(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
12 July 2018 (12.07.2018)

WIPO | PCT

(10) International Publication Number
WO 2018/127762 A1

(51) International Patent Classification:
A61K 31/422 (2006.01) *A61P 7/02* (2006.01)
A61K 31/5355 (2006.01) *C07D 413/14* (2006.01)
A61K 31/5377 (2006.01)

(21) International Application Number:
PCT/IB2017/058245

(22) International Filing Date:
21 December 2017 (21.12.2017)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
201721000351 04 January 2017 (04.01.2017) IN

(71) Applicant: **UNICHEM LABORATORIES LTD** [IN/IN]; Unichem Bhavan, Prabhat Estate, Off. S. V. Road, Jogeshwari (W), Mumbai, Maharashtra 400102 (IN).

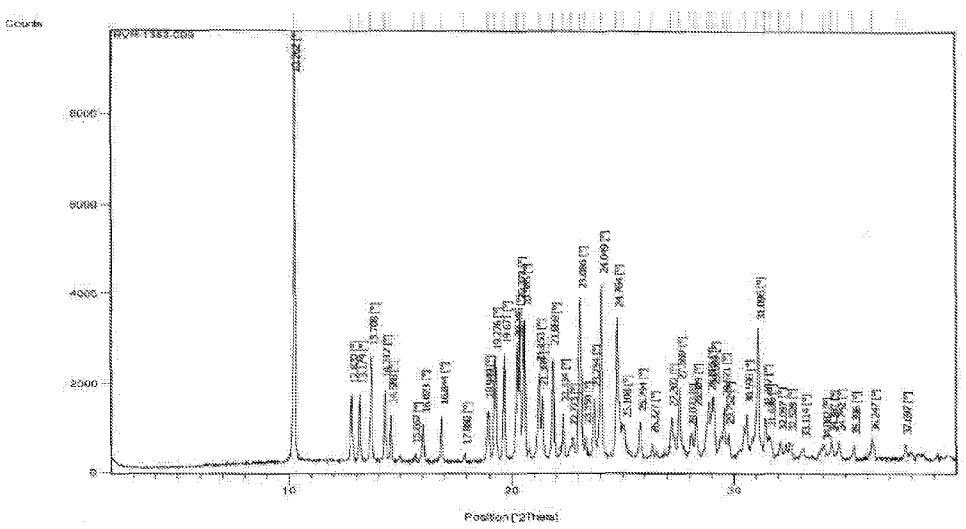
(72) Inventors: **SATHE, Dhananjay G.**; 202/A-1, Golden Park, L.B.S., Marg Panchpakhadi,, Thane, Maharashtra 400601 (IN). **DAS, Arijit**; Sapana Habitat, Bld-A1, Apt No-6, Chogam Road, Porvorim, Goa 403521 (IN). **RAIKAR, Sanjay**; Behind Government Primary School, Lobo ward, Bardez, Goa 403510 (IN). **SURVE, Yashwant S.**; 2A/304, OMKAR SOCIETY, New MHADA Colony, Near NNP-I & II, DINDOSHI, Goregaon (East), MUMBAI, Maharashtra 400 065 (IN). **PANDIT, Bhushan S.**; Manas Society B, Geetanagar, Mhasrul, Nashik, Maharashtra 422004 (IN).

(74) Agent: **KHURANA & KHURANA, ADVOCATES & IP ATTORNEYS**; E-13, UPSIDC, Site-IV, Behind-Grand Venice, Kasna Road, Greater Noida, National Capital Region, Uttar Pradesh 201310 (IN).

(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, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JO, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, 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, SA,

(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF RIVAROXABAN INVOLVING NOVEL INTERMEDIATE

Fig 1: XRPD pattern of Compound of Formula-5



(57) Abstract: The present invention relates to the novel key intermediate, 4-{4-[(5S)-(Aminomethyl)-2- oxo-l,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate, in the synthesis of rivaroxaban. The invention further relates to the crystalline form of novel intermediate, the process to prepare the novel intermediate and method of preparing rivaroxaban using this novel intermediate. The invention provides an improved and efficient process for preparation of Rivaroxaban.

WO 2018/127762 A1

[Continued on next page]

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, ST, SZ, TZ, 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).

Published:

— *with international search report (Art. 21(3))*

— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments (Rule 48.2(h))*

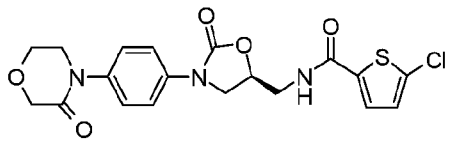
AN IMPROVED PROCESS FOR THE PREPARATION OF RIVAROXABAN INVOLVING NOVEL INTERMEDIATE

TECHNICAL FIELD

The present invention provides novel intermediate, process to prepare novel intermediate and an efficient and improved process for preparation of Rivaroxaban or its pharmaceutically acceptable salt using novel intermediate.

