



- (51) International Patent Classification: Not classified
- (21) International Application Number: PCT/IN2013/000413
- (22) International Filing Date: 5 July 2013 (05.07.2013)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
2838/CHE/2012 12 July 2012 (12.07.2012) IN
4298/CHE/2012 15 October 2012 (15.10.2012) IN
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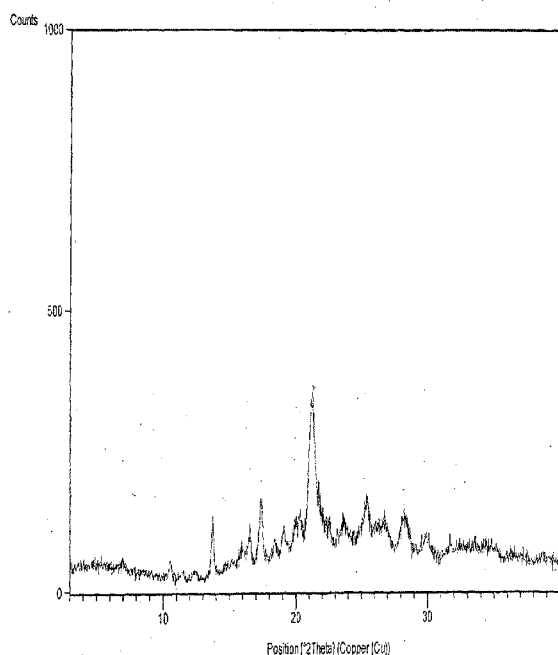
(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, SZ, TZ,

[Continued on next page]

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF DABIGATRAN ETEXILATE MESYLATE AND ITS INTERMEDIATES THEREOF

X-Ray Powder Diffraction (XRPD) pattern of crystalline form A of single prodrug of Dabigatran



(57) Abstract: An improved process for the preparation of Dabigatran Etexilate Mesylate and the processes for the preparation of Dabigatran single prodrug and Dabigatran Etexilate are described in this invention



UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

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- *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

- *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*
- *of inventorship (Rule 4.17(iv))*

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- *without international search report and to be republished upon receipt of that report (Rule 48.2(g))*

SPECIFICATION

Title of the invention

An improved process for the preparation of DabigatranEtexilateMesylate and its intermediates thereof

5 Cross reference to related application

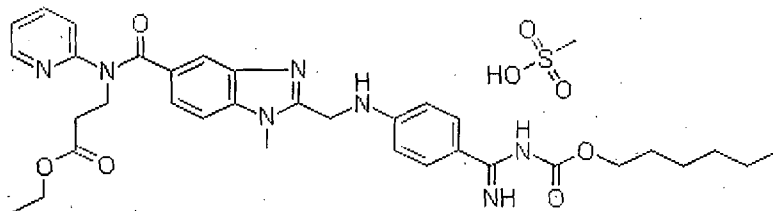
[0001] This application claims priority from the provisional specifications No. 2838/CHE/2012 filed on 12.07.2012 and 4298/CHE/2012 filed on 15.10.2012.

Field of the invention

[0002] The present invention relates to an improved process for the preparation of
10 DabigatranEtexilateMesylate and the processes for the preparation of Dabigatran
single prodrug and DabigatranEtexilate thereof.

Background of the invention

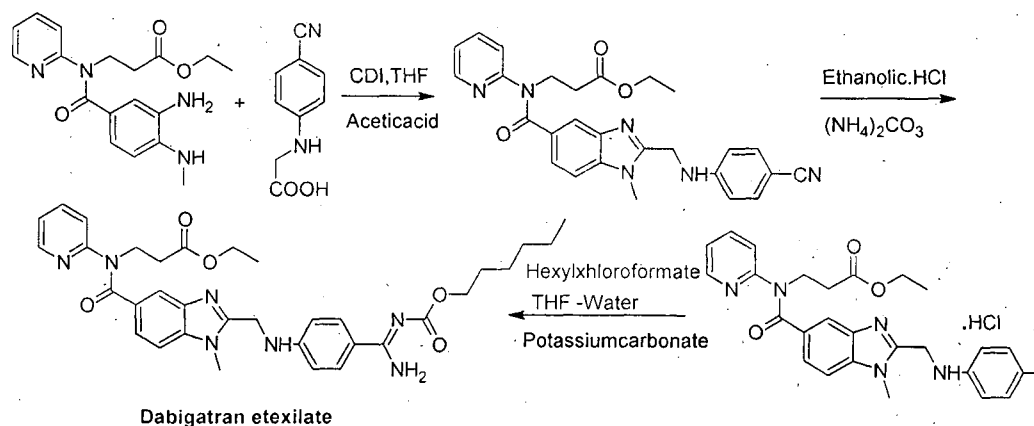
[0003] DabigatranEtexilateMesylate chemically know as N-[[2-[[[4-[[[(hexyloxy) carbonyl] amino]-iminomethyl] phenyl] amino] methyl]-1-methyl-1H-
15 benzimidazol-5-yl] carbonyl]-N-2- pyridinyl-beta-Alanine ethyl ester
methanesulfonate having the formula I as provided below,



Formula I

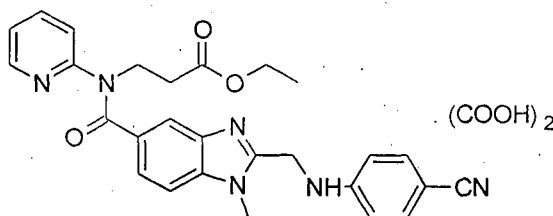
is a direct thrombin inhibitor having anti - coagulant activity when administered orally.

[0004] DabigatranEtexilate is first time reported in the US patent 6087380 (hereinafter referred as US'380) in which the process for the preparation of DabigatranEtexilate is disclosed in the Example 49, 58a and Example 59, said process for the preparation of DabigatranEtexilate is depicted below:

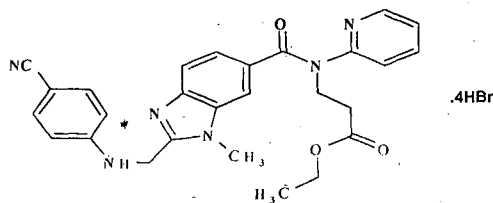


[0005] In accordance to the process in the Patent US'380 the substance requires complex purifying operations, such as chromatography for the production of high-quality API. Further the chromatographic purification is expensive and difficult to implement in large scale. The impurity in the Dabigatran single prodrug and DabigatranEtexilate affects the purity of the final product DabigatranEtexilateMesylate. Hence there is a necessity to maintain the purity level of every intermediate involved in the preparation of DabigatranEtexilateMesylate.

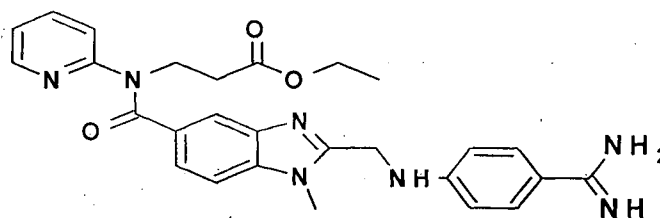
[0006] The patent application US2011082299 discloses a process for the preparation Dabigatran from 3- ([2-[(4-cyanophenyl amino)-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) ethyl propionate oxalate as one of the intermediate in order to overcome the problem of the process depicted in the product patent.



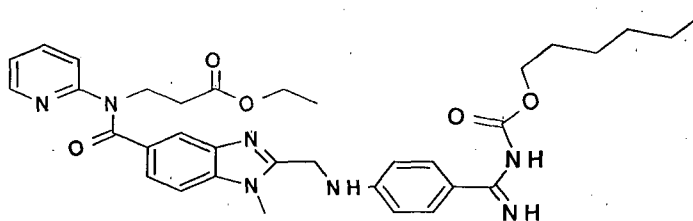
[0007] The patent US8119810 discloses the process for the preparation Dabigatran from 3- ([2-[(4-cyanophenylamino)-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) ethyl propionate hydro bromide as one of the intermediate in order to overcome the problem of the process depicted in the product patent.



[0008] The single prodrug of Dabigatran having the formula-II,



and double prodrug of the Dabigatran having the formula-III,



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which is DabigatranEtexilate are exemplified in the examples of the patent US'380. The patent US'380 has no information about the solid state properties of the single prodrug of Dabigatran and DabigatranEtexilate. However, a similar process described in a publication of Huel et al in Journal of Medicinal Chemistry, 2002, 45, 1757 – 1766, wherein DabigatranEtexilate is characterized by 128 – 129°C.

[0009] The PCT publication WO2006131491 discloses the anhydrous form I of DabigatranEtexilate having the melting point 135°C, anhydrous form II of DabigatranEtexilate having the melting point 150°C, and hydrate form of DabigatranEtexilate having the melting point 90°C.

[0010] The PCT publication WO2008059029 discloses anhydrous form III of DabigatranEtexilate having melting point 128°C, anhydrous form IV of DabigatranEtexilate having the melting point 133°C, and mono hydrate form I of DabigatranEtexilate having melting point 128°C and mono hydrate form II of DabigatranEtexilate having melting point 123°C.

[0011] The different forms of the single prodrug of Dabigatran and/or the DabigatranEtexilate are disclosed in the patent applications of WO2012027543, WO2012004396 and WO 2012044595.

[0012] The patent application US2007185333 discloses the process for the

preparation of DabigatranEtexilateMesylate from the DabigatranEtexilate by adding acetone solution of methanesulfonic acid in an acetone solution of DabigatranEtexilate.

[0013] The patent application US 20060183779 discloses the process for the preparation of DabigatranEtexilateMesylate from the DabigatranEtexilate by adding ethylacetate solution of methanesulfonic acid in an ethylacetate solution of DabigatranEtexilate.

[0014] Therefore, there is a need for an economically efficient and improved process for the preparation of DabigatranEtexilateMesylate and a process for the DabigatranEtexilate, Dabigatran single prodrug and novel intermediates thereof.

Brief Description of the Drawings

[0015] Figure 1 depicts X-Ray Powder Diffraction (XRPD) pattern of crystalline form A of single prodrug of Dabigatran.

[0016] Figure 2 depicts X-Ray Powder Diffraction (XRPD) pattern of crystalline form IC of DabigatranEtexilate.

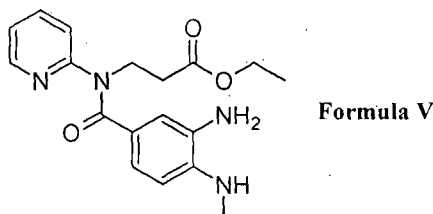
[0017] Figure 3 depicts Differential Scanning Calorimetry (DSC) pattern of crystalline form IC of DabigatranEtexilate.

Summary of the invention

[0018] The main objective of the present invention is to provide an improved process for the preparation of DabigatranEtexilateMesylate.

[0019] The first aspect of the present invention is to provide a process for the preparation of DabigatranEtexilateMesylate comprising the steps of:

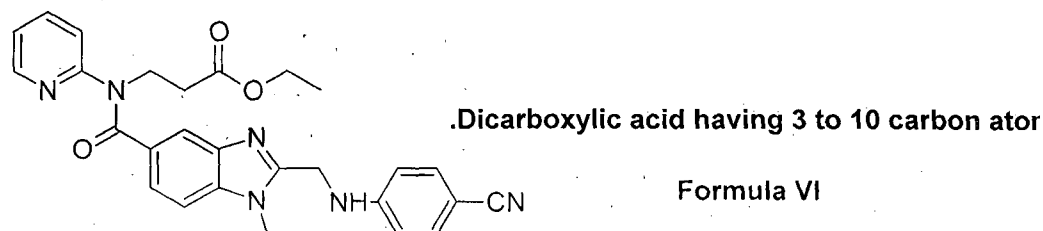
a) reacting ethyl-3-{1-[3-amino-4-(methylamino)benzoyl]-N-(pyridin-2-yl)amino}propanoate of formula V,



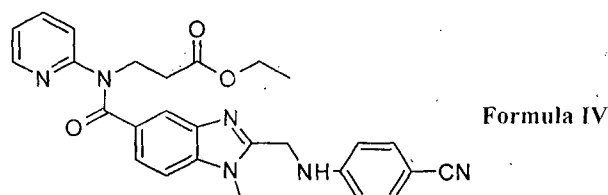
with 2-[(4-cyanophenyl)amino]acetic acid in the presence of a coupling reagent in an organic solvent to obtain a reaction mixture;

b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain a compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-

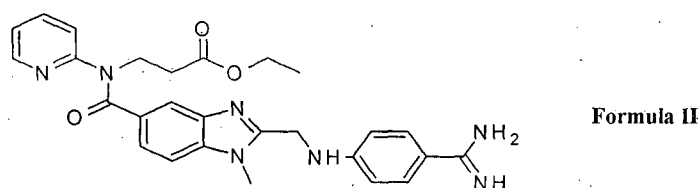
5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid addition salt having 3 to 10 carbon atoms having the formula-VI;



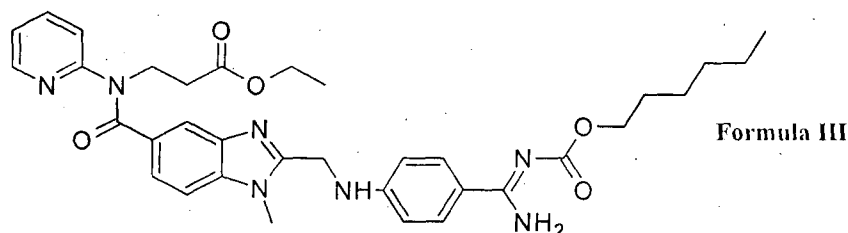
- 5 c) basifying the compound of formula-VI prepared in the step (b) to obtain the ethyl 3-[1-(2-{[(4-cyanophenyl)amino] methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate free base of formula-IV;



- d) dissolving the compound of formula IV obtained in step (c) in a mixture of ethanol and esters thereof;
- 10 e) adding hydrochloride to the reaction mixture obtained in step (d);
- f) adding an ammonia source periodically to the reaction mixture prepared in step (e) and maintaining the reaction mixture for a sufficient time to obtain a compound of formula II;



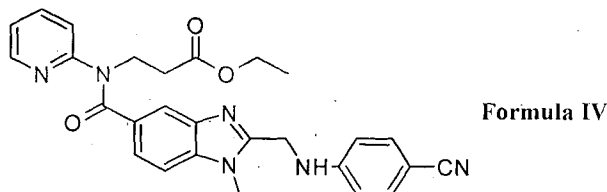
- 15 g) treating the compound of formula II with hexylchloroformate in the presence of base and maintaining the reaction mixture for sufficient time to obtain a compound of formula III;



- 20 h) treating the compound of formula III with methane sulfonic acid to obtain

DabigatranEtexilateMesylate.

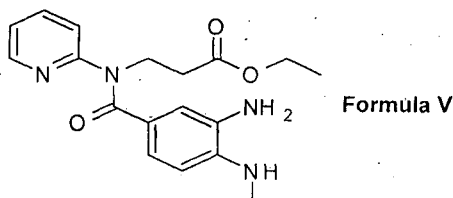
[0020] The second aspect of the present invention provides a process for the pure 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV



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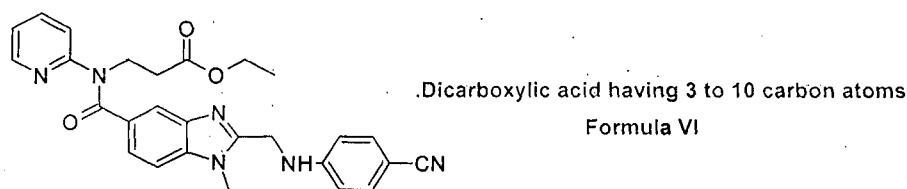
comprising the steps of:

a) reacting ethyl 3-{1-[3-amino-4-(methylamino)benzoyl]-N-(pyridin-2-yl)amino}propanoate of formula V,



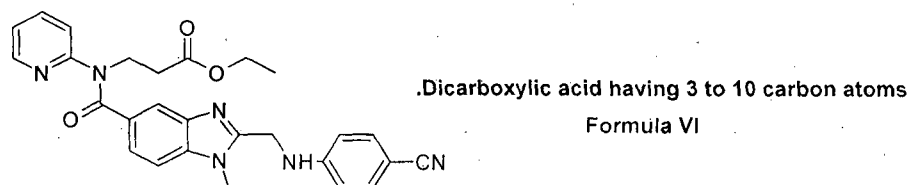
10 with 2-[(4-cyanophenyl)amino] acetic acid in the presence of a coupling reagent in an organic solvent to obtain a reaction mixture;

b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain a compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid having 3 to 10 carbon atoms having the formula-VI

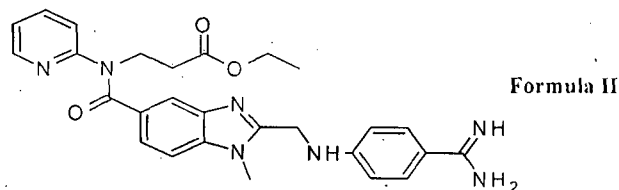


c) basifying the compound of formula VI prepared in the step (b) to obtain the ethyl 3-[1-(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate free base of formula-IV.

[0021] The third aspect of the present invention provides a novel compound 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester dicarboxylic acid having 3 to 10 carbon atoms of formula VI.

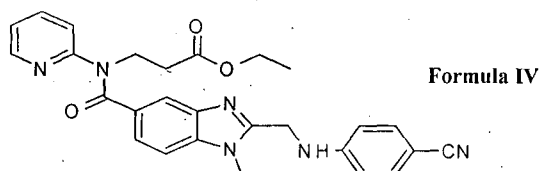


[0022] The fourth aspect of the present invention provides a process for the preparation of the compound of formula II as a free base in pure form,



5 comprising the steps of:

a) dissolving compound of formula IV,

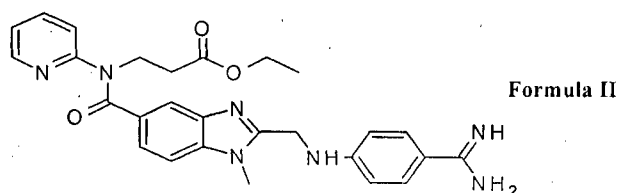


in a mixture of ethanol and ester;

b) adding hydrochloride to the reaction mixture obtained in step (a);

10 c) adding an ammonia source periodically to the reaction mixture prepared in step (b) and maintaining the reaction mixture for a sufficient time to obtain a compound of formula II.

[0023] The fifth aspect of the present invention is to provide a process for the preparation of the compound of formula II as free base in pure form

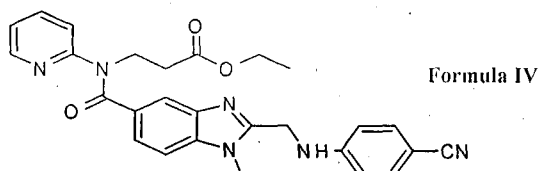


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comprising the steps of:

a) adding hydrochloride to the mixture of ethanol and ester;

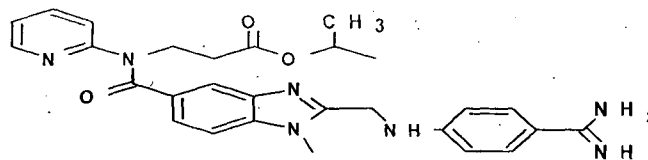
b) adding the compound of the formula IV



to the reaction mixture prepared in step (a) ;

c) adding an ammonia source periodically to the reaction mixture obtained in step (b) and maintaining sufficient time to obtain the compound of formula II.

[0024] The sixth aspect of the present invention is to provide a novel compound of formula VII



Formula VIII

[0025] The seventh aspect of the present invention is to provide a novel process for the purification of DabigatranEtexilate involving the step of crystallizing Crude DabigatranEtexilate in isopropanol.

[0026] The eighth aspect of the present invention provides a process for the preparation of DabigatranEtexilateMesylate comprising the steps of:

a) dissolving DabigatranEtexilate in acetone or a solvent mixture containing acetone;

b) adding a mixture of methane sulphonic acid in ethylacetate to the mixture prepared in step (a); and

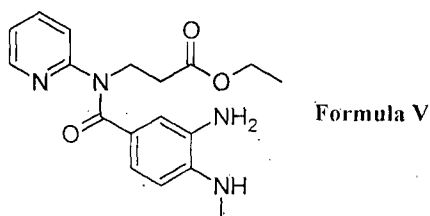
c) obtaining the DabigatranEtexilateMesylate.

[0027] The ninth aspect of the present invention is to provide a crystalline form of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazol-5-carbonyl)-pyridin-2-yl-amino]-propionate, designated as the Form IC characterized by X-ray powder diffraction pattern (Fig 2) having characteristic peaks at reflection angle 2θ ($\pm 0.2^\circ$) 5.84, 6.5, 11.7, 17.47, 19.9, 20.49, 24.77, 26.44, 27.02.

Detail description of the invention

[0028] The present invention is providing the improved process for the preparation of DabigatranEtexilateMesylate with a novel intermediate comprising the steps of:

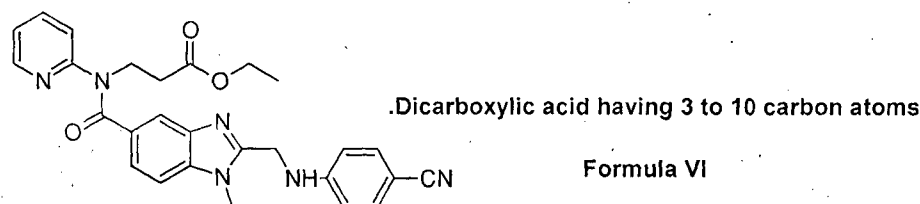
a) reacting ethyl 3-{1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl)amino}propanoate of the formula V



Formula V

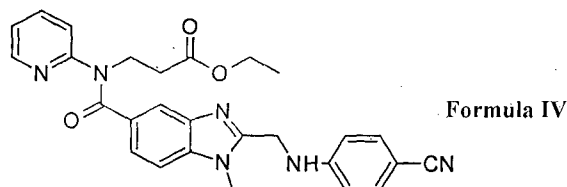
with 2-[(4-cyanophenyl)amino] acetic acid in the presence of a coupling reagent in an organic solvent to obtain a reaction mixture;

- b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain a compound of 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid addition salt having 3 to 10 carbon atoms having the formula-VI,



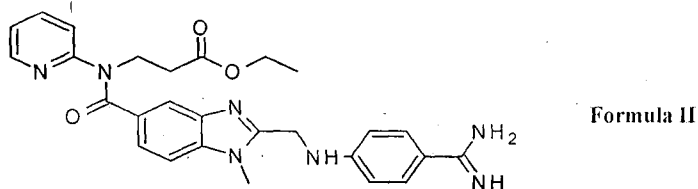
Formula VI

- c) basifying the compound of formula VI prepared in the step (b) to obtain the ethyl 3-[1-(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate free base of formula IV;



Formula IV

- d) dissolving the compound of formula IV in ethanol and esters or its mixtures thereof ;
- e) adding hydrochloride to the reaction mixture obtained in step (d);
- f) adding an ammonia source periodically to the reaction mixture obtained in step (e) and maintaining sufficient time to obtain the compound of formula II;

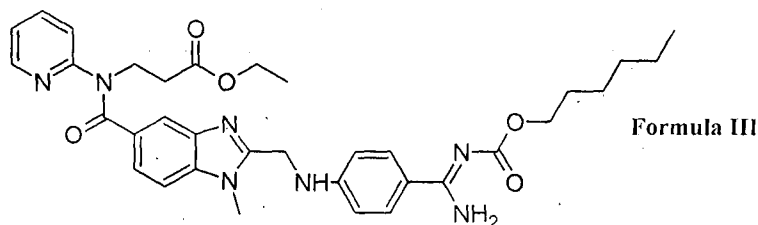


Formula II

- g) filtering the compound obtained in the step (d);

h) purifying the compound obtained in step (e) with a polar organic solvent or mixtures thereof;

i) treating the compound of formula II with hexylchloroformate in the presence of base and maintaining the reaction mixture for sufficient time to obtain a compound of formula III;



j) treating the compound of formula III with methane sulfonic acid to obtain the DabigatranEtexilateMesylate.

[0029] The coupling reagent employed in the step (a) is selected from the group comprising of O-(Benzotriazol-1-yl)-N, N, N', N'-tetramethyluroniumhexafluorophosphate (HBTU) and O-(Benzotriazol-1-yl)-N, N, N', N'-tetramethyluroniumtetrafluoroborate (TBTU) 3-(Diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one, N,N'-Carbonyldiimidazole, preferably N,N'-Carbonyldiimidazole.

[0030] The organic solvent employed in the step (a) is selected from the group comprising of dimethylacetamide, N-methyl-2-pyrrolidone, MDC, dimethylformamide, HMPA, esters containing C1 to C6 carbon atoms such as Butyl acetate Sec-Butyl acetate, Tert-Butyl acetate, Ethyl acetoacetate, Ethyl butyrate, Ethyl lactate, Isopropyl acetate, Methyl acetate and mixtures thereof preferably mixture of dimethylformamide and Methylene chloride.

[0031] The dicarboxylic acid having C3 to C10 carbon atoms employed in the step (b) is selected from the group comprising of acetonedicarboxylic acid, camphoric acid, diaminopimelic acid, dimercapto succinic acid, folic acid, glutaconic acid, adipic acid, maleic acid, phthalic acid, tartaric acid, fumaric acid, succinic acid, malonic acid, glutamic acid, preferably succinic acid.

[0032] The esters employed in the step (d) is selected from the group comprising of Butyl acetate Sec-Butyl acetate, Tert-butyl acetate, Ethyl acetoacetate, Ethyl butyrate, Ethyl acetate, Isopropyl acetate, Methyl acetate and mixtures thereof.

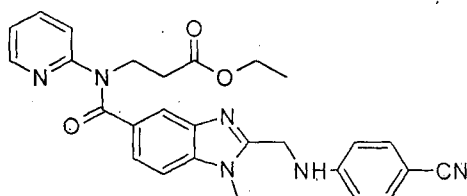
[0033] The ammonium source employed in step (f) is selected from the group comprising of ammonium hydroxide, ammonium carbonate and ammonium

chloride. Preferably the ammonium source is ammonium carbonate.

[0034] The polar solvent employed in the step (h) is selected from the group of alcohol solvents containing C3 to C10 carbons such as propanols water or substituted propanols, butanols or substituted butanols preferably isopropyl alcohol and or ketone such as butanone, pentanone, water and mixture thereof preferably a mixture of acetone and water.

[0035] The base employed in step (i) is selected from the group of alkali metal bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate and others such as ammonium hydroxide and ammonium carbonate.

[0036] In another embodiment, the present invention provides a process for the preparation of compound 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzoimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV

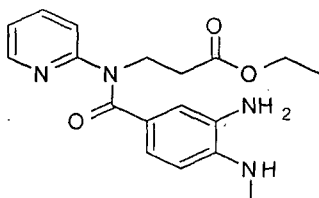


Formula IV

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comprising the steps of:

a) reacting ethyl 3-{1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl)amino}propanoate of the formula V

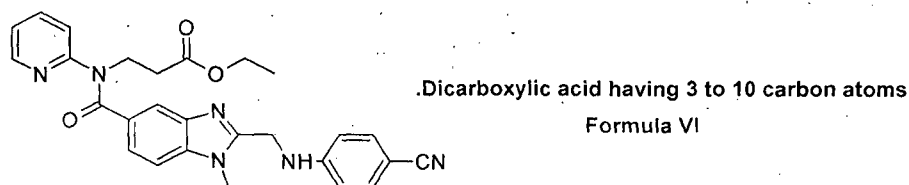


Formula V

20 with 2-[(4-cyanophenyl)amino] acetic acid in the presence of a coupling reagent in an organic solvent to obtain a reaction mixture;

b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain a compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid addition salt having 3 to 10 carbon atoms salt of the compound having the formula-VI;

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c) basifying the compound of formula VI prepared in the step (b) to obtain the 3-
(2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzimidazole-5-

5 carbonyl)pyridin-2-ylamino)propionic acid ethyl ester free base of formula IV.

[0037] The employment of the dicarboxylic acid having 3 to 10 carbon atoms to
the reaction mixture in step (b) in the process for the preparation of compound 3-
(2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl)
pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV
10 enhances the recovery of the final product from the reaction mixture.

[0038] The coupling reagent employed in the step (a) is selected from the group
comprising of O-(Benzotriazol-1-yl)-N, N, N', N'-
tetramethyluroniumhexafluorophosphate (HBTU) and O-(Benzotriazol-1-yl)-N,
N, N', N'-tetramethyluroniumtetrafluoroborate (TBTU) 3-
15 (Diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one, preferably N, N'-
Carbonyldiimidazole.

[0039] The organic solvent employed in the step (a) is selected from the group
comprising of dimethylacetamide, N-methyl-2-pyrrolidone, MDC,
Dimethylformamide and HMPA, esters containing C1 to C6 carbon atoms such as
20 Butyl acetate Sec-Butyl acetate, Tert-Butyl acetate, Ethyl acetoacetate, Ethyl
butyrate, Ethyl lactate, Isopropyl acetate, Methyl acetate and mixtures thereof
preferably mixture of dimethylformamide and methylene chloride.

[0040] The dicarboxylic acid having C3 to C10 carbon atoms employed in step
(b) is selected from the group comprising of acetonedicarboxylic acid, adipic acid,
25 camphoric acid, diaminopimelic acid, dimercapto succinic acid, folic acid,
glutaconic acid, maleic acid, phthalic acid, tartaric acid, fumaric acid, succinic
acid, malonic acid, glutamic acid, preferably succinic acid.

[0041] The step (a) for the preparation of compound 3-((2-[(4-cyano-
phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl) pyridin-2-
30 ylamino) propionic acid ethyl ester of the compound of formula IV may be carried
out in the time ranging from 30 minutes to 5 hours, preferably 4 hours.

[0042] The step (a) for the preparation of compound 3-((2-[(4-cyano-

phenylamino) methyl]-1-methyl-1H-benzoimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV may be carried out in temperature ranging between 25°C to 100°C, preferably 35°C to 50°C.

[0043] The maintaining of the reaction mixture in step (b) for the preparation of compound 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzoimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV may be carried out in time ranging from 2 to 10 hours, preferably 5 to 6 hours.

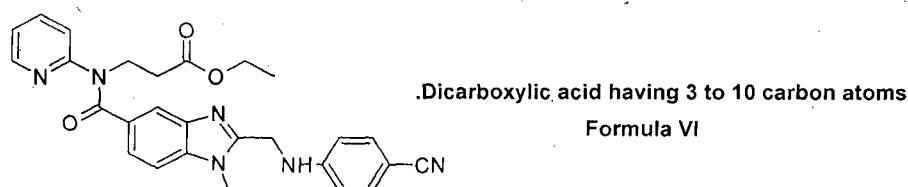
[0044] The maintaining of the reaction mixture in step (b) for the preparation of compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester of the compound of formula IV may be carried out in temperatures ranging between 25°C to 100°C, preferably 15°C to 35°C.

[0045] The basifying in step (c) for the preparation of compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester of the compound of formula IV carried out in the presence of a base with an organic solvent for a sufficient time to obtain compound of formula IV. The base employed in step (c) is selected from inorganic and organic bases; the organic bases according to the present invention are selected from the group comprising of isopropyl amine, diisopropyl amine, diisopropyl ethyl-amine, N-methyl morpholine, N-methyl piperidine, N-methyl piperazine, N-methyl pyridine, DBU, DABCO and triethylamine; and the inorganic bases according to the present invention are selected from the group comprising of alkali metals such as sodium, potassium, lithium; alkali metal carbonates such as sodium carbonate, potassium carbonate, cesium carbonate, lithium carbonate; alkali metal bicarbonates such as sodium bicarbonate, potassium bicarbonate, lithium bicarbonate, cesium bicarbonate; alkali metal hydroxides such as sodium hydroxide, calcium hydroxide, potassium hydroxide; metal alkoxides such as alkoxides of sodium, lithium or potassium, sodium tert-butoxide; alkali metal hydrides such as sodium hydride; alkali metal chlorides such as calcium chloride; alkali metal acetates such as acetate of calcium, potassium or lithium; and ammonia source such as ammonium carbonate, ammonia, ammonium hydroxide. The solvent employed in step (c) is selected from the group comprising of hydrocarbons such as pentane, hexane, heptanes,

octane, petroleum ether; aromatic hydrocarbons such as toluene, xylenes; chlorinated hydrocarbons such as chlorobenzene, o-dichlorobenzene, 1,2-dichloroethane; esters such as ethyl acetate; ethers such as tetrahydrofuran, diethyl ether, methyl tert-butyl ether, 1,4-dioxane, dimethoxyethane; N,N-dimethyl formamide, dimethyl sulfoxide, N,N-dimethyl acetamide; alcohols such as methanol, ethanol, propanol, isopropanol, butanol, t-butanol; or mixtures thereof.

[0046] The step (a) of reacting ethyl 3-[1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl) amino]propanoate with 2-[(4-cyanophenyl)amino] acetic acid in presence of a coupling reagent in an organic solvent of the present invention may be carried out in single or two step process.

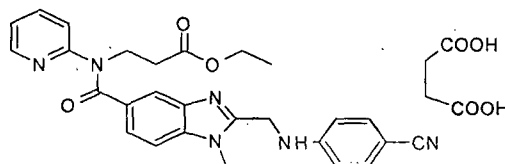
[0047] In yet another embodiment of the present invention is to provide a novel compound Ethyl-3-[1-(2-[[[(4-cyanophenyl) amino] methyl]-1-methyl-1H-1, 3-benzodiazol-5-yl)-N-(pyridin-2-yl) formamido] propanoate]dicarboxylic acid having C3 to C10 carbon atoms of formula VI.



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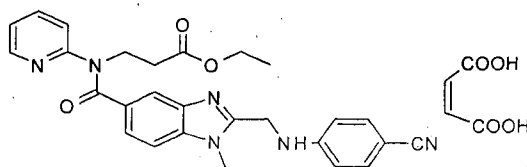
[0048] Some novel compounds of Ethyl 3-[1-(2-[[[(4-cyanophenyl) amino] methyl]-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate]dicarboxylic acid having C3 to C10 carbon atoms of formula VI are mentioned below:

Ethyl-3-[1-(2-[[[(4-cyanophenyl) amino] methyl]-1-methyl-1H-1, 3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido]propanoate succinate

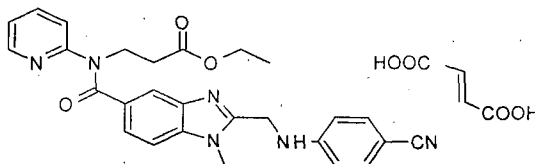


Ethyl-3-[1-(2-[[[(4-cyanophenyl) amino] methyl]-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate maleate

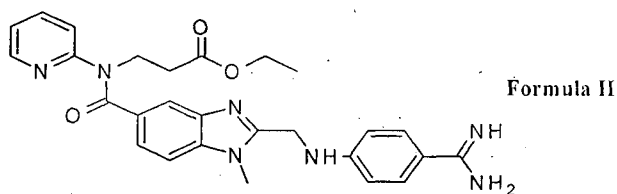
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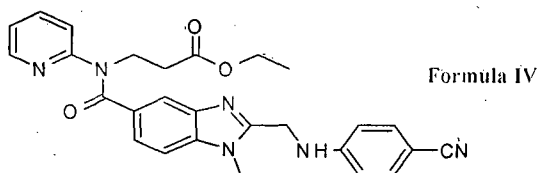
Ethyl-3-[1-(2-{{(4-cyanophenyl) amino] methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoatefumarate.



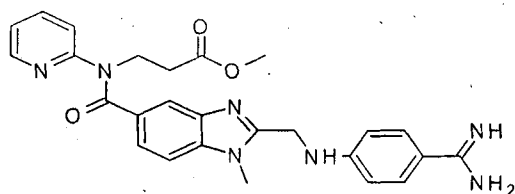
5 [0049] The prior art process for the preparation of formula II,



from the compound of formula IV



employs ethanol and hydrochloride. The present inventors found a potential
10 impurity formed

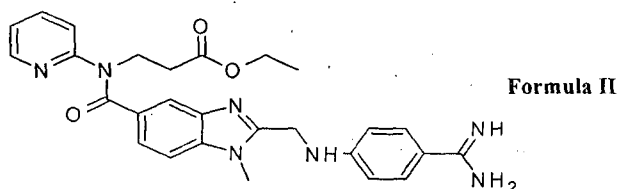


during such prior art processes. This potential impurity is not removed after
repeated purification procedures and also present in the final product
DabigatranEtexilateMesylate in ppm. The presence of this potential impurity in
15 DabigatranEtexilateMesylate is not pharmaceutically acceptable.

[0050] Unexpectedly the present inventors have observed that employment of
ester along with ethanol in the process for the preparation of the compound of
formula II as a pure free base from the compound of formula-IV decreases
formation of this potential impurity.

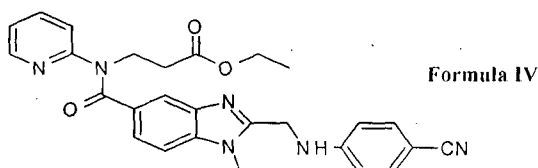
20 [0051] In yet another embodiment, the present invention provides a process for

the preparation of the compound of formula II as a pure free base,



comprising the steps of:

a) dissolving compound of formula IV



5

in a mixture of ethanol and esters ;

b) adding hydrochloride to the reaction mixture obtained in step (a);

c) adding an ammonia source periodically to the reaction mixture obtained in step (b) and maintaining sufficient time to obtain the compound of formula II;

10 d) filtering the compound obtained in the step (c); and

e) purifying the compound obtained in step (d) with a polar organic solvent or mixtures thereof.

[0052] The esters employed in the step (a) is selected from the group of comprising of Butyl acetate ,Sec-Butyl acetate , Tert-Butyl acetate, Ethyl acetoacetate , Ethyl butyrate, Ethyl lactate, Isopropyl acetate, Methyl acetate and mixtures thereof preferably Ethyl acetate.

15

[0053] The "polar solvents " employed in the step (e) is selected from the group comprising of water, alcohols containing C3 to C10 carbons such as propanol or substituted propanol, butanols or substituted butanols, isopropyl alcohol ketone such as butanone, pentanone and mixtures thereof preferably mixture of acetone and water.

20

[0054] The ammonium source employed in step (c) is selected from the group comprising of ammonium hydroxide, ammonium carbonate and ammonium chloride. Preferably the ammonium source is ammonium carbonate.

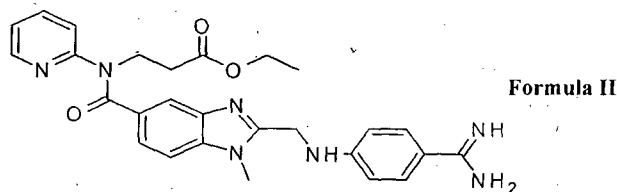
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[0055] The maintaining of the reaction mixture for a sufficient time in step (b) for the preparation of the compound of formula II may be carried out in time ranging from 10 to 50 hours, preferably 11 to 30 hours.

[0056] The maintaining of the reaction mixture for a sufficient time in step (b) for

the preparation of the compound of formula II may be carried out in temperatures ranging from 0°C to 100°C, preferably 15°C to 35°C.

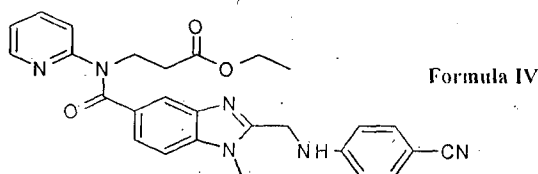
[0057] In yet another embodiment of the invention is to provide a process for the preparation of the compound of formula II as a pure free base



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comprising the steps of:

- a) adding hydrochloride to a mixture of ethanol and ester;
- b) adding the compound of the formula IV



- c) adding an ammonia source periodically to the reaction mixture obtained in step (b) and maintaining sufficient time to obtain the compound of formula II;
- d) filtering the compound obtained in the step (c); and
- e) purifying the compound obtained in step (d) with a polar solvent or mixtures thereof.

15

[0058] The esters employed in the step (a) is selected from the group comprising of Butyl acetate, Sec-Butyl acetate, Tert-Butyl acetate, Ethyl acetoacetate, Ethyl butyrate, Ethyl acetate, Isopropyl acetate, Methyl acetate and mixtures thereof.

20

[0059] The ammonium source employed in step (c) is selected from the group comprising of ammonium hydroxide, ammonium carbonate and ammonium chloride. Preferably the ammonium source is ammonium carbonate.

25

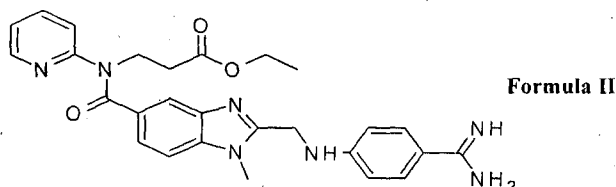
[0060] The "polar solvent" employed in the step (e) is selected from the group of alcohol solvents containing C3 to C10 carbons such as propanols water or substituted propanols, butanols or substituted butanols preferably isopropyl alcohol and or ketone such as butanone, pentanone, water and mixture thereof preferably a mixture of acetone and water.

[0061] The maintaining of the reaction mixture for a sufficient time in step (b) for the preparation of the compound of formula II may be carried out in time ranging

from 10 to 50 hours, preferably 11 to 30 hours.

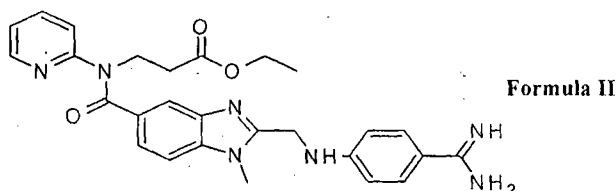
[0062] The maintaining of the reaction mixture for a sufficient time in step (b) for the preparation of the compound of formula II may be carried out in temperatures ranging from 0°C to 100°C, preferably 15°C to 35 °C.

- 5 [0063] In yet another embodiment, the present invention is to provide a crystalline form of Dabigatran single prodrug of formula II



- designated as the Form A, characterized by X-ray powder diffraction pattern (Fig 1) having characteristic peaks at reflection angle $2\theta (\pm 0.2^\circ 2\theta)$ 6.66, 9.40, 11.37, 10 14.65, 15.61, 16.2, 17.54, 21.91, 23.45, 27.64, 28.35.

[0064] The present invention also provides a process for DabigatranEtexilate from Dabigatran single prodrug comprising the steps of: (a) treating the compound of formula II



- 15 with n-hexyl chloroformate in the presence of a base in a ketones solvent or mixture containing at least ketone solvent. The "base" is selected from the group of alkali metal bases such as sodium hydroxide, potassium hydroxide, sodium carbonate, sodium bicarbonate, potassium carbonate, potassium bicarbonate and others such as ammonium hydroxide and ammonium carbonate. The 'ketones solvent' is selected from the group of ketones containing C3-C10 carbon atoms, 20 such as propanone, butanone, pentanone preferably acetone.

- [0065] The present inventors found that the prior art of diluting methane sulfonic acid with the acetone develops a black reddish color on standing, which is pharmaceutically not acceptable during the preparation of the 25 DabigatranEtexilateMesylate in commercial scale. Further the present inventors have found that dissolving the DabigatranEtexilate in ethyl acetate requires more amount of ethyl acetate which increases the expenditure of the process for DabigatranEtexilate

[0066] Surprisingly the present inventors found a process for the preparation of DabigatranEtexilateMesylate comprising the steps of:

- a) dissolving DabigatranEtexilate in acetone or a solvent mixture containing acetone;
- 5 b) adding a mixture of methansulphonic acid in ethylacetate to the mixture prepared in step (a); and
- c) obtaining the DabigatranEtexilateMesylate.

[0067] Thereby process for the preparation of DabigatranEtexilateMesylate from DabigatranEtexilate is economical efficient and also pharmaceutically acceptable
10 during the manufacturing process of DabigatranEtexilateMesylate.

[0068] The maintaining of the reaction mixture for a sufficient time in step (b) for the preparation of the compound of DabigatranEtexilateMesylate may be carried out in time ranging from 1 to 15 hours, preferably 2 to 6 hours.

[0069] The maintaining of the reaction mixture for a sufficient time in step (b) for
15 the preparation of the compound of DabigatranEtexilateMesylate may be carried out in temperatures ranging from 0°C to 100°C, preferably 15°C to 35°C.

[0070] The present inventors have found that the solvents employed in prior arts do not efficiently purify the Crude DabigatranEtexilate. The purification of the Crude DabigatranEtexilate is essential for the purity of the final product, the
20 DabigatranEtexilateMesylate.

[0071] Unexpectedly, the present inventors found a novel process for the purification of DabigatranEtexilate involving the step of crystallizing Crude DabigatranEtexilate in isopropanol.

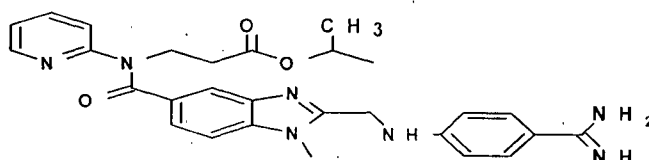
[0072] In an embodiment of the invention, the present invention provides a
25 crystalline form of Ethyl 3-[(2-{[4-(hexyloxy carbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, designated as the Form IC characterized by X-ray powder diffraction pattern (Fig 2) having characteristic peaks at reflection angle 2θ ($\pm 0.2^\circ$) 2θ) 5.84, 6.5, 11.7, 17.47, 19.9, 20.49, 24.77, 26.44, 27.02. Form IC exhibits a
30 melting point 82-85°C (DSC endothermic peak) (Fig 3)

[0073] Another embodiment of the present invention provides a process for the preparation of virtually anhydrous crystalline form IC of Ethyl-3-[(2-{[4-(hexyloxy carbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate comprising the steps

of:

- a) dissolving the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base in isopropanol;
- 5 b) optionally stir up till precipitation of the solid ;
- c) filtering the solid and drying the obtained solid.

[0074] The present invention also provides a novel compound of formula VII



Formula VIII

- [0075] The compound of formula-VII is found by the present inventors during the preparation of Dabigatran single prodrug.

[0076] Some aspects and embodiments of this disclosure are described in the examples below, which are provided only for the purpose of illustration and are not intended to limit the scope of the disclosure in any manner.

Examples

- 15 **Example-1a: Preparation of ethyl 3-[(2-[(4-cyanophenyl) amino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino] propionate succinic acid salt.**

- [0077] N, N'-Carbonyldiimidazole (0.14 mol) was dissolved in mixture of methylenechloride (200 ml) DMF (40 ml), added 2-[(4-cyanophenyl) amino] acetic acid (0.13 mol) stirred for 1 hr at 20-30°C. The Ethyl 3-{1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl) amino} propionate (0.12 mol) in methylene chloride solution was added to the reaction mixture and raised the reaction mass temperature to 35-40°C, monitored the reaction by HPLC. After the completion of the reaction, the reaction mass was washed with water and separated the organic layer. The solvent was distilled under vacuum and resulted residue was dissolved in isopropyl acetate (280 ml) and acetic acid (16 ml), heated the reaction mass up to 80-90°C, monitored the reaction by HPLC. After reaction completion, the mass was cooled to 65-70°C, washed with water and added succinic acid to the separated organic layer at the same temperature. The reaction mass was cooled to 25-30°C and stirred for 5 hours at the same temperature. The

reaction mass was further cooled to 0-5°C and continued stirring for 2 hours. Filtered the isolated solid and washed with isopropyl acetate, dried at 55-60°C. Yield: 85%

5 **Example-1b: Preparation of ethyl 3-([2-[(4-cyanophenyl) amino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) propionate succinic acid salt.**

[0078] N, N'-Carbonyldiimidazole (0.14 mol) was dissolved in THF (340 ml), added 2-[(4-cyanophenyl) amino] acetic acid at 35-40°C and stirred for 1 hrs at 10 35-40°C. The solution of Ethyl 3-{1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl) amino} propanoate in THF was added to the reaction mixture and the reaction temperature was raised to 50°C and monitored the reaction by HPLC. After completion of the reaction the solvent was distilled under vacuum. The residue was dissolved in isopropyl acetate and acetic acid at 80-90°C and 15 monitored the reaction by HPLC. After the completion of the reaction, the reaction mass was cooled to 65-70°C washed with water and added succinic acid to the separated organic layer at the same temperature. The reaction mass was cooled to 25-30°C, stirred for 5 hours at the same temperature. The reaction mass was further cooled to 0-5°C and continued stirring for 2 hours. Filtered the isolated 20 solid and washed with isopropyl acetate, dried at 55-60°C. Yield: 87%

[0079] **Example-2: Preparation of 3-([2-[(4-cyanophenyl) amino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) ethyl propionate fumarate** was prepared according to the procedure described in example 1, in the place of succinic acid, fumaric acid was used. Yield: 85% HPLC: 95%.

25 [0080] **Example-3: Preparation of 3-([2-[(4-cyanophenyl) amino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) ethyl propionate maleate** was prepared according to the procedure described in example 1, in the place of succinic acid maleic acid was used. Yield: 85% HPLC: 95%.

Example-4: Preparation of ethyl 3-([2-[(4-cyanophenyl) amino]-methyl]-1-methyl-1H-benzimidazole-5-carbonyl]-pyridin-2-yl-amino) propionate free 30 base.

[0081] The dried compound from example-1 to 4 was dissolved in methylene chloride (280 ml) and basified with sodium carbonate solution, separated the methylene chloride layer and distilled the solved under vacuum, finally isolated

the compound in ethyl acetate. Yield: 80 % and HPLC: 99.5%.

Example-5: Preparation of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

[0082] The compound from example-4 (0.2 mol) was dissolved in ethyl acetate and ethanolic hydrochloride solution (1000 ml) and stirred for 12-15 hours at 25-30°C. The excess of ethanol was distilled under vacuum, the resulted residue dissolved in ethanol (1000 ml), ammonium carbonate (2.08 mol) was added to the reaction mixture and stirred for 16 hours at 25-30°C, monitored the reaction by HPLC. Upon completion of the reaction methylene chloride (300 ml) was added and filtered. The filtrate was taken and distilled the solvent under vacuum and added aqueous acetone (500 ml), stirred for product isolation. The resulting solid was filtered and dried under vacuum. Yield: 95 % & HPLC: 95%.

Example-6: Preparation of 1-methyl-2-[N-(4-amidinophenyl)-aminomethyl]-benzimidazol-5-yl-carboxylic acid-N-(2-pyridyl)-N-(2-ethoxycarbonylethyl)-amide

[0083] The compound from example-4 (0.2 mol) was dissolved in ethyl acetate, sulfuric acid and ethanolic hydrochloride solution (1000 ml) and stirred for 12-15 hours at 25-30°C. The excess of ethanol was distilled under vacuum, the resulted residue dissolved in ethanol (1000 ml), ammonium carbonate (2.08 mol) was added to the reaction mixture and stirred for 16 hours at 25-30°C, monitored the reaction by HPLC. Upon completion of the reaction methylene chloride (300 ml) was added and filtered. The filtrate was taken and distilled the solvent under vacuum and added aqueous acetone (500 ml), stirred for product isolation. The resulting solid was filtered and dried under vacuum. Yield: 95 % & HPLC: 98%.

Example-7: Preparation of N-[[2-[[[4-[[[(Hexyloxy) carbonyl]-amino] imino methyl] phenyl] amino] methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]-N-2-pyridinyl -β- alanine ethyl ester.

[0084] The compound from example-5 was dissolved in acetone and added potassium carbonate (0.5 mol) (700 ml) followed by hexylchloroformate (0.25 mol) and stirred for 1.0 hr at 25-30 °C and monitored the reaction by HPLC. Upon reaction completion water (200ml) was charged into reaction mass and stirred for product isolation. The isolated product was filtered; the wet solid was dissolved in

methylen chloride. The clear methylen chloride layer was washed with potassium carbonate solution followed by water (650 ml) and finally passed through hyflo bed. The filtrate was taken and distilled the solvent under vacuum and the residue obtained was dissolved in ethyl acetate (800 ml) and stirred at the same temperature to obtain solid. The isolated solid was filtered and dried under vacuum. Yield: 75 % & HPLC: 98%.

Example 8: Process for the preparation of virtually crystalline form IC of N-[[2-[[[4-[[[(Hexyloxy) carbonyl]-amino] imino methyl] phenyl] amino] methyl]-1-methyl-1H-benzimidazol-5-yl] carbonyl]-N-2-pyridinyl - β - alanine ethyl ester

[0085] Wet material obtained in the example-7 was dissolved in isopropyl alcohol (150 ml) and stirred for 4 hours at 25–30°C, and then the compound was filtered and dried under vacuum.

Example-9: Process for the preparation of DabigatranEtexilateMesylate from DabigatranEtexilate

[0086] The DabigatranEtexilate (0.04 mol) was dissolved in acetone (250.0 ml) and added Methanesulfonic acid (0.04 mol) in Ethyl acetate (25 ml) at 25–30°C. Stirred the reaction mass for 3 hrs at the same temperature, the isolated solid was filtered and washed with acetone, dried under vacuum to get the DabigatranEtexilateMesylate. Yield: 85 %, Purity: Not less than 99.0%

Example 10: Process for the preparation of DabigatranEtexilateMesylate

[0087] To a solution of DabigatranEtexilate (0.04 mol) in Acetone (8 volumes) and Ethanol (2 volumes), Methanesulfonic acid solution [Methanesulfonic acid (0.04 mol) was dissolved in Ethyl acetate (25 ml) was added at 25–30°C and stirred for 3 hrs at the same temperature. After completion of the reaction, the resultant solid was filtered, washed with acetone and dried under vacuum. Yield: 93%.

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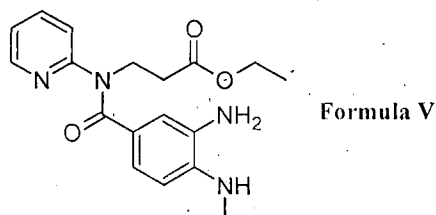
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Claims

We Claim:

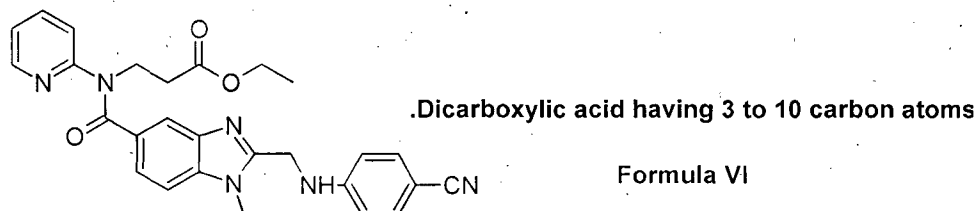
1. A process for the preparation of dabigatranetexilatemesylate comprising the steps of:

a) reacting ethyl 3-{1-[3-amino-4-(methylamino)benzoyl]-N-(pyridin-2-yl)amino}propanoate of formula V,

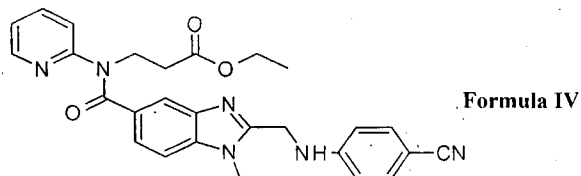


with 2-[(4-cyanophenyl)amino]acetic acid in the presence of a base and a coupling reagent in an organic solvent to obtain a reaction mixture;

b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain a compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid having 3 to 10 carbon atoms having the formula-VI;

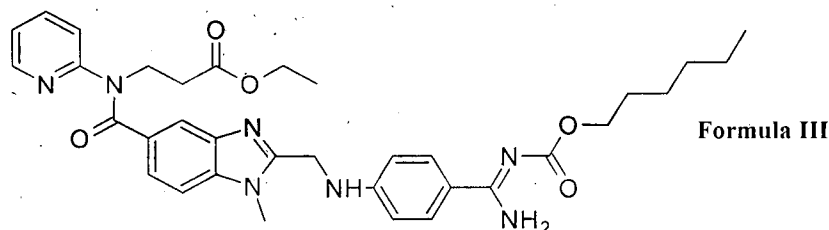
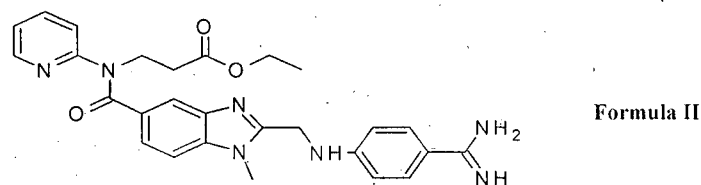


c) basifying the compound 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzoimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid of formula-VI prepared in the step (b) to obtain the ethyl 3-[1-(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido]propanoate free base of formula-IV;



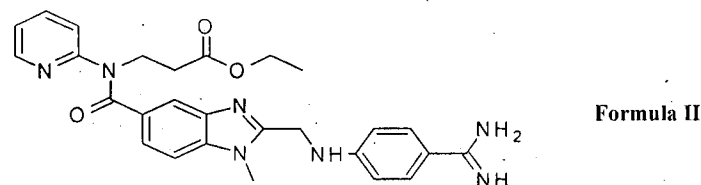
d) dissolving the compound of formula IV obtained in step (c) in a mixture of

ethanol and esters thereof;



e) adding hydrochloride to the reaction mixture obtained in step (d);

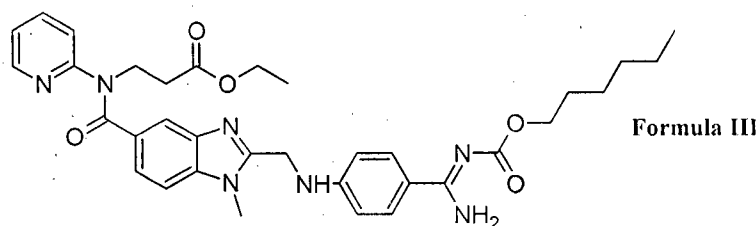
- 5 f) adding an ammonia source periodically to the reaction mixture obtained in step (e) and maintaining sufficient time to obtain the compound of formula II;



g) filtering the compound obtained in the step (d);

- h) purifying the compound obtained in step (e) with a polar organic solvent or
10 mixtures thereof;

i) treating the compound of formula II with hexylchloroformate in the presence of base and maintaining the reaction mixture for sufficient time to obtain a compound of formula III;



- 15 j) treating the compound of formula III with methane sulfonic acid to obtain the dabigatranetexilatemesylate.

2. The process for the preparation of dabigatranetexilatemesylate according to claim-1, wherein said coupling reagent in step (a) is selected from the group comprising of O-(Benzotriazol-1-yl)-N, N', N'-
20 tetramethyluroniumhexafluorophosphate (HBTU) and O-(Benzotriazol-1-yl)- N,

N, N', N'-tetramethyluroniumtetrafluoroborate (TBTU) 3-(Diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one, N,N'-Carbonyldiimidazole.

3. The process for the preparation of dabigatranetexilatemesylate according to claim-1, wherein said organic solvent in step a) is selected from the group comprising of dimethylacetamide, N-methyl-2-pyrrolidone, HMPA, MDC, dimethylformamide, esters containing C1 to C6 carbon atoms and mixtures thereof.

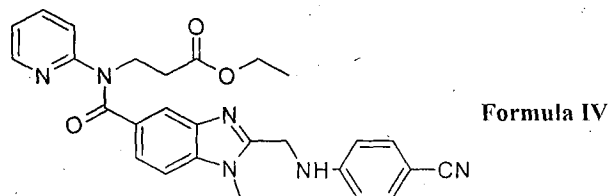
4. The process for the preparation of dabigatranetexilatemesylate according to claim-1, wherein said dicarboxylic acid having C3 to C10 carbon atoms is selected from the group comprising of acetone dicarboxylic acid, camphoric acid, diaminopimelic acid, dimercapto succinic acid, folic acid, glutaconic acid, maleic acid, phthalic acid, tartaric acid, fumaric acid, malonic acid, glutamic acid, adipic acid and succinic acid.

5. The process for the preparation of dabigatranetexilatemesylate according to claim-1, wherein said esters employed in step d) is selected from the group comprising of butyl acetate, sec-butyl acetate, tert-butyl acetate, ethyl acetoacetate, ethyl butyrate, ethyl acetate, isopropyl acetate, methyl acetate and mixtures thereof.

6. The process for the preparation of DabigatranEtexilatemesylate according to claim-1, wherein said polar organic solvent employed in the step h) is selected from the group of alcohol solvents containing C3 to C10 carbons, water, ketones and mixtures thereof.

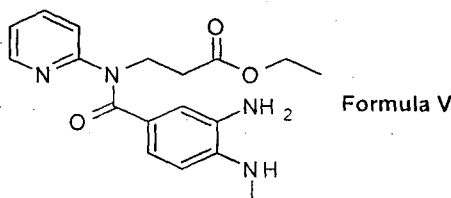
7. The process for the preparation of dabigatranetexilatemesylate according to claim-1, wherein said base employed in step i) is selected from the group of alkali metal bases, ammonium hydroxide and ammonium carbonate.

8. A process for the preparation of 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzoimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester of the compound of formula IV



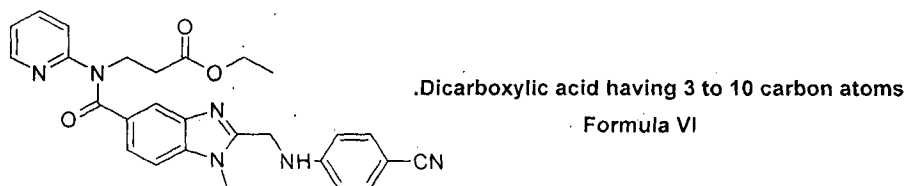
comprising the steps of:

a) reacting ethyl 3-{1-[3-amino-4-(methylamino) benzoyl]-N-(pyridin-2-yl)amino}propanoate of formula V



with 2-[(4-cyanophenyl)amino] acetic acid in the presence of a base and a coupling reagent in an organic solvent to obtain a reaction mixture;

b) adding dicarboxylic acid having 3 to 10 carbon atoms to the reaction mixture obtained in step(a) and maintaining the mixture for a sufficient time to obtain an intermediate 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzimidazole-5-carbonyl}pyridin-2-ylamino) propionic acid ethyl ester, dicarboxylic acid having 3 to 10 carbon atoms having the formula VI;



c) the intermediate 3-({2-[(4-cyano-phenylamino)methyl]-1-methyl-1H-benzimidazole-5-carbonyl}pyridin-2-ylamino)propionic acid ethyl ester, dicarboxylic acid of formula VI prepared in the step (b) is basified to obtain the ethyl 3-[1-(2-{[(4-cyanophenyl)amino]methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propionic acid ethyl ester free base of formula IV.

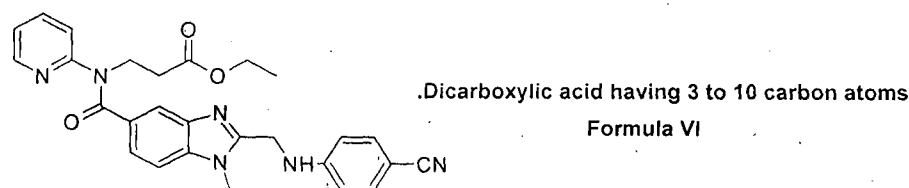
9. The process for the preparation of 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester according to claim-8, wherein said coupling reagent employed in the step a) is selected from the group comprising of O-(Benzotriazol-1-yl)-N, N, N', N'-tetramethyluroniumhexafluorophosphate (HBTU) and O-(Benzotriazol-1-yl)- N, N, N', N'-tetramethyluroniumtetrafluoroborate (TBTU) 3-(Diethylphosphoryloxy)-1,2,3-benzotriazin-4(3H)-one and N, N'-carbonyldiimidazole.

10. The process for the preparation of 3-({2-[(4-cyano-phenylamino) methyl]-1-

methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester according to claim-8, wherein said organic solvent employed in the step a) is selected from the group comprising of dimethylacetamide, N-methyl-2-pyrrolidone, HMPA, MDC, dimethylformamide, esters containing C1 to C6 carbon atoms and mixtures thereof.

11. The process for the preparation of 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester according to claim-8, wherein said dicarboxylic acid having C3 to C10 carbon atoms is selected from the group comprising of succinic acid, acetone dicarboxylic acid, camphoric acid, diaminopimelic acid, dimercapto succinic acid, folic acid, glutaconic acid, maleic acid, phthalic acid, tartaric acid, fumaric acid, malonic acid, adipic acid, and glutamic acid.

12. A novel compound of 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester dicarboxylic acid having 3 to 10 carbon atoms of formula VI

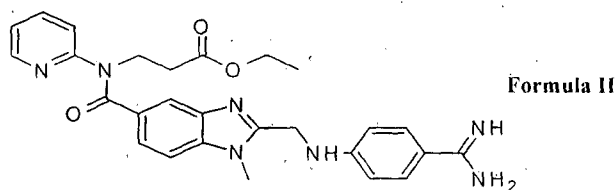


13. The novel compound of 3-({2-[(4-cyano-phenylamino) methyl]-1-methyl-1H-benzimidazole-5-carbonyl} pyridin-2-ylamino) propionic acid ethyl ester dicarboxylic acid having 3 to 10 carbon atoms according to claim-12, wherein said novel compound is ethyl-3-[1-(2-{{[(4-cyanophenyl) amino] methyl}-1-methyl-1H-1, 3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido]propanoate succinate.

14. The novel compound according to claim-12, wherein said novel compound is ethyl 3-[1-(2-{{[(4-cyanophenyl) amino] methyl}-1-methyl-1H-1, 3-benzodiazol-5-yl)-N-(pyridin-2-yl) formamido] propanoate maleate.

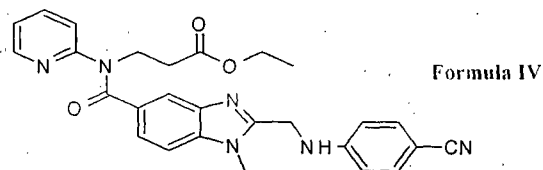
15. The novel compound according to claim-12, wherein said novel compound is ethyl 3-[1-(2-{{[(4-cyanophenyl) amino] methyl}-1-methyl-1H-1,3-benzodiazol-5-yl)-N-(pyridin-2-yl)formamido] propanoate fumarate.

16. A process for the preparation of the compound of formula II as free base in pure form

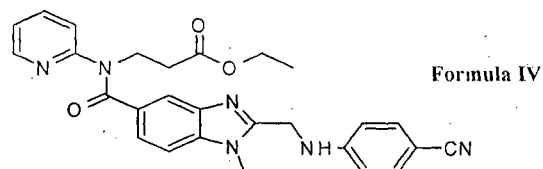


comprising the steps of:

a) dissolving compound of formula IV

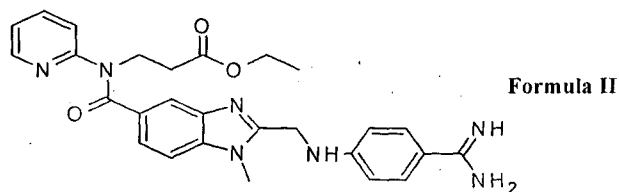


- 5 in a mixture of ethanol and esters ;
- b) adding hydrochloride to the reaction mixture obtained in step (a);
- c) adding an ammonia source periodically to the reaction mixture obtained in step (b) and maintaining sufficient time to obtain the compound of formula II;
- d) filtering the compound obtained in the step (c); and
- 10 e) purifying the compound obtained in step (d) with a polar organic solvent or mixtures thereof.

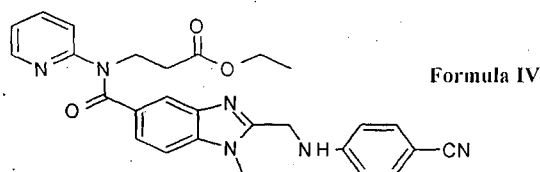


17. The process for the preparation of the compound of formula II as free base in pure form according to claim-16, wherein said esters employed in the step a) is
- 15 selected from the group comprising of butyl acetate, sec-butyl acetate, tert-butyl acetate, ethyl acetoacetate, ethyl butyrate, ethyl acetate, isopropyl acetate, methyl acetate and mixtures thereof .

18. A process for the preparation of the compound of formula II as free base in pure form

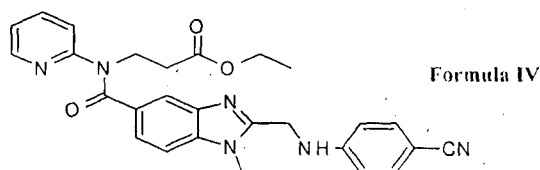


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comprising the steps of:

- a) adding hydrochloride to a mixture of ethanol and ester;
- b) adding the compound of the formula IV



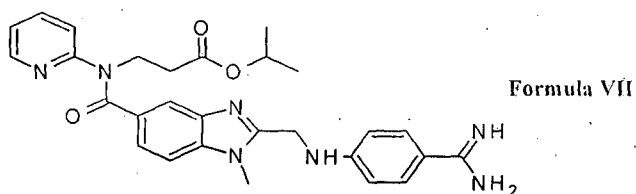
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to the reaction mixture obtained in step (a);

- c) adding an ammonia source periodically to the reaction mixture obtained in step (b) and maintaining sufficient time to obtain the compound of formula II;
- d) filtering the compound obtained in the step (c); and
- 10 e) purifying the compound obtained in step (d) with a polar solvent or mixtures thereof.

19. The process for the preparation of the compound of formula II as free base in pure form according to the claim-18, wherein said esters employed in the step a) is selected from the group comprising of butyl acetate, sec-butyl acetate, tert-butyl acetate, ethyl acetoacetate, ethyl butyrate, ethyl acetate, isopropyl acetate, methyl acetate and mixtures thereof.

20. A novel compound of formula VII



20 21. A process for the preparation of dabigatranetexilatemesylate comprising the steps of:

- a) dissolving or suspending dabigatranetexilate in acetone, or a solvent mixture containing acetone;
- b) adding a mixture of methanesulphonic acid in ethylacetate to the mixture prepared in step (a); and
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c) obtaining the dabigatranetexilate mesylate.

22. A crystalline form of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, designated as the form IC characterized by x-ray powder diffraction pattern having characteristic peaks at reflection angle 2θ ($\pm 0.2^\circ 2\theta$) 5.84, 6.5, 11.7, 17.47, 19.9, 20.49, 24.77, 26.44, 27.02.

23. A process for the preparation of crystalline form of ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate, designated as the form IC characterized by x-ray powder diffraction pattern having characteristic peaks at reflection angle 2θ ($\pm 0.2^\circ 2\theta$) 5.84, 6.5, 11.7, 17.47, 19.9, 20.49, 24.77, 26.44, 27.02, comprising the steps of:

- a) dissolving the ethyl 3-[(2-{[4-(hexyloxycarbonylamino-imino-methyl)-phenylamino]-methyl}-1-methyl-1H-benzimidazole-5-carbonyl)-pyridin-2-yl-amino]-propionate base in isopropanol;
- b) optionally stir up till precipitation of the solid;
- c) filtering the solid and drying the obtained solid.

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DavuluriRamamohanRao

An improved process for the preparation of DabigatranEtexilateMesylate
and its intermediates thereof

X-Ray Powder Diffraction (XRPD) pattern of crystalline form A of single
prodrug of Dabigatran

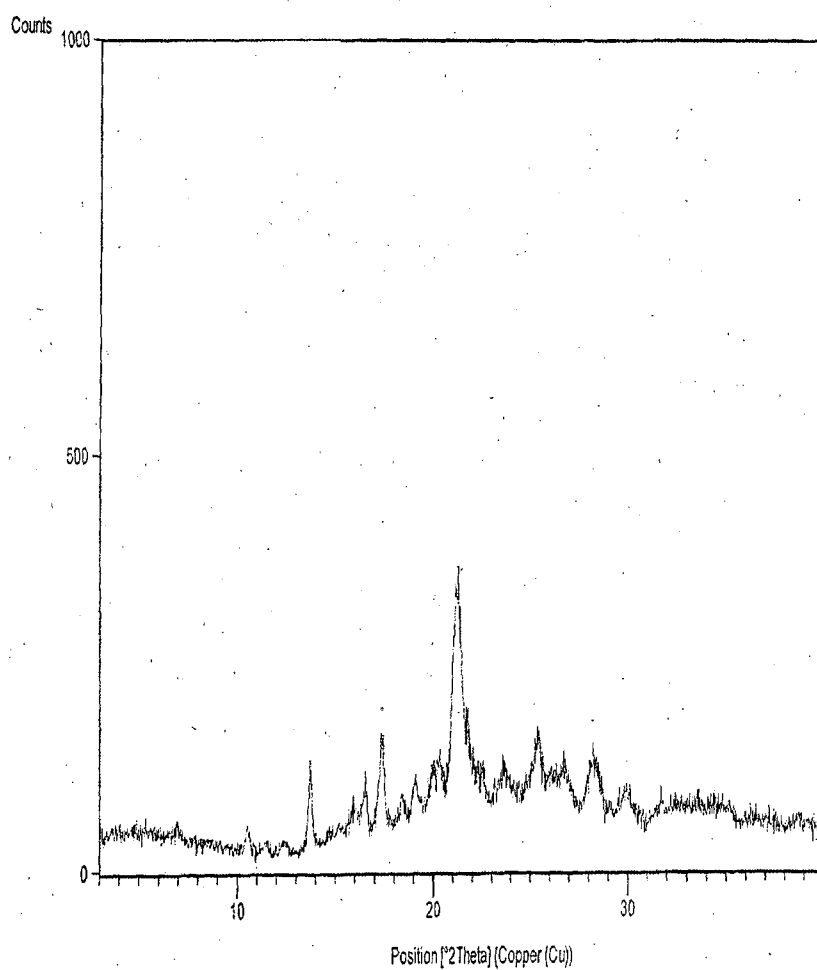


Figure 1

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An improved process for the preparation of DabigatranEtexilateMesylate
and its intermediates thereof

X-Ray Powder Diffraction (XRPD) pattern of crystalline form IC of
DabigatranEtexilate

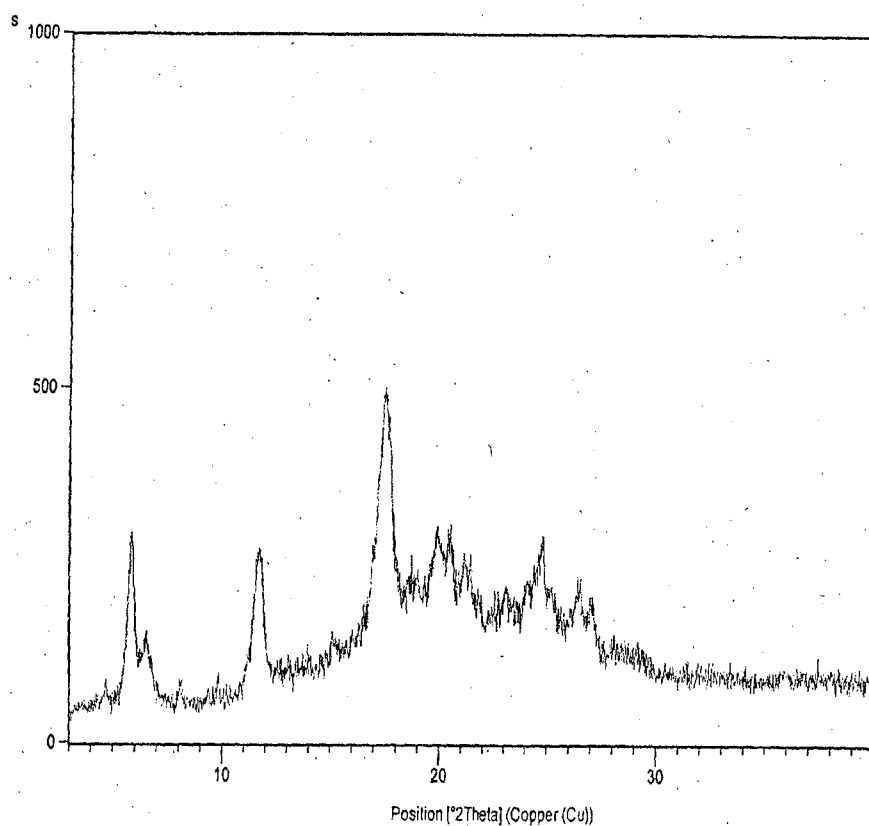


Figure 2

Signature:

N. Ramaswami
Advocate & Patent Agent
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DavuluriRamamohanRao

An improved process for the preparation of DabigatranEtexilateMesylate
and its intermediates thereof

Differential Scanning Calorimetry (DSC) pattern of crystalline form IC of
DabigatranEtexilate

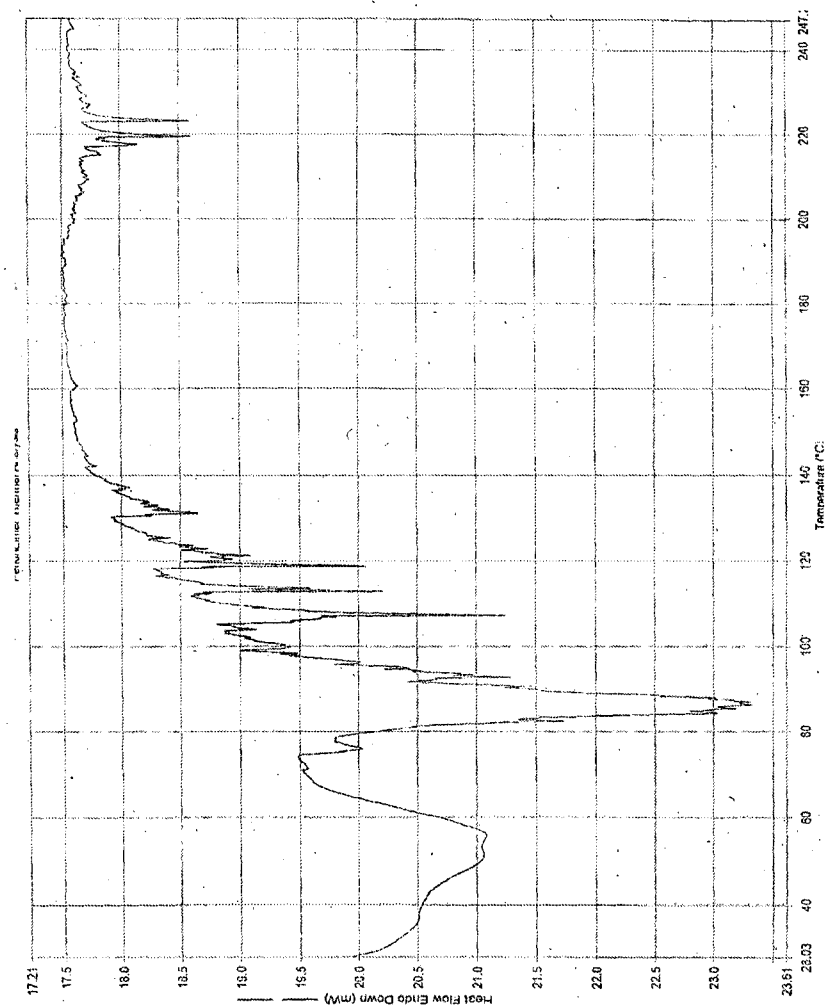


Figure 3

Signature:

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