like.

In one embodiment, the present invention provides a process for recrystallizing the compound of formula IA, from methyl tertiary butyl ether.

In one embodiment, the present invention provides a process for preparing the compound of formula IA, by slurrying with methyl tertiary butyl ether.
In one embodiment, the present invention provides a process for preparation of dabigatran etexilate mesylate, compound of formula IA, comprising

a. reacting the compound of formula I with methanesulfonic acid to form dabigatran etexilate mesylate, compound of formula IA; and

b. isolating the dabigatran etexilate mesylate, compound of formula IA from methyl tert-butyl ether.

In one embodiment, the present invention provides a process for preparing the compound of formula IA, comprising reacting a compound of formula I with methanesulphonic acid in ethyl acetate.

**HPLC Methodology**

**Reagents, Solvents and Standards:**

Water (Milli Q or equivalent); Perchloric Acid (Merck, GR Grade) Acetonitrile (HPLC Grade) Methanol (HPLC Grade)

**Apparatus:** A High Performance Liquid Chromatograph equipped with quaternary gradient pumps, variable wavelength UV detector attached with data recorder and integrator software. **Column:** Inertsil ODS 3V, 250 X 4.6mm, 5µ; **Column temperature:** 30°C; **Sample cooler temperature:** 5°C; **Mobile Phase A:** Buffer: 0.1% perchloric acid in water. **Mobile Phase B:** Acetonitrile

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**Diluent:** Water: Acetonitrile: Methanol (60:10:30, v/v); **Flow Rate:** 1.0mL/minute; **Detection:** UV 225nm; **Injection Volume:** 20µL

**Preparation of Reference solution (a):**
Transfer about 35.0mg of Dabigatran etexilate mesylate in-house reference standard, accurately weighed into a 100mL volumetric flask. Add about 50-60ml of diluent and sonicate to dissolve. Make up to the mark with diluent and mix. Dilute 5.0mL of this solution to 50mL with diluent and mix. Further dilute 1.0mL of this solution to 100mL with diluent and mix.

Preparation of Reference solution (b):
Transfer about 10.5mg of compound of formula VIII standard, accurately weighed into a 100mL volumetric flask. Add 10.0ml of acetonitrile, 30.0ml of methanol in it and sonicate to dissolve. Make up to the mark with water and mix.

Preparation of Reference solution (c):
Transfer about 10.5mg of compound of formula XII standard, accurately weighed into a 100mL volumetric flask. Add 10.0ml of acetonitrile, 30.0ml of methanol in it and sonicate to dissolve. Make up to the mark with water and mix.

Preparation of Reference solution (d):
Transfer about 10.5mg of compound of formula XIII standard, accurately weighed into a 100mL volumetric flask. Add 10.0ml of acetonitrile, 30.0ml of methanol in it and sonicate to dissolve. Make up to the mark with water and mix.

Preparation of Reference solution (e):
Transfer about 10.5mg of compound of formula XIV standard, accurately weighed into a 100mL volumetric flask. Add 10.0ml of acetonitrile, 30.0ml of methanol in it and sonicate to dissolve. Make up to the mark with water and mix.

Preparation of Reference solution (f):
Transfer about 10.5mg of compound of formula XI standard, accurately weighed into a 100mL volumetric flask. Add 10.0ml of acetonitrile, 30.0ml of methanol in it and sonicate to dissolve. Make up to the mark with water and mix.

Preparation of Reference solution (g):
Transfer 5.0mL each of reference solution (b), (c), (d), (e) and (f) into 50mL volumetric flask and mix well. Make up to the mark with diluent and mix.

Preparation of Reference solution (h):
Transfer about 35.0mg of Dabigatran etexilate mesylate in-house reference standard, accurately weighed into a 100mL volumetric flask. Add about 50-60ml of diluent and sonicate to dissolve. Add 5.0mL of reference solution (g) in it and mix well. Make up to the mark with diluent and mix. **Note: Reference solution (h) should be freshly prepared for analysis.**

Preparation of Test Solution:
Transfer about 35mg of sample into a 100mL volumetric flask. Add about 50-60ml of diluent and sonicate to dissolve. Make up to the mark with diluent and mix. **Note: Test Solution should be freshly prepared for analysis.**

**Procedure**

Separately inject the equal volumes of blank solution, reference solution (h) and six replicate injections of reference solution (a). Then inject test solution in duplicate and record the chromatogram for all injections eliminating the peaks due to blank. The retention time of main peak i.e. Dabigatran etexilate is about 30.0 minutes under these conditions. **Relative retention time** for compound of formula VIII is about 0.27, for compound of formula XII is about 0.72, compound of formula XIII is about 0.90, compound of formula X is 1.04, compound of formula XIV is about 1.14, compound of formula XI is about 1.23 and for compound of formula XV is 0.62 with respect to main peak i.e. dabigatran etexilate.

The present invention provides novel process for preparation of dabigatran etexilate and salt thereof.

In one embodiment the present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or salt thereof

![Formula I](image)

comprising reacting a compound of Formula II, wherein R is selected from the group consisting of H or Cl-C₇ alkyl, with a compound of Formula III
In one embodiment the present invention provides a process for the preparation of dabigatran etexilate as depicted in Scheme 1.

Scheme I for preparation of dabigatran etexilate

In scheme 1, R is selected from the group consisting of H or C1-C7 alkyl.
The present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or salt thereof

![Formula I](image)

comprising

(a) reacting a compound of Formula II, wherein R is selected from the group consisting of H or C\textsubscript{1}--C\textsubscript{7} alkyl, with a compound of Formula IV or derivative thereof to obtain a compound of Formula V or derivative thereof; and

![Formula II](image)

![Formula IV](image)

![Formula V](image)

(b) treating the compound of Formula V or derivative thereof with a compound of Formula VI

![Formula VI](image)

to obtain a compound of Formula I.

The term "compound of Formula IV or derivative thereof" includes the acid derivatives of compound of formula IV such as the acid chloride, acid anhydride, ester derivatives represented by compound of formula IVA wherein R\textsubscript{1} is selected from halogen, -Oalkyl, -Oalkylaryl, -OCOalkyl.
The term "compound of Formula V or derivative thereof" includes the acid derivatives of compound of formula V such as the acid chloride, acid anhydride, ester derivatives represented by compound of formula VA wherein R1 is selected from halogen, -Oalkyl, -Oalkylaryl, -OCOalkyl.

The term alkyl includes C1-C7 alkyl such as methyl, ethyl, propyl and the like. The term halogen includes chlorine, bromine, iodine and fluorine. The term alkylaryl includes benzyl, ethyl benzene and the like.

In one embodiment the present invention provides a process for the preparation of dabigatran etexilate as depicted in Scheme II.
Scheme II for preparation of dabigatran etexilate

In scheme II, R is selected from the group consisting of H or C₁-C₇ alkyl.

The present invention provides a compound of Formula V.
The present invention provides a compound of Formula II, wherein R is selected from the group consisting of H or C\textsubscript{1}-C\textsubscript{7} alkyl.

In one embodiment the present invention provides a compound of formula II wherein R is H.

The present invention provides a compound of Formula VII, wherein R is selected from the group consisting of H or C\textsubscript{1}-C\textsubscript{7} alkyl.

In one embodiment, the present invention provides compound of formula VII wherein R is H.

The present invention provides a process for preparing a compound of formula II wherein R is selected from the group consisting of H or C\textsubscript{1}-C\textsubscript{7} alkyl as depicted in Scheme III.
In scheme III, R is selected from the group consisting of H or C1-C7 alkyl; X is a halogen selected from chlorine, bromine, iodine and fluorine.
In one embodiment, the present invention provides a process for preparing a compound of Formula II, wherein R is selected from the group consisting of H or C_{1-7}alkyl comprising reacting a compound of Formula VII, wherein R is selected from the group consisting of H or C_{1-7}alkyl, with n-hexylhaloformate.

The compound of formula II obtained by Scheme III may be converted to dabigatran or pharmaceutically acceptable salt by methods disclosed earlier.

In one embodiment, the present invention provides a process for preparing a compound of Formula V comprising reacting the compound of formula II obtained by the process of the present invention with a compound of Formula IV or derivative thereof, to obtain a compound of Formula V or derivative thereof.
In one embodiment, the present invention provides a process for preparing a compound of Formula V as depicted in scheme IV.

**Scheme IV for preparation of compound of formula V**

In one embodiment, the present invention provides a process for the preparation of dabigatran etexilate, a compound of Formula I or salt thereof.
Formula I

comprising reacting a compound of Formula VIII, with a compound of Formula IX

\[ \text{Formula VIII} \]

\[ \text{Formula IX} \]

The compound of formula IX may be prepared by reacting 1-hydroxybenzotriazole with hexylchloroformate.

In one embodiment, the present invention provides a process for the preparation of compound of formula I by a process comprising reacting hexylchloroformate with N-hydroxysuccinimide and reacting the resulting complex with compound of formula VIII.

In one embodiment, the present invention provides a process for the preparation of compound of formula I by a process comprising reacting hexylchloroformate with N-hydroxyphthalimide and reacting the resulting complex with compound of formula VIII.

The compound of formula I obtained by following the process of the present invention may be recrystallized in an organic solvent for example ethyl acetate.

The compound of formula I obtained by following the process of the present invention may be converted to its pharmaceutically acceptable salt like hydrochloride, sulphate, mesylate, bismesylate.

The following examples are provided to enable one skilled in the art to practice the invention and are merely illustrative of the invention. The examples should not be read as limiting the scope of the invention as defined in the features and advantages.
Examples

Example 1: Preparation of \(\{4-[\text{imino(ethoxyamino)methyl]phenyl}\text{amino}\}\text{acetic acid}\)

To a solution of 75 ml saturated ethanolic HCl, charged 5 gms of \([4\text{-cyanophenyl}\text{amino}\]\text{acetic acid} (0.0284 mmol) and 1.26 gms calcium chloride(0.01 136 mmol), and stirred the reaction mass at about 20-25°C for about 12 hours. The solvent was distilled out completely under vacuum at about 45-50°C, and the concentrate obtained was stirred in 50 ml ethanol at 25-30°C, and residue was filtered out. The filtrate was concentrated under vacuum at 45-50°C to obtain 6.2 gms of title compound.

Example 2: Preparation of \(\{4\text{-famino(imino)methyl]phenyl}\text{amino}\}\text{acetic acid, compound of formula VII}:

To a solution of 25 ml saturated Ethanolic Ammonia charged 6.2 gms of \([4\text{-imino(ethoxyamino)methyl]phenyl}\text{amino}\]\text{acetic acid}, and stirred at about 20-25°C for about 10 hours. The solvent was distilled out completely under vacuum at about 45-50°C, and the concentrate obtained was stirred in 50 ml ethanol at about 25-30°C, and the residue was filtered out. The filtrate was concentrated under vacuum at 45-50°C completely. The above concentrate was slurried in 15ml ethanol and 100ml ethyl acetate at 60-65°C for 15 min. and at 20-25°C for 120 min. The solid was filtered and washed with 15ml ethyl acetate to obtain 5.0 gms of title compound.

Example 3: Preparation of \(\{4\text{-((Z)-amino(hexyloxy)carbonylimino)methyl]phenyl]amino}\text{acetic acid, compound of formula II, wherein R is H}\)

Charged 5.0 gms of \([4\text{-amino(imino)methyl]phenyl}\text{amino}\]\text{acetic acid} (0.0155 mmol) to ml 50 ml methylene chloride and cooled to 10-15°C. Charged 3.93 gms of triethylamine (0.0389 mmol) and stirred for 15 mins. Charged gradually a solution of h- hexyl chloroformate 3.84 gms (0.0233 mmol) in 10 ml methylene chloride in about 15-20 mins. Stirred for 3.0 hours at 10-15°C. Charged 25 ml distilled water to reaction mass and stirred for 5 min. Aqueous layer was separated and extracted with 15 ml methylene chloride. Organic layer washed with 25 ml distilled water, and treated with anhydrous sodium sulfate. The solvent was distilled out completely under vacuum at 45-50°C. Stirred the above concentrate in 50 ml isopropyl ether at 25-30°C for 30 min. The solid was filtered and washed with 5ml isopropyl ether to obtain 2.5 gm of title compound.