BACKGROUND OF THE INVENTION

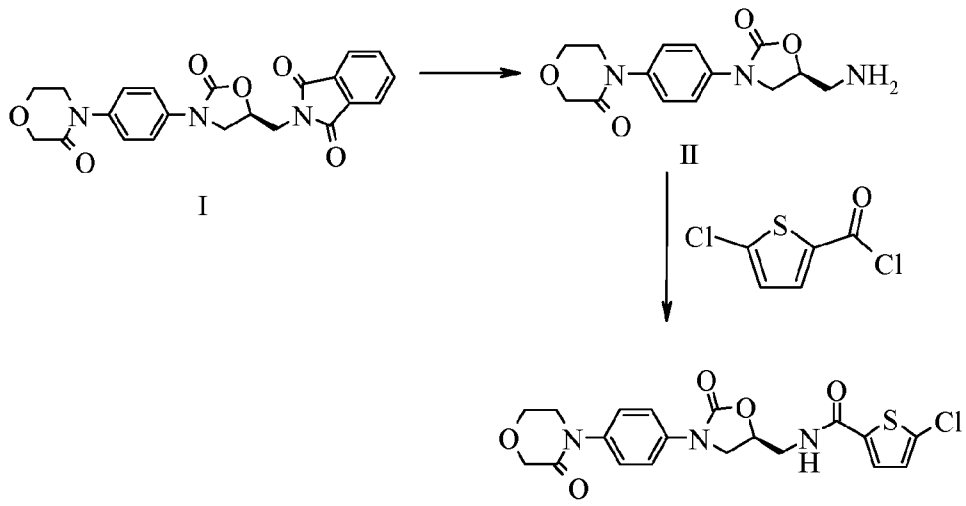
Rivaroxaban chemically known as (S)-5-chloro-N-{[2-oxo-3-[4-(3-oxomorpholin-4-yl) phenyl]oxazolidin-5-yl]methyl} thiophene-2-carboxamide (FORMULA-1), is an oral anticoagulant and is marketed under brand name Xarelto. It is the first available orally active direct factor Xa inhibitor. On July 1, 2011, the U.S. Food and Drug Administration (FDA) approved Rivaroxaban for prophylaxis of deep vein thrombosis (DVT), which may lead to pulmonary embolism (PE), in adults undergoing hip and knee replacement surgery. On November 4, 2011, the U.S. FDA approved rivaroxaban for stroke prophylaxis in people with non-valvular atrial fibrillation.



FORMULA-1

A process for the preparation of the Rivaroxaban and its intermediate was first disclosed in WO2001047919 (US7157456 B2) as shown in Scheme I, which includes:

i.Reaction between I with aq. Methylamine in ethanol to produce 4-[{4-[(5S)-5-(-Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}]-morpholin-3-one (Oxazolidine amine II);



FORMULA-1

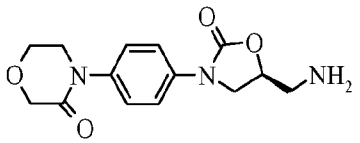
Scheme I

ii. Further condensation of 4-[{4-[(5S)-5-(-Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}]-morpholin-3-one (Oxazolidine amine II) with 5-chlorothiophene-2-carbonyl chloride in pyridine to produce (S)-5-chloro-N{[2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]oxazolidin-2-yl]methyl}thiophene-2-caboxamide (Rivaroxaban of FORMULA-1). In this process all intermediates and final API are purified using flash chromatography. Moreover use of excess dichloromethane and pyridine as a solvent limits its commercial scale production due to handling difficulties.

Similar process is disclosed in Journal of medicinal chemistry, 2005, 48, 5900-5908.

US7351823 discloses a process to prepare rivaroxaban by slightly modifying the process disclosed in US7157456 to get the better yield of the product as compared to US7157456. However the yields of US7157456 still provide the scope for improvement. In the said process, intermediate VI in scheme I is converted into its hydrochloride salt and then reacted with 5-chlorothiophene-2-carbonyl chloride to get Rivaroxaban. The patent however does not mention the purity of the final product. Dimeric impurities are formed in the process disclosed in US7351823.

On the similar lines as that of US7351823, many processes for preparation of rivaroxaban have been claimed and disclosed in the patents thereafter, wherein the step of converting compound VI in scheme I to Rivaroxaban is modified.



Compound VI the key intermediate

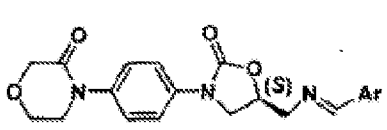
Either different salts of compound VI have been prepared or the base used in the reaction is changed or the solvents are selected in such a way that the yield, ease of handling and the affordability of the reaction of the overall process improves.

US8188270 claims novel modifications and solvates of rivaroxaban and in Example 2. The patent discloses the process to prepare rivaroxaban in which compound VI as HCl salt is reacted with 5-chlorothiophene-2-carbonyl chloride in presence of triethyl amine and N-methyl-2-pyrrolidone (NMP) as solvent. Use of NMP in larger amount on industrial scale is undesirable, highly dangerous and environmentally unfriendly.

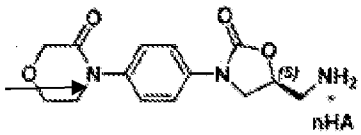
US2013253187 discloses a process to prepare rivaroxaban by reacting compound VI as its salt (preferably sulphate) with 5-chlorothiophene-2-carbonyl chloride in presence of organic base having pKa higher than 5.3, or mixtures thereof. Particularly preferred organic bases are organic bases with a pKa higher than 8.5, more preferably organic bases with a pKa higher than 10.0. The most preferred base being N,N-diisopropyl ethylamine (DIPEA). The application further mentions that, 'the use of an organic base instead of an inorganic base gives more versatility to the reaction' and 'the organic base easily dissolves in both organic media and water, which provides a more effective reaction and therefore better yield'. Use of excess of costly CDI, elaborate purification to separate byproducts from desired product and extensive purification process of two crystallizations to obtain pure Rivaroxaban compromises yields and makes the process lengthy and undesirable.

WO2013053739 provides a process to prepare rivaroxaban using compound VI, wherein compound VI is in its acid addition salt form and wherein the acid is specifically an organic acid. The drawback of the process are the extremely low yields (65 -85%) of acid addition salts and conversion of acid addition salt to crude rivaroxaban gives product in not more than 90% yield. Further purification of this low yielded crude rivaroxaban decreases the yield of final pure rivaroxaban.

In WO2013120465 the process used in the preparation of acid addition salt of compound VI is:



(S)-(9)



(S)-(11) n = 1/2, 1

wherein HA stands for an acid selected from the group of methanesulfonic, benzenesulfonic, p-toluenesulfonic, (R)- and (S)- camphorsulfonic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, D- and L- tartaric, benzoic, oxalic and trifluoroacetic acid. Use of unstable

reagents such as aldehyde and imine, lower carbon efficiency, lengthy process to prepare Rivaroxaban via imine are undesirable features of the process. Also low yield of 51% in imine formation and 68% in coupling of imine with amino morpholine derivative, drastically reduces the overall yield of the process. Use costly & pyrophoric t-BuOLi makes process unsafe on larger scales and costly.

WO2013098833 provides compounds of formula VI in various inorganic and organic salt forms and their solid state forms. It claims a process to prepare rivaroxaban using these salts and rivaroxaban with high purity. The process uses sulphonyl halides to prepare rivaroxaban which are potential source of genotoxic impurity after reacting with alcoholic solvent.

A process claimed by WO2015198259 uses Nitrate salt of compound VI and the overall yield of rivaroxaban is low.

It has been observed that plain base or an amine when treated with 5-chlorothiophene-2-carbonyl chloride leads to formation of Rivaroxaban with extremely poorer yields. It was also observed that when a salt of the amine is used for reaction with 5-chlorothiophene-2-carbonyl chloride, better yields and purity are obtained. It is also noticed that different salts give different purity and yield for the reaction. It makes it very clear that the amine is different from its salts in many aspects, primarily salts are significantly different from each other and from the amine from which they are formed. Different salts behave differently in the reaction. Stability and reactivity or the ability of different salts of amine to form quality of rivaroxaban is unpredictable. Therefore salts are not same as the amine from which they are formed.

In view of the drawbacks associated with prior art processes, there is a need to provide a better, highly energy efficient, cheap, safe process without the use of corrosive and pyrophoric chemicals, to prepare rivaroxaban which is suitable for industrial scale ups and which produces all the intermediates and the final product substantially free of impurities and in high yields.

OBJECT OF THE INVENTION

The main object of the present invention is to provide a process to prepare rivaroxaban using novel key intermediate, wherein the process is highly energy efficient, cheap, safe and easily scalable.

Another object of the invention is to provide novel key intermediates in the synthesis of rivaroxaban, which are high yielding, easily purified and easy to handle.

Yet another object of the invention is to provide a process to prepare key intermediate in the synthesis of rivaroxaban wherein the process is high yielding and easy to carry out on larger scale.

Yet another object of the invention is to provide highly pure crystalline form of the key intermediate in the synthesis of rivaroxaban.

Yet another object of the invention is provide a process to prepare a crystalline form of the key intermediate in the synthesis of rivaroxaban.

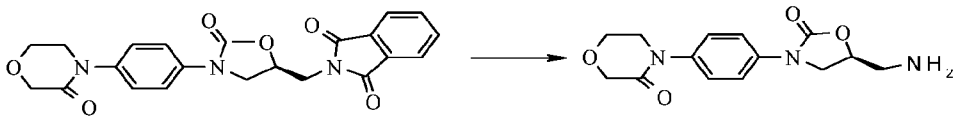
SUMMARY OF THE INVENTION:

The present invention provides a process to prepare Rivaroxaban using 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) as a novel key intermediate.

The present invention further provides a novel intermediate 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5).

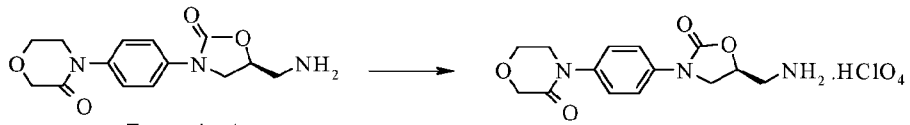
The present invention provides a process to prepare 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises:

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with methylamine to obtain amine of Formula-4a *in-situ*;



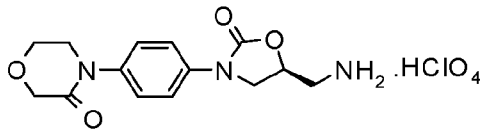
Formula-4 Formula-4a

ii. converting *in-situ* prepared amine of Formula-4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

In the present invention there is provided a crystalline 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5).



Formula-5

As per one more aspect of the present invention there is provided a process to prepare highly pure, crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5, wherein the process comprises the steps of:

i. Crystallization of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate using solvent selected form methanol IPA, Ethanol, Dichloromethane or mixture thereof at a temperature of 30°C -82°C;

ii. Separation of crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate from the solvent.

There is also provided a process to prepare rivaroxaban using crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises:

BRIEF DESCRIPTION OF THE DRAWINGS

Fig 1: XRPD pattern of crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-oneperchlorate (Formula-5)

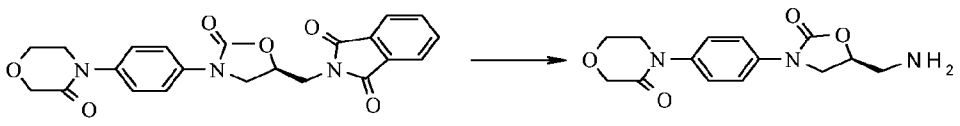
Peak List: List of Peaks as depicted in Fig 1

Fig 2: Differential scanning calorimetry of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-oneperchlorate (Formula-5)

DETAILED DESCRIPTION OF THE INVENTION

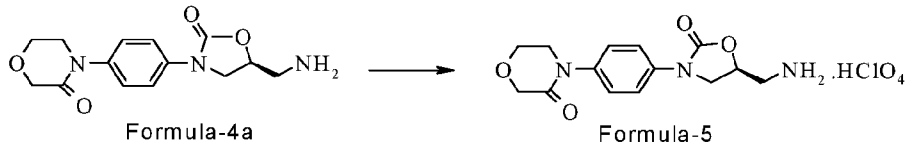
The present invention provides a process to prepare Rivaroxaban using 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of formula-5 as a novel key intermediate, wherein the process comprises:

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with aqueous methylamine to obtain amine of Formula-4a *in-situ*;



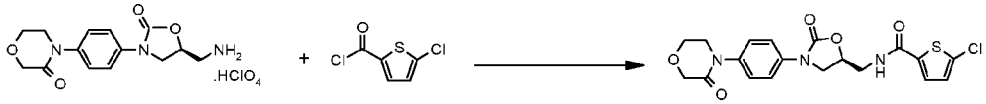
Formula-4 Formula-4a

ii. converting *in-situ* prepared amine of Formula 4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

iii. reacting 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5, obtained in step ii with 5-chlorothiophene-2-carbonyl chloride in presence of a base and solvent to obtain Rivaroxaban of Formula-1.



Formula-5 5-chlorothiophene -2-carbonylchloride Rivaroxaban

The compound of the Formula-4 is prepared by the processes known in the prior art. The reaction in step i is carried out using excess of aqueous methylamine in presence of solvent selected from methanol, ethanol, isopropyl alcohol (IPA), water or mixture thereof; preferably IPA, at temperature from 30°C to 60°C preferably at 45°C to 50°C. The *in-situ* prepared amine in step i is acidified using perchloric acid in the same solvent as that in step i to produce 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5.

4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 formed in step ii is in crystalline form. Formula-5 in its crystalline form is used as a starting material in the synthesis of rivaroxaban in step iii.

The reaction between perchlorate of Formula-5 with 5-chlorothiophene-2-carbonyl chloride as in step iii is carried out in presence of an inorganic base selected from Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate, Potassium carbonate, Lithium carbonate, or an organic base selected from Triethylamine, N,N diisopropylethyl amine, Pyridine; preferably Sodium carbonate in a solvent selected from ketones such as Acetone, Methyl ethyl ketone, N-methylpyroolidone, Methyl isobutyl ketone (MIBK), aromatic hydrocarbons such as Toluene, Xylene, chlorinated solvents such as Dichloromethane, Chloroform, Chlorobenzene, esters such as Ethyl acetate, Methyl acetate, amides such as Dimethylformamide, Dimethylacetamide, or solvents selected from Acetonitrile, water, Dimethyl sulfoxide, ethers such as Tetrahydrofuran, Dioxane, and mixtures thereof; preferably in mixture of Acetone, Toluene and water, in the ratio of 2.4:2.2:5.17.

Final yield of Rivaroxaban was upto 98%. The purity of final product was as per ICH standards. The process of the present invention was high yielding as compared to processes in the prior art. Raw materials used in the process were cheap and easy to handle, thus making the process cost effective, energy efficient and highly efficient.

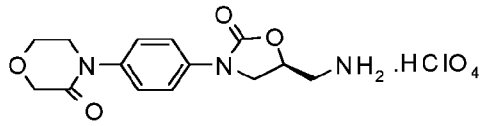
Use of perchloric acid to form 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is normally unheard of. The reason may be that the perchloric acid per se is highly reactive and has strong oxidizing effect. The reason may be the fact that perchloric acid being a very strong oxidizing agent and oxidizes the compound very fast, the moment it comes into contact with it. As a result an effort to form a salt with perchloric acid may result into unstable salt and would foul the purpose of preparing a perchloric acid salt.

However, surprisingly it was noticed that 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is stable, highly pure, crystalline and is produced in very good yields.

Unlike the salts used in the prior art, perchlorate salt was found to be high yielding making the process efficient, easy to handle therefore easily scalable and could be prepared *in situ* in reaction mixture during amine preparation. It also gives highly pure product, both the salt as well as rivaroxaban in the next step. Use of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) of Formula-5 as a key intermediate in the synthesis of rivaroxaban makes the entire process cost effective, energy efficient and easily scalable.

US2013253187 states that the use of organic base in the reaction between sulphate of 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one and 5-chlorothiophene-2-carbonyl chloride, provides a more effective reaction and therefore better yield. Surprisingly it was noticed that, Sodium carbonate, an inorganic base, made this reaction high yielding, easy to handle and highly efficient. Also the cost of inorganic base as compared to DIPEA, used in US2013253187 is considerably less, making process cheaper. The yields of reaction in present invention are better than those of US2013253187. Also the time required in the present invention to prepare rivaroxaban is lesser than that disclosed in US2013253187. Use of inorganic bases makes the process user friendly and nature friendly.

As per one aspect of the invention, there is provided 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5).

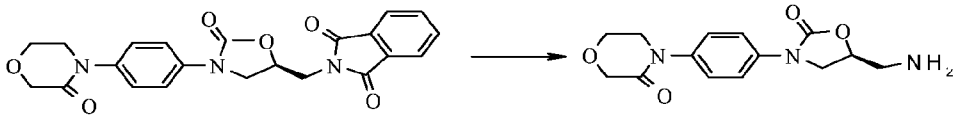


Formula-5

It was surprisingly found that as compared to other known salts of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one, the yield of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) was high and the product obtained was in highly pure form. Surprisingly it was noticed that although perchloric acid is a strong oxidizing agent, use of perchloric acid could yield a stable salt. The salt was easy to handle and easily scalable. The yield of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate was higher than that of widely used hydrochloric acid salt mentioned in prior art US7351823.

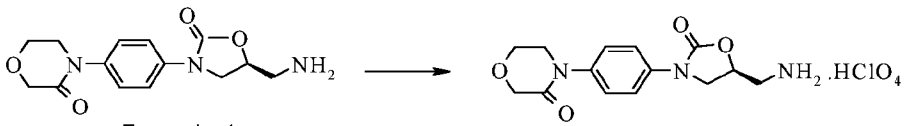
In another aspect of the invention, there is provided a process to prepare 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises;

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with methylamine to obtain amine of Formula-4a *in-situ*;



Formula-4 Formula-4a

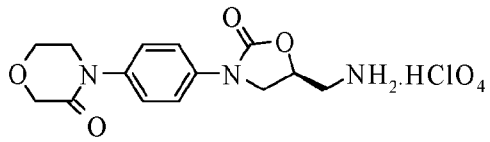
ii. converting *in-situ* prepared amine of Formula-4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

The reaction in step i is carried out using excess of aqueous methylamine in presence of solvent selected from methanol, ethanol, IPA water or mixture thereof; preferably IPA, at temperature from 30°C to 60°C preferably at 45°C to 50°C. The *in-situ* obtained amine is acidified using perchloric acid to produce 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5.

In another aspect of the invention there is provided a highly pure crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5).



Formula-5

Crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is characterized by XRPD pattern with 2θ values at 10.26, 19.27, 20.24, 20.58, 24.04 and 31.09 +/- 0.2θ.

Crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is characterized by XRPD pattern with 2θ values at 10.26, 13.70, 19.67, 20.37, 23.08, 24.76 +/- 0.2θ.

Crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is characterized by XRPD pattern with 2θ values at 13.70, 19.27, 20.24, 20.37, 24.04 +/- 0.2θ.

Accordingly, crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is characterized by XRPD pattern with 2θ values at 10.26, 13.70, 19.27, 19.67, 20.24, 20.37, 20.58, 23.08, 24.04, 24.76 and 31.09 +/- 0.2θ.

The crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is further characterized by the XRPD patter with 2θ values at 12.81, 13.17, 14.31, 14.58, 16.84, 18.94, 21.25, 21.39, 21.88, 22.33, 23.75, 27.58, 28.88, 29.06, 29.57, 30.59, +/- 0.2θ.

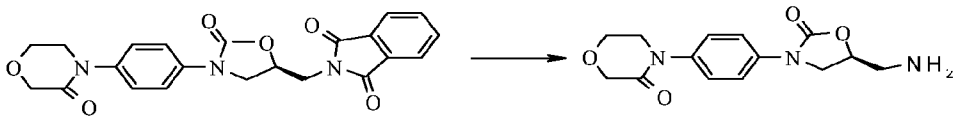
The crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) is characterized by the XRPD pattern as shown in Fig 1.

The crystalline form is further characterized by DSC. The product showed DSC endotherm at 206.84°C as shown in Fig 2.

A compound is said to be in highly pure form, when the purity of the compound is measured by HPLC and gives value of more than 99%.

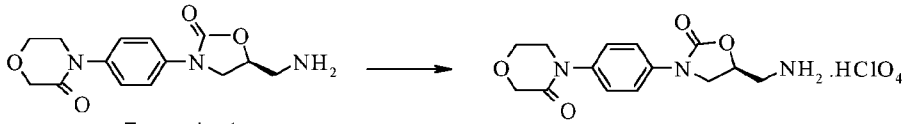
As per one aspect of the invention there is provided a process to prepare highly pure crystalline form of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises the steps of:

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with methylamine to obtain amine of Formula-4a *in-situ*;



Formula-4 Formula-4a

ii. converting *in-situ* prepared amine of Formula-4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

iii. crystallizing 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 obtained in step ii in a solvent selected from Acetic acid, methanol, IPA, ethanol, Dichloromethane and mixture thereof at a temperature of 30°C to 82°C to obtain crystals of 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula 5.

iv. Separating crystal of 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate from the solvent.

The reaction in step i is carried out using excess of aqueous methylamine in presence of solvent selected from methanol, ethanol, IPA water or mixture thereof; preferably IPA, at temperature from 30°C to 60°C preferably at 45°C to 50°C. The amine obtained in step i is acidified using perchloric acid to produce 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5.

Crystallization of 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is carried out using solvent selected from acetic acid, methanol, IPA, ethanol, dichloromethane or mixture thereof; preferably in the mixture of dichloromethane and methanol in the ratio of 1:3 to 3:1, preferred being 4:2, at a temperature of 30°C to 82°C The crystals of Formula-5 were separated by Filtration.

As described earlier, the very nature of perchloric acid discourages its use to form a salt for use in the reactions. Surprisingly the crystal form of Formula 5 was found to be stable, and was produced in very good yields with excellent purity. The deprotection reaction was carried out in Isopropyl alcohol. When the perchloric acid was added to the reaction mass 4-

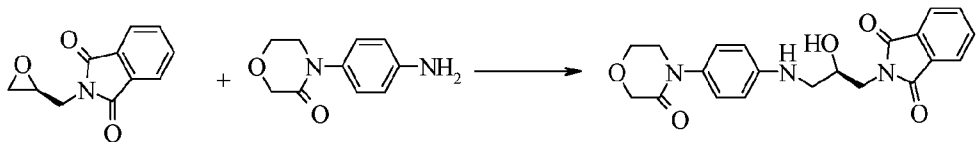
{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula 5 separated out from the reaction mass.

Surprisingly, the accidently obtained crystalline 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula 5 is obtained in high yield (94%) and in highly pure form. This negated the necessity to purify intermediates separately and therefore made the process cost effective, easy to perform, industrially scalable and environment friendly. This also gave the pure rivaroxaban in high yield and purity.

The very fact that use of perchlorate i.e. 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate results into better yields and better purity of Rivaroxaban than use of mere 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one means the two are not same and cannot be presumed to be same. These two are technically, structurally and constitutionally dissimilar and are not superimposable. They significantly differ in their performance in reaction dynamics because of inherent differences in them which result into differential yields and purity of the product. The below given examples demonstrate best mode of carrying out the present invention and do not limit invention in any manner.

EXAMPLES

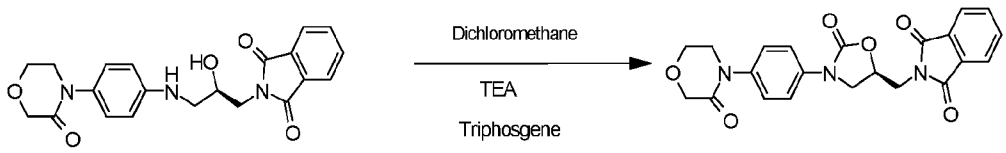
EXAMPLE-1: Preparation of 2-(2R)-hydroxy-3-{[4-(3-oxo-4-morphonyl)phenylamino]propyl}-1H-isoindole-1,3(2H)-dione (Formula-3) from 4-(4-aminophenyl)morpholinone (Formula-2) and (S)-(+)glycidyl phthalimide



(S)-(+) glycidyl phthalimide Formula-2 Formula-3

4-(4-aminophenyl)morpholinone 100 gm, 0.5202 moles and (S)-(+)glycidyl phthalimide 106.6 gm (0.5246 moles) was charged to the mixture of, methanol and water 1000 ml (9:1) and heated to 65°C-70°C. Continued stirring for next 20 hrs at 65°C-70°C. Add second lot of S)-(+)glycidyl phthalimide 10.6 gm (0.05246 moles) and 200 ml (9:1) methanol water mixture and stir for next 12 hrs. Cooled the reaction mass to 25°C-30°C and filter the slurry on Buckner funnel, suck dried well. Wet cake washed with 100 ml mixture of methanol and water (9:1). The solid obtained was dried at 50°C to 55°C to get 190 gm compound of Formula-3 as dry material. Yield-92%

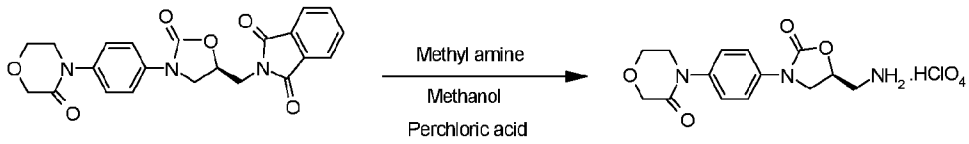
EXAMPLE-2: Preparation of 2-{(5S)-2-oxo-3-[4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3 (2H)-dione (Formula-4) from 2-(2R)-hydroxy-3-{[4-(3-oxo-4-morphonyl)phenylamino]propyl}-1H-isoindole-1,3(2H)-dione (Formula-3)



Formula-3 Formula-4

Amino alcohol 170 gm, 0.4293 moles and Triethylamine 4114.72 gms, 0.9459 moles, was charged to Dichloromethane 2380 ml and cooled reaction mass to 0°C - 5°C. To the cooled reaction mass added triphosgene solution, 51.09 gms in 340 ml MDC, 0.18 moles drop wise at 5°C - 10°C in 60 min, and stirred for 60 - 90 min. Reaction mass quenched with water and distilled out MDC layer atmospherically till thick solid mass obtained. To the thick solid, charged tetrahydrofuran 1360 ml, distilled out 130 ml under vacuum. Cooled slurred mass to 25°C -30°C, stirred for 30 min, filtered. Wet material dried at 55°C -60°C to afford 162 gm dry material. Yield- 89%

EXAMPLE-3: Preparation of 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) and its crystalline form from 2-{(5S)-2-oxo-3-[4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3 (2H)-dione (Formula-4)



Formula-4 Formula-5

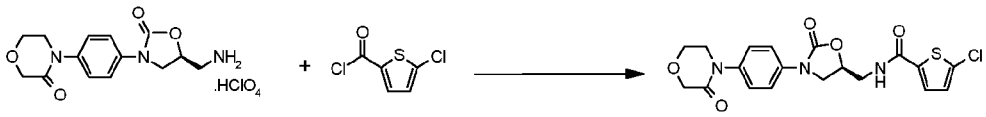
To the slurry of Formula-4 160 gm, 0.379 moles in 800 ml Isopropyl alcohol, Charged 40% methylamine solution130 gm, 1.677 moles. Reaction mass was heated up to 45°C-50°C for 2-3 Hrs. Distilled out IPA under vacuum and charged fresh 800 ml Isopropyl alcohol Cooled reaction mass to 45°C-50°C and added 70% solution of Perchloric acid 59.6 gm, 0.415 moles. Stirred reaction mass for 1 Hrs at 45-50°C. Cooled reaction mass to 0-5°C, filtered and dried at 50°C-55°C to afford 160 gm crude 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate. The crude 4-{4-[(5S)-5-

(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate has a crystalline nature and is in considerably pure form.

Preparation of pure crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) from crude

To Above crude 4-{4-[(5S)-5-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate charged 640 ml Dichloromethane (4 vol of starting material) and charged 320 ml methanol. Heated the slurry to 38°C - 40°C and stirred for 30 min. Cooled the slurry to 20°C. Filtered and suck dried. Product obtained after drying was 138.7 gm pure crystalline perchlorate salt having purity more than 99.5% (Yield-94%)

EXAMPLE-4: Preparation of Rivaroxaban from 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5).



Formula-5 | 5-chlorothiophene -2-carbonylchloride | Rivaroxaban

To the chilled solution of sodium carbonate 5.83 gm, 0.55 moles in 51 ml water, charged 10 gms, (0.0255 moles) of compound of Formula-5 followed by acetone 24 ml. Stirred for 10 min., Meanwhile prepared dil. solution of 5-chlorothiophene-2-carbonyl chloride (5.7 gm Chloro compound diluted with 22 ml of toluene). Toluene solution of 5-chlorothiophene-2-carbonyl chloride was added drop wise at 0°C - 5°C, to the reaction mass. White solid separated out during addition of Toluene solution. Stirred for next 30 min at 0°C - 5°C, raised the temperature of reaction mass to 50°C and charged 35 ml acetone.

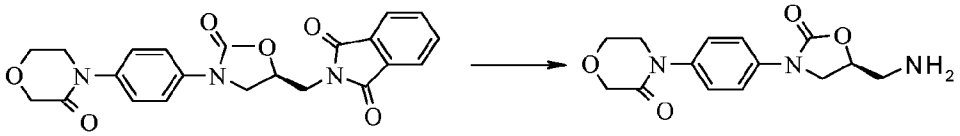
Stirred for 30 min at 45°C to 50°C, followed by cooling and filtration, wet cake was slurred in water at 55°C - 60°C to afford 10.9 gms dry product (Yield-98%).

Above material was purified using methanol Dichloromethane mixture followed by acetic acid to afford pure material having HPLC purity 99.8% chiral purity-99.95%.

We Claim:

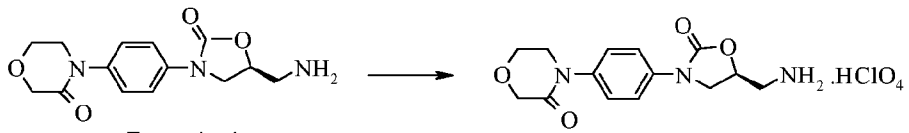
1. A process to prepare rivaroxaban using 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises:

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with aqueous methylamine to obtain amine of Formula-4a *in-situ*;



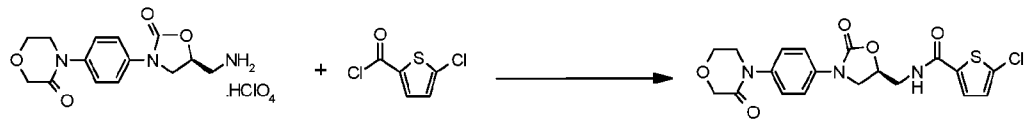
Formula-4 Formula-4a

ii. converting *in-situ* prepared amine of Formula 4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

iii. reacting 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5, obtained in step ii with 5-chlorothiophene-2-carbonyl chloride in presence of a base and solvent to obtain Rivaroxaban of Formula-1.



Formula-5 5-chlorothiophene -2-carbonylchloride Rivaroxaban

2. The process as claimed in claim 1, wherein a solvent in step i and ii is selected from methanol, ethanol, IPA water or mixture thereof.

3. The process as claimed in claim 1, wherein the base used in step iii is selected from an inorganic base selected from Sodium bicarbonate, Sodium carbonate, Potassium bicarbonate, Potassium carbonate, Lithium carbonate, or an organic base selected from Triethylamine, N,N diisopropylethyl amine, Pyridine.

4. The process as claimed in claim 1, wherein the solvent used in step iii is selected from ketones such as Acetone, Methyl ethyl ketone, N-methylpyroolidone, MIBK, aromatic hydrocarbons such as Toluene, Xylene, chlorinated solvents such as

Dichloromethane, Chloroform, Chlorobenzene, esters such as Ethyl acetate, Methyl acetate, amides such as Dimethylformamide, Dimethylacetamide, or solvents selected from Acetonitrile, water, Dimethyl sulfoxide, ethers such as Tetrahydrofuran, Dioxane, and mixtures thereof.

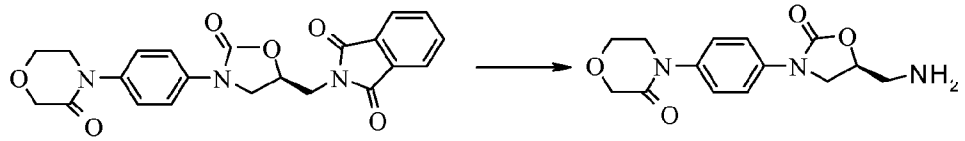
5. The process as claimed in claim 4, wherein the mixture of acetone, toluene and water is in the ratio of 2.4:2.2:5.17.

6. The process as claimed in claim 1, wherein 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) