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(71) **Applicant**: **MEGAFINE PHARMA (P) LTD.** [IN/IN]; Sethna, 4th Floor, 55, Maharishi Karve Road, Marine Lines, Mumbai 400002 (IN).

(72) **Inventors**: **MATHAD, Vijayavitthal Thippannachar**; Flat no. 05, Nirman Classic, Behind HDFC Bank, Thatte, Nagar, Gangapur Road, Nashik 422007, Maharashtra (IN). **SOLANKI, Pavankumar Vrajlal**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur, Tal. Dindori, Dist. Nashik (IN). **UPPELLI, Sekhar Babu**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur, Tal. Dindori, Dist. Nashik (IN). **SARODE, Ganesh Gitaram**; Megafine Pharma (P) Ltd., Plot No. 31 to 35 & 48 to 51/201, Lakhmapur, Tal. Dindori, Dist. Nashik (IN).

(74) **Agent**: **MAYUR DHAYGUDE**; Intellectual Property Management, Megafine Pharma (P9 Ltd., Plot No. 31 to 35 & 48 to 51/201, Lkhmapur, Tal. Dindori, Dist. Nashik 422202, Maharashtra (IN).

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(54) **Title**: A PROCESS FOR PREPARATION OF DABIGATRAN ETEXILATE MESYLATE AND INTERMEDIATES THEREOF

(57) **Abstract**: The present invention relates to an improved process for the preparation of Dabigatran etexilate and its acid addition salts thereof, wherein the said process substantially eliminates the potential impurities. The present invention also relates to an intermediate of Dabigatran etexilate and process for preparation thereof.

WO 2015/128875 A2

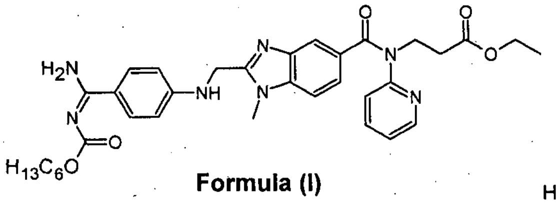
TITLE OF THE INVENTION

A PROCESS FOR PREPARATION OF DABIGATRAN ETEXILATE MESYLATE AND INTERMEDIATES THEREOF

This application claims the priority from our provisional Indian patent application number 675/MUM/2014 filed on February 26, 2014 which is incorporated herein by reference.

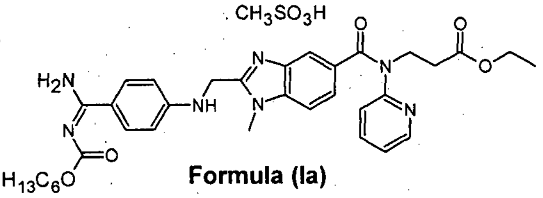
FIELD OF THE INVENTION:

The present invention relates to an improved process for preparation of 1-methyl-2-[N-[4-(N-nhexyloxycarbonylamidino)phenyl]aminomethyl]benz imidazol-5-yl-carboxylicacid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide compound of formula (I) also known as dabigatran etexilate and its methane sulfonate salt compound of formula (Ia), represented by the following structural formulae:



Formula (I)

Dabigatran Etexilate

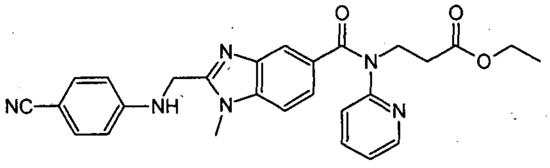


Formula (Ia)

Dabigatran Etexilate Mesylate

The process of the present invention is an improved, commercially viable and industrially advantageous process for the preparation of Dabigatran etexilate mesylate wherein, the said process substantially eliminates the impurities formed during the preparation of Dabigatran etexilate mesylate.

Further, the present invention also provides novel acid additions salts of ethyl N-[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1-H-benzimidazol-5-yl0carbonyl]-N-pyridin-2-yl-beta-alaninate (DEM-III),preferably p-toluene sulfonic acid salt, represented by structural formula (V), an useful intermediate in the synthesis of highly pure compound (Ia).



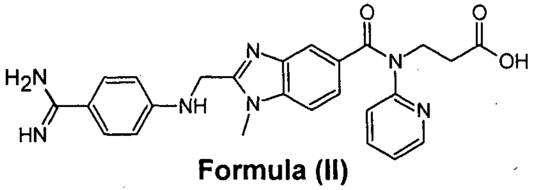
.p-toluene sulfonic acid addition salt

Formula (V)

BACKGROUND OF THE INVENTION:

Dabigatran etexilate mesylate is an oral anticoagulant from the class of the direct thrombin inhibitors. Direct thrombin inhibitors (DTIs) are a class of medication that act as anticoagulants (delaying blood clotting) by directly inhibiting the enzyme thrombin. It is used to help prevent strokes or serious blood clots in people who have atrial fibrillation (a condition in which the heart beats irregularly, increasing the chance of clots forming in the body and possibly causing strokes) without heart valve disease. Dabigatran etexilate mesylate is approved in both US and Europe and commercially available under the brand name of Pradaxa.

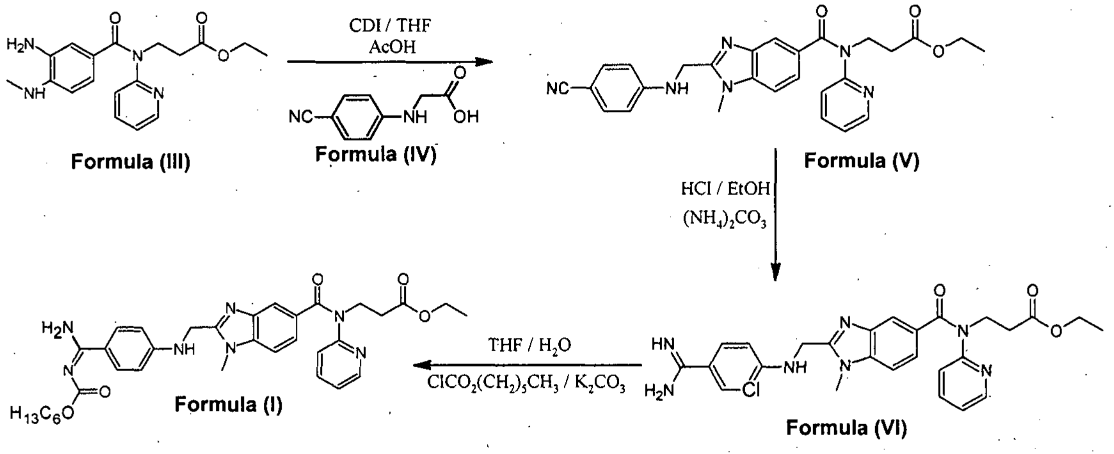
Dabigatran etexilate mesylate is a double prodrug of the active substance, Dabigatran of formula **(II)**. It is the pharmacologically active molecule formed through hydrolysis catalyzed by plasma and liver esterase



Formula (II)

Dabigatran and process for its preparation was first disclosed in WO9837075 (henceforth '075) disclosed process involves the reaction of 1-methyl-2-[N-[4amidinophenyl]aminomethyl]benzimidazol-5-yl-carboxylicacid-N-(2-pyridyl)- N-(2-ethoxycarbonylethyl)amide hydrochloride of formula (VI) with hexylchloroformate in presence of potassium carbonate in tetrahydrofuran/water to provide l-methyl-2-[N -[4-(N -n-hexyloxycarbonylamidino) phenyl]aminomethyl]benzimidazol- 5-yl-carboxylicacid- N-(2-pyridyl)- N-(2-ethoxy carbonylethyl)amide (herein after referred as dabigatran etexilate) of compound of formula (I). But WO'075 does not discuss or exemplify process for preparation of Dabigatran etexilate mesylate salt.

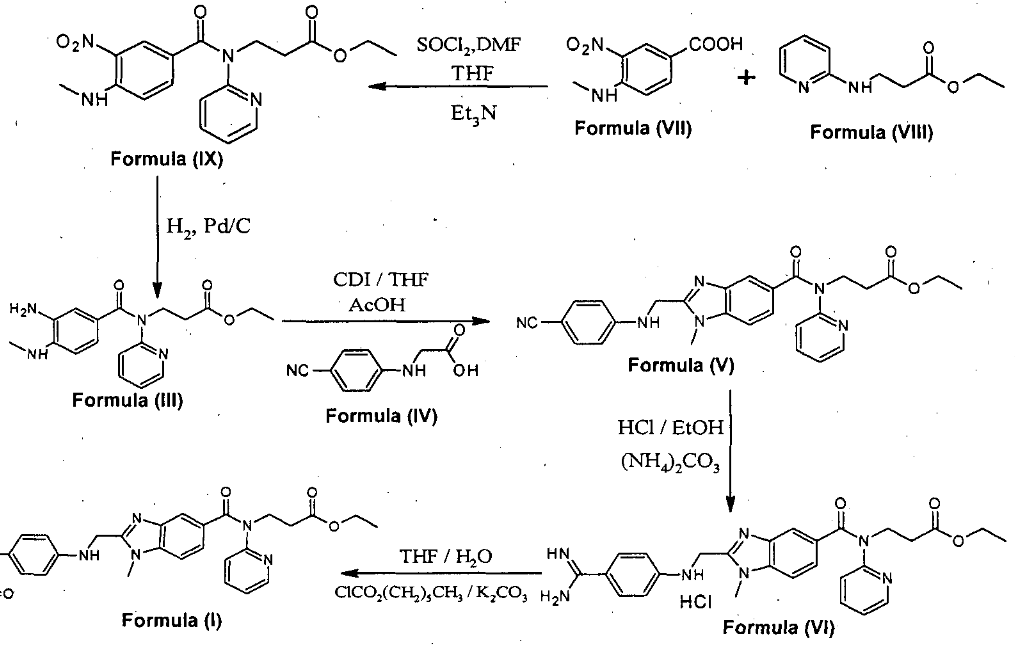
The key step of the disclosed process is the conversion of the nitrile of the Formula (V) into the amidine hydrochloride of formula (VI) by pinner reaction. The low yields of the pinner reaction can be derived from the water sensibility of the reaction on the one hand while the realization of the reaction is rendered more difficult on the other by the fact that the ester as well as amide function of the molecule is susceptible to hydrolysis. According to Example 58b of said patent in an analogous manner to Example 25d 1.2 g of l-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonylethyl]-amide (V) is reacted with ethanol saturated with hydrochloric acid in large dilution. The evaporated crude product is then converted to hydrochloric acid salt of l-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5- benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonyl)-ethyl]- amide compound of formula(VI) using ethanol and ammonium carbonate. The disclosed process was not suitable for large scale production because of tedious workup procedures, less yield, low purity, separation by column chromatography, which in turn results in excessive production time and costlier process and less eco-friendly. The purification step performed by using large dilutions and column chromatography makes scale up and commercialization of the process strongly limited. Hence, this process is not commercially viable.



SCHEME - I

Example 113 of WO'075 reveals the total yield of the final compound (I) is 22%.

J.Med.Chem. 2002, 45, 1757-1766 describes a process for preparation of compound of formula (III) as depicted in scheme-II.



SCHEME - II

The process for preparation of mesylate salt of dabigatran etexilate and its polymorphic forms was disclosed in US2005/234104. The disclosed process involves the reaction of Dabigatran etexilate with methane sulfonic acid in acetone to provide Dabigatran etexilate mesylate.

According to WO 2012/153158 (henceforth WO'158) dabigatran etexilate base compound of formula (I) is characterized by mass spectrum, ^{1}H NMR and melting point (128-129°C).WO 2008/059029 reports the melting point of 128 ±3°C for the anhydrous form-III. Further WO'158 discloses that according to WO2006/000353 dabigatran etexilate of formula (I) is prepared as described in Examples 5A and 5B by reacting the tosylate salt of (6) and hexylchloroformate in an acetone-aqueous medium, obtained product is dried at 45°C and is not characterized by analytical data. On the basis of the calculations the product is presumed to be anhydrous. Thus according to WO 2006/000353 dabigatran etexilate is prepared by crystallization from an acetone/water system (Example 5A) and in said process no drying agent or other dehydrating agent is used.

Further WO'158 reveals that on following the example 5A of WO 2006/000353 authors failed to obtain anhydrous dabigatran etexilate but rather modification thereof containing four moles of water was observed in dabigatran etexilate.

Further WO'158 discloses that two anhydrous and tetrahydro form of dabigatran etexilate are described in WO 2006/131491. In this international patent application no process is disclosed for preparation of dabigatran etexilate but reference is made rather to basic patent and hence the said new forms are obtained by recrystallization from ethyl acetate (anhydrous form-I and anhydrous II Examples 1 and 2) and a mixture of acetone and water (tetrahydrate form, example 3).

According to disclosure of WO'158, WO 2007/007142 three further variants are disclosed for the preparation of dabigatran etexilate (1) starting from the tosylate salt of the amidine (6); said procedures differ from each other in the reaction conditions and the work-up method. Thus Example 6A is identical with Example 5A of WO 2006/000353, however in the working up method of new variants 6B and 6C an azeotropic distillation is employed using butyl acetate for dehydration. Accordingly in these cases actually the anhydrate of dabigatran etexilate (1) is formed and consequently the yield is lower (yield of 1 using ditosylate of 6).

As per WO'158, an article published in 2009 (UP.Com. Journal 2009, 9, 20) reports a detailed process for the realization of the Pinner-reaction mentioned in the basic patent, wherein the hydrolysis of the nitrile derivative of formula (V) is carried out at room temperature with the aid of an approximately 100 molar amount of hydrochloric acid. The process involves five re-crystallization steps to obtain pure di-hydrochloride (characterized by XRD). The disadvantages of the disclosed process are high dilution ratio, low yield, process is restricted to smaller batch size at commercial scale, process results in formation of impurities and is not cost effective at commercial scale, and involve 5 purification steps thereby making the said process unsuitable at industrial scale.

WO 2010/045900 discloses the preparation of free base of dabigatran etexilate of formula (I), from oxalate salt of nitrile compound of formula (V) via monohydrochloride and dihydrochloride of the amidine of formula (VI). These salts are found to degrade and lead to the formation of impurities and thereby yield dabigatran etexilate with low purity. Thus making the process less favorable at industrial scale.

Like any synthetic compound, Dabigatran etexilate mesylate contain extraneous compounds or impurities that can come from many sources. They may be un-reacted starting materials, by-products of reaction, products of side reaction, and/or degradation products. To meet the regulatory quality norms, identification, isolation, synthesis and characterization of the impurities followed by their control to the ICH levels in the final drug compound is a must. Potential impurities of Dabigatran etexilate mesylate are disclosed in EP2522662 and it also addresses the stability issues associated with dabigatran etexilate mesylate. Additionally WO'158 discloses the additional set of impurities which are formed due to the use of poor quality of hexyl chloroformate. Hence, there is a need of simple, efficient and production friendly process for the preparation of dabigatran etexilate mesylate with high purity, yield and higher throughput.

OBJECTS OF THE PRESENT INVENTION:

The primary object of the present invention is to provide an improved, economic, efficient, production friendly process for preparation of dabigatran etexilate mesylate of formula (Ia).

Yet another object of the present invention is to provide a novel process for the preparation of crystalline form-I of dabigatran etexilate mesylate compound of formula- la

Yet another object of the present invention is to provide a process for the preparation of hexyl-4-nitrophenyl carbonate compound of formula (XII).

Yet another object of the present invention is to provide a process for preparation of Dabigatran etexilate mesylate of formula (Ia); wherein the said process eliminates laborious workup. Hence, makes the process simple, easy and user friendly.

Yet another object of the present invention is to provide a process for preparation of Dabigatran etexilate mesylate of formula (Ia);wherein the obtained Dabigatran etexilate mesylate of formula (Ia); is substantially free from impurities and thereby eliminating the required purification steps and further making the process cost effective and efficient.

Yet another object of the present invention is to provide an isolated acid addition salt of compound of formula (v).

Yet another object of the present invention is to provide a crystalline form of acid addition salt of compound of formula (v).

Another object of the present invention is to provide an improved process for the preparation of pure dabigatran etexilate mesylate wherein the overall yield and quality is consistent during production.

BRIEF DESCRITPION OF DRAWINGS

Figure 1 of the present invention illustrates X-ray powder diffraction (XRD) pattern of p-toluene sulfonate of compound of formula (V), prepared according to example h.

Figure 2 of the present invention illustrates Infrared spectrum (IR) pattern of p-toluene sulfonate of compound of formula (V), prepared according to example h.

DETAILED DESCRIPTION OF THE INVENTION

Before the present invention is described, it is to be understood that this invention is not limited to particular methodologies and materials described, as these may vary as per the person skilled in the art. It is also to be understood that the terminology used in the description is for the purpose of describing the particular embodiments only, and is not intended to limit the scope of the present invention.

Before the present invention is described, it is to be understood that unless defined otherwise, all technical and scientific terms used herein have the same meaning as commonly understood by one of ordinary skill in the art to which this invention belongs. Further, it is to be understood that the present invention is not limited to the methodologies and materials similar or equivalent to those described herein can be used in the practice or testing of the present invention, the preferred methods and materials are described, as these may vary within the specification indicated. Unless stated to the contrary, any use of the words such as "including," "containing," "comprising," "having" and the like, means "including without limitation" and shall not be construed to limit any general statement that it follows to the specific or similar items or matters immediately following it. Embodiments of the invention are not mutually exclusive, but may be implemented in various combinations. The described embodiments of the invention and the disclosed examples are given for the purpose of illustration rather than limitation of the invention as set forth the appended claims. Further the terms disclosed embodiments are merely exemplary methods of the invention, which may be embodied in various forms.

A term herein “reflux temperature” means the temperature at which the solvent or the solvent system refluxes or boils at atmospheric pressure.

As used herein the present invention the term "suitable solvents" refers to solvents selected from "**Ester solvents**" like ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate, Sec-butyl acetate, tert-butyl acetate; "**Ether solvents**" like tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropyl ether, Di-tert-butyl ether and the like; "**Hydrocarbon solvents**" like toluene, xylene, hexane, heptane, pentane, cyclohexane, cycloheptane, cyclopentane, cyclooctane and like; "**Polar aprotic solvents**" like dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide; "**ketone solvents**" like acetone, methyl ethyl ketone/butanone, methyl isobutyl ketone, methyl isopropyl ketone,; "**Alcoholic solvents**" like methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol, sec-butanol, ter-butanol, ethylene glycol, 2-ethyl hexanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, 2-pentanol, propylene glycol, hexylene glycol, triethylene glycol, tripropylene glycol; "**Chlorinated solvents**" like dichloro methane, chloroform, chlorobenzene and dichloro ethane; "**Nitrile solvents**" like acetonitrile and propionitrile, butyronitrile; "**Nitro solvents**" like nitro methane, nitro ethane, nitro benzene and the like; polar solvents like water; and mixtures thereof. “Suitable solvent" means a single or a combination of two or more solvents.

As used herein the present invention the term "suitable bases" refers to the bases selected from inorganic bases like alkali metal hydroxides such as lithium hydroxide, sodium hydroxide, potassium hydroxide, rubidium hydroxide, cesium hydroxide; alkali metal alkoxides such as sodium methoxide, sodium ethoxide, sodium tert-butoxide, potassium tert-butoxide; titanium isopropoxide, titanium ethoxide, zirconium ethoxide, aluminium isopropoxide, tentalum ethoxide; alkali metal carbonates like sodium carbonate, potassium carbonate, and cesium carbonate; and alkali metal bicarbonates like sodium bicarbonate potassium bicarbonate, calcium bicarbonate and ammonium bicarbonate, ; and organic bases like triethylamine, isopropyl ethylamine, diisopropyl amine, diisopropyl ethylamine, N- methyl morpholine, piperidine, pyridine and their mixtures thereof.

The term "acid" herein the present invention is selected from inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; organic acids such as trifluoroacetic acid, acetic acid, methane sulfonic acid, 2,5-dihydroxy benzoic acid, ethanedisulfonic acid, p-toluene sulfonic acid (PTSA), benzene sulfonic acid, ethane disulfonic acid, ethane sulfonic acid, naphthalene disulfonic acid, naphthalene-2- sulfonic acid, camphor sulfonic acid, acetic acid, oxalic acid, fumaric acid, maleic acid, oleic acid, malic acid, adipic acid, stearic acid, cinnamic acid, succinic acid, malonic acid, mandelic acid, palmitic acid, pamoic acid, ascorbic acid, lactic acid, citric acid, tartaric acid, gentisic acid, cyclamic acid, D-glucuronic acid, glycolic acid, isethionic acid, saccharine, salicylic acid, naphthalene- 1 ,5-disulfonic acid and the like.

When a molecule or other material is identified herein as "substantially pure", it generally means, unless specified otherwise, that the material is about 99% pure or more. In general, this refers to purity with regard to unwanted residual solvents, reaction byproducts, impurities and unreacted starting materials.

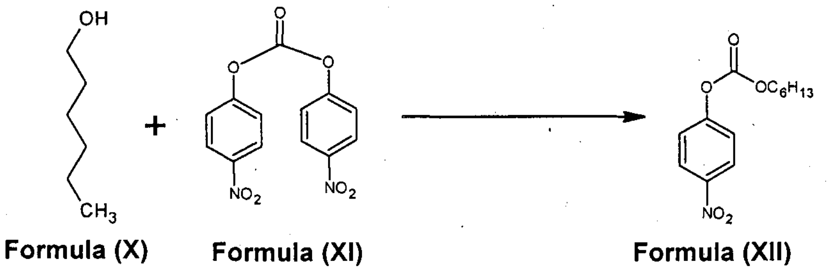
As used here in the term "obtaining" may include filtration, filtration under vacuum, centrifugation, and decantation to isolate product. The product obtained may be further or additionally dried to achieve the desired moisture values. For example, the product may be dried in a hot air oven, tray drier, dried under vacuum and/or in a Fluid Bed Drier.

The term "crystallizing" herein means heating a "slurry" or "suspension" or "solution" of compound from about 25°C to about 10°C above or below of the reflux temperature of solvent, and optionally cooling to the ambient temperature to obtain crystalline form of compound. The term "ambient temperature" herein means temperature of about 20°C or less.

EMBODIMENT - 1:

According to one of the embodiment of the present invention, there is provided a process for the preparation of hexyl-4-nitrophenyl carbonate compound of formula (XII) comprising:

a) reacting n-hexanol of formula **(X)** with bis-(4-nitrophenyl) carbonate compound of formula **(XI)** in a solvent and in presence of a base to obtain hexyl-4-nitrophenyl carbonate compound of formula **(XII)**, and optionally isolating compound of formula (XII).



The solvent used in step (a) is selected from ether solvents, hydrocarbon solvents, polar aprotic solvents, chlorinated solvents, nitrile solvents and the like; or mixtures thereof.

The base used in step (a) is an organic or inorganic base; organic bases selected from such as but not limited to 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like. inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or liquor ammonia and the like;

The compound of formula (XII) can also be isolated and purified as per the conventional techniques known in the prior art like recrystallization, re-saltification, solvent purification, high vacuum distillation and the like;

The isolation of compound of formula (XII) comprises the steps of:

i. treating the reaction mass of step (a) with water;
ii. extracting the aqueous layer of step (i) with an organic solvent;
iii. separating the organic layer of step (ii) followed by washing it with suitable aqueous base; and
iv. removing the solvent from the organic layer of step (iii) to obtain the compound of formula (XII) as syrup/oil.

The organic solvent used in step (ii) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

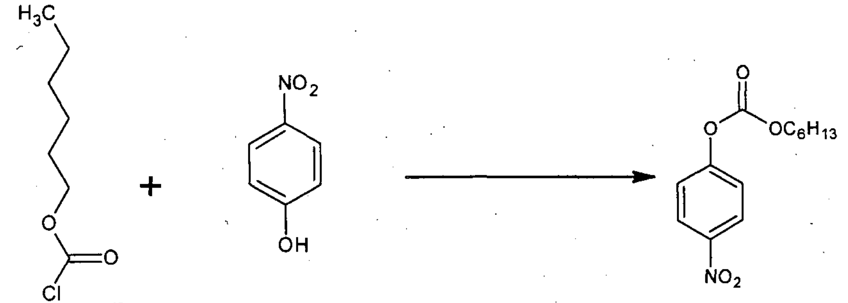
The aqueous base used in step (iii) is selected from aqueous solution of alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates.

The solvent in step (iv) may be removed by the known techniques in the art like filtration, decantation, centrifugation, spray drying, evaporation and the like.

EMBODIMENT – 2

According to another embodiment of the present invention, there is provided a process for the preparation of hexyl-4-nitrophenyl carbonate compound of formula **(XII)**, comprising:

a) Reacting hexyl chloroformate of formula **(XIII)** with p-nitro phenol of compound of formula **(XIV)** in a solvent and in presence of a base to provide hexyl-4-nitrophenyl carbonate compound of formula **(XII)**;and optionally isolating compound of formula (XII);



Formula (XIII) **Formula (XIV)** **Formula (XII)**

The solvent used in step (a) is selected from ether solvents, hydrocarbon solvents, polar aprotic solvents, chlorinated solvents, nitrile solvents and the like.

The base used in step (a) is an organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like. inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or liquor ammonia and the like.

The isolation of compound of formula (XII) comprises the steps of:

i. treating the reaction mass of step (a) with water;
ii. extracting the aqueous layer of step (i) with an organic solvent;
iii. separating the organic layer of step (ii) followed by washing it with suitable aqueous base;
iv. removing the solvent from the organic layer of step (iii) to obtain the compound of formula (XII) as a syrup/oil.

The organic solvent used in step (ii) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbons such as dichloromethane and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

The aqueous base used in step (iii) is selected from aqueous solution of alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates.

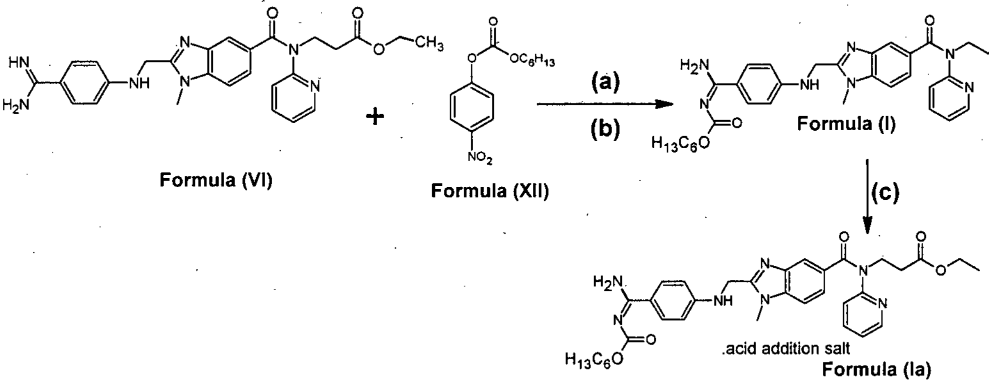
The solvent in step (iv) may be removed by the known techniques in the art like filtration, decantation, centrifugation, spray drying, evaporation and the like.

