Abstract:

Disclosed herein are novel, commercially viable and industrially advantageous processes for the preparation of Dabigatran or a salt thereof, in high yield and purity, using novel intermediate compounds.

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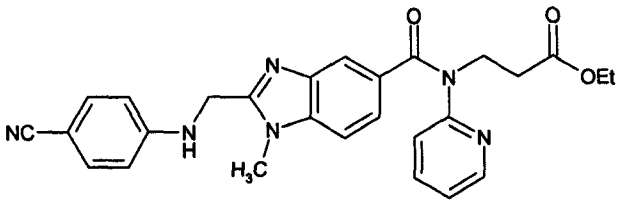
We claim:

1. A process for the preparation of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:



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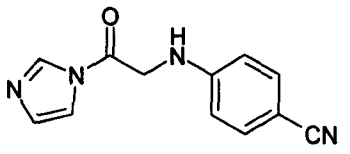
or an acid addition salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



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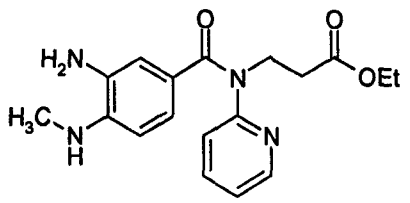
or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



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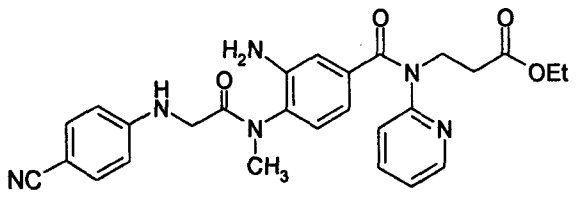
or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III:



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or an acid addition salt thereof;

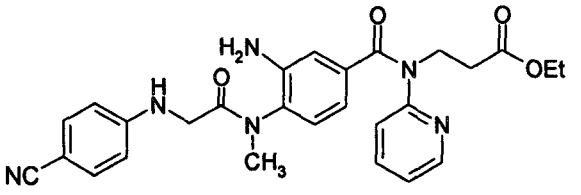
b) reacting the compound of formula III with a suitable reagent to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base.

2. The process of claim 1, wherein the reaction in steps-(a) and (b) is, each independently, carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof; wherein the reaction in step-(a) is carried out at a temperature of about 25°C to the reflux temperature of the solvent used; wherein the reagent used in step-(b) is an acid selected from the group consisting of an organic acid, an inorganic acid or a combination thereof; and wherein the reaction in step-(b) is carried out at a temperature of about 35°C to the reflux temperature of the solvent used.

3. The process of claim 2, wherein the reaction inert solvent used in steps-(a) and (b) is, each independently, selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof; wherein the reaction in step-(a) is carried out at the reflux temperature of the solvent used; wherein the acid used in step-(b) is selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, 4-hydroxybenzoic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof; and wherein the reaction in step-(b) is carried out at the reflux temperature of the solvent used while removing the water formed during the reaction.

4. The process of claim 3, wherein the reaction inert solvent used in step-(a) is dichloromethane; wherein the reaction inert solvent used in step-(b) is toluene; and wherein the acid used in step-(b) is acetic acid.

5. A process for the preparation of 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III:



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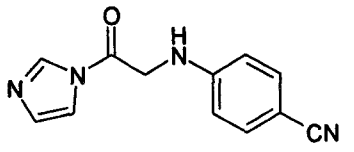
or an acid addition salt thereof, comprising reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



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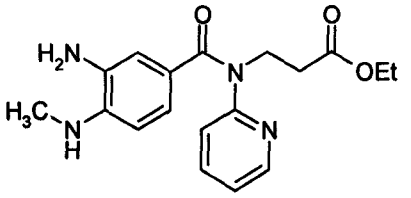
or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



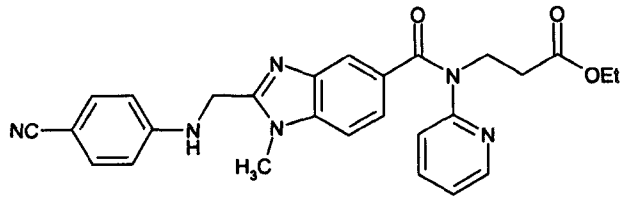
---------- VII

or an acid addition salt thereof to produce the compound of formula III or an acid addition salt thereof.

6. The process of claim 5, wherein the reaction is carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof; and wherein the reaction is carried out at a temperature of about 25°C to the reflux temperature of the solvent used.

7. The process of claim 6, wherein the reaction inert solvent is dichloromethane; and wherein the reaction is carried out at the reflux temperature of the solvent used.

8. A process for the preparation of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:



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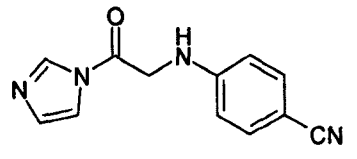
or an acid addition salt thereof, comprising reacting 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III or an acid addition salt thereof with a suitable reagent to produce the compound of formula VIII or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base.

9. The process of claim 8, wherein the reagent used is an acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, 4-hydroxybenzoic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof; and wherein the reaction is carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof.

10. The process of claim 9, wherein the acid used is acetic acid; and wherein the reaction inert solvent is toluene.

11. A process for the preparation of 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile of formula II:



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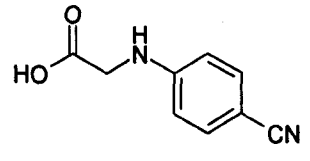
or an acid addition salt thereof comprising reacting N-(4-Cyanophenyl)-glycine of formula XI:



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or an acid chloride derivative, or an acid anhydride derivative thereof,

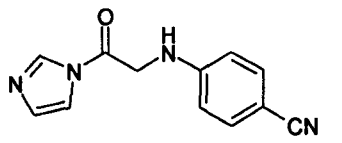
with carbonyldiimidazole in a suitable solvent to produce the 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile of formula II or an acid addition salt thereof.

12. The process of claim 11, wherein the reaction is carried out in the presence of a reaction inert solvent selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof; and wherein the reaction is carried out at a temperature of about 25°C to the reflux temperature of the solvent used.

13. The process of claim 12, wherein the reaction inert solvent is dichloromethane; and wherein the reaction is carried out at the reflux temperature of the solvent used.

14. A process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



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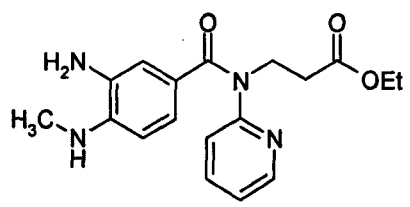
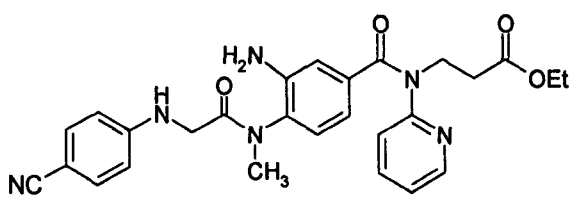
or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



---------- VII

or an acid addition salt thereof, to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III:



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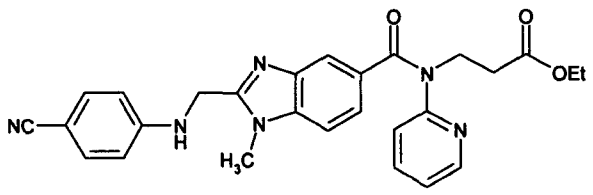
or an acid addition salt thereof;

b) reacting the compound of formula III with a suitable reagent to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:



---------- VIII

or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base; and

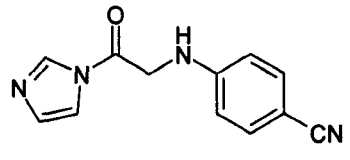
c) converting the compound of formula VIII obtained in step-(b) into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof.

15. The process of claim 14, wherein the reagent used in step-(b) is an organic or inorganic acid selected from the group consisting of hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, 4-hydroxybenzoic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof; and wherein the reaction in step-(b) is carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof.

16. The process of claim 15, wherein the reagent used in step-(b) is acetic acid; and wherein the reaction inert solvent used in step-(b) is toluene.

17. A process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



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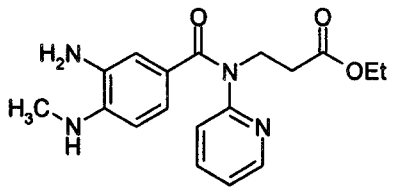
or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



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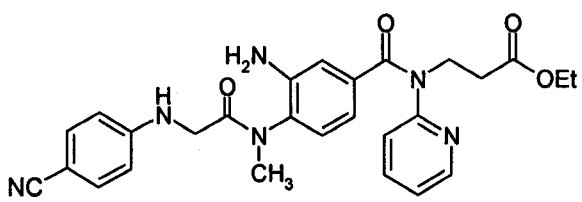
or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III:



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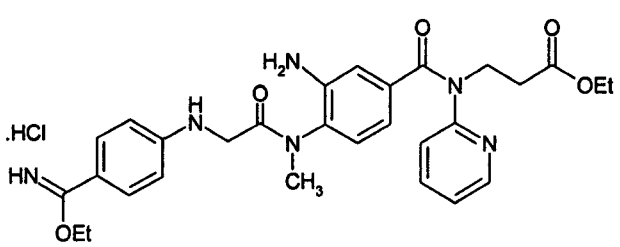
or an acid addition salt thereof;

b) reacting the compound of formula III or an acid addition salt thereof with a suitable reagent to produce 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



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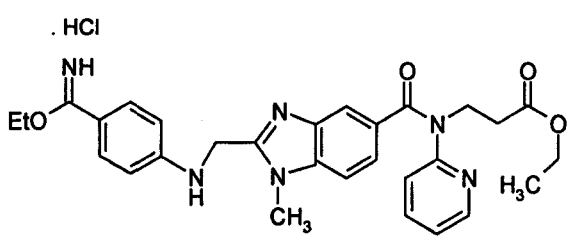
c) reacting the compound of formula IV with a suitable reagent to produce 1-methyl-2-[N-(4-ethoxyimidoylphenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IX:



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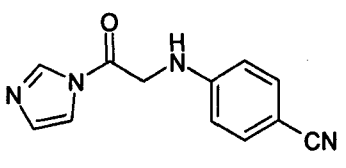
d) converting the compound of formula IX obtained in step-(c) into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof.

18. The process of claim 17, wherein the reagent used in step-(b) is ethanolic-HCl; wherein the reagent used in step-(c) is an organic or inorganic acid; and wherein the reaction in step-(c) is carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof.

19. The process of claim 18, wherein the reagent used in step-(c) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, or a combination thereof; and wherein the reaction inert solvent used in step-(c) is selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof.

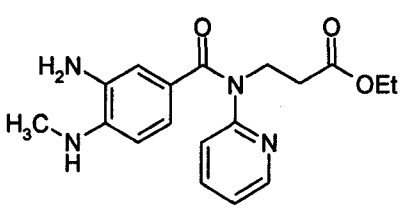
20. A process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



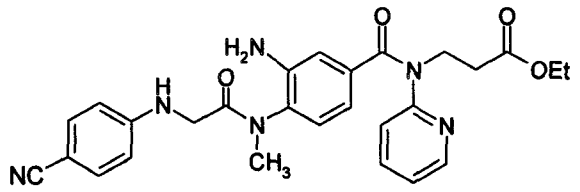
——— II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



——— VII

or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III:



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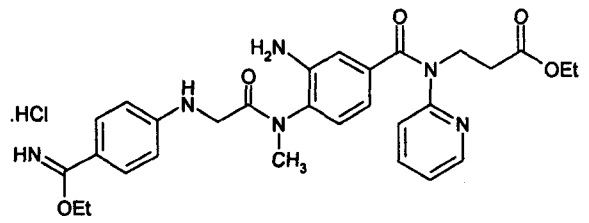
or an acid addition salt thereof;

b) reacting the compound of formula III or an acid addition salt thereof with a suitable reagent to produce 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



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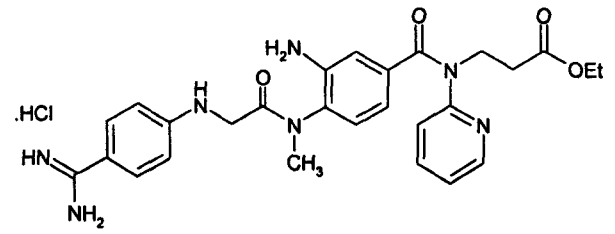
c) reacting the compound of formula IV with a suitable reagent in a solvent to produce 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula V:



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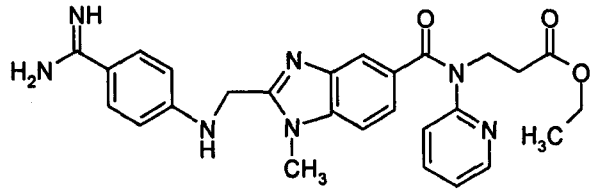
d) reacting the compound of formula V with a suitable reagent to produce 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (Dabigatran) of formula X:



---------- X

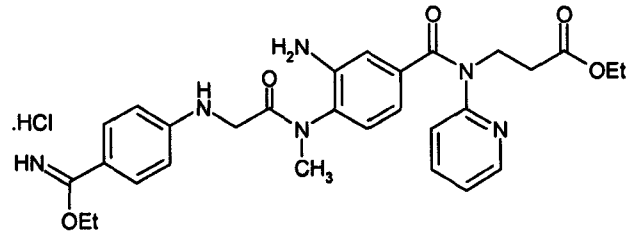
or an acid addition salt thereof; and

e) optionally converting the compound of formula X or an acid addition salt thereof obtained in step-(d) into Dabigatran etexilate or a pharmaceutically acceptable salt thereof.

21. The process of claim 20, wherein the reagent used in step-(c) is ethanolic ammonia or ammonium carbonate; wherein the solvent used in step-(c) is ethanol; and wherein the reagent used in step-(d) is an organic or inorganic acid.

22. The process of claim 21, wherein the reagent used in step-(d) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, or a combination thereof.

23. A process for the preparation of 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino) acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



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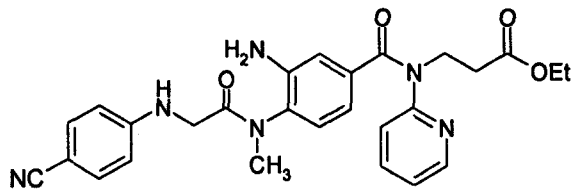
comprising reacting the compound of formula III:



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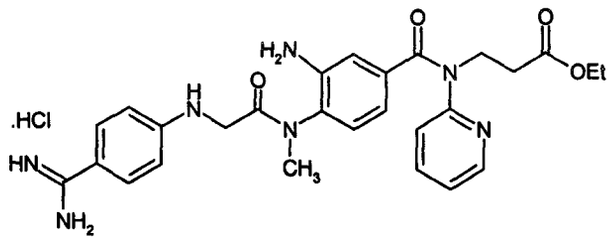
or an acid addition salt thereof with a suitable reagent to produce the compound of formula IV.

24. The process of claim 23, wherein the reagent used is ethanolic-HCl.

25. A process for the preparation of 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula V:



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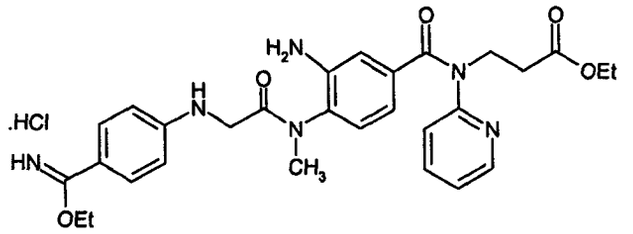
comprising reacting 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:

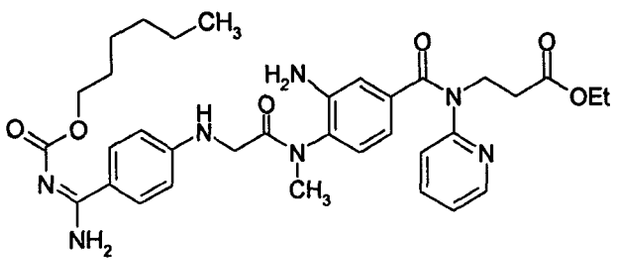


---------- IV

with a suitable reagent to produce the compound of formula V.

26. The process of claim 25, wherein the reagent used is ethanolic ammonia or ammonium carbonate.

27. A process for the preparation of 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonyl amidino)phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VI:



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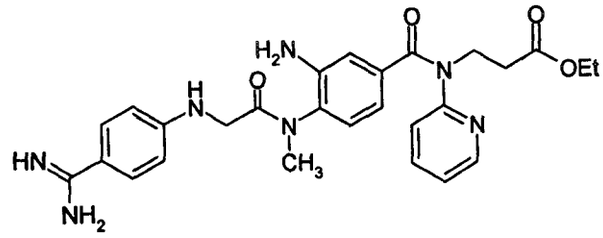
or an acid addition salt thereof, comprising reacting 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula Va:



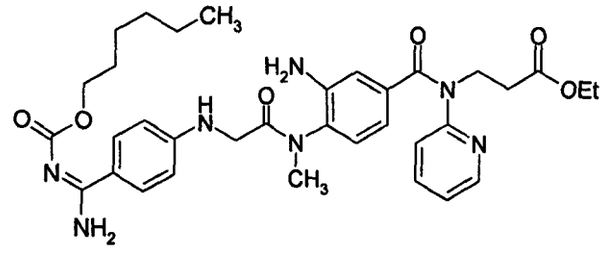
---------- Va

or an acid addition salt thereof with n-hexylchloroformate or n-hexyl 1H-imidazole-1-carboxylate in the presence of a suitable base to produce the compound of formula VI or an acid addition salt thereof.

28. The process of claim 27, wherein the reaction is carried out in the presence of a reaction inert solvent comprising water, an alcohol, a ketone, and mixtures thereof; wherein the base used is an inorganic base selected from the group comprising hydroxides, alkoxides, bicarbonates and carbonates of alkali or alkaline earth metals.

29. The process of claim 28, wherein the base is sodium carbonate or potassium carbonate.

30. A process for the preparation of Dabigatran etexilate or a pharmaceutically acceptable salt thereof, comprising reacting 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonyl amidino)phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula VI:



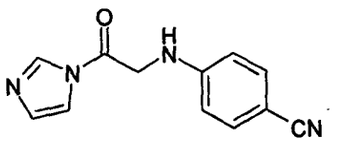
---------- VI

or an acid addition salt thereof with a suitable reagent to produce Dabigatran etexilate or a pharmaceutically acceptable salt thereof.

31. The process of claim 30, where in the reagent used is an organic or inorganic acid; and wherein the reaction is carried out in the presence of a reaction inert solvent selected from the group consisting of a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof.

32. The process of claim 31, where in the reagent used is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof; and wherein the reaction inert solvent is dichloromethane.

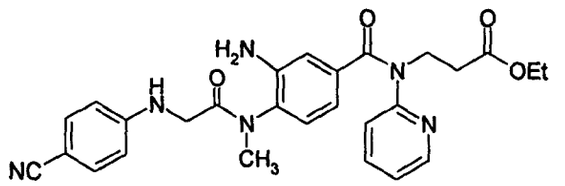
33. A compound, 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



---------- II

or an acid addition salt thereof.

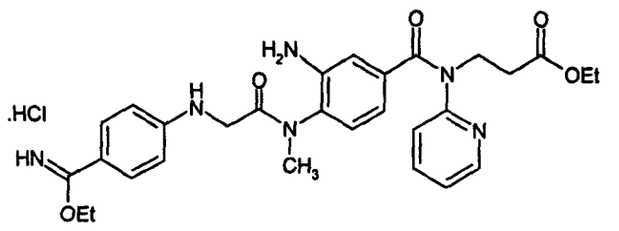
34. A compound, 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula III:



---------- III

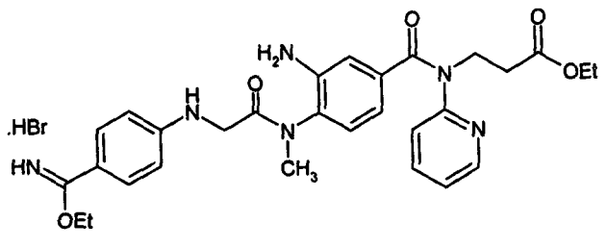
or an acid addition salt thereof.

35. A compound, 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



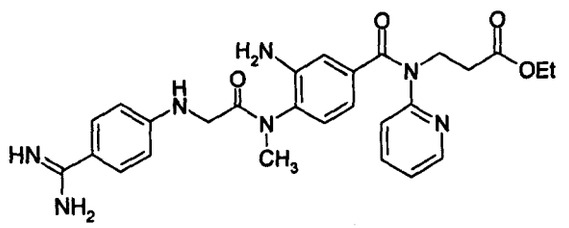
---------- IV

36. A compound, 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrobromide salt, of formula IVa:



---------- IVa

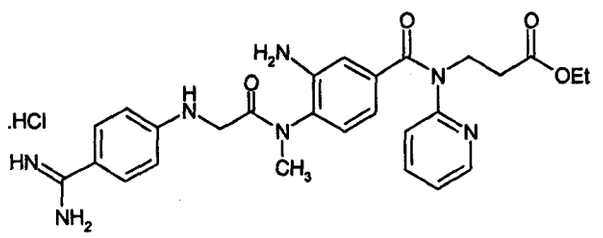
37. A compound, 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula Va:



---------- Va

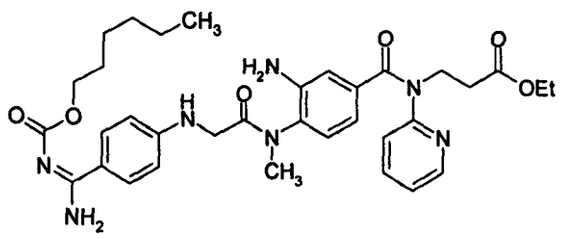
or an acid addition salt thereof.

38. A compound, 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt, of formula V:



---------- V

39. A compound, 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino)phenylamino] acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula VI:



---------- VI

or an acid addition salt thereof.

40. Use of the compounds of formulae II, III, IV, IVa, V, Va and VI, or an acid addition salt thereof, in the preparation of Dabigatran, or Dabigran etexilate, or a pharmaceutically acceptable salt thereof.

41. The compound of any one of claims 33, 34, 37 and 39, wherein the acid addition salt of the compounds of formulae II, III, Va and VI is selected from the group consisting of hydrochloride, hydrobromide, dihydrochloride, dihydrobromide, sulphate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, citrate and tartrate.

42. The compound of any one of claims 33, 34, 37 and 39, wherein the acid addition salt of the compounds of formulae II, III, Va and VI is hydrochloride.

43. Solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt.

44. The solid state form of Claim 43, characterized by a powder X-ray diffraction pattern having peaks at about 7.73, 9.0, 10.07, 11.74, 12.07, 12.77, 15.48, 16.30, 16.67, 17.38, 17.74, 18.14, 18.37, 19.17, 19.52, 20.37, 20.86, 21.83, 23.53, 24.27, 24.99, 25.77, 26.77 and 27.14 ± 0.2 degrees 2-theta substantially in accordance with Figure 1.

Dated this Third (3rd) day of March 2014

(Signed)_____

SURESH REDDY VELAGALA
Dy. General Manager - IPM
SYMED LABS LIMITED

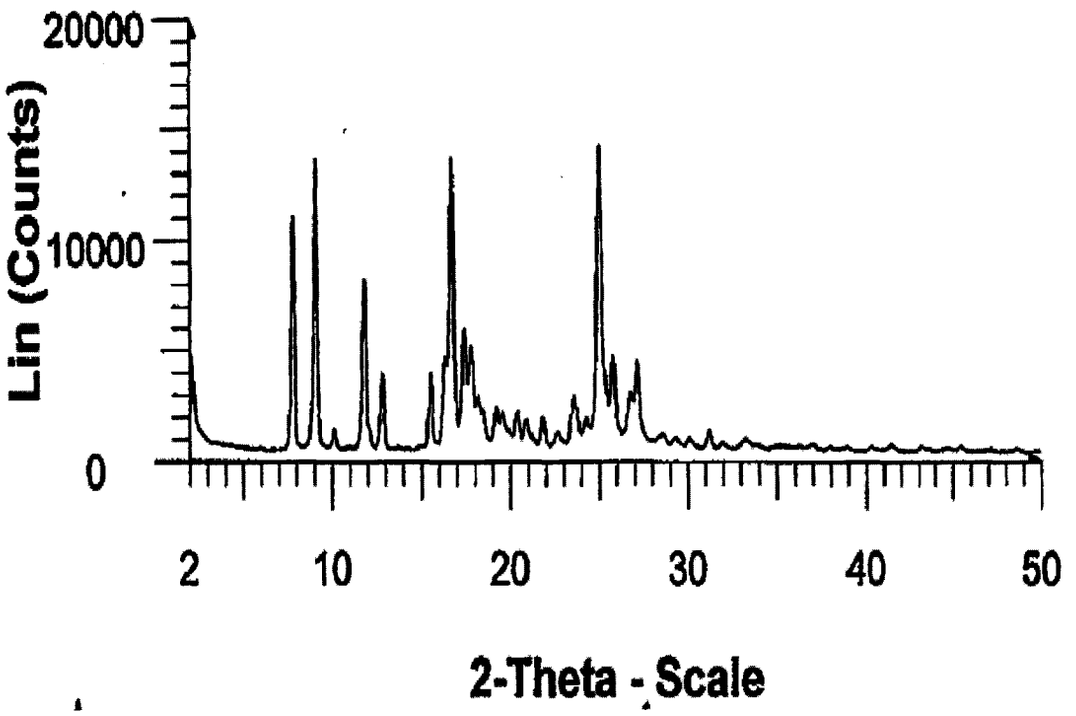


Figure 1: Powder X-ray diffraction (XRPD) pattern of solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt

Dated this Third (3rd) day of March 2014

(Signed)_____

SURESH REDDY VELAGALA
Dy. General Manager - IPM
SYMED LABS LIMITED

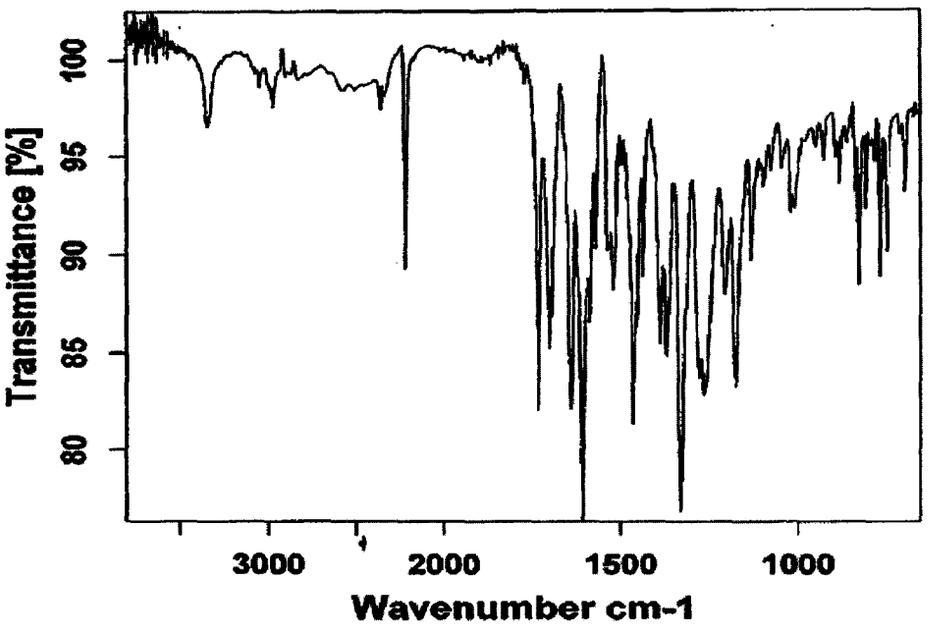


Figure 2: Infra-red (IR) spectrum of solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt

Dated this Third (3rd) day of March 2014

(Signed)_____

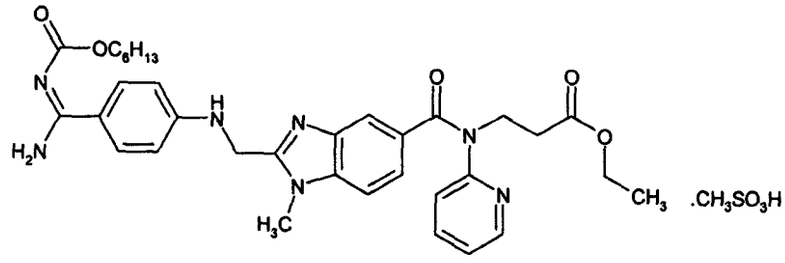
SURESH REDDY VELAGALA
Dy. General Manager - IPM
SYMED LABS LIMITED

FIELD OF THE INVENTION

The present invention relates to novel, commercially viable and industrially advantageous processes for the preparation of Dabigatran or a salt thereof, in high yield and purity, using novel intermediates.

BACKGROUND OF THE INVENTION

U.S. Patent No. 6,087,380 (hereinafter referred to as the US'380 patent) discloses a variety of disubstituted bicyclic heterocycle derivatives and their pharmaceutically acceptable salts, processes for their preparation, pharmaceutical compositions comprising the derivatives, and methods of use thereof. These compounds have valuable pharmacological properties, particularly a thrombin-inhibiting activity and the effect of extending thrombin time, and are useful for the prophylaxis or treatment of venous and arterial thrombotic diseases such as deep leg vein thrombosis, reocclusion after a bypass operation or angioplasty, occlusion in peripheral arterial disease, pulmonary embolism, disseminated intravascular coagulation, coronary thrombosis, stroke, and the occlusion of a shunt or stent. Among them, Dabigatran etexilate mesylate, chemically named ethyl 3-[[[2-[[[4-[[[(hexyloxy)carbonyl]amino]iminomethyl]phenyl]amino]methyl]-1-methyl-1*H*-benzimidazol-5-yl]carbonyl](pyridin-2-yl)amino]propanoate mesylate salt, is a direct thrombin inhibitor indicated to reduce the risk of stroke and systemic embolism in patients with non-valvular atrial fibrillation (AF). Dabigatran etexilate mesylate is represented by the following structural formula:



Dabigatran etexilate mesylate is marketed by Boehringer Ingelheim under the brand name PRADAXA®, and it is orally administered as capsules containing 75 mg and 150 mg of Dabigatran etexilate mesylate.

The synthesis of Dabigatran etexilate was first described in the US 6087380. Various processes for the preparation of Dabigatran etexilate, its intermediates, and pharmaceutically acceptable salts thereof are apparently described in U.S. Patent Nos. US 7202368, US 7932273, US 8119810, US 8394961, US8394962, US 8399678, US 8471033; U.S. Patent Application Publications US 2006/0276513, US 2009/0042948, US2010/0087488, US 2013/116440 and US 2013/116441; PCT Patent Publications WO 2008/059029, WO 2009/111997, WO 2010/045900, WO 2011/110876, WO 2011/061080, WO 2012/004396, WO 2012/004397, WO 2012/044595, WO 2012/077136, WO 2012/152855, WO 2012/153158 and WO 2013/144903; and Journal of Medicinal Chemistry, 2002, 45(9), 1757-1766.

As per the process exemplified in Example 59, in an analogous manner to examples 25 & 26, of the US '380 patent, Dabigatran, chemically named 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide is prepared by the following sequence of reaction steps:

a) 4-methylamino-3-nitro-benzoic acid chloride is reacted with N-(2-ethoxycarbonylethyl)-2-pyridylamine in the presence of triethylamine in tetrahydrofuran solvent to produce 4-methylamino-3-nitro-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide intermediate;

b) the nitro-compound obtained in step-(a) is then hydrogenated in ethanol and dichloromethane in the presence of palladium/charcoal to produce 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide;

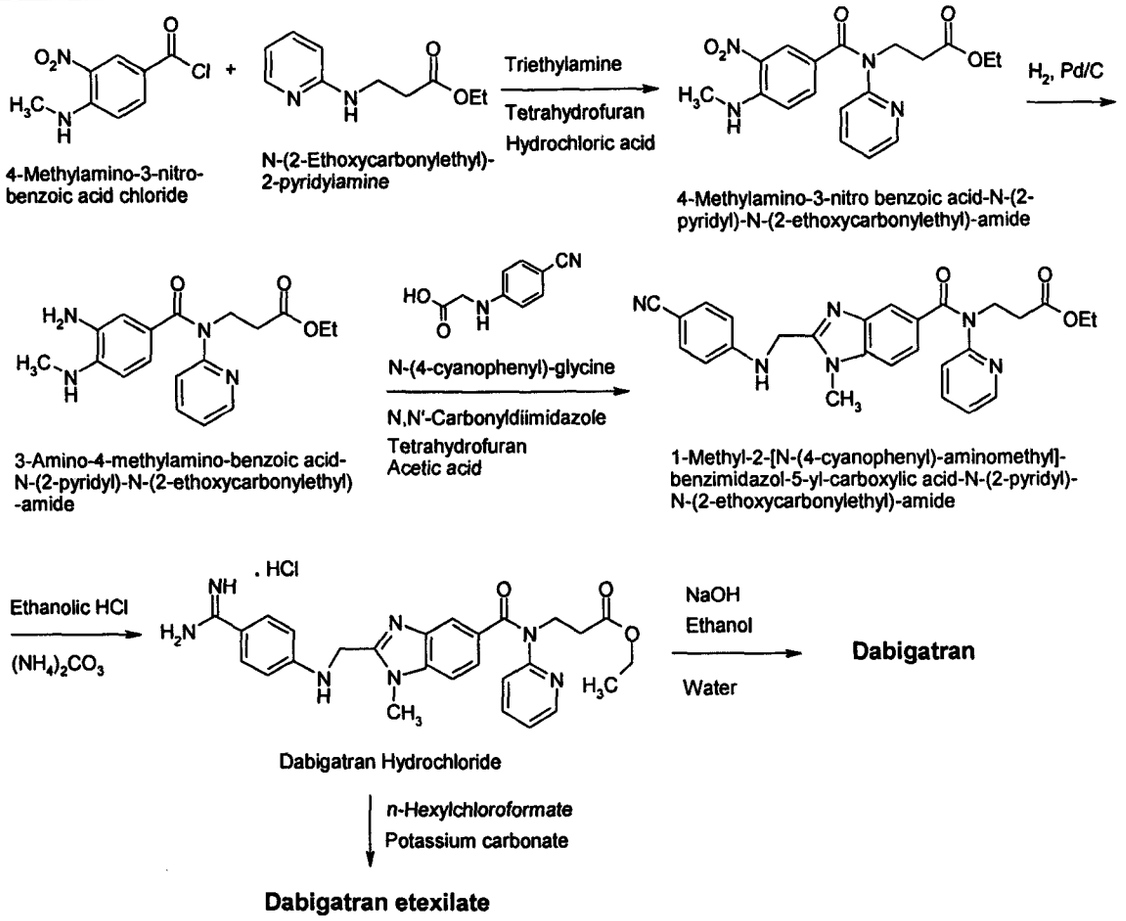
c) the amino-compound obtained in step-(b) is then condensed with N-(4-cyanophenyl)-glycine in the presence of N,N'-carbonyldiimidazole in tetrahydrofuran to produce a reaction mass, followed by treating with glacial acetic acid and then subjecting to usual work up methods and column chromatographic purifications to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (hereinafter referred to as the cyano-benzimidazole intermediate);

d) the cyano-benzimidazole intermediate obtained in step-(c) is then reacted with saturated ethanolic hydrochloric acid and subsequently with ammonium carbonate followed by usual work up and column chromatographic purifications to produce

Dabigatran hydrochloride, which is then treated with sodium hydroxide to produce Dabigatran.

The synthetic route of Dabigatran as described in the US'380 patent is shown in the below scheme-1:

Scheme-1:



As per the process exemplified in Example 113 of the US '380 patent, 1-methyl-2-[N-(4-(N-n-hexyloxycarbonylamidino)phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (Dabigatran Etexilate) is prepared, analogously to the example 90, by reacting 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl ethyl)-amide hydrochloride salt (Dabigatran hydrochloride) with n-hexyl chloroformate in the presence of potassium carbonate in a solvent medium comprising tetrahydrofuran and

water, followed by isolation using column chromatography to produce Dabigatran etexilate.

The processes for the preparation of Dabigatran, pharmaceutically acceptable salts and derivatives thereof as described in the aforementioned prior art suffer from several disadvantages such as the use of highly flammable solvents like tetrahydrofuran; use of expensive column chromatographic purifications; use of excessive amounts of corrosive organic acids like acetic acid; use of multiple solvents and in excess amounts; and use of tedious and cumbersome procedures like prolonged reaction time periods, multiple distillations and extractions, multiple isolations/re-crystallizations, and thus resulting in a poor product yield and quality. Methods involving column chromatographic purifications are generally undesirable for large-scale operations, thereby making the process commercially unfeasible.

For example, the preparation of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide as described in the prior art involves the use of 15 volumes of acetic acid with respect to 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, whereas the process of the present invention requires the use of 0.25 to 0.3 volumes of acetic acid.

The most important reaction step in the synthesis of Dabigatran as reported in the aforesaid prior art is the condensation reaction between 3-amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and N-(4-cyanophenyl)-glycine in the presence of N,N'-carbonyldiimidazole to produce the corresponding cyano-benzimidazole intermediate "1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide". The major drawback of this condensation step is that the purity of the resulting cyano-benzimidazole intermediate obtained by the prior art process is below 50% (measured by HPLC), which intern requires multiple purification steps thereby leading to the poor product yields (i.e. below about 30%).

The cyano-benzimidazole intermediate obtained by the processes described in the prior art does not have satisfactory purity (Purity by HPLC: 50%) since unacceptable amounts of impurities are formed during the condensation reaction between 3-amino-4-

methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide and N-(4-cyanophenyl)-glycine in the presence of N,N'-carbonyldiimidazole, which are persistent impurities and cannot be removed completely.

SUMMARY OF THE INVENTION

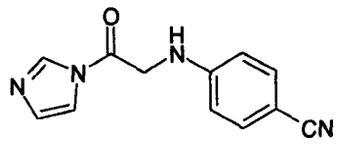
The present inventors have surprisingly and unexpectedly found that 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, which is a key intermediate in the synthesis of Dabigatran, can be prepared advantageously with high purity and with high yield, by reacting N-(4-Cyanophenyl)-glycine with Carbonyldiimidazole to produce a novel intermediate compound 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, which is then reacted with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide to produce a novel intermediate compound 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, followed by treating with a suitable reagent to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl ethyl)-amide. The novel process solves the drawbacks associated with the prior processes and is commercially viable for preparing Dabigatran and its salts or derivatives thereof.

The present inventors have further surprisingly and unexpectedly found that Dabigatran or a salt or a derivative thereof can be prepared, in high purity and with high yield, by reacting N-(4-Cyanophenyl)-glycine with Carbonyldiimidazole to produce a novel intermediate compound 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, which is then reacted with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide to produce a novel intermediate compound 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, followed by converting it into Dabigatran or salt or a derivative thereof.

In one aspect, provided herein are efficient, industrially advantageous and environmentally friendly processes for the preparation of Dabigatran and its key intermediates 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-

carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, in high yield and with high purity using novel intermediate compounds.

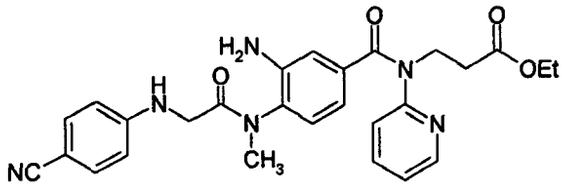
In another aspect, provided herein is a novel compound, 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



---------- II

or an acid addition salt thereof.

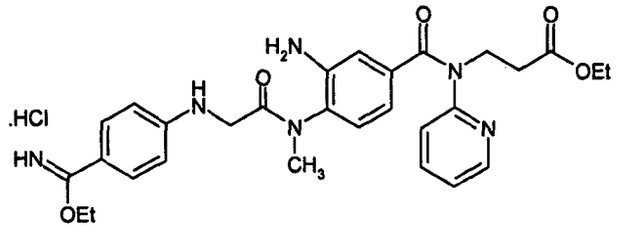
In another aspect, provided herein is a novel intermediate compound, 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula III:



---------- III

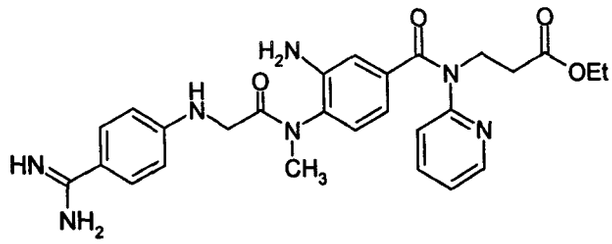
or an acid addition salt thereof.

In another aspect, provided herein is a novel intermediate compound, 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



---------- IV

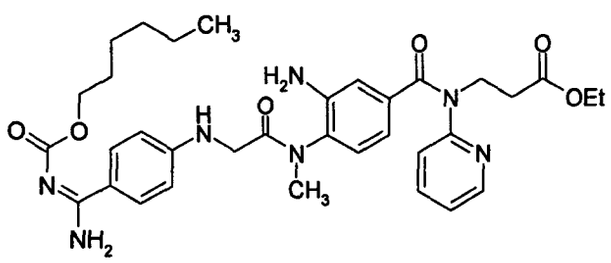
In another aspect, provided herein is a novel intermediate compound, 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula Va:



---------- Va

or an acid addition salt thereof.

In another aspect, provided herein is a novel intermediate compound, 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino) phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula VI:



---------- VI

or an acid addition salt thereof.

The processes for the preparation of Dabigatran and its intermediates disclosed herein have the following advantages over the processes described in the prior art:

i) the process involves the use of novel intermediate compounds;

ii) the overall yield of the Dabigatran and its intermediates is increased and the purity of the product is increased without additional purifications such as multiple isolations and column chromatographic purifications;

iii) the process avoids the use of highly flammable solvents like tetrahydrofuran;

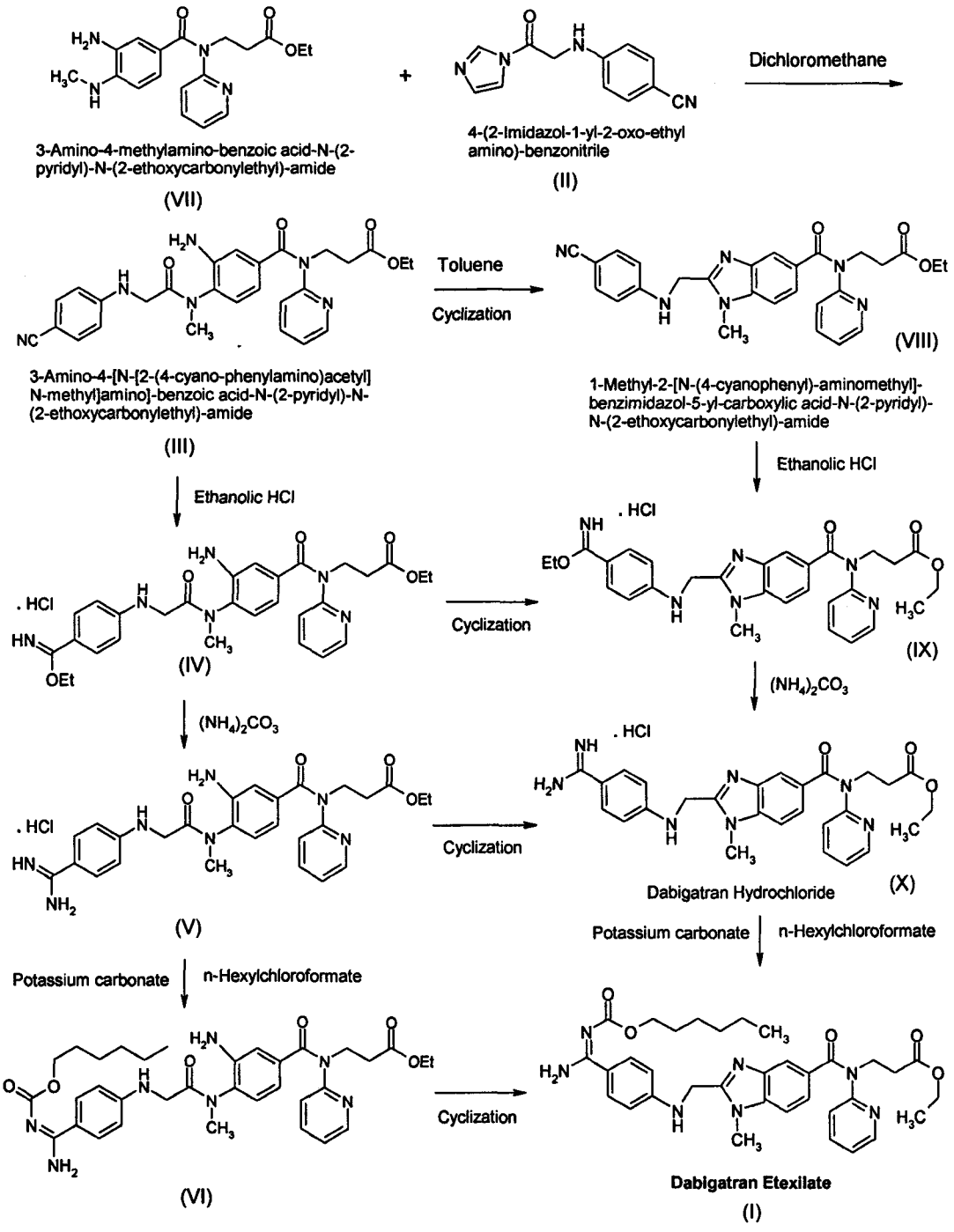
iv) the process avoids the use of excessive amounts of corrosive organic acids like acetic acid and toluenesulfonic acid;

v) the process avoids the use of additional and excess amounts of solvents, multiple isolation steps, column chromatographic purifications;

vi) the processes involve easy work-up methods and simple isolation processes, and there is a reduction in chemical waste.

The processes for the preparation of Dabigatran hydrochloride and Dabigatran etexilate using novel intermediates disclosed herein may be represented by a schematic diagram as depicted in scheme-2:

Scheme-2:



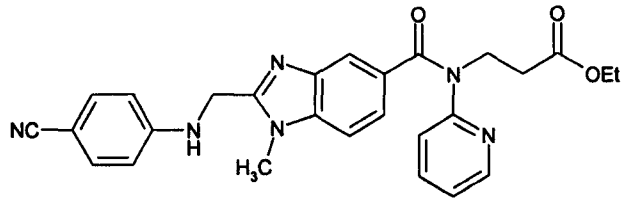
BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a characteristic powder X-ray diffraction (XRPD) pattern of solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt.

Figure 2 is a characteristic infra-red (IR) spectrum of solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt.

DETAILED DESCRIPTION OF THE INVENTION

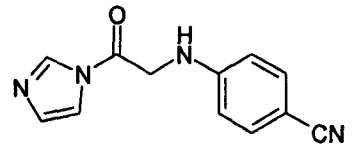
According to one aspect, there is provided a process for the preparation of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:



---------- VIII

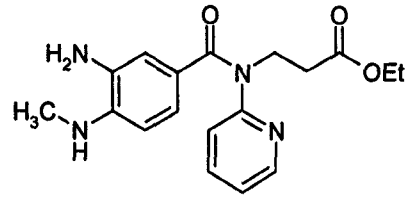
or an acid addition salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



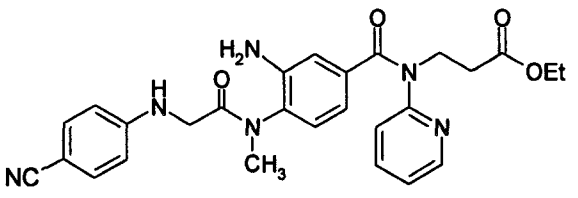
---------- II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



---------- VII

or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula III:



---------- III

or an acid addition salt thereof;

b) reacting the compound of formula III with a suitable reagent to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base.

The use of the novel intermediate compounds of formulae II and III disclosed herein for the preparation of Dabigatran and its key intermediate of formula VIII allows the products to be easily isolated with high purity and with high overall yield, thereby avoiding additional and unnecessary purification steps.

In one embodiment, the reaction in steps-(a) and (b) is, each independently, carried out in the presence of a reaction inert solvent. Exemplary inert solvents may include, but are not limited to, a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof. Specifically, the solvent used in steps-(a) and (b) is, each independently, selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof, and a most specific solvent is dichloromethane or toluene.

In another embodiment, the reaction in step-(a) is carried out at a temperature of about 25°C to the reflux temperature of the solvent used, specifically at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used. The reaction time may vary between about 2 hours to about 8 hours, and most specifically about 3 hours to about 5 hours.

The reaction mass containing the 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III or an acid addition salt thereof obtained in step-(a) may be subjected to usual work up such as a washing, a filtration, an extraction, a pH adjustment, an evaporation, a layer separation or a combination thereof. The reaction mass may be used directly in the next step to produce the compound of formula VIII, or the compound of formula III may be isolated and then used in the next step.

In one embodiment, the compound of formula III is isolated from a suitable solvent by conventional methods such as cooling, seeding, partial removal of the solvent from the solution, by adding an anti-solvent to the solution, evaporation, vacuum distillation, or a combination thereof. The solvent used to isolate the compound of formula III is selected from the group consisting of water, an alcohol, an ether, an ester, a hydrocarbon solvent, a chlorinated hydrocarbon, and mixtures thereof. Specifically, the solvent is selected from the group consisting of water, methanol, ethanol, iso-propanol, diisopropyl ether, methyl tert-butyl ether, ethyl acetate, n-pentane, cyclohexane, toluene, xylene, dichloromethane, dichloroethane, chloroform, and mixtures thereof. A most specific solvent is methanol or toluene.

In one embodiment, the reagent used in step-(b) is an acid. The acid can be an organic acid or an inorganic acid or a combination thereof.

Exemplary acids used in step-(b) include, but are not limited to, hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, 4-hydroxybenzoic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof. Specifically, the acid is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, or a combination thereof; and a most specific acid is acetic acid.

The reaction in step-(b) is carried out at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used while removing the water formed during the reaction through Dean-Stark apparatus.

In one embodiment, the acid in step-(b) is used in a ratio of about 0.15 to 1 equivalents, specifically about 0.25 to 0.5 equivalents, with respect to the compound of formula III in order to ensure a proper course of the reaction.

The reaction mass containing the compound of formula VIII or an acid addition salt thereof obtained in step-(b) may be subjected to usual work up, and then isolated and/or crystallized from a suitable solvent as per the methods described hereinabove.

The compounds of formulae III and VIII obtained in the above process steps-(a) and (b) may be collected by filtration, filtration under vacuum, decantation, centrifugation, filtration employing a filtration media of a silica gel or celite, or a combination thereof.

In one embodiment, the conversion of the acid addition salt of the compound of formula VIII into its free base is carried out by treating with a suitable base. The base used in the above conversion is an organic or inorganic base, and specifically an inorganic base. Exemplary inorganic bases include, but are not limited to, hydroxides, alkoxides, bicarbonates and carbonates of alkali or alkaline earth metals, and ammonium hydroxide. A most specific inorganic base is ammonium hydroxide. In another embodiment, the conversion is carried out in a suitable solvent selected from the group consisting of water, a chlorinated hydrocarbon solvent, a hydrocarbon solvent, and mixtures thereof. Specifically, the solvent is a mixture of water and dichloromethane.

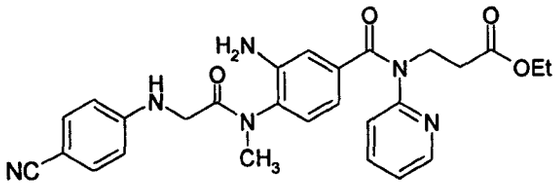
Exemplary acid addition salts of the compound of formula VIII obtained by the process disclosed herein include, but are not limited to, hydrochloride, hydrobromide, dihydrochloride, dihydrobromide, sulphate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, citrate, tartrate, and the like. A most preferred acid addition salt of the compound of formula VIII obtained by the process disclosed herein is acetate salt.

In one embodiment, the acetate salt of the compound of formula VIII obtained by the process disclosed herein is in the form of a solid state form.

According to another aspect, there is provided a solid state form of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt. In one embodiment, the solid state form of the 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt, obtained by the process

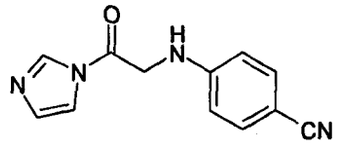
exemplified in step-3 of example 1, is a crystalline form characterized by a powder X-ray diffraction pattern having peaks at about 7.73, 9.0, 10.07, 11.74, 12.07, 12.77, 15.48, 16.30, 16.67, 17.38, 17.74, 18.14, 18.37, 19.17, 19.52, 20.37, 20.86, 21.83, 23.53, 24.27, 24.99, 25.77, 26.77 and 27.14 ± 0.2 degrees 2-theta substantially in accordance with Figure 1.

According to another aspect, there is provided a process for the preparation of 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III:



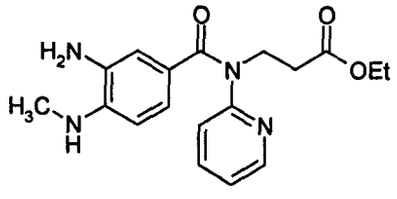
---------- III

or an acid addition salt thereof, comprising reacting 4-(2-imidazol-1-yl-2-oxo-ethyl amino)-benzonitrile, of formula II:



---------- II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:

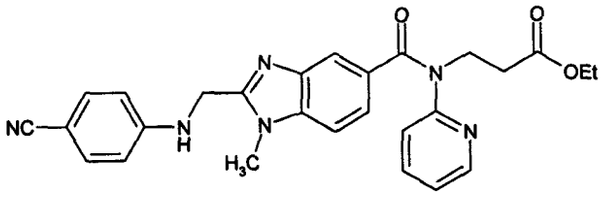


---------- VII

or an acid addition salt thereof to produce the compound of formula III or an acid addition salt thereof.

The reaction between the compound of formula II with the compound of formula VII to produce the compound of formula III is carried out by using the methods and conditions as described hereinabove.

According to another aspect, there is provided a process for the preparation of 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:

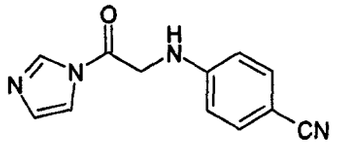


---------- VIII

or an acid addition salt thereof, comprising reacting 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl ethyl)-amide of formula III or an acid addition salt thereof with a suitable reagent to produce the compound of formula VIII or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base.

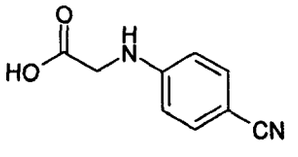
The preparation of the compound of formula VIII or an acid addition salt thereof from the compound of formula III is carried out by using the suitable reagents, methods and conditions as described hereinabove.

According to another aspect, there is provided a process for the preparation of 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile of formula II:



---------- II

or an acid addition salt thereof comprising reacting N-(4-Cyanophenyl)-glycine of formula XI:



---------- XI

or an acid chloride derivative, or an acid anhydride derivative thereof,

with carbonyldiimidazole in a suitable solvent to produce the 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile of formula II or an acid addition salt thereof.

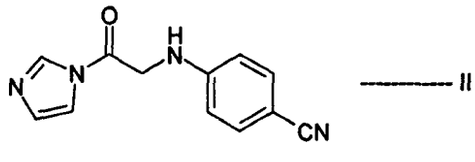
In one embodiment, the reaction between the N-(4-Cyanophenyl)-glycine of formula XI or a derivative thereof and carbonyldiimidazole is carried out in the presence of a reaction inert solvent. Exemplary reaction inert solvents may include, but are not limited to, a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof. Specifically, the reaction inert solvent is selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof. A most specific solvent is dichloromethane.

In another embodiment, the reaction between the N-(4-Cyanophenyl)-glycine of formula XI or a derivative thereof and carbonyldiimidazole is carried out at a temperature of about 25°C to the reflux temperature of the solvent used, specifically at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used.

The reaction mass containing the compound of formula II obtained above may be subjected to usual work up, and then isolated and/or crystallized from a suitable solvent as per the methods described hereinabove.

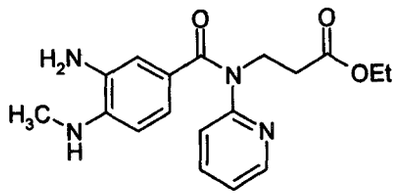
According to another aspect, there is provided a process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



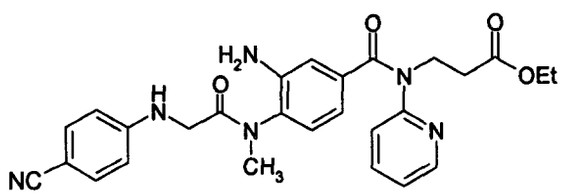
——— II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



---------- VII

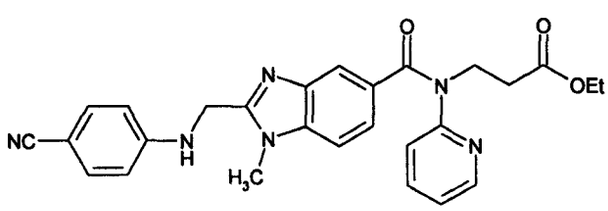
or an acid addition salt thereof, to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III:



---------- III

or an acid addition salt thereof;

b) reacting the compound of formula III with a suitable reagent to produce 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VIII:



---------- VIII

or an acid addition salt thereof, and optionally converting the acid addition salt of the compound of formula VIII obtained into its free base; and

c) converting the compound of formula VIII obtained in step-(b) into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof.

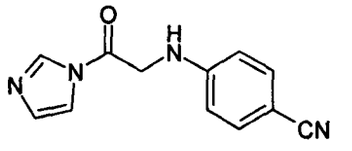
The reaction steps-(a) and (b) are carried out by using the methods, conditions and reagents as described hereinabove.

In one embodiment, the conversion of the acid addition salt of the compound of formula VIII into its free base in step-(b) is carried out by treating with a suitable base according to the methods as described hereinabove.

The conversion of the intermediate compound of formula VIII into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof in step-(c) can be carried out either as per the methods described in the prior art, for example, as per the processes described in the US Patent No. 6,087,380, or as per the processes described hereinafter.

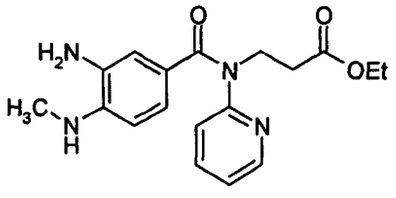
According to another aspect, there is provided a process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



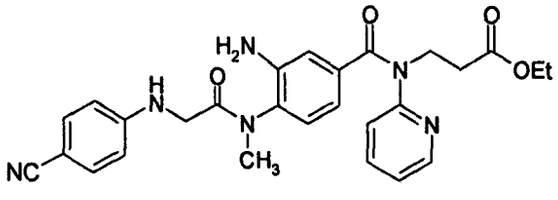
——— II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



——— VII

or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III:

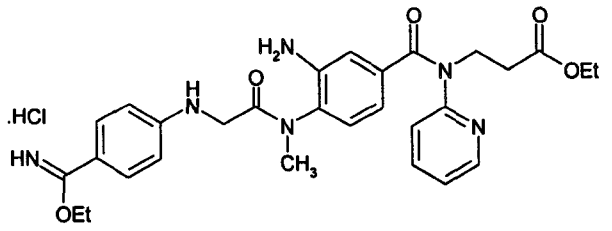


---------- III

or an acid addition salt thereof;

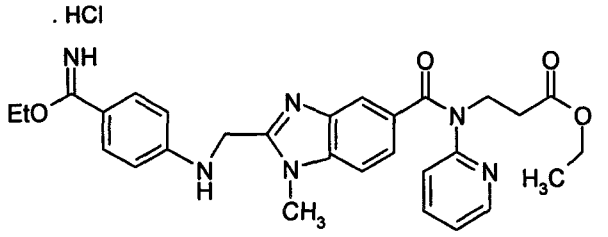
b) reacting the compound of formula III or an acid addition salt thereof with a suitable reagent to produce 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-

methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



---------- IV

c) reacting the compound of formula IV with a suitable reagent to produce 1-methyl-2-[N-(4-ethoxyimidoylphenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IX:



---------- IX

d) converting the compound of formula IX obtained in step-(c) into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof.

The reaction in step-(a) is carried out by using the methods, conditions and reagents as described hereinabove.

In one embodiment, the reagent used in step-(b) is ethanolic-HCl. In another embodiment, the reaction in step-(b) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 20°C to the 50°C, and more specifically at a temperature of about 25°C to the 35°C.

The reaction mass containing the compounds of formula IV obtained in steps-(b) may be subjected to usual work up methods as described hereinabove. The compound of formula IV obtained in step-(b) may be used directly in the next step to produce the compound of formula IX, or the compound of formula IV may be isolated by the methods described hereinabove and then used in the next step.

In another embodiment, the reagent used in step-(c) is an organic or inorganic acid selected from the group as described hereinabove. Specifically, the reagent used in step-(c) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, or a combination thereof; and a most specific acid is acetic acid.

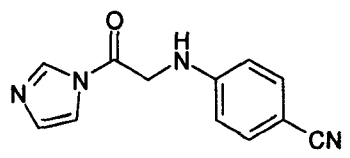
In one embodiment, the reaction in step-(c) is carried out in the presence of a reaction inert solvent such as a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof. The reaction in step-(c) is carried out at a temperature of about 20°C to the reflux temperature of the solvent used, specifically at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used.

The reaction mass containing the compound of formula IX obtained in steps-(c) may be subjected to usual work up methods as described hereinabove. The compound of formula IX obtained in step-(c) may be used directly in the next step to produce Dabigatran or Dabigatran etexilate or a pharmaceutically acceptable salt thereof, or the compound of formula IX may be isolated and/or recrystallized by the methods described hereinabove and then used in the next step.

The conversion of the intermediate compound of formula IX into Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof in step-(d) can be carried out by the methods described in the prior art, for example, as per the processes described in the US Patent No. 6,087,380.

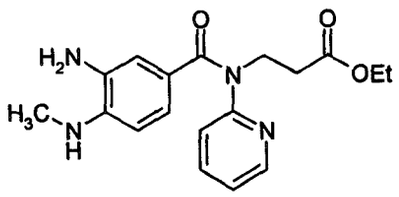
According to another aspect, there is provided a process for the preparation of Dabigatran, or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof, comprising:

a) reacting 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



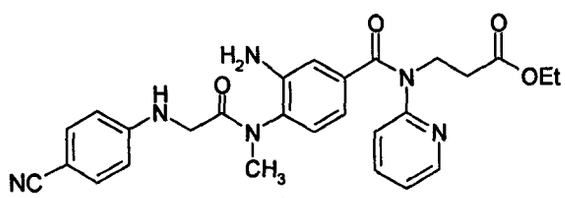
——— II

or an acid addition salt thereof with 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VII:



---------- VII

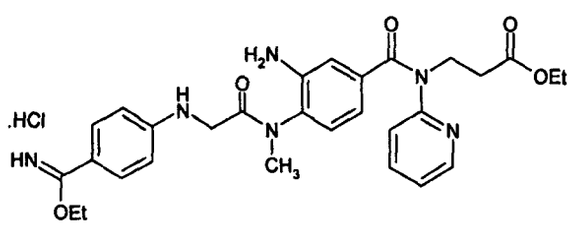
or an acid addition salt thereof to produce 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula III:



---------- III

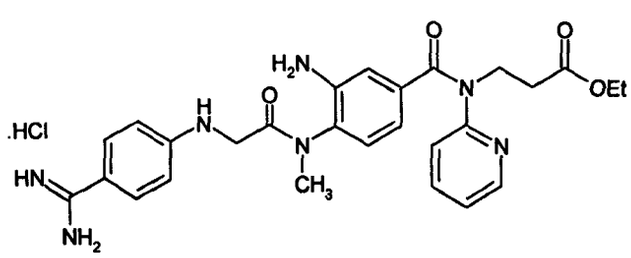
or an acid addition salt thereof;

b) reacting the compound of formula III or an acid addition salt thereof with a suitable reagent to produce 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



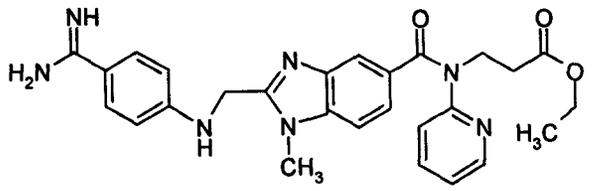
---------- IV

c) reacting the compound of formula IV with a suitable reagent in a suitable solvent to produce 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula V:



---------- V

d) reacting the compound of formula V with a suitable reagent to produce 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (Dabigatran) of formula X:



---------- X

or an acid addition salt thereof; and

e) optionally converting the compound of formula X or an acid addition salt thereof obtained in step-(d) into Dabigatran etexilate or a pharmaceutically acceptable salt thereof.

The reaction steps- (a) and (b) are carried out by using the methods, conditions and reagents as described hereinabove.

In one embodiment, the reagent used in step-(c) is ethanolic ammonia or ammonium carbonate. In another embodiment, the solvent used in step-(c) is ethanol.

In another embodiment, the reaction in step-(c) is carried out at a temperature of about 0°C to the reflux temperature of the solvent used, specifically at a temperature of about 20°C to the 50°C, and more specifically at a temperature of about 25°C to the 35°C.

The reaction mass containing the compounds of formula V obtained in steps-(c) may be subjected to usual work up methods as described hereinabove. The compound of formula V obtained in step-(c) may be used directly in the next step to produce the Dabigatran of formula X, or the compound of formula V may be isolated and/or recrystallized by the methods described hereinabove and then used in the next step.

In another embodiment, the reagent used in step-(d) is an organic or inorganic acid selected from the group as described hereinabove for such purpose. Specifically, the reagent used in step-(d) is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, p-toluene sulfonic acid, or a combination thereof; and a most specific acid is acetic acid.

In another embodiment, the reaction in step-(d) is carried out in the presence of a reaction inert solvent such as a chlorinated hydrocarbon solvent, an ether solvent, a

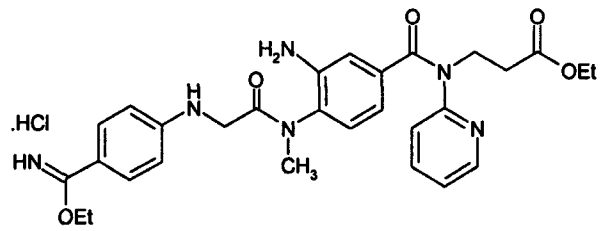
hydrocarbon solvent, and mixtures thereof. Specifically, the solvent used in step-(d) is selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof.

The reaction in step-(d) is carried out at a temperature of about 20°C to the reflux temperature of the solvent used, specifically at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used.

The reaction mass containing the Dabigatran of formula X or an acid addition salt thereof obtained in steps-(d) may be subjected to usual work up methods as described hereinabove. The Dabigatran of formula X or an acid addition salt thereof obtained in step-(d) may be used directly in the next step to produce the Dabigatran etexilate, or the compound of formula X or an acid addition salt thereof may be isolated and/or recrystallized by the methods described hereinabove and then used in the next step.

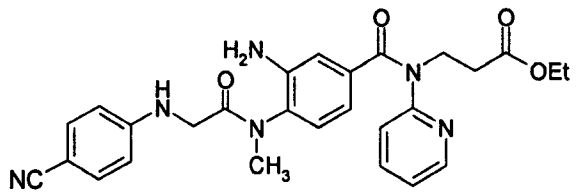
The conversion of the dabigatran of formula X or an acid addition salt thereof into dabigatran etexilate or a pharmaceutically acceptable salt thereof in step-(e) can be carried out by the methods described in the prior art, for example, as per the processes described in the US Patent No. 6,087,380.

According to another aspect, there is provided a process for the preparation of 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



---------- IV

comprising reacting the compound of formula III:

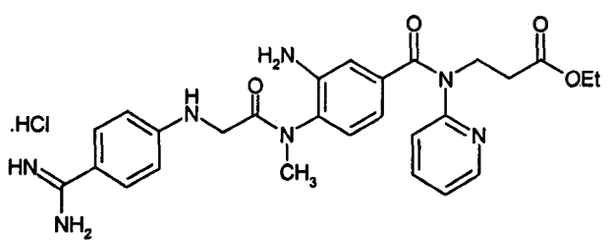


---------- III

or an acid addition salt thereof with a suitable reagent to produce the compound of formula IV.

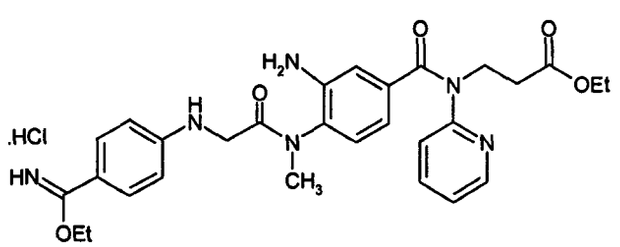
The preparation of the compound of formula IV from the compound of formula III is carried out by using the suitable reagents, methods and conditions as described hereinabove. In one embodiment, the reagent used in the above reaction is ethanolic-HCl.

According to another aspect, there is provided a process for the preparation of 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula V:



---------- V

comprising reacting 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:

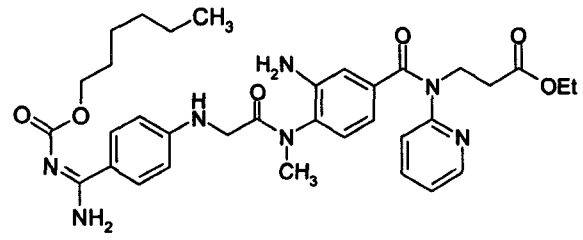


---------- IV

with a suitable reagent to produce the compound of formula V.

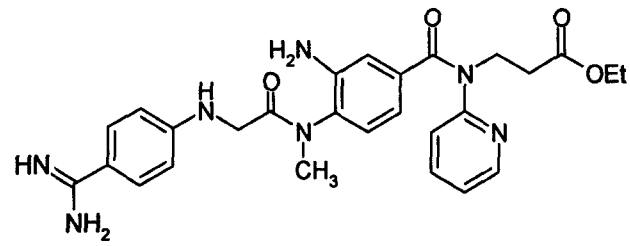
The preparation of the compound of formula V from the compound of formula IV is carried out by using the suitable reagents, methods and conditions as described hereinabove. In one embodiment, the reagent used in the above reaction is ethanolic ammonia or ammonium carbonate.

According to another aspect, there is provided a process for the preparation of 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino)phenylamino]acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula VI:



---------- VI

or an acid addition salt thereof, comprising reacting 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonyl ethyl)-amide of formula Va:



---------- Va

or an acid addition salt thereof with n-hexylchloroformate or n-hexyl 1H-imidazole-1-carboxylate in the presence of a suitable base to produce the compound of formula VI or an acid addition salt thereof.

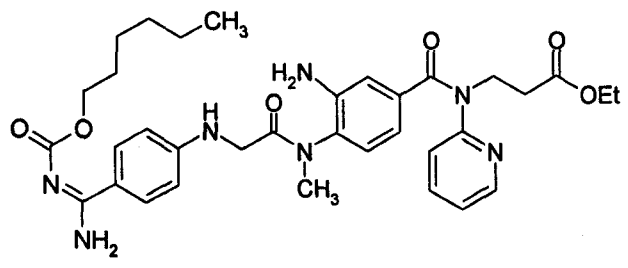
A most preferred acid addition salt of the compound of formula Va is 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonyl ethyl)-amide hydrochloride salt of formula V.

The above reaction is carried out in the presence of a reaction inert solvent comprising water, an alcohol, a ketone, and mixtures thereof. Specifically the solvent is selected from the water, acetone, and mixtures thereof.

The base used in the above reaction is an organic or inorganic base, and specifically an inorganic base. Exemplary inorganic bases include, but are not limited to, hydroxides, alkoxides, bicarbonates and carbonates of alkali or alkaline earth metals. A most specific inorganic base is sodium carbonate or potassium carbonate.

In another embodiment, the above reaction is carried out at a temperature of below about 50°C, specifically at a temperature of about 0°C to the 35°C, and more specifically at a temperature of about 10°C to the 20°C.

According to another aspect, there is provided a process for the preparation of Dabigatran etexilate or a pharmaceutically acceptable salt thereof, comprising reacting 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino)phenylamino]acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide of formula VI:



---------- VI

or an acid addition salt thereof with a suitable reagent to produce Dabigatran etexilate or a pharmaceutically acceptable salt thereof.

In one embodiment, the reagent used in the above reaction is an acid. The acid can be an organic acid or an inorganic acid or a combination thereof selected from the group as described hereinabove. Specifically, the acid is selected from the group consisting of hydrochloric acid, sulfuric acid, acetic acid, methanesulfonic acid, p-toluene sulfonic acid, or a combination thereof; and a most specific acid is acetic acid.

In another embodiment, the reaction is carried out in the presence of a reaction inert solvent. Exemplary inert solvents may include, but are not limited to, a chlorinated hydrocarbon solvent, an ether solvent, a hydrocarbon solvent, and mixtures thereof. Specifically, the solvent is selected from the group consisting of dichloromethane, ethylene dichloride, chloroform, toluene, xylene and mixtures thereof, and a most specific solvent is dichloromethane.

The reaction is carried out at a temperature of about 35°C to the reflux temperature of the solvent used, and more specifically at the reflux temperature of the solvent used while removing the water through Dean-Stark apparatus.

The compounds of formulae II, III, IV, IVa, V, Va and VI, and their salts, disclosed herein are novel and constitute another aspect of the present invention.

The use of the novel compounds of formulae II, III, IV, IVa, V, Va and VI, or an acid addition salt thereof, in the preparation of Dabigatran, or Dabigran etexilate, or a

pharmaceutically acceptable salt thereof is novel and forms further aspect of the present invention.

Unless otherwise specified, the term "acid addition salt" as used herein, includes the salt that is derived from organic and inorganic acids. For example, the acid addition salt is derived from a therapeutically acceptable acid such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, oxalic acid, acetic acid, propionic acid, phosphoric acid, succinic acid, maleic acid, fumaric acid, citric acid, glutaric acid, tartaric acid, methanesulfonic acid, benzenesulfonic acid, toluenesulfonic acid, di-p-toluoyl-L-(+)-tartaric acid, malic acid, ascorbic acid, and the like.

Exemplary acid addition salts of the compounds of formulae II, III, Va and VI include, but are not limited to, hydrochloride, hydrobromide, dihydrochloride, dihydrobromide, sulphate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, citrate, tartrate, and the like. Specific acid addition salts are hydrochloride, oxalate, methanesulfonate and p-toluenesulfonate. A most specific acid addition salt is hydrochloride salt.

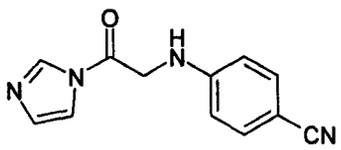
Exemplary pharmaceutically acceptable salts of Dabigatran or Dabigatran etexilate include, but are not limited to, hydrochloride, hydrobromide, sulfate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate, toluenesulfonate, citrate, and tartrate. A most specific pharmaceutically acceptable salt of Dabigatran etexilate is methanesulfonate salt.

Advantageously, the novel intermediate compounds of Dabigatran disclosed herein are obtained as solid state forms in substantially pure form.

The term "substantially pure" as used herein refers to the compounds of formulae II, III, IV, IVa, V, Va and VI, or an acid addition salt thereof, disclosed herein, having a purity of greater than about 97 wt%, specifically greater than about 98 wt%, more specifically greater than about 99 wt%, and still more specifically greater than about 99.5 wt%. The purity is preferably measured by High Performance Liquid Chromatography (HPLC). For example, the purity of the compounds of formulae II, III, IV, IVa, V, Va and VI, or an acid addition salt thereof obtained by the processes disclosed herein can be about 97% to about 99.9% as measured by HPLC.

The Dabigatran or Dabigatran etexilate, or a pharmaceutically acceptable salt thereof obtained by the processes disclosed herein has a purity of greater than about 98%, specifically greater than about 99%, more specifically greater than about 99.9%, and most specifically greater than about 99.95% as measured by HPLC.

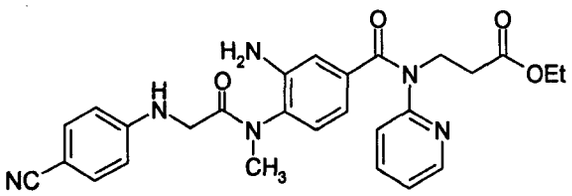
According to another aspect, there is provided a novel compound, 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile, of formula II:



II

or an acid addition salt thereof.

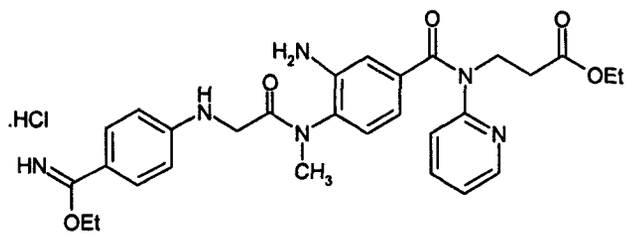
According to another aspect, there is provided a novel intermediate compound, 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide, of formula III:



III

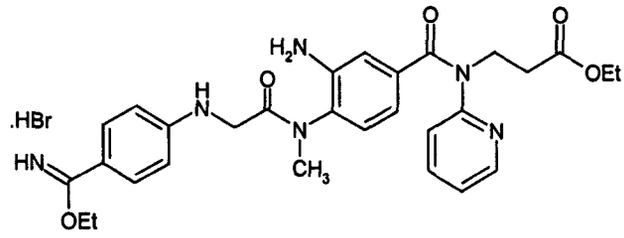
or an acid addition salt thereof.

According to another aspect, there is provided a novel compound, 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula IV:



IV

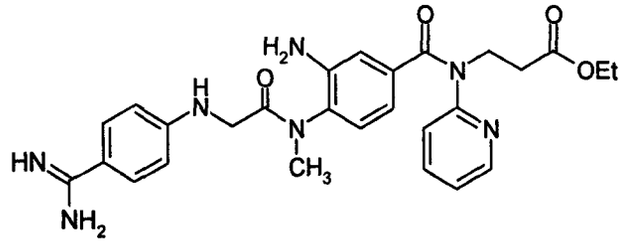
According to another aspect, there is provided a novel compound, 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrobromide salt of formula IVa:



---------- IVa

The compound of formula IVa can be prepared by reacting the compound of formula III or an acid addition salt thereof with ethanolic-hydrobromide analogously to the process for the preparation of compound of formula IV as described hereinabove.

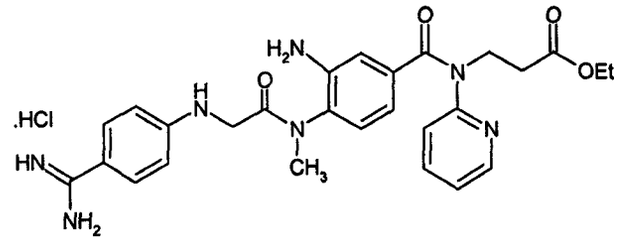
According to another aspect, there is provided a novel compound, 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide of formula Va:



---------- Va

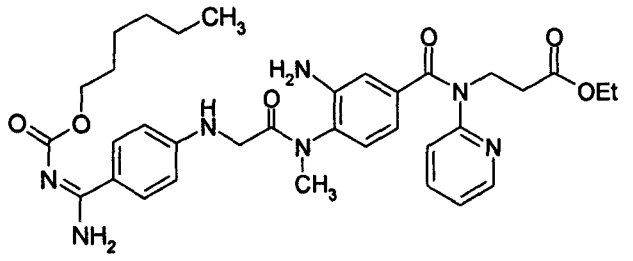
or an acid addition salt thereof.

According to another aspect, there is provided a novel compound, 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt of formula V:



---------- V

According to another aspect, there is provided a novel compound, 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino)phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide, of formula VI:



---------- VI

or an acid addition salt thereof.

In one embodiment, the acid addition salt of the compounds of formulae II, III, Va & VI is, each independently, derived from an organic or inorganic acid. Specific acid addition salts of the compounds of formulae II, III, Va & VI include, but are not limited to, hydrochloride, hydrobromide, dihydrochloride, dihydrobromide, sulphate, nitrate, phosphate, acetate, propionate, oxalate, succinate, maleate, fumarate, methanesulfonate, benzenesulfonate, p-toluenesulfonate, citrate and tartrate. A most specific acid addition salt of the compounds of formulae II, III, Va & VI is hydrochloride salt.

As used herein, the term "reflux temperature" means the temperature at which the solvent or solvent system refluxes or boils at atmospheric pressure.

As used herein, the term "room temperature" or "RT" refer to a temperature of about 15°C to about 35°C. For example, "RT" can refer to a temperature of about 20°C to about 30°C.

INSTRUMENTAL DETAILS:

X-Ray Powder Diffraction (P-XRD):

The X-ray powder diffraction spectrum was measured on a BRUKER AXS D8 FOCUS X-ray powder diffractometer equipped with a Cu-anode (copper-Kα radiation). Approximately 1 gm of sample was gently flattered on a sample holder and scanned from 2 to 50 degrees 2-theta, at 0.03 degrees to theta per step and a step time of 38 seconds. The sample was simply placed on the sample holder. The sample was rotated at 30 rpm at a voltage 40 KV and current 35 mA.

Infra-Red Spectroscopy (FT-IR):

FT-IR spectroscopy was carried out with a Bruker vertex 70 spectrometer. For the production of the KBr compacts approximately 5 mg of sample was powdered with 200

mg of KBr. The spectra were recorded in transmission mode ranging from 3800 cm^{-1} to 650 cm^{-1}.

Differential Scanning Calorimetry (DSC):

Differential Scanning Calorimetry (DSC) measurements were performed with a Differential Scanning Calorimeter (DSC Q200 V23.10 Build 79, Universal V4.4A TA Instruments).

HPLC Method for measuring Chemical Purity:

The chemical purity was measured by HPLC using Shimadzu LC-2010 CHT system with LC solutions software or its equivalent under the following conditions: Column = Kromasil 100 C18, 150 mm x 4.6 mm, 5µ or Equivalent; Detector wavelength = 210 nm; Flow Rate = 1.0 mL/minute; Diluent = Methanol; Elution = Gradient; Mobile Phase-A = 0.02M potassium dihydrogen orthophosphate (95): Acetonitrile (5); Mobile Phase-B = Acetonitrile.

COMPARATIVE EXAMPLE

The present applicant has repeated the Process for the Preparation of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide as exemplified in step-(c) of Example 25 (in an analogous manner to Example 59) of the U.S. Patent No. 6,087,380

N-(4-Cyanophenyl)-glycine (61.7 g) and Carbonyldiimidazole (56.8 g) were added to tetrahydrofuran (3000 ml) at 25-35°C and the resulting mixture was heated to reflux for 30 minutes, followed by the addition of 3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (106 g) at reflux temperature. The reaction mass was refluxed for 5 hours and the solvent was removed by distillation under vacuum to form a residue. The residue was dissolved in glacial acetic acid (1500 ml) and then refluxed for 1 hour, followed by distillation of acetic acid under vacuum to form a residue. The resulting residue was dissolved in dichloromethane and the resulting organic layer was washed two times with water (1500 ml), followed by distillation of solvent under vacuum to produce the titled compound as a residue (HPLC Purity: 48%; and Residue weight: 125 g).

The following examples are given for the purpose of illustrating the present invention and should not be considered as limitation on the scope or spirit of the invention.

EXAMPLES

Example 1

Preparation of Dabigatran hydrochloride

Step-1: Preparation of 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile

N-(4-Cyanophenyl)-glycine (133 g) was added to dichloromethane (2000 ml) while stirring at room temperature and then stirred for 5 minutes to form a solution. Carbonyldiimidazole (222 g) was added to the resulting solution and the resulting mass was heated to reflux, followed by stirring the reaction mass at reflux for 2 to 3 hours. After completion of the reaction the reaction mass was cooled to 25-35°C and then stirred for 15 minutes at the same temperature. The resulting mass was filtered and then washed with dichloromethane (300 ml) to produce 183 g of 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile (Purity by HPLC: 99.5%).

Infra-red (FT-IR) Data (KBr pellet): 3380, 3145, 3126, 2215, 1728, 1609, 1526, 1396, 1300 and 1230 cm^{-1}; Mass (m/z): 227.1 (M+1); DSC Endotherm peak: 118.93°C.

Step-2: Preparation of 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl] amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

3-Amino-4-methylamino-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (150 g) and 4-(2-imidazol-1-yl-2-oxo-ethylamino)-benzonitrile (215 g) were subsequently added to dichloromethane (1560 ml). The resulting mixture was heated to reflux and then stirred for 4 hours at reflux. After completion of the reaction the reaction mass was cooled to room temperature, the separated solid was filtered and then washed with dichloromethane (150 ml). The resulting filtrate was distilled under vacuum at 60°C to obtain a residue (weight: 335 g). Methanol (600 ml) was added to the resulting residue at 25-30°C and the mass was heated at 55-60°C to form a solution, followed by maintaining the solution for 10 minutes at the same temperature. The reaction mass was filtered and the filtrate was cooled to 0 - 5°C, followed by stirring the mass for 1 hour at the same temperature. The resulting mass was filtered and then washed with chilled methanol (150 ml) to produce 220 g of 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]

amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (Purity by HPLC: 99%).

Infra-red (FT-IR) Data (KBr pellet): 3358, 3243, 2214, 1719, 1699, 1662, 1609, 1532, 1515, 1276 and 1176 cm^{-1}; Mass (m/z): 501.1 (M+1).

Step-3: Preparation of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt

Toluene (2240 ml) was taken in a reaction flask equipped with Dean-Stark apparatus and then 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (220 g) was added into toluene at 25-30°C. The resulting mass was heated to reflux and then stirred for 30 minutes at reflux while removing the collected water through Dean-Stark apparatus. Acetic acid (61 ml) was slowly added to the reaction mass under reflux for 30 minutes. A clear solution was formed after complete addition of acetic acid and the collected water was removed from Dean-Stark apparatus. The reaction mass was initially cooled to 25-30°C and then cooled the resulting mass to 0-5°C, followed by stirring for 30 minutes at the same temperature. The separated solid was filtered, washed with chilled toluene (100 ml) and the dried the material at 60-65°C for 4 hours 30 minutes to produce 139 g of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt (Purity by HPLC: 99.5%).

Infra-red (FT-IR) Data (KBr pellet): 3346, 2218, 1733, 1699, 1640, 1608, 1370, 1330, 1264 and 1174 cm^{-1}; Mass (m/z): 483.2 (M+1).

P-XRD Data: 7.73, 9.0, 10.07, 11.74, 12.07, 12.77, 15.48, 16.30, 16.67, 17.38, 17.74, 18.14, 18.37, 19.17, 19.52, 20.37, 20.86, 21.83, 23.53, 24.27, 24.99, 25.77, 26.77 and 27.14 degrees 2-theta.

Step-4: Preparation of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide free base

1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide acetate salt (65.5 g, obtained in step-3) was added to dichloromethane (655 ml) and water (327.5 ml) at 25-35°C, followed by stirring the reaction mixture at the same temperature. Ammonium hydroxide (65.5 ml) was added drop-wise to the reaction mass over a period of 10 to 15 minutes while adjusting the pH of

the resulting mass to 9 to 9.5 and the reaction mass was stirred for 10 minutes at 25-35°C. The resulting organic layer was separated, the aqueous layer was extracted with dichloromethane (200 ml), followed by combining the total organic layer. The resulting organic layer was subsequently washed with water (400 ml) and 20% sodium chloride solution and then distilled the solvent under vacuum at 50°C to obtain a residue (wt. 59 g). Ethyl acetate (176 ml) was added to the residue at 25-35°C, followed by stirring the mass for 30 minutes at the same temperature. The separated solid was filtered and then washed with ethyl acetate (125 ml) and then dried at 55-60°C to produce 55 g of 1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide free base.

Infra-red (FT-IR) Data (KBr pellet): 3265, 2216, 1730, 1640, 1605, 1372, 1329, 1271 and 1179 cm^{-1}; Mass (m/z): 483.2 (M+1).

Step-5: Preparation of Dabigatran hydrochloride

1-Methyl-2-[N-(4-cyanophenyl)-aminomethyl]-benzimidazole-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (210 g, obtained in step-4) was added to saturated ethanolic hydrochloride solution (1000 ml) at 10-12°C, followed by slowly increasing the temperature of the reaction mass to 25-35°C and then stirring the mass for 24 hours at the same temperature. Solvent was distilled from the reaction mass under vacuum at 40-45°C to form a residue, followed by the addition of saturated ethanolic ammonia solution (2300 ml) at 25-35°C. The reaction mass was stirred for 10-12 hours at 25-35°C and then distilled the solvent under vacuum at 75-80°C to obtain a residue. A solvent medium comprising ethyl acetate and ethanol (2:1) (1750 ml) was added to the above residue and then heated to reflux, followed by maintaining the reaction mass at reflux for 30 minutes. The resulting mass was filtered and the mother liquor was distilled under vacuum to obtain a residue. Isopropanol (2000 ml) was added to the resulting residue and then heated for 2 hours at 70°C. The separated solid was filtered to produce 130 g of Dabigatran hydrochloride.

Example 2

Preparation of Dabigatran hydrochloride

Ethanol (150 ml) was taken into a reaction flask, followed by purging of hydrogen chloride gas into ethanol at 0-10°C until the weight of the ethanol increases to 80 to 90 g. 3-Amino-4-[N-[2-(4-cyano-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide (30 g) was added to the ethanolic-HCl solution at 0-10°C and the temperature was raised to 25-35°C, followed by stirring the reaction mass at room temperature for 16 hours. After completion of the reaction, the solvent was distilled off from the reaction mass under vacuum at 45-50°C to produce 3-Amino-4-[N-[2-(4-ethoxyimidoyl-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt. The resulting residue was added to saturated ethanolic ammonia solution (600 ml) at 25-35°C and the resulting mass was stirred for 4 hours 30 minutes at the same temperature. The solvent was removed from the reaction mass by distillation under vacuum at 70-75°C to produce 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt. Water (500 ml) was added to the resulting solid at 25-35°C, followed by stirring the mass for 10 to 15 minutes at the same temperature. The resulting aqueous layer was extracted three times with toluene (250 ml x 3), followed by combining the toluene layers. The combined organic layer was heated to reflux and the collected water was removed through Dean-Stark apparatus. Acetic acid (8 ml) was added to the resulting organic layer at reflux. The toluene layer reflux was continued until water collection is stopped from Dean-Stark apparatus. The resulting toluene layer was initially cooled to room temperature, followed by further cooling to 0-5°C. The separated solid was filtered, washed with chilled toluene (50 ml) and then dried the material under vacuum at 60-65°C to produce pure Dabigatran hydrochloride (Purity by HPLC: 99.95%).

Example 3

Preparation of 1-methyl-2-[N-(4-(N-n-hexyloxycarbonylamidino)phenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonyl ethyl)-amide (Dabigatran Etexilate)

Acetone (437 ml) and water (273 ml) were taken into a reaction flask, followed by the addition of Dabigatran hydrochloride (55 g) at 25-30°C and then stirring for 15-20 minutes to form a clear solution. Potassium carbonate (34 g) was added to the above solution at 25-30°C and the resulting mass was cooled to 10-15°C, followed by the addition of n-hexyl chloroformate (16.5 g) at the same temperature. The reaction mass was stirred for 12-14 hours at 10-15°C and then filtered the solid. The resulting solid was dissolved in dichloromethane (1000 ml) and the resulting organic layer was washed two times with 10% potassium carbonate solution (500 ml x 2). The resulting organic layer was then washed with 20% sodium chloride solution, followed by distillation under vacuum to produce 55.5 g of Dabigatran Etexilate as solid.

Example 4

Preparation of Dabigatran Etexilate

Step-1: 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino) phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide

Acetone (437 ml) and water (273 ml) were taken into a reaction flask, followed by the addition of 3-Amino-4-[N-[2-(4-amidino-phenylamino)acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide hydrochloride salt (55 g) at 25-30°C and then stirring for 15-20 minutes to form a clear solution. Potassium carbonate (34 g) was added to the above solution at 25-30°C and the resulting mass was cooled to 10-15°C, followed by the addition of n-hexyl chloroformate (16.5 g) at the same temperature. The reaction mass was stirred for 12-14 hours at 10-15°C and then filtered the solid. The resulting solid was dissolved in dichloromethane (1000 ml) and the resulting organic layer was washed two times with 10% potassium carbonate solution (500 ml x 2). The resulting organic layer was then washed with 20% sodium chloride solution, followed by distillation under vacuum to produce 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino) phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-pyridyl)-N-(2-ethoxy carbonylethyl)-amide.

Step-2: Dabigatran Etexilate

Dichloromethane (550 ml) was added to 3-Amino-4-[N-[2-[(4-N-n-hexyloxycarbonylamidino) phenylamino]acetyl]-N-methyl]amino]-benzoic acid-N-(2-

pyridyl)-N-(2-ethoxycarbonylethyl)-amide (obtained in step-1) at 25-30°C. The resulting mass was heated to reflux and then stirred for 10-15 minutes at reflux while removing the collected water through Dean-Stark apparatus. Acetic acid (15 ml) was added to the reaction mass at reflux and then stirred for 4 to 5 hours at reflux. After completion of the reaction the reaction mass was cooled to room temperature and then water (250 ml) was added to the mass at the same temperature. The resulting mass was further cooled to 10-15°C, followed by adjusting the pH of the mass to 8-9 with potassium carbonate. The aqueous layer was separated and the organic layer was washed with water (200 ml), followed by distillation of dichloromethane solvent under vacuum at 50°C to produce 50 gm of Dabigatran Etexilate.

All ranges disclosed herein are inclusive and combinable. While the invention has been described with reference to a preferred embodiment, it will be understood by those skilled in the art that various changes may be made and equivalents may be substituted for elements thereof without departing from the scope of the invention. In addition, many modifications may be made to adapt a particular situation or material to the teachings of the invention without departing from essential scope thereof. Therefore, it is intended that the invention not be limited to the particular embodiment disclosed as the best mode contemplated for carrying out this invention, but that the invention will include all embodiments falling within the scope of the appended claims.