Example 4: Preparation of Dabigatran etexilate, compound of formula I

1) Using polyphosphoric acid

Charged 2.5 gm \([4\text{-((Z)-amino(hexyloxy)carbonylimino)methyl]phenyl]amino}\]\text{acetic acid }, 2.6 gms of ethyl 3-[[3-amino-4-(methylamino)phenyl]carbonyl(pyridin-2-yl)amino]propanoate and 5 ml poly
phosphoric acid. The reaction mass was heated to 110-120°C for 12 hours. The reaction mass was cooled and charged 25 ml water and basified using potassium carbonate. The reaction mass was extracted with 20 ml methylene chloride. The organic layer was washed with 10 ml distilled water and sodium sulfate. The organic layer was concentrated and slurried in 25 ml ethyl acetate obtain title compound (1.0 g).

II) Using 1,1'-Carbonyl diimidazole

Charged 2.5 gms [(4-((Z)-amino)[(hexyloxy)carbonyl]iminomethyl)phenylamino]acetic acid and 1.25 gm 1,1'- Carbonyl diimidazole in 10 ml tetrahydrofuran, and stirred for 20 min. The above solution was charged in a solution of 2.4 gms ethyl 3-[[3-amino-4-(methylamino)phenyl]carbonyl](pyridin-2-yl)amino]propanoate in 10 ml dimethyl formamide. The reaction mass was heated to about 100°C for about 5 hours. The reaction mass was concentrated under vacuum and extracted with ethyl acetate after adding water. The combined organic layer was washed with water and distilled off under vacuum. The above concentrate was refluxed in 5 ml acetic acid for 1 hr. After removal of solvent the residue was extracted in methylene chloride, washed with water and distilled off under vacuum to give title compound (1.0 g).


50 gms of Ethyl 3-[[2-[[4-(N'-[(hexyloxy) carbonyl] carbamimidoyl] phenyl) amino]methyl]-1-methyl-lH-benzimidazol-5-yl]carbonyl] (2-pyridinylamino) propionate was dissolved in ethyl acetate at about 35-60 °C and a solution of methane sulfonic acid in 100ml of ethyl acetate was added in 30-60 min. The reaction mass was cooled to about 25-30°C for 2 hours. The crude product was filtered and washed with 100ml of ethyl acetate and dried at 45-50 °C in vacuum tray drier to get 48 gm of title compound.


50 gms of Ethyl 3-[[2-[[4-(N'-[(hexyloxy) carbonyl] carbamimidoyl] phenyl) amino]methyl]-1-methyl-lH-benzimidazol-5-yl]carbonyl] (2-pyridinylamino) propionate was dissolved in acetone at about 35-60 °C and a solution of methane sulfonic acid in 100ml of acetone was added in 30-60 min. The reaction mass was cooled to about 25-30°C for 2 hours. The crude product was filtered and washed with 100ml of acetone and dried at 45-50 °C in vacuum tray drier to get 48 gm of title compound.
Example 7: Preparation of N-[2-(4-Amidinophenylaminomethyl)-1-methyl-lH-benzimidazol-5-ylcarbonyl]-N-(2-pyridyl)-beta-alanine ethyl ester HCl

Dissolved 100 gms of [(3-[N-2-(4-Cyanophenylaminomethyl)-1-methyl-lH-benzimidazol-5-ylcarbonyl]-N-(2-pyridyl)aminolpropionic acid ethyl ester (207.2 mmol) in 700 ml dichloromethane and added 300 ml solution of saturated ethanolic hydrogen chloride and purged hydrogen chloride gas under stirring at about 5°C to 35°C. The reaction mass was concentrated completely under vacuum at about 45-50°C. The oily mass was dissolved in 200 ml ethanol or in a mixture of 200 ml MDC and 700 ml IPA at 25-30°C and the pH of the reaction mass was adjusted to about 8.9 by ethanolic ammonia or IPA ammonia. The reaction mass was charged in the autoclave and stirred at about 1050°C for about 5 to 8 hours. The reaction was carried out at ammonia pressure of about 2-10 kg/cm². After completion of reaction, the reaction mass was filtered, and the filtrate was concentrated to dryness. The solid was isolated using ethanol: isopropyl alcohol mixture (80 g) which was further crystallized using ethanol: isopropyl alcohol mixture to afford 75 g of the desired product.

The above reaction was also carried out in absolute ethanol using same quantity of reagents under similar condition, and isolated a much purer form of desired product after crystallization from ethanol (70-80 g).

Example 8: Preparation of N-f2-(4-Amidinophenylaminomethyl)-1-methyl-lH-benzimidazol-5-ylcarbonyl]-N-(2-pyridyl)-beta-alanine ethyl ester HCl

[(3-[N-2-(4-Cyanophenylaminomethyl)-1-methyl-lH-benzimidazol-5-ylcarbonyl]pyridin-2-ylamino]propionic acid ethyl ester (100 gm) was dissolved in dichloromethane (300 ml), and cooled to 0-5°C. Saturated ethanolic hydrogen chloride solution (35%, 1200 ml) was slowly added to it, and reaction mixture was stirred at 15-20°C for 30-35 hours. The reaction mass was concentrated under vacuum, maintaining temperature 30-35°C, and stripped out twice with ethanol (200 mL). The oily mass was dissolved in ethanol (400 ml), cooled to 0-5°C, and pH was adjusted to 8.5-9.5 using 10% ethanolic ammonia (300-400 mL). The reaction mass was stirred at 25-30°C for 12-16 hours, and completion of reaction was monitored by HPLC. The reaction mass was filtered, and the solid was refluxed twice with ethanol (400 mL), and filtered at ambient temperature. The combine filtrate was concentrated to dryness, and re-dissolved in ethanol (700 mL). Ethyl acetate (800 mL) was slowly added under stirring to get a solid which was collected by filtration, washed with a mixture of ethanol and ethyl acetate, and dried in oven at 50-60°C for 12 h to get the desired product (80 g). The HPLC purity of the product was 98.0%.

Example 9: Preparation of i-{ffHexyloxy)carbonylloxy]-IH-1,2,3-benzotriazole, compound of formula IX
IH-1,2,3-Benzotriazol-1-ol 100 gm, dissolved in 1 L of dichloromethane, was treated with 184 gm of n-hexylchloroformate in presence of 187 gm of triethyl amine at 5-35 °C. After stirring for about 12 hours, reaction mass was quenched in saturated aq ammonium chloride solution. The organic layer was separated and the aqueous layer was washed and extracted with 200 ml methylene chloride. The combined organic layer was washed with 200 ml water twice. Organic layer was distilled off, and the residue was triturated with 1 L of diisopropyl ether, stirred at room temperature for 1 hr. The solid was filtered, and dried under vacuum at 25-50°C. The crude solid was crystallized using ethanol and diisopropyl ether 1:1 mixture to get the desired compound (80 g).

**Example 10: Preparation of Dabigatran etexilate, compound of formula I**

Dissolved 50 gms of N-[2-(4- Amidinophenylaminomethyl)-1-methyl- lH-benzimidazo 1-5-yIcarbonyl]-N-(2-pyridyl)-beta-alanine ethyl ester HC1 in to the mixture of 850 ml of Acetone and 350 ml of water. A solution of 38.6 gm of potassium carbonate in water (150 ml) was added at 0-30°C. A solution of 49 gm of above prepared l-[(Hexyloxy)carbonyloxy]-lH-1,2,3-benzotriazole, compound of formula IX in 150 ml acetone was added, and stirred the reaction mass at about 0-30°C. After completion of the reaction, the solid was filtered, washed with acetone water, and dried at about 50-55°C to get 55 gm of title compound.

The above preparation was also carried out using n-hexylchloroformate under above reaction condition.

**Example 11: Preparation of Dabigatran etexilate, compound of formula I**

N-[2-(4- Amidinophenylaminomethyl)-1-methyl- lH-benzimidazol-5-yIcarbonyl]-N-(2-pyridyl)-beta-alanine ethyl ester HC1 (50 g) was dissolved into a mixture of 850 ml of acetone and 350 ml of water. A solution of 38.6 gm of potassium carbonate in 150 ml of water was slowly added at 0-30 °C, followed by addition of 22 g of n-hexylchloroformate in 50 ml of acetone, and the reaction mixture was stirred at 0-30 °C for 4-5 h. Progress of the reaction was monitored by HPLC (for consumption of starting material), and additional calculated quantity of n-hexylchloroformate mixed with acetone was added if significant quantity (more than 2%) of starting material was left un-reacted. The precipitated product was filtered, washed with a mixture of acetone and water, and dried at 50-55 °C to get the desired product (55 g). The isolated crude product was purified by stirring with a mixture of acetone and water (8:8 vol), followed by 1-2 re-crystallizations from ethyl acetate: ethanol (7: 0.3 vol.) to get the desired product, having HPLC purity 99.7%.

**Example 12: Preparation of Dabigatran etexilate, compound of formula I**
N-[2-(4-Amidinophenylaminomethyl)-1-methyl-1H-benzimidazol-5-ylcarbonyl]-N-(2-pyridyl)-beta-alanine ethyl ester HC1 (50 g) was dissolved into a mixture of 850 ml of acetone and 350 ml of water. A solution of 51.5 gm of potassium carbonate dissolved in 300 ml of water was slowly added at 0-30 °C, followed by addition of 42.86 g of n-hexylchloroformate in 300 ml of acetone, and the reaction mixture was stirred at 0-30 °C for 0-4 hours. If required additional quantity of n-hexylchloroformate mixed with acetone and potassium carbonate in water was added if unreacted starting material was more than 3.0%. The precipitated product was filtered, washed with water to obtain a crude compound of formula I with HPLC purity of 92.5%; compound of formula X-1.26%; compound of formula XV-0.84%. The crude compound was purified with a mixture of acetone and water (10vol:10vol), followed by crystallization by a mixture of Ethyl acetate: Acetone (7.0vol: 3.0 vol) to get the desired product, having HPLC purity 99.7%; compound of formula X-0.01%; compound of formula XV-0.01%.

Example 13: Preparation of Hexyl phenyl carbonate
Phenol (100 gm) was dissolved in 100 ml of dichloromethane, and treated with 262 gm of ri-hexyl chloro carbonate in presence of triethyl amine (268.0 g) at 0-35 °C. After stirring for about 6 hours, the reaction mass was quenched in saturated aq ammonium chloride solution. The organic layer was separated, and aqueous layer was extracted with 200ml methylene chloride. The combined organic layer was washed with 200 ml water twice. The organic layer was concentrated, and the residue was added with 1000 ml diisopropyl ether, and stirred at room temperature. The solid was filtered, washed and dried under vacuum at 25-50 °C and recrystallized from a mixture of ethanol and diisopropyl ether to get the desired compound (60-75 g).

Example 14: Preparation of l-[[{(Hexyloxy) carbonyl oxy} pyrrolidine-2,5-dione:]
1-Hydroxypyrrrolidine-2,5-dione 100 gm was treated with 215 gm n-hexyl chloro carbonate in presence of triethyl amine (220 gm) in dichloromethane (1000 ml). The reaction was carried out at about 0-35 °C. After completion of reaction, the reaction mass was quenched in sat. aq ammonium chloride solution. The organic layer was separated, and the aqueous layer was extracted with 200ml methylene chloride. The combined organic layer was washed with 200 ml water twice. The organic layer was concentrated to get a residue which was triturated with 1000 ml of diisopropyl ether at room temperature, and filtered to get the desired solid (70-80 g).

Example 15: Preparation of Dabigatran etexilate mesylate
Ethyl 3-[[2-[[4-[[N'-{(hexyloxy) carbonyl} carbamimidoyl} phenyl] amino]methyl]-1-methyl-1H-benzimidazol-5-yl]carbonyl] (2-pyridinyl)amino] propionate (50 g), was suspended in ethyl acetate (1250
ml) at 35-60 °C, and heated to 75-80 °C to get a clear solution. The reaction mass was filtered in hot (50-55 °C), cooled to 30-35 °C, and methane sulfonic acid (7.50 g) dissolved in 50 ml (1.0 vol) of ethyl acetate was added slowly at 30-35 °C. The reaction mixture was stirred at this temperature for 2-3 h. The precipitate was filtered, and washed with ethyl acetate. The wet cake was suspended in methyl tertiary butyl ether (250 ml), and stirred for 30 min at 25-30 °C. The solid was filtered and washed with methyl tertiary butyl ether, and sucked-dried under vacuum. The solid was dried under vacuum in oven at 45-50 °C for 8-10 h to get 48 gm of the title compound with HPLC purity of 99.8%.

**Example 16: Preparation of compound of formula X**

Ethyl 3-(2-(((4-cyanophenyl)amino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo[d]imidazole-5-carboxamido)propanoate (5.0 g) was dissolved in EtOH-HCl (50 ml), and stirred in a closed flask at room temperature for 36 h. The reaction mass was concentrated, and stripped twice with ethanol. The residue was added with EtOH-NH₃, and stirred in a closed flask for 15 hours. After completion of reaction, the reaction mass was concentrated to get a residue. The residue was refluxed with dichloromethane (25 ml), cooled and filtered. The filtrate was concentrated, and the residue was triturated with ethanol to get a solid which was filtered to get a desired solid (2.7 g). This solid was dissolved in DMF (20 ml), and cooled to 0-5 °C. Triethyl amine (1.04 g) was added, and the reaction mass was stirred for 30 min. A solution of n-hexylchloroformate in DMF (2 ml) was slowly added, and the reaction mass was stirred for 2 hours. After completion of the reaction, the reaction mass was poured over ice-water, stirred, and extracted with dichloromethane. After drying, the solvent was evaporated to get a viscous liquid which was purified by prep-HPLC to get a 90% pure desired compound.

**Example 17: Preparation of compound of formula XI**

(E)-ethyl 3-(2-(((4-((N-(hexyloxy)carbonyl)carbamimidoyl)phenyl)amino)methyl)-1-methyl-N-(pyridin-2-yl)-1H-benzo[d]imidazole-5-carboxamido)propanoate methanesulfonate (2.0 g) was suspended in 15 ml water, and heated at 55-60 °C for 48 hours. After completion of reaction, the mass was cooled to r.t., and filtered. The solid was washed with water, dried, and triturated with n-hexane to get the desired compound (1.2 g).

**Example 17: Preparation of compound of formula XV**

To a solution of 2.8gm of 3-[[2-[[4-([hexyloxy]carbonyl] amino)methanimidoyl](phenyl)amino)methyl]-1-methyl-IH-1,3-benzodiazol-5-yl]-N-(pyridin-2-yl)formamido} propanoic acid in 14ml of dimethyl formamide, 0.95gm of 1.1' -carbonyldimidazole at 20-25°C was added under stirring. The mixture was stirred for 15-20 min and 1.12gm of ammonium carbonate was added and heated to 35-
40°C for 4 hours. 1.12gm of ammonium carbonate was added in three lots at 4.0 hours interval. To the above reaction mass 50ml water was added and extracted with ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution followed by 20ml brine solution. The organic layer was concentrated under vacuum and precipitated with diisopropyl ether. The solid obtained was filtered and dried at 50°C to get 1.2gm of product. Mass M+: 599.39 and 1HNMR (300MHz, DMSO-d6) δ: 0.86 (3H, t), 1.28 (6H, qt), 1.57 (2H, qu), 2.50 (2H, t), 3.76 (3H, s), 3.94-3.96 (2H, t), 4.14 (2H, t), 4.58 (2H, s), 6.74-6.84 (2H, d), 6.97-7.16 (1H, d), 7.11-7.16 (2H, d), 7.37-7.40 (1H, d), 7.47 (1H, s), 7.55-7.57 (1H, t), 7.78-7.80 (2H, d), 8.28 (1H, d).

**Example 18: Preparation of f(3-fN-f2-(4-Cyanophenylaminomethyl)-1-methyl-IH-benzimidazol-5-ylcarbonyl pyridin-2-ylaminol propionic acid ethyl ester:**

In a clean and dry 4-neck round bottom flask fitted with reflux condenser, overhead stirrer, thermowell pocket kept in a water bath a mixture of solvent methylene chloride and dimethyl formamide [(4-cyanophenyl)amino] acetic acid (125gm) was added and cooled the reaction mixture to 20-25°C followed by the addition of 1,1'-Carbonyldiimidazole (CDI) (15gm). The reaction mixture was maintained for 1 hour and the temperature was raised to 35-40°C. To this a solution of Ethyl 3-[[3-amino-4-(methylamino)benzoyl][pyridin-2-yl]amino]propanoate (200gm) in 600ml (3.0 volume) methylene chloride was added at 18-22°C. The reaction mixture was maintained at 35-40°C for 6 hours. After completion of the reaction, water was added and organic layer was separated. The solvent was distilled out and to the degassed mass a mixture of (2:1) glacial acetic acid and ethyl acetate was added and maintained at 75-80°C for 6 hours. After the reaction the product was extracted with methylene chloride and basified with aqueous ammonia (25%) solution and distilled out methylene chloride and isolated crude in ethyl acetate: acetone mixture. The isolated crude was purified with a mixture of solvent methanohethyl acetate followed by acetone:ethyl acetate and finally with Industrial solvent to get [f(3-N-[2-(4-cyanophenylaninomethyl)]-1-methyl- IH-benzimidazol-5 -ylcarbonyl[pyridin-2-ylamino] propionic acid ethyl ester with purity 99.80% by HPLC with yield 75-85% w/w.
We claim

1. A process for the preparation of dabigatran etexilate, a compound of Formula I or a salt thereof

   \[
   \text{Formula I}
   \]

   in a purity of at least 99.0% and wherein the level of compound of formula X and XV is less than 0.15% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof, as determined by HPLC

   \[
   \text{Formula X} \quad \text{Formula XV}
   \]

   comprising

   (a) subjecting a crude compound of formula I to treatment with alkyl acetate and ketone to form a reaction mixture;

   (b) optionally heating the reaction mixture; and

   (c) isolating the compound of Formula I.

2. A process as claimed in claim 1 wherein the ketone is selected from the group consisting of acetone, butanone and pentanone.

3. A process as claimed in claim 1 wherein the alkyl acetate is selected from the group consisting of ethyl acetate, propyl acetate and butyl acetate.

4. A process as claimed in claim 1 further comprising
a. reacting the compound of formula I with methanesulfonic acid to form dabigatran etexilate mesylate, compound of formula IA; and
b. isolating the dabigatran etexilate mesylate, compound of formula IA from methyl tert-butyl ether.

5 5. A compound of formula XV.

6. Dabigatran etexilate mesylate wherein the level of compound of formula X and XV

7. Formula X

8. Formula XV.

is less than 0.15% w/w relative to the amount of dabigatran etexilate, a compound of Formula I or salt thereof as determined by HPLC.