EMBODIMENT – 3

According to another embodiment of the present invention, there is provided a process for the preparation of Dabigatran etexilate of formula (I) or its acid addition salts of formula (Ia) comprising the steps of:

a) treating hexyl-4-nitrophenyl carbonate compound of formula **(XII)** with 1-methyl-2-[N-[4-amidinophenyl]aminomethyl]benzimidazol-5-yl-carboxylicacid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide compound of formula (VI) or its acid addition salt in presence of a base in a suitable solvent to provide Dabigatran etexilate of formula (I);
b) crystallizing dabigatran etexilate of formula (I) in a suitable solvent to obtain substantially pure dabigatran etexilate of formula (I); and
c) treating dabigatran etexilate (I) with an acid in an organic solvent to obtain acid addition salt of dabigatran etexilate (I); and

d) isolating the acid addition salt of dabigatran etexilate (Ia) from reaction mixture of step (c).



The suitable base used in step (a) of the reaction is an organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like. inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or liquor ammonia and the like.

The solvent used in step (a) of the reaction is selected from but not limited to alcohols such as but not limited to methanol, ethanol, isopropanol, n-butanol, t-butanol; ketone selected from but not limited to acetone, methyl ethyl ketone; esters selected from but not limited to ethyl acetate, isopropyl acetate, butyl acetate; ethers selected from tetrahydrofuran, 2-methyl tetrahydrofuran; polar aprotic solvents selected from but not limited to dimethylformamide, dimethylacetamide, N-methylpyrrolidine, dimethylsulfoxide; hydrocarbons selected from but not limited to toluene, xylene; nitriles like acetonitrile and proprionitrile; water and mixtures thereof.

The solvent used for crystallization in step (b) is selected from the group comprising of alcohols such as but not limited to methanol, ethanol, isopropanol, n-butanol, t-butanol; ketone selected from but not limited to acetone, methyl ethyl ketone; esters selected from but not limited to ethyl acetate, isopropyl acetate, butyl acetate; polar aprotic solvents selected from but not limited to dimethylformamide, dimethylacetamide, N- methylpyrrolidine, dimethylsulfoxide; hydrocarbons selected from but not limited to toluene, xylene; nitriles like acetonitrile and proprionitrile; water and mixtures thereof.

The acid addition salt of step (c) may be an organic or inorganic acid addition salt.

The organic acids is selected from but not limited to maleic, fumaric, benzoic, ascorbic, succinic, oxalic, bis-methylenesalicylic, camphor sulfonic, methanesulfonic, ethanesulfonic, acetic, propionic, tartaric, salicylic, citric, gluconic, lactic, malic, mandelic, cinnamic, citraconic, aspartic, stearic, palmitic, itaconic, glycolic, p-aminobenzoic, glutamic, benzene sulfonic and theophylline acetic acids, 8-halotheophylline; inorganic acids such as but not limited to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid.

The solvent used for preparation of acid additions salt of step (c) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water and mixtures thereof.

EMBODIMENT – 4

According to another embodiment of the present invention, there is provided a process for the preparation of Dabigatran etexilate of formula (I) or its acid addition salt of formula (Ia) comprising the steps of:

a. reacting n-hexanol of formula **(X)** with bis-(4-nitrophenyl) carbonate compound of formula **(XI)** in a solvent and in presence of a base to obtain hexyl-4-nitrophenyl carbonate compound of formula **(XII)**,and optionally isolating compound of formula (XII);

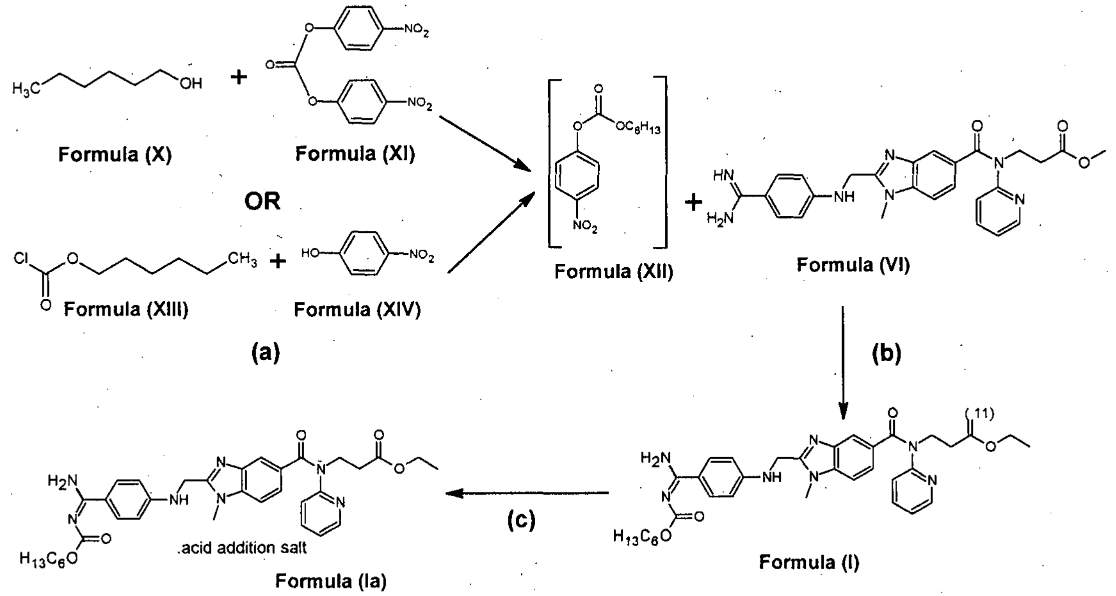
OR

a. reacting hexyl chloroformate of formula **(XIII)** with p-nitrophenol of compound of formula **(XIV)** in a solvent and in presence of a base to provide hexyl-4-nitrophenyl carbonate compound of formula **(XII)**,and optionally isolating compound of formula (XII);

b. treating reaction mass of step (a) containing hexyl-4-nitrophenyl carbonate compound of formula **(XII)**with 1-methyl-2-[N-[4-amidinophenyl]aminomethyl]benzimidazol-5-yl-carboxylicacid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide compound of formula (VI) or its acid addition salt in a solvent and in presence of a base to provide Dabigatran etexilate of formula (I);crystallizing dabigatran etexilate of formula (I) in a suitable solvent to obtain substantially pure dabigatran etexilate of formula (I); and

c. optionally, treating dabigatran etexilate (I) with an acid in an organic solvent to obtain acid addition salt of dabigatran etexilate (I); and

d. isolating the acid addition salt of dabigatran etexilate (Ia) from reaction mixture of step (c).



The solvent used in step (a) is selected from ether solvents, hydrocarbon solvents, polar aprotic solvents, chlorinated solvents, nitrile solvents and the like.

The base used in step (a) and (b) is an organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like. inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or liquor ammonia and the like.

The solvent used in (b) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile, proprionitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water and mixtures thereof.

The solvent used for crystallization in step (b) is selected from the group comprising of alcohols such as but not limited to methanol, ethanol, isopropanol, n-butanol, t-butanol; ketone selected from but not limited to acetone, methyl ethyl ketone; esters selected from but not limited to ethyl acetate, isopropyl acetate, butyl acetate; polar aprotic solvents selected from but not limited to dimethylformamide, dimethylacetamide, N- methylpyrrolidine, dimethylsulfoxide; hydrocarbons selected from but not limited to toluene, xylene; nitriles like acetonitrile and proprionitrile; water and mixtures thereof.

The acid additions salt of step (c) may be an organic acid or inorganic acid addition salt.

The organic acids is selected from but not limited to fumaric acid, benzoic acid, ascorbic, acid succinic acid, oxalic acid, bis-methylenesalicylic acid, camphor sulfonic acid, methanesulfonic acid, ethanesulfonic acid, acetic acid, propionic acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, maleic acid, mandelic acid, cinnamic acid, citraconic acid, aspartic acid, stearic acid, palmitic acid, itaconic acid, glycolic acid, p-aminobenzoic acid, glutamic acid, benzene sulfonic acid, theophylline acetic acids, 8-halotheophylline acid; inorganic acids such as but not limited to hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid; preferably selected from oxalic acid, methanesulfonic acid, camphor sulfonic acid.

The solvent used for preparation of acid additions salt of step (c) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water and mixtures thereof.

Optionally, the isolation of compound of formula (XII) comprises the steps of:

i. treating the reaction mass of step (a) with water;
ii. extracting the aqueous layer of step (i) with an organic solvent;
iii. separating the organic layer of step (ii) followed by washing it with suitable aqueous base;
iv. removing the solvent from the organic layer of step (iii) to obtain the compound of formula (XII) as oil.

The organic solvent used in step (ii) is selected from the group comprising of aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbons such as dichloromethane, chloroform and the like; carboxylic acid esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; ethers such as diethyl ether, diisopropyl ether, di-methyl ether, methyl tertiary butyl ether and the like; substituted cyclic ether such as 2-methyltetrahydrofuran and the like; or mixtures thereof.

The aqueous base used in step (iii) is selected from aqueous solution of alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates.

The solvent in step (iv) may be removed by the known techniques in the art like filtration, decantation, centrifugation, spray drying, evaporation and the like.

EMBODIMENT-5

According to another embodiment of the present invention, there is provided a process for preparation of Dabigatran Etexilate Mesylate (Ia), which comprises of the following steps:

a) dissolving the dabigatran etexilate compound of formula (I) in a suitable solvent at 40°C to reflux temperature of solvent;
b) filtering the reaction mixture;
c) cooling the obtained filtrate;
d) adding a solution of methane sulfonic acid in suitable solvent to the obtained filtrate of step (c);
e) cooling the obtained suspension of step (d);
f) filtering the solid obtained in step (f) and washing with a solvent;
g) drying the solid to obtain crystalline dabigatran etexilate mesylate compound of formula (Ia).

The solvent used in (a), (d) and (f) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water and mixtures thereof.

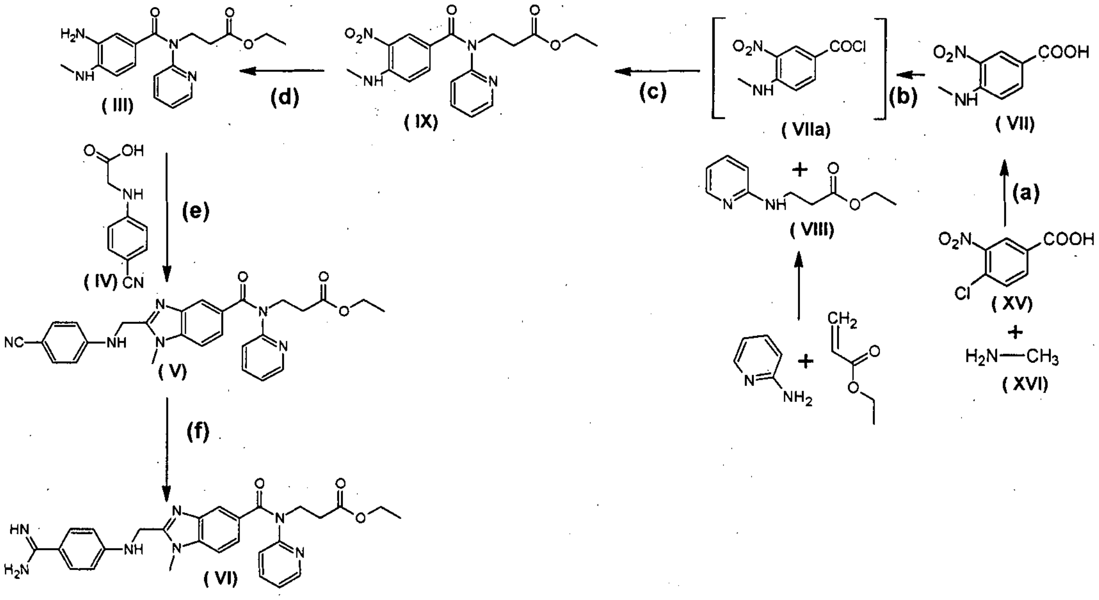
The process for the preparation of dabigatran etexilate mesylate (Ia) are described herein above embodiment as well as those described in the examples.

EMBODIMENT – 6

According to another embodiment of the present invention, there is provided a process for the preparation of compound of formula (VI) or its acid addition salt comprising the steps of:

a) reacting 4-chloro-3-nitrobenzoic acid of formula (XV) with monomethyl amine of formula (XVI) to obtain 4-(methyl amino)-3-nitrobenzoic acid of formula (VII);
b) reacting 4-(methyl amino)-3-nitrobenzoic acid of formula (VII) with a halogenating agent in a solvent to obtain corresponding 4-(methyl amino)-3-nitrobenzoyl halide of formula (VIIa);
c) reacting 4-(methyl amino)-3-nitrobenzoyl halide of formula (VIIa) in-situ with ethyl 3-(pyridine-2-ylamino) propanoate of formula (VIII) in a solvent and in presence of a base to obtain ethyl-3-(4-(methylamino)-3-nitro-*N*-(pyridine-2-yl)benzamido)propanoateof formula (IX) and optionally isolating and purifying compound of formula (IX);
d) reducing compound of formula (IX) in a solvent to obtain 3-(3-amino-4-(methylamino)-*N*-(pyidin-2-yl)benzamido)propanoate of formula (III); optionally isolating and purifying compound of formula (III);
e) reacting compound of formula (III) with 2-(4-cyanophenylamino)acetic acid of formula (IV) in presence of a coupling agent, solvent and acid to obtain 1-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonylethyl]-amide of formula (V); and optionally isolating and purifying compound of formula (V);

f) reacting compound of formula (V) with an acid in a solvent to obtain reaction mixture, basifying the reaction mixture to obtain1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5- benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonyl)-ethyl]- amide of formula (VI); and
g) optionally isolating and purifying compound of formula (VI).



The compound of formula (VI) is used for preparation of dabigatran etexilate of formula (I) and its acid addition salt of formula (Ia).

The suitable solvent used in step (b) and step (c) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane, chloroform and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; water and mixtures thereof.

The halogenating agent used in step (b) is selected from thionyl chloride, phosphorous trichloride, phosphorous pentachloride, phosphorus oxychloride, oxalyl chloride and the like.

The reaction step (b) may be performed in presence of catalytic amount of dimethylformamide.

The suitable base used in step (c) of the reaction is an organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like; inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or liquor ammonia and the like.

Compound of formula (IX) obtained in step (c) and compound of formula (III) obtained in step (d) can also be purified by the process like crystallization, recrystallization, re-saltification or by solvent purification.

The solvent used for isolation and crystallization of compound of formula (IX) obtained in step (c) and compound of formula (III) obtained in step (d) may be same or different and is selected from is selected from "Ester solvents" such as but not limited to ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate, Sec-butyl acetate, tert-butyl acetate; "Ether solvents" such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropyl ether, and Di-tert-butyl ether; "Hydrocarbon solvents" such as but not limited to toluene, xylene, hexane, heptane, pentane, cyclohexane, cycloheptane, cyclopentane, and cyclooctane; "Polar aprotic solvents" such as but not limited to dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide; "ketone solvents" such as but not limited to acetone, methyl ethyl ketone/butanone, methyl isobutyl ketone, and methyl isopropyl ketone; "Alcoholic solvents" such as but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol, sec-butanol, ter-butanol, ethylene glycol, 2-ethyl hexanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, 2-pentanol, propylene glycol, hexylene glycol, triethylene glycol, tripropylene glycol; "Chlorinated solvents" such as but not limited to dichloro methane, chloroform and dichloro ethane; "Nitrile solvents" such as but not limited to acetonitrile and propionitrile, butyronitrile; "Nitro solvents" such as but not limited to nitro methane, nitro ethane, and nitro benzene; polar solvents like water; and mixtures thereof.

The reducing agent used in step (d) is selected from but not limited to Sn/HCl, Fe/HCl, $Na_2S_2O_4$, sodium borohydride, lithium aluminium hydride, Raney nickel, Pd/C and Pt/C.

The solvent used in reduction step (d) is selected from the group comprising "Ester solvents" such as but not limited to ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate, Sec-butyl acetate, tert-butyl acetate; "Ether solvents" such as but not limited to tetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropyl ether, and Di-tert-butyl ether; "Hydrocarbon solvents" such as but not limited to toluene, xylene, hexane, heptane, pentane, cyclohexane, cycloheptane, cyclopentane, and cyclooctane; "Polar aprotic solvents" such as but not limited to dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide; "ketone solvents" such as but not limited to acetone, methyl ethyl ketone/butanone, methyl isobutyl ketone, and methyl isopropyl ketone; "Alcoholic solvents" such as but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol, sec-butanol, ter-butanol, ethylene glycol, 2-ethyl hexanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, 2-pentanol, propylene glycol, hexylene glycol, triethylene glycol, tripropylene glycol.

Optionally, the process further includes removal of solvent from step (d) to obtain compound of formula (III).

The compound of formula (V) obtained in step (e) can be optionally converted into its acid addition salt before isolating and purifying the compound of formula (V). The acid addition salt of (V) is further converted to its free base and further purified by crystallization process to obtain highly pure compound of formula (V).

The solvent used in step (e) is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The acid used in step (e) is selected from acetic acid, and halogenated acetic acid.

The coupling agent used in step (e) is selected from but not limited to Pivaloyl chloride, N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminoprpyl) carbodiimide (EDCI) or its salts, 1,1'-carbonyldiimidazole (CDI), diphenylphosphorylazide (DPPA), diethylphosphoryl cyanide (DEPC), 3-(Diethoxyphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one (DEPBT), 4-(4,6-Dimethoxy-1,3,5-triazin-2-yl)-4-methylmorpholinium chloride (DMTMM), 1-[Bis(dimethylamino)methylene]-1H-1,2,3-triazolo[4,5-b]pyridinium 3-oxid hexafluorophosphate (HATU), (O-(7-Azabenzotriazole-1-yl)-N,N,N',N'-tetramethyluroniumtetrafluoroborate) (TATU),2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetramethyluroniumhexafluorophosphate (HBTU), 1-Hydroxy-7-azabenzotriazole(HOAt),2-(1H-Benzotriazole-1-yl)-1,1,3,3-tetra methyluroniumtetrafluoroborate (TBTU), and the like.

The step (e) further comprises isolation of compound of formula (v) followed by purification of it; wherein the said process of isolation and purification comprises the steps of:

i. removal of solvent from the reaction mass of step (e) to obtain compound of formula (v) as residue;
ii. treating the residue of compound of formula (v) of step (i) with solvent and water; basifying the mixture obtained, separating the organic layer, followed by washing with water;
iii. distilling the organic layer of step (ii) to obtain residue;
iv. dissolving the residue in a suitable solvent by heating to obtain solution and treating the solution with an acid in suitable solvent to get suspension;
v. cooling the obtained suspension of step (iv);
vi. filtering the obtained solid and washing with a solvent to obtain wet solid of acid addition salt of compound of formula (v);
vii. optionally, drying the obtained wet solid of step (vi);
viii. basifying the acid addition salt of compound of formula (v) in a suitable solvent to obtain free base of compound of formula (v), and extracting the compound of formula (V) in a suitable solvent;
ix. distilling the organic layer of step (v) to obtain residue of compound of formula (v); and
x. crystallizing compound of formula (v) obtained in step (ix) using solvent to obtain pure compound of formula (v).

The solvent in step (i) may be removed by the known techniques in the art like filtration, decantation, centrifugation, spray drying, evaporation and the like.

The solvent used in step (ii), (iv), (vi), (viii) and (x) may be same or different and is selected from alcohols such as methanol, ethanol, isopropanol, n-butanol and the like; aromatic hydrocarbons such as toluene, xylene, and the like; aliphatic hydrocarbons such as hexane, heptane and the like; halogenated hydrocarbon such as dichloromethane, dichloroethane, chloroform and the like; formamide such as N,N-dimethylformamide, N,N-dimethylacetamide and the like; sulfoxides such as dimethylsulfoxide and the like; cyclic amides such as N-Methylpyrrolidinone and the like; nitriles such as acetonitrile and the like; ketones such as acetone, methyl isobutyl ketone and the like; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether and the like; esters such as ethyl acetate, methyl acetate, isopropyl acetate and the like; or a mixture thereof.

The base used in step (ii) and (viii) is an organic or inorganic base; organic bases such as but not limited 1, 8-diazabicyclo[5.4.0]undec-7-ene; 1,5-diazabicyclo[4.3.0]non-5-ene; primary amines such as but not limited to methylamine, propyl amine, 2-propyl amine, butyl amine, and the like; secondary amines such as but not limited to N,N-diisopropyl amine, dimethylamine, diethyl amine, N-methyl propyl amine, morpholine, and the like; tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine or substituted pyridine such as but not limited to 2,6 lutidine, 2,4 lutidine, 3,5 lutidine and the like; pyrimidine, N,N-dimethylethyl amine and the like metal alkoxides and the like and inorganic bases such as but not limited to alkali metal carbonates such as but not limited to potassium carbonate, sodium carbonate, cesium carbonate and the like; alkali metal bicarbonates such as but not limited to sodium bicarbonate, potassium bicarbonate and the like; alkali metal hydroxides such as but not limited to sodium hydroxide, potassium hydroxide, barium hydroxide , lithium hydroxide and the like; metal hydrides, metal alkoxides such as but not limited to sodium methoxide, sodium ethoxide, potassium tertbutoxide and the like; metal amides or ammonia gas, ammonium carbonate, liquor ammonia and the like.

The acid used in step (iv) may be selected from organic or inorganic acid, inorganic acids is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; organic acids such as trifluoroacetic acid, acetic acid, methane sulfonic acid, 2,5-dihydroxy benzoic acid, ethanedisulfonic acid, p-toluene sulfonic acid (PTSA), benzene sulfonic acid, ethane disulfonic acid, ethane sulfonic acid, naphthalene disulfonic acid, naphthalene-2- sulfonic acid, camphor sulfonic acid, acetic acid, oxalic acid, fumaric acid, maleic acid, oleic acid, malic acid, adipic acid, stearic acid, cinnamic acid, succinic acid, malonic acid, mandelic acid, palmitic acid, pamoic acid, ascorbic acid, lactic acid, citric acid, tartaric acid, gentisic acid, cyclamic acid, D-glucuronic acid, glycolic acid, isethionic acid, saccharine, salicylic acid, naphthalene- 1 ,5-disulfonic acid and the like.

The acid used in step (f) may be selected from organic or inorganic acid and is selected from but not limited to formic acid, acetic acid, trifluoroacetic acid, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like.

The hydrochloric acid used in step (f) may be aqueous hydrochloric acid, hydrochloric acid gas or solution of hydrochloric acid in a solvent like methanol, ethanol, isopropanol, acetone, ethyl acetate and the like. In particular, alcoholic hydrochloric acid in alcoholic solvents like ethanol may be used.

The base used for basifying reaction mixture in step (f) is selected from ammonia gas, ammonium carbonate, ammonical solution in alcohols like methanol, ethanol, isopropanol, butanol and the like or mixture thereof.

The solvent used in step (f) is selected from "Ester solvents" such as but not limited to ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate, Sec-butyl acetate, tert-butyl acetate; "Ether solvents" such as but not limited totetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropyl ether, and Di-tert-butyl ether; "Hydrocarbon solvents" such as but not limited to toluene, xylene, hexane, heptane, pentane, cyclohexane, cycloheptane, cyclopentane, and cyclooctane; "Polar aprotic solvents" such as but not limited to dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide; "ketone solvents" such as but not limited to acetone, methyl ethyl ketone/butanone, methyl isobutyl ketone, and methyl isopropyl ketone; "Alcoholic solvents" such as but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol, sec-butanol, ter-butanol, ethylene glycol, 2-ethyl hexanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, 2-pentanol, propylene glycol, hexylene glycol, triethylene glycol, tripropylene glycol; "Chlorinated solvents" such as but not limited to dichloro methane, chloroform and dichloro ethane; "Nitrile solvents" such as but not limited to acetonitrile and propionitrile, butyronitrile; "Nitro solvents" such as but not limited to nitro methane, nitro ethane, and nitro benzene; polar solvents like water; and mixtures thereof.

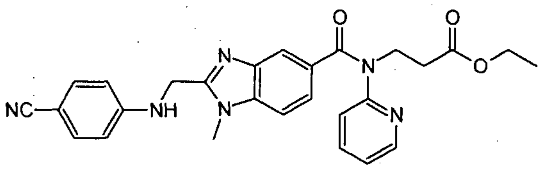
The step (g) further comprises isolation of crude compound of formula (VI) followed by purification of it; wherein the said process of isolation and purification comprises the steps of:

i. removal of solvent from reaction mass of step (f) which comprises of filtering the reaction mass and evaporation of the solvent to obtain compound of formula (VI) or its acid addition salt as residue;
ii. treating the residue of compound of formula (VI) or its acid addition salt of step (i) with solvent; heating at 60 to 90°C, cooling the solution to 0 to 30 °C, filtering the precipitate, washing the obtained precipitate with solvent followed by drying to obtain pure compound of formula (VI);

The solvent used for crystallization step (ii) is selected from "Ester solvents" such as but not limited to ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate, Sec-butyl acetate, tert-butyl acetate; "Ether solvents" such as but not limited totetrahydrofuran, 2-methyl tetrahydrofuran, diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropyl ether, and Di-tert-butyl ether; "Hydrocarbon solvents" such as but not limited to toluene, xylene, hexane, heptane, pentane, cyclohexane, cycloheptane, cyclopentane, and cyclooctane; "Polar aprotic solvents" such as but not limited to dimethyl acetamide, dimethyl formamide, dimethyl sulfoxide; "ketone solvents" such as but not limited to acetone, methyl ethyl ketone/butanone, methyl isobutyl ketone, and methyl isopropyl ketone; "Alcoholic solvents" such as but not limited to methanol, ethanol, n-propanol, isopropanol, n-butanol and isobutanol, sec-butanol, ter-butanol, ethylene glycol, 2-ethyl hexanol, 2-methyl-1-butanol, 2-methyl-1-pentanol, 3-methyl-2-butanol, 2-pentanol, propylene glycol, hexylene glycol, triethylene glycol, tripropylene glycol; "Chlorinated solvents" such as but not limited to dichloro methane, chloroform and dichloro ethane; "Nitrile solvents" such as but not limited to acetonitrile and propionitrile, butyronitrile; "Nitro solvents" such as but not limited to nitro methane, nitro ethane, and nitro benzene; polar solvents like water; and mixtures thereof.

The dabigatran etexilate mesylate of Formula (Ia) prepared by the process of present invention is crystalline form-I is substantially free from impurities.

According to another embodiment, the present invention provides an isolated acid addition salt of compound of formula (V).

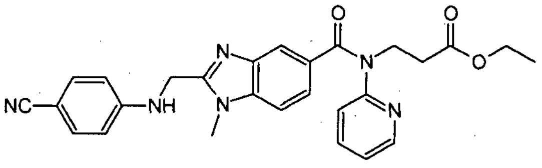


.acid addition salt

Formula (V)

The acid addition salt of compound of formula (V) may be prepared by using acid selected from organic or inorganic acid, inorganic acids is selected from hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid and the like; organic acids such as trifluoroacetic acid, acetic acid, methane sulfonic acid, 2,5-dihydroxy benzoic acid, ethanedisulfonic acid, p-toluene sulfonic acid (PTSA), benzene sulfonic acid, ethane disulfonic acid, ethane sulfonic acid, naphthalene disulfonic acid, naphthalene-2- sulfonic acid, camphor sulfonic acid, acetic acid, oxalic acid, fumaric acid, maleic acid, oleic acid, malic acid, adipic acid, stearic acid, cinnamic acid, succinic acid, malonic acid, mandelic acid, palmitic acid, pamoic acid, ascorbic acid, lactic acid, citric acid, tartaric acid, gentisic acid, cyclamic acid, D-glucuronic acid, glycolic acid, isethionic acid, saccharine, salicylic acid, naphthalene- 1 ,5-disulfonic acid and the like.

In a preferred embodiment of the present invention, the acid addition salt is p-toluenesulfonic acid.



.p-toluene sulfonic acid

Formula (V)

According to another embodiment, the present invention provides a crystalline form of p-toluene sulfonate of compound of formula (V).

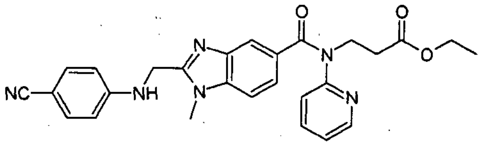
Figure 1 of the present invention illustrates X-ray powder diffraction (XRD) pattern of p-toluene sulfonate of compound of formula (V), prepared according to example h, exhibits the characteristic peaks at 4.78, 9.54, 14.85, 15.07, 15.32, 16.92, 17.24, 19.14, 19.57, 19.89, 22.69 and 24.
37 ± 0.2° 2θ.The X-ray diffractogram was measured on BrukerAxe, DS advance Power X-ray Diffractometer with Cu K alpha-1 Radiation source having the wavelength 1.541A°.

Figure 2 of the present invention illustrates Infrared spectrum (IR) pattern of p-toluene sulfonate of compound of formula (V), prepared according to example h. The IR spectrum of p-toluene sulfonate of compound of formula (V) having characteristic peaks at 3277.1, 2977,2214.9, 1735.5, 1609.8, 1641.9, 1533.2, 1468.8, 1397.4, 1333.2, 1222.9, 1176.8, 1159.4 cm^{-1}.The IR spectra of co-precipitates of the invention has been recorded on a Fourier Transform Infrared Spectroscopy, Perkin Elmer model 100 instrument using potassium bromide pellet method.

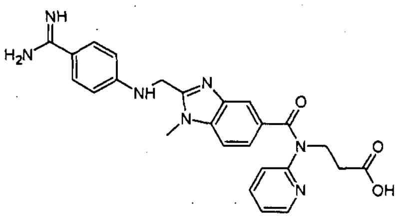
The term "substantially free" herein means dabigatran etexilate mesylate having about 99.0% purity. In particular, dabigatran etexilate mesylate has about 99.50 % purity. More particular, dabigatran etexilate mesylate having about 99.81% purity, when measured by HPLC.

Dabigatran etexilate (I) or its acid addition salt (Ia) prepared according to any of the processes of the present invention has less than about 0.2% of the following impurities:

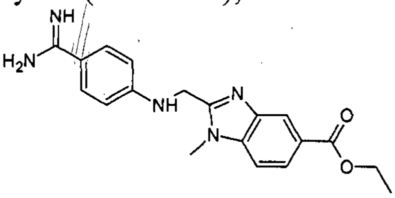
1. 3-[[[2-[[(4-Cyanophenyl)amino]methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]
   Pyridine-2-ylamino]propionic acid ethyl ester (DBIMP-1);



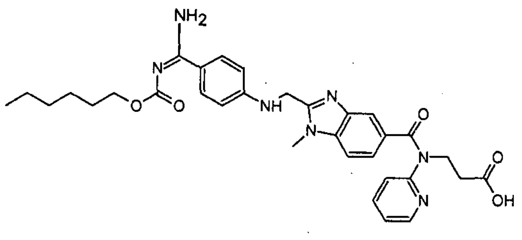
2. (3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoic acid (DBIMP-2);



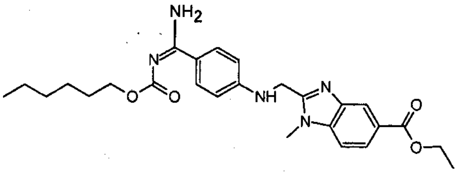
3. Ethyl 2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-carboxylate (DBIMP-3);



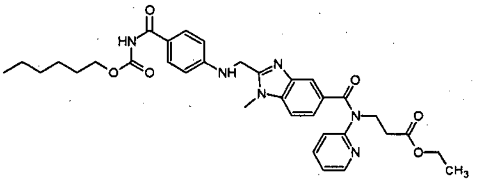
4. 3-{[(2-{[(4-{[(hexyloxy)carbonyl]carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoic acid (DBIMP-4);



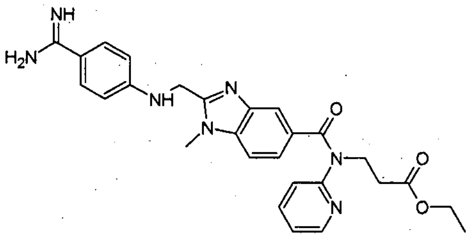
5. ethyl 2-{[(4-{[(hexyloxy)carbonyl]carbamimidoyl}phenyl)amino]methyl-1-methyl-1H-benzimidazol-5-carboxylate (DBIMP-5);



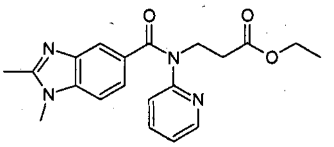
6. 3-{[(2-{[(4-{[(hexyloxy}carbonyl)amino]carbonyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate (DBIMP-6);



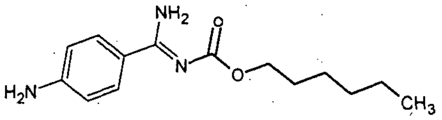
7. 3-{[(2-{[(4--{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate (DBIMP-7);



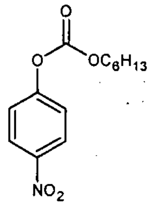
8. Ethyl 3-{[(1,2-dimethyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate (DBIMP-8);



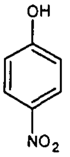
9. 4-{[(hexyloxy)carbonyl]carbamimidoyl}aniline (DBIMP-9);



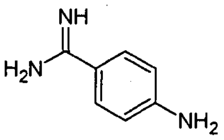
10. Hexyl 4-nitrophenyl carbonate (DBIMP-10);



11. Para nitro phenol (DBIMP-11);



12. 4-amino benzamidine (DBIMP-12);



BEST MODE OR EXAMPLES FOR WORKING OF THE INVENTION

The present invention is described in the examples given below; further these are provided only to illustrate the invention and therefore should not be construed to limit the scope of the invention.

Example: Synthesis of dabigatran etexilate mesylate

a)4-(Methylamino)-3-nitrobenzoic acid (VII):

300 g (1.49mol) of 4-chloro-3-nitrobenzoic acid was suspended in 769 g of a 25-30% aqueous solution of methylamine. After heating to reflux temperature, a clear

solution was obtained. The solution was kept at reflux temperature for 2 hours and the completion of reaction was checked by TLC. The solution was cooled to room temperature, and pH of reaction mixture was adjusted to about 1 by addition of 2M aqueous sulphuric acid. Precipitation of a yellow solid was observed, which was isolated by filtration. The filtered cake was washed with water and subsequently with methanol to obtain 338 g of wet 4-(methylamino)-3-nitrobenzoic acid as a yellow powder.

Yield: 280g (95.90%); Purity by HPLC: 99.10 %.

b) Ethyl 3-(2-pyridylamino) propanoate (VIII):

75.2 g (0.80 mol) of 2-aminopyridine was dissolved in 88.0 g (0.88 mol) of ethyl acrylate and 20 mL of acetic acid. The mixture was heated to 80°C and stirred for 24 hours at the same temperature. Solvent was removed under vacuum, and the title compound was isolated by vacuum distillation to obtain 77.0 g of ethyl 3-(2-pyridylamino)propionate as a white solid.

Yield: 77.0g (49.67%); Purity by HPLC: 98.5%.

c) Ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl} carbonyl](pyridyn-2-yl)amino]propanoate (IX):

100 g (0.50mol) of 4-(methylamino)-3-nitrobenzoic acid as obtained in step (a) was suspended in 800 ml dichloromethane. To the obtained suspension was added of 200 ml of thionyl chloride diluted with 200 ml dichloromethane. Finally to the reaction mixture was added 2 ml of N,N-dimethylformamide. The mixture was stirred at reflux temperature for 4-5 hr. completion of reaction was monitored by TLC. Excess thionyl chloride was removed by vacuum distillation. The residue was dissolved in 100 ml of dichloromethane which was distilled under vacuum. Finally to the obtained residue was charged 700 ml of dichloromethane and solution was cooled to 0-5°C. To the cooled solution was added mixture of 213 ml triethylamine and 100 ml

dichloromethane at 0-10°C temperature and stirred for 10-15 min. Finally to the reaction mixture was added 93 gm (0.48 mol) Ethyl 3-(2-pyridylamino)propanoate dissolved in 200 ml dichloromethane at 0-10°C temperature and stirred for 10-15 min. Reaction mixture was then warmed to 25-30°C and stirred for 4-5 hr and completion of reaction was monitored by TLC. Upon completion of reaction, reaction mixture was quenched with 1.0 Lit purified water at 0-10°C and stirred for 30 min. Layers were then allowed to separate for 30 min. Organic layer was separated and was washed with purified water 1.0 Lit at 0-10°C. Finally organic layer was washed with 2% HCl solution 1.0 Lit X 3 times. The obtained organic layer was then washed with 10% sodium bicarbonate solution 1.0 lit X 2 times. Dichloromethane layer was then distilled under vacuum to obtain crude Ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate.

Yield: 180 g (94.82%); Purity by HPLC: 97.6 %.

d)Purification of Ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate (IX):

100 gm of crude ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate was dissolved in 300 ml isopropyl alcohol at 65-70°C. To the obtained clear solution was added 5.0 gm activated charcoal and stirred for 20 min. Solution was then filtered over celite bed and bed was subsequently washed with 100 ml isopropyl alcohol, combined filtrate was cooled to 0-5°C and stirred for 60 min. precipitated product was filtered and dried at 50-55°C to obtain pure ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate.

Yield: 83.0g (83%); Purity by HPLC: 99.4 %.

e)Ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate (III):

100 gm of crude ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate as obtained in example c) was dissolved in 1.0 lit ethyl acetate

to the obtained clear solution. Then to this solution (20 gm) was added Raney nickel and reaction mixture was hydrogenated at 60-65°C under 10 bar pressure. Completion of reaction was monitored by TLC. Upon completion of reaction, reaction mixture was filtered over celite bed and bed was subsequently washed with 200 ml ethyl acetate. Combined filtrate was concentrated under vacuum to obtain crude ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate.

Yield: 90.0g (97.88%); Purity by HPLC: 96.5 %.

f)Purification of ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate (III):

100gm of crude ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}

Propanoate as obtained in example e) was dissolved in 100 ml ethyl acetate at 75-80°C. To the obtained clear solution was added slowly 100 ml diisopropyl ether at 75-80°C and stirred for 10-15 min. Cool the solution to 0-5°C and 400 ml diisopropyl ether was added which was further cooled to 0-5°C and stirred for 60 min. precipitated product was filtered and dried at 50-55°C to obtain pure ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate.

Yield: 92.73g (92.73%); Purity by HPLC: 98.51 %.

g)Ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate (III):

100gm (0.268 mol) pure ethyl3-{[{1-(methylamino)-2-nitrophen-4-yl}carbonyl](pyridyn-2-yl)aminol propanoate as obtained in example c) was dissolved in 1.0 lit ethyl acetate to obtain clear solution. To this clear solution (20 gm) Raney nickel was added and reaction mixture was hydrogenated at 60-65°C under 10 bar pressure. Completion of reaction was monitored by TLC. Upon completion of reaction, reaction mixture was filtered over celite bed and bed was subsequently washed with 200 ml ethyl acetate. Combined filtrate was concentrated under vacuum to obtain crude Ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}Propanoate.

Yield: 85.4g (9286%); Purity by HPLC: 99.40 %.

h)Ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate (v):

66 gm (0.379mol) of 2-(4-cyanophenylamino) acetic acid was suspended in 500ml tetrahydrofuran and suspension was cooled to 0-5°C. To the cooled suspension to 45.7 gm (0.379 mol) pivaloyl chloride was added and stirred at 0-5°C for 10-15 min. To the obtained clear solution was added 49 gm (0.379 mol) diisopropyl ethyl amine and stirred for 10 min.

To the reaction mixture was added 100 gm (0.292 mol) ethyl3-{[{2-amino-1-(methylamino)phen-4-yl}carbonyl](pyridyn-2-yl)amino}propanoate and stirred for 5 min at 0-5°C. To the reaction mixture was charged 200 ml acetic acid and stirred for 10-15 min at 0-15°C. Reaction mixture was then heated to 80-85°C and maintained the temperature for 2-4 hr. Completion of reaction was monitored by TLC. Upon completion of reaction, reaction mass was concentrated under vacuum at below 70°C to obtain residue. Obtained residue was cooled to 25-30°C. To the obtained residue was charged purified 500 ml water and 500 ml dichloromethane, pH of the reaction mass was adjusted to 8-9 using aq.ammonia. Reaction mixture was stirred for 30 min. and layers were separated. Aqueous layer was again extracted with 500 ml dichloromethane. Combined organic layer was washed with water 500 ml Dichloromethane layer was then distilled out under vacuum at below 45°C to obtain residue. Obtained residue was cooled to 25-30°C and was charged with 500 ml acetone and stirred to dissolve. The obtained solution was heated to 50-55°C and was charged with para toluene sulphonic acid solution prepared by using 55 gm paratoluenesulphonic acid and 100 ml ethanol, reaction mixture was stirred for 20-30 min. at 50-55°C and then cooled to 0-5°C. Precipitated solid was stirred at 0-5°C for around 60 min. and filtered. Obtained wet cake was dried under vacuum at 50-55°C to obtain p-toluene sulfonate salt of ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1h-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

Yield: 172 g (89.59 %); Purity by HPLC: 97.1%.

172 gm of p-toluene sulfonate salt of ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1h-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was suspended in mixture of 860 ml dichloromethane and 860 ml water. The obtained suspension was basified using aq. Ammonia to pH 8-10 and stirred for 20-25 min. Layers were then separated and aq. Layer was again extracted with 860 ml dichloromethane. Dichloromethane layers were combined and washed with 860 ml water, finally dichloromethane layer was distilled out under vacuum at below 45°C to obtain residue. Obtained reside was finally crystallized from mixture of ethyl acetate and acetone to obtain ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1h-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

Yield: 118g (95.5%); Purity by HPLC: 99. 81%.

i)Ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate (VI):

Varient-01

100 gm (0.192 mol) of Ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was added to 465 ml ethanolic hydrochloride solution having HCl content between 34 to 36 at temperature not more than 35°C. Upon complete addition reaction mixture was stirred for 10-15 min. and temperature of reaction was raised to 38-42°C. Completion of reaction was monitored by HPLC. Reaction mixture was then cooled to 25-30°C and diluted with

ethanol 1400 ml. reaction mixture was then cooled to 0-5°C and was purged with ammonia gas till to achieve neutral pH. To the reaction mixture was added ammonium carbonate 93 gm and reaction mixture was warmed to 28-32°C and stirred for 10-12 hr. completion of reaction was monitored by HPLC. Reaction mixture was filtered and the residue was washed with ethanol 465 ml. combined filtrate was concentrated under vacuum to obtain residue. To the obtained residue was added ethanol 465 ml and 930 ml ethyl acetate. Mixture was refluxed for 30 min. and then cooled to 25-30°C. precipitated product was stirred for 60 min. at 25-30°C and then filtered and dried at 40-45°C to obtain crude Ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

Yield: 97g (93.71%); Purity by HPLC: 94.0 %.

Varient-02

100 gm (0.207 mol) Ethyl3-{[(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was added to 500 ml ethanolic hydrochloride solution having HCl content between 34 to 36 at temperature not more than 35°C. Upon complete addition reaction mixture was stirred for 10-15 min. and temperature of reaction was raised to 38-42°C. Completion of reaction was monitored by HPLC. Reaction mixture was then cooled to 25-30°C and diluted with 1500 ml ethanol. reaction mixture was then cooled to 0-5°C and was purged with ammonia gas till to achieve neutral pH. To the reaction mixture was added 75 gm ammonium carbonate and reaction mixture was warmed to 28-32°C and stirred for 10-12 hr. completion of reaction was monitored by HPLC. Reaction mixture was filtered and the residue was washed with ethanol 500 ml. combined filtrate was concentrated under vacuum to obtain residue. To the obtained residue was added 500 ml ethanol and 1000 ml ethyl acetate. Mixture was refluxed for 30 min. and then cooled to 25-30°C. precipitated product was stirred for 60 min. at 25-30°C and then

filtered and dried at 40-45°C to obtain crude Ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

Yield: 100g (96.61%); Purity by HPLC: 95.3 %.

j)Purification of crude ethyl3-{[(2-{[(4-{carbamimidoyl} phenyl)amino] methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

100 gm of crude ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was suspended in mixture of 500 ml ethanol and 250 ml ethyl acetate. obtained suspension was refluxed for 60 min. and then cooled to 25-30°C and stirred for 60 min. precipitated product was filtered and dried at 40-45°C to obtain 95 gm of pure Ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate.

Yield: 95g (95.0%): Purity by HPLC: 97.4 %.

k)hexyl-4-nitrophenyl carbonate:

Varient-01:

100 gm (0.328 mol) Bis-(4-nitrophenyl) carbonate was dissolved in 1500 ml dichloromethane. To the obtained clear solution was added 33.2 gm (0.328 mol) triethylamine. To the reaction mixture was added 33.59 gm (0.329 mol) n-hexanol. Reaction mixture was stirred at 25-30°C for 5-6 hr. completion of reaction was monitored by TLC. Upon completion of reaction, reaction mixture was quenched with 1000 ml water. Organic layer was separated and aqueous layer was extracted with 500 ml dichloromethane. Combined dichloromethane layer was washed two times with 1000 ml 1% NaOH solution. Finally dichloromethane layer was washed

two times with 1000 ml purified water. Dichloromethane was removed under vacuum to obtain title compound.

Yield: 83.3 g (94.84%); Purity by HPLC: 96.65%.

Varient-02:

100 gm (0.718 mol) para nitro phenol was dissolved in 1000 ml dichloromethane. To the obtained clear solution was added 80 gm (0.790 mol) triethylamine. Reaction mixture was then cooled to 0-5°C. To the reaction mixture was added pure 165 gm (1.0 mol) n-hexyl chloroformate at 0-5°C. Reaction was then stirred at 0-5°C for 5-6 hr. the completion of reaction was monitored by TLC. Upon completion of reaction, reaction mixture was quenched with 1000 ml water. Organic layer was separated and aqueous layer was extracted with 500 ml dichloromethane. Combined dichloromethane layer was washed two times with 1000ml 0.5N NaOH solution. Finally dichloromethane layer was washed two times with 1000 ml purified water. Dichloromethane was removed under vacuum to obtain title compound.

Yield: 132 g (68.71%); Purity by HPLC:99.73%.

l)Dabigatran etexilate:

Varient-01

100 gm (0.200 mol) ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was added to the mixture of 900 ml acetonitrile, 150 ml purified water and 82.8 gm (0.6 mol) potassium carbonate at 25-30°C. To the reaction mixture was added 72.2 gm (0.27 mol) hexyl-4-nitrophenyl carbonate. Reaction mixture was then stirred for 4-6 hr. at 25-30°C. Completion was monitored by HPLC. Upon completion of reaction, reaction mixture was cooled to 0-5°C and stirred for 60 min. Precipitated product was filtered to obtain wet solid. To the obtained wet solid 1000ml purified water was

added and stirred for 60 min to form slurry, filtered and dried at 50-55°C to obtain dabigatran etexilate.

Yield: 100 g (79.61%); Purity by HPLC: 99.11%.

Varient-02

100 gm (0.200 mol) ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was added to the mixture of 2-methyl tetrahydrofuran, 1580 ml purified water and 82.8 gm (0.6mol) potassium carbonate at 25-30°C. To the reaction mixture was added 58.8 gm (0.22mol) hexyl-4-nitrophenyl carbonate. Reaction mixture was then stirred for 5-6 hr. at 25-30°C. Completion of reaction was monitored by HPLC. Upon completion of reaction, 2-methyl tetrahydrofuran was distilled out under vacuum. To the concentrated mass was charged 300 ml dichloromethane and stirred for 15-20 min. Organic layer was separated and aqueous layer was extracted with 300 ml dichloromethane. Finally combined organic layer was washed three times 500 ml with. Finally the organic layer was concentrated under vacuum to obtain residue. To the obtain residue was added 400 ml acetone and mixture was heated to 40-45°C to obtain clear solution. Clear solution was cooled to 25-30°C. Purified 500 ml water was added slowly through dropping funnel to the clear solution of dabigatran etexilate in acetone. Precipitate soild was stirred at 25-30°C for 60 min. and then filtered and dried at 50-55°C to obtain dabigatran etexilate.

Yield: 88 g (70.03%); Purity by HPLC: 90.78%.

Varient-03

100 gm (0.200 mol) ethyl3-{[(2-{[(4-{carbamimidoyl}phenyl)amino]methyl}-1-methyl-1H-benzimidazol-5-yl)carbonyl](pyridin-2-yl)amino}propanoate was added to the mixture of 5000 ml tetrahydrofuran, 1000 ml purified water and 69 gm (0.5mol) potassium carbonate at 25-30°C. To the reaction mixture was added 58.8

gm (0.22 mol) hexyl-4-nitrophenyl carbonate. Reaction mixture was then stirred for 7-8 hr. at 25-30°C. Completion of reaction was monitored by HPLC. Upon completion of reaction, tetrahydrofuran layer was separated. To the obtained tetrahydrofuran layer was added 10% saline solution 1000 ml X 2. Finally the organic layer was concentrated under vacuum to obtain residue. To the obtain residue was added 400 ml acetone and mixture was heated to 40-45°C to obtain clear solution. Clear solution was cooled to 25-30°C. 500 ml purified water was added slowly through dropping funnel to the clear solution of dabigatran etexilate in acetone. Precipitate soild was stirred at 25-30°C for 60 min. and then filtered and dried at 50-55°C to obtain dabigatran etexilate.

Yield: 88 g (70.03%); Purity by HPLC: 94.43%.

m)Purification of Dabigatran etexilate:

Varient-01

100 gm Dabigatran etexilate obtained from the either of the variants as mentioned in example (l) was added to mixture of 500 ml ethyl acetate and 6 ml purified water. Crystallization mixture was then refluxed for 60 min. The obtain clear solution was then seeded with dabigatran etexilate dihydrate and cooled to 0-5°C. Precipitated product was stirred at 0-5°C for 60 min. filtered and dried at 40-45°C to obtain dabigatran etexilate. Moisture content of the dabigatran etexilate dihydrate was 5.5%.

Yield: 87 g (87%); Purity by HPLC: 99.45%.

Varient-02

100 gm Dabigatran etexilate obtained from the either of the variants as mentioned in example (l) was added to mixture of 700 ml acetone and 6 ml purified water. Crystallization mixture was then refluxed for 60 min. The obtain clear solution was then seeded with dabigatran etexilate dihydrate and cooled to 0-5°C. Precipitated

product was stirred at 0-5°C for 60 min. filtered and dried at 40-45°C to obtain dabigatran etexilate. Moisture content of the dabigatran etexilate dihydrate was 5.9%.

Yield: 87g (97%); Purity by HPLC: 99.43%.

Varient-03

100 gm Dabigatran etexilate obtained from the variant 1, as mentioned in example (l) was added to mixture of 500 ml acetone, solution was heated to 45-50° C which was further stirred till clear solution was obtained. The solution was cooled to 25-30°C, to this 400 ml purified water was added slowly then stirred for 60 min at 25-30° Precipitated product was stirred at 0-5°C for 60 min. and then filtered and dried at 40-45°C to obtain dabigatran etexilate. Moisture content of the dabigatran etexilate dihydrate was 5.4%.

Yield: 96g (96%); Purity by HPLC: 99.31%.

Varient-04

100 gm Dabigatran etexilate obtained from the variant 1 as mentioned in example (l) was dissolved in 800 ml acetonitrile at 65-70° C and was stirred for 15 min. The solution was cooled to 25-30°C, stirred for 60 min. The Precipitated product was filtered and dried at 40-45°C to obtain dabigatran etexilate. Moisture content of the dabigatran etexilate dihydrate was 5.4%.

Yield: 95g (95%); Purity by HPLC: 99.75%.

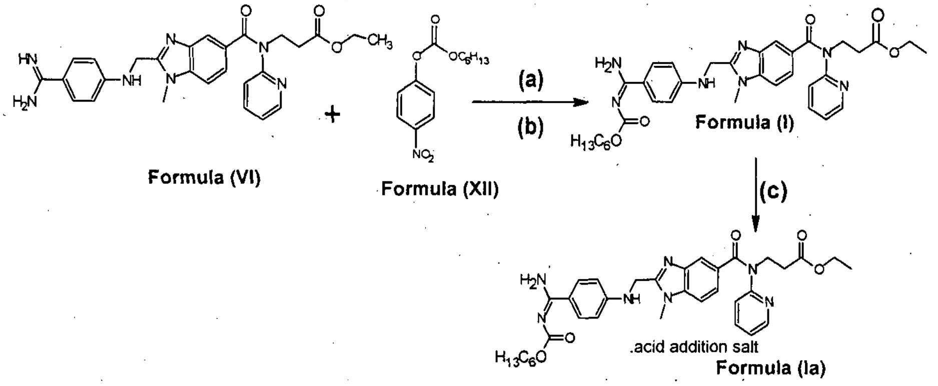
n)Dabigatran etexilate mesylate:

52.6 gm of ethyl 3-[(2{[4(hexyloxycarbonylaminoiminomethyl)phenylamino] methyl}-1-methyl-1H-benzimidazole-5-carbonyl)pyridin-2-ylamino]propionate dihydrate was added to 293 gm of acetone. The obtained mixture was heated to 40-46° C. with stirring. After a clear solution has formed, the contents of the apparatus was filtered and the filtrate was cooled to 30° C. to 36° C. 42 gm of acetone was precooled to 0° C. to 5° C and to it was added 7.5gm of 99.5% methanesulfonic acid. The obtained methanesulfonic acid solution was added in to the solution of ethyl 3-[(2-{[4-(hexyloxycarbonylaminoiminomethyl)phenylamino]methyl}-1-methyl-1H-benzimi-dazole-5-carbonyl)pyridin-2-ylamino]propionate base at 26° C. to 36° C. within 15 to 40 minutes. Then the mixture was stirred for 40 to 60 minutes at 26° C. to 33° C. It was then cooled to 17° C. to 23° C. and stirred for a further 40 to 80 minutes. The crystal suspension was filtered and washed 270 ml of acetone. The product was dried under vacuum at 45-50° C. for at least 4 hours.

Yield: 53g (91.93%); Purity by HPLC: 99.81%.

We Claim:

1. A process for the preparation of dabigatran etexilate of formula (I) or its acid addition salts thereof, comprising;
   a. reacting hexyl-4-nitrophenyl carbonate compound of formula (XII) with 1-methyl-2-[N-[4-amidinophenyl]aminomethyl]benzimidazol-5-yl-carboxylicacid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide (VI) or its acid addition salt in presence of a base and in a suitable organic solvent to provide dabigatran etexilate (I);



   b. crystallizing dabigatran etexilate (I) in a suitable organic solvent to obtain substantially pure dabigatran etexilate of formula (I); and
   c. treating dabigatran etexilate (I) with an acid in an organic solvent to obtain acid addition salt of dabigatran etexilate (I); and
   d. isolating the acid addition salt of dabigatran etexilate (Ia) from reaction mixture of step (c).

2. The process as claimed in claim 1, wherein base used in step (a) is selected from inorganic bases such as alkali metal carbonates such as potassium carbonate, sodium carbonate and the like; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate and the like.

3. The process as claimed in claim 1, wherein suitable organic solvent used in step (a) is selected from ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran; nitriles such as acetonitrile and proprionitrile; water and mixtures thereof.

4. The process as claimed in claim 1, wherein suitable organic solvent for crystallization used in step (b) is selected from nitriles such as acetonitrile and proprionitrile; ketone such as acetone, methyl ethyl ketone; esters such as ethyl acetate, isopropyl acetate: water and mixtures thereof.

5. The process as claimed in claim 1, wherein the acid used for preparation of acid addition salts of dabigatran etexilate (I) in step (c) is selected from fumaric acid, benzoic acid, ascorbic acid, succinic acid, oxalic acid, camphor sulfonic acid, methanesulfonic acid, ethanesulfonic acid, acetic acid, propionic acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, maleic acid , mandelic acid, cinnamic acid, benzene sulfonic acid, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and the like.

6. The process as claimed in claim 1, wherein the solvent used for preparation of acid addition salts of dabigatran etexilate (I) in step (c) is selected from ketones such as acetone, methyl isobutyl ketone; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether; water and mixtures thereof.

7. A process for the preparation of dabigatran etexilate of formula (I) or its acid addition salt of formula (Ia) comprising:
    a. reacting n-hexanol of formula (X) with bis-(4-nitrophenyl) carbonate compound of formula (XI) in a solvent and in presence of a base to obtain

hexyl-4-nitrophenyl carbonate compound of formula (XII), and optionally isolating compound of formula (XII);

OR

a. reacting hexyl chloroformate of formula (XIII) with p-nitrophenol of compound of formula (XIV) in a solvent and in presence of a base to provide hexyl-4-nitrophenyl carbonate compound of formula (XII), and optionally isolating compound of formula (XII);
b. reacting hexyl-4-nitrophenyl carbonate compound of formula (XII) with 1-methyl- 2 [N-[4-amidinophenyl]aminomethyl]benzimidazol-5-yl-carboxylicacid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)amide (VI) or its acid addition salt in presence of base and in a solvent to provide dabigatran etexilate (I); crystallizing dabigatran etexilate of formula (I) in a suitable solvent to obtain substantially pure dabigatran etexilate of formula (I); and
c. optionally, treating dabigatran etexilate (I) with an acid in an organic solvent to obtain acid addition salt of dabigatran etexilate (I); and
d. isolating the acid addition salt of dabigatran etexilate (Ia) from reaction mixture of step (c).

8. The process according to claim 7, hexyl-4-nitrophenyl carbonate compound of formula (XII) obtained in step (a) can be further used without isolation in step (b).

9. The process as claimed in claim 7, wherein suitable organic solvent used in step (a) is selected from chlorinated solvent such as dichloromethane and chloroform.

10. The process as claimed in claim 7, wherein base used in step (a) is selected from tertiary amines such as triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine.

11. The process as claimed in claim 7, wherein the step (a) further comprises isolation of compound (XII);The said process comprises the steps of:
    i. treating the reaction mass of step (a) with water;
    ii. extracting the aqueous layer of step (i) with an organic solvent;
    iii. washing the organic layer of step (ii) with suitable aqueous base;
    iv. removing the solvent from the organic layer of step (iii) to obtain the compound of formula (XII) as oil.

12. The process as claimed in claim 11, wherein solvent used in step (ii) is selected from halogenated hydrocarbons such as dichloromethane, chloroform.

13. The process as claimed in claim 11, wherein aqueous base used in step (iii) is selected from aqueous solution of alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates.

14. The process as claimed in claim 7, wherein suitable organic solvent used in step (b) is selected from ethers such as tetrahydrofuran, 2-methyl tetrahydrofuran; nitriles such as acetonitrile and proprionitrile; water and mixtures thereof.

15. The process as claimed in claim 7, wherein suitable organic solvent for crystallization used in step (b) is selected from nitriles such as acetonitrile and proprionitrile; ketone such as acetone, methyl ethyl ketone; esters such as ethyl acetate, isopropyl acetate; water and mixtures thereof.

16. The process as claimed in claim 7, wherein the acid used for preparation of acid addition salts of dabigatran etexilate (I) in step (c) is selected from fumaric acid, benzoic acid, ascorbic acid, succinic acid, oxalic acid, camphor sulfonic acid,

methanesulfonic acid, ethanesulfonic acid, acetic acid, propionic acid, tartaric acid, salicylic acid, citric acid, gluconic acid, lactic acid, maleic acid , mandelic acid, cinnamic acid, benzene sulfonic acid, hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid and the like.

17. The process as claimed in claim 7, wherein the solvent used for preparation of acid addition salts of step (c) is selected from ketones such as acetone, methyl isobutyl ketone; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether; water and mixtures thereof.

18. A process for preparation of dabigatran etexilate mesylate (Ia), comprising:
    a. dissolving the dabigatran etexilate compound (I) in a suitable solvent at 40° C to reflux temperature of the solvent ;
    b. filtering the solution;
    c. adding a solution of methane sulfonic acid in suitable solvent to the obtained filtrate of step (c);
    d. cooling the obtained suspension of step (d);
    e. filtering the solid obtained in step (f) and washing with a solvent;
    f. drying the solid to obtain crystalline dabigatran etexilate mesylate compound of formula (la).

19. The process as claimed in claim 18, wherein solvent used in steps (a), (d) and (f) is selected from ketones such as acetone, methyl isobutyl ketone; esters such as ethyl acetate, methyl acetate, isopropyl acetate; water and mixture thereof.

20. The process for the preparation of compound of formula (VI) or its acid addition salt comprising the steps of:

a. reacting 4-chloro-3-nitrobenzoic acid of formula (XV) with monomethyl amine of formula (XVI) to obtain 4-(methyl amino)-3-nitrobenzoic acid of formula (VII);
b. reacting 4-(methyl amino)-3-nitrobenzoic acid of formula (VII) with a halogenating agent in a suitable solvent to obtain corresponding 4-(methyl amino)-3-nitrobenzoyl halide of formula (VIIa);
c. reacting 4-(methyl amino)-3-nitrobenzoyl halide of formula (VIIa) in-situ with ethyl 3-(pyridine-2-ylamino) propanoate of formula (VIII) in a suitable solvent in presence of a suitable base to obtain ethyl-3-(4-(methylamino)-3-nitro-N-(pyridine-2-yl)benzamido)propanoateof formula (IX) and optionally isolating and purifying compound of formula (IX);
d. reducing compound of formula (IX) with a suitable reducing agent in a suitable solvent to obtain 3-(3-amino-4-(methylamino)-N-(pyidin-2-yl)benzamido)propanoate of formula (III); optionally isolating and purifying compound of formula (III);
e. reacting compound of formula (III) with 2-(4-cyanophenylamino)acetic acid of formula (IV) in presence of a coupling agent in a solvent in presence of an acid to obtain l-methyl-2-[N-(4-cyanophenyl)-aminomethyl]-5-benzimidazole-carboxylicacid-N-(2-pyridyl)-N-[2-(ethoxycarbonylethyl]-amide of formula (V), and optionally isolating and purifying compound of formula (V);
f. reacting compound of formula (V) with an acid in a suitable organic solvent, basifying the reaction mixture to obtainl-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-5- benzimidazole-carboxylic acid-N-(2-pyridyl)-N-[2-(ethoxycarbonyl)-ethyl]- amide of formula (VI); and
g. optionally isolating and purifying compound of formula (VI).

21. The process as claimed in claim 20, wherein suitable solvent used in step (b) and (c) is selected from halogenated hydrocarbon such as dichloromethane, dichloroethane, chloroform; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran.

22. The process as claimed in claim 20, wherein halogenating agent used in step (b) is selected from thionyl chloride, phosphorous trichloride, phosphorous pentachloride, phosphorus oxychloride, oxalyl chloride and the like;

23. The process as claimed in claim 20, wherein step (b) may be optionally performed in the presence of catalytic amount of dimethylformamide.

24. The process as claimed in claim 20, wherein the base used in step (c) is selected from tertiary amines like triethylamine, N,N-dimethyl aniline, N,N-diisopropyl ethyl amine, trimethyl amine, pyridine.

25. The process as claimed in claim 20, wherein compound (IX) obtained in step (c) and compound (III) obtained in step (d) can also be purified by the process like crystallization, recrystallization, re-saltification or by solvent purification.

26. The process as claimed in claim 20, wherein solvent used for isolation and crystallization of compound of formula (IX) obtained in step (c) and compound of formula (III) obtained in step (d) is selected from alcohols such as methanol, ethanol, n-propanol, isopropanol; esters such as ethyl acetate, methyl acetate, isopropyl acetate; ethers such as diethyl ether, methyl tert-butyl ether, ethyl tert-butyl ether, 1,4- dioxane, dimethoxy ethane, dimethoxy methane, diisopropylether.

27. The process as claimed in claim 20, wherein reducing agent used in step (d) is selected from but not limited to Sn/HCl, Fe/HCl, Na2S2O4, sodium borohydride, lithium aluminium hydride, Raney nickel, Pd/C and Pt/C.

28. The process as claimed in claim 20, wherein solvent used in reduction step (d) is selected from alcohols such as methanol, ethanol, n-propanol, isopropanol; esters such as ethyl acetate, methyl acetate, isopropyl acetate.

29. The process as claimed in claim 20, wherein solvent used in in step (e) is selected from ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, diisopropyl ether, methyl tert-butyl ether, preferably tetrahydrofuran.

30. The process as claimed in claim 20, wherein acid used in step (e) is selected from acetic acid, and halogenated acetic acid.

31. The process as claimed in claim 20, wherein coupling agent used in step (e) is selected from pivaloyl chloride, N,N'-dicyclohexylcarbodiimide (DCC), 1-ethyl-3-(3-dimethylaminoprpyl) carbodiimide (EDCI) or its salts, 1,1'-carbonyldiimidazole (CDI),preferably pivaloyl chloride.

32. The process as claimed in claim 20, wherein step (e) further comprises isolation of compound of formula (V) followed by purification; wherein the said process of isolation, purification comprises the steps of:
    i. removal of solvent from the reaction mass of step (e) to obtain compound of formula (v) as residue;
    ii. treating the residue of compound of formula (v) of step (i) with solvent and water; basifying the mixture obtained, separating the organic layer, followed by washing with water;

iii. distilling the organic layer of step (ii) to obtain residue;
iv. dissolving the residue in a suitable solvent by heating to obtain solution and treating the solution with an acid in suitable solvent to get suspension;
v. cooling the obtained suspension of step (iv);
vi. filtering the obtained solid and washing with a solvent to obtain wet solid of acid addition salt of compound of formula (v);
vii. optionally, drying the obtained wet solid of step (vi);
viii. basifying the acid addition salt of compound of formula (v) in a suitable solvent to obtain free base of compound of formula (v), and extracting the compound of formula (V) in a suitable solvent;
ix. distilling the organic layer of step (v) to obtain residue of compound of formula (v); and
x. crystallizing compound of formula (v) obtained in step (ix) using solvent to obtain pure compound of formula (v).

33. The process as claimed in claim 32, wherein solvent used in step (ii), (iv), (vi), (viii), and (x) is selected from halogenated hydrocarbon such as dichloromethane, dichloroethane, chloroform; ketones such as acetone, methyl isobutyl ketone; alcohols such as methanol, ethanol, isopropanol, n-butanol; esters such as ethyl acetate, methyl acetate, isopropyl acetate.

34. The process as claimed in claim 32, wherein base used in step (ii) and (viii) is selected from ammonia gas, ammonium carbonate, liquor ammonia and the like.

35. The process as claimed in claim 32, wherein acid used in step (iv) may be selected from methane sulfonic acid, p-toluene sulfonic acid (PTSA), benzene sulfonic acid.

36. The process as claimed in claim 20, wherein acid used in step (f) may be selected from hydrochloric acid, hydrobromic acid, sulfuric acid and the like.

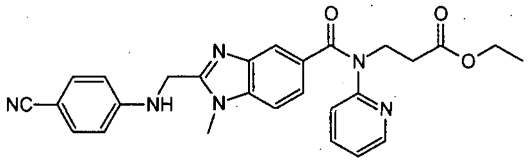
37. The process as claimed in claim 20, wherein solvent used in step (f) is an alcoholic solvent such as methanol, ethanol, propanol and isopropanol.

38. The process as claimed in claim 20, wherein base used for basifying reaction mixture in step (f) is selected from ammonia gas, ammonium carbonate, ammonical solution in alcohols like methanol, ethanol, isopropanol.

39. The process as claimed in claim 20, wherein step (g) further comprises isolation of crude compound of formula (VI) followed by purification; wherein the said process of isolation and purification comprises the steps of:
    i. removal of solvent from reaction mass of step (f) which comprises of filtering the reaction mass and evaporation of the solvent to obtain compound of formula (VI) or its acid addition salt as residue;
    ii. treating the residue of compound of formula (VI) or its acid addition salt of step (i) with solvent; heating at 60 to 90°C, cooling the solution to 0.to 30 °C, filtering the precipitate, washing the obtained precipitate with solvent followed by drying to obtain pure compound of formula (VI).

40. The process as claimed in claim 39, wherein solvent used for crystallization in step (ii) is selected from alcohols such as methanol, ethanol, and isopropanol; esters such as ethyl acetate, methyl acetate, isopropyl acetate, hexyl acetate, butyl acetate and mixture thereof, preferably mixture of ethanol and ethyl acetate.

41. A compound (V);



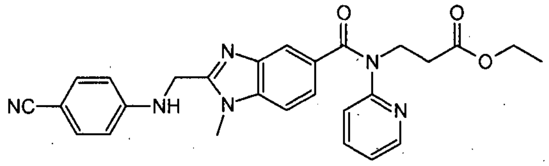
.acid addition salt

Formula (V)

wherein said compound is crystalline in nature.

42. A compound as claimed in claim 40, where in acid addition salt of compound of formula (V) may be prepared by using acid selected from methane sulfonic acid, 2,5-dihydroxy benzoic acid, ethanedisulfonic acid, p-toluene sulfonic acid (PTSA), benzene sulfonic acid, ethane disulfonic acid, ethane sulfonic acid, oxalic acid, fumaric acid, maleic acid, oleic acid, malic acid, succinic acid, malonic acid and the like;

43. A compound as claimed in claim 42, where in acid addition salt is preferably p-toluenesulphonate of formula (V),



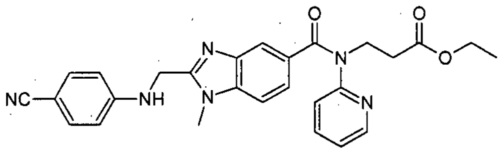
.p-toluene sulfonic acid addition salt

Formula (V)

Wherein said compound is crystalline in nature and is characterized by their X-ray diffraction having characteristic peaks at 4.78, 9.54, 14.85, 15.07, 15.32, 16.92, 17.24, 19.14, 19.57, 19.89, 22.69 and 24.37 ± 0.2° 2θ.

44. The process as claimed in claim 18, wherein the form-I of dabigatran etexilate mesylate has purity greater than 99%; preferably 99.5%; more preferably 99.81% when determined by HPLC.

45. The process of any of the preceding claims, dabigatran etexilate of formula (I) or its acid addition salt of formula (Ia) has less than about 0.2% of DBIMP-1 impurity, has less than about 0.2% of DBIMP-2 impurity, has less than about 0.2% of DBIMP-3 impurity, has less than about 0.2% of DBIMP-4 impurity, has less than about 0.2% of DBIMP-5 impurity, has less than about 0.2% of DBIMP-6 impurity, has less than about 0.2% of DBIMP-7 impurity, has less than about 0.2% of DBIMP-8 impurity, has less than about 0.2% of DBIMP-9 impurity, has less than about 0.2% of DBIMP-10 impurity, has less than about 0.2% of DBIMP-11 impurity, has less than about 0.2% of DBIMP-12 impurity.



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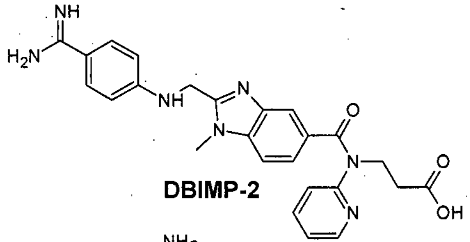

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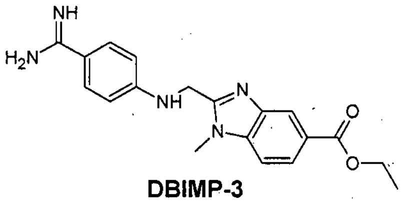

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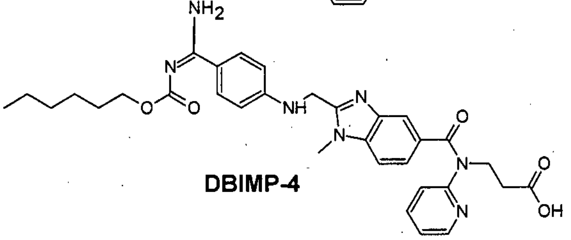

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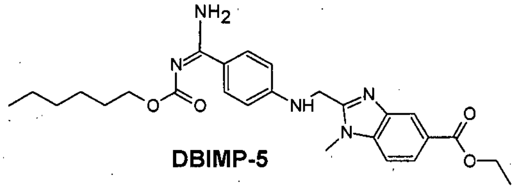

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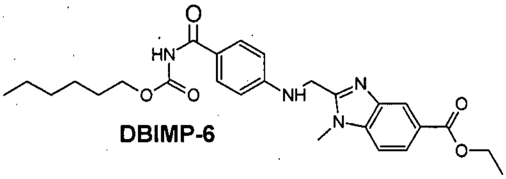

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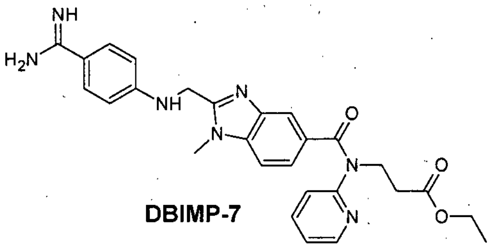

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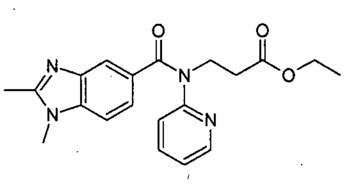

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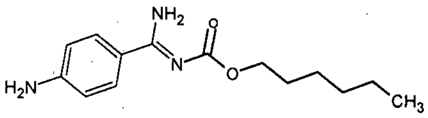

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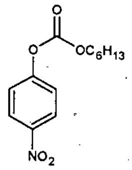
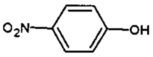
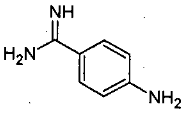


DBIMP-10



DBIMP-11



DBIMP-12

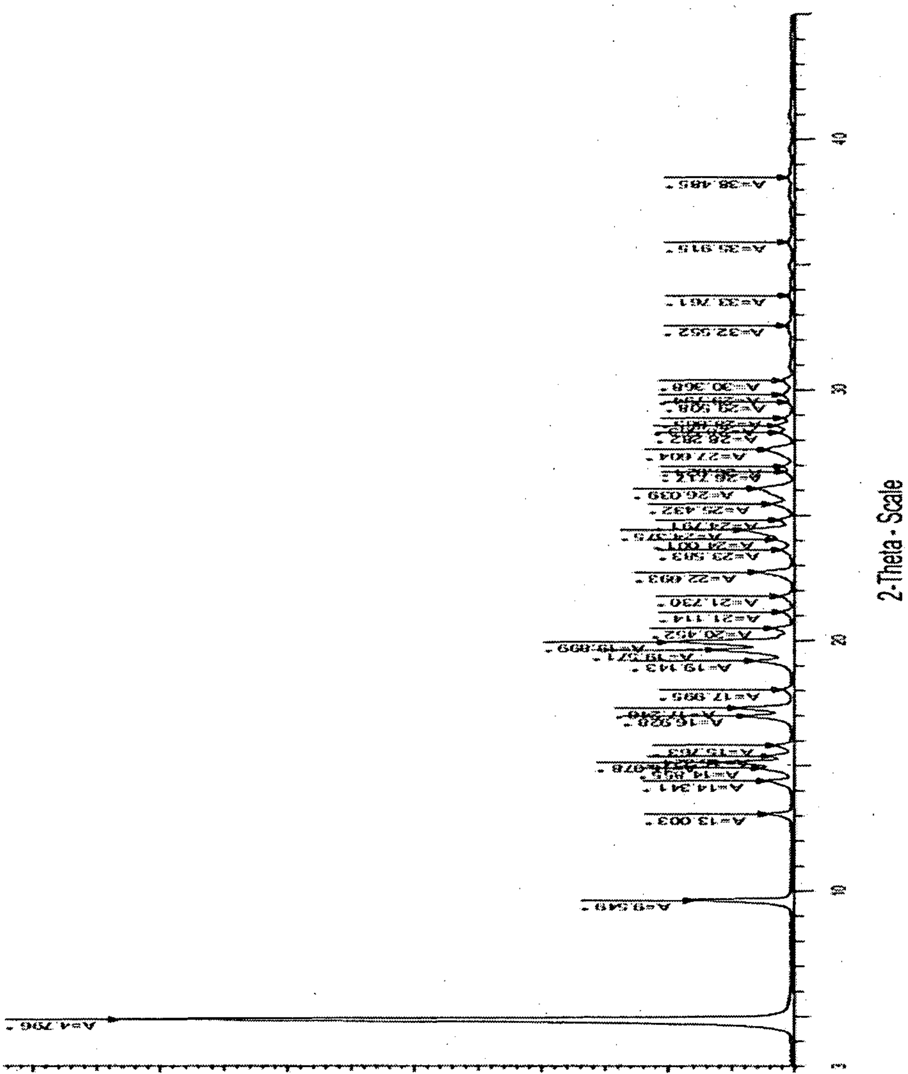

A=4.796 °
A=9.549 °
A=13.003 °
A=14.341 °
A=14.895 °
A=15.078 °
A=15.763 °
A=16.928 °
A=17.246 °
A=17.995 °
A=19.143 °
A=19.371 °
A=19.899 °
A=20.452 °
A=21.114 °
A=21.730 °
A=22.693 °
A=23.583 °
A=24.001 °
A=24.375 °
A=24.791 °
A=25.432 °
A=26.039 °
A=27.004 °
A=28.282 °
A=29.508 °
A=30.368 °
A=32.552 °
A=33.761 °
A=35.915 °
A=38.485 °
Lin (Counts)
3
10
20
30
40
2-Theta - Scale

Figure 1

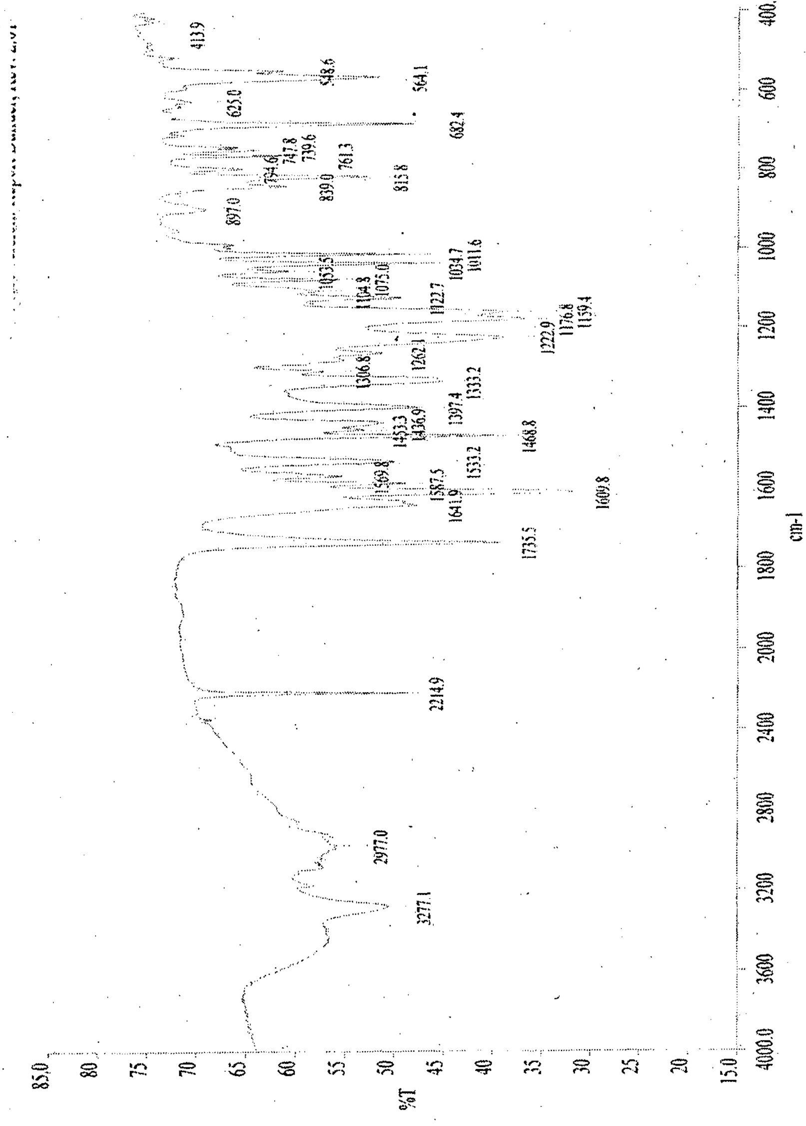

%T
85.0
80
75
70
65
60
55
50
45
40
35
30
25
20
15.0
4000.0
3600
3200
2800
2400
2000
1800
1600
1400
1200
1000
800
600
400.0
cm-1
3277.1
2977.0
2214.9
1735.5
1641.9
1609.8
1587.5
1569.8
1533.2
1468.8
1453.3
1436.9
1397.4
1333.2
1306.8
1262.1
1222.9
1176.8
1159.4
1122.7
1104.8
1075.0
1053.5
1034.7
1011.6
897.0
839.0
815.8
794.6
761.3
747.8
739.6
682.4
625.0
564.1
548.6
413.9

Figure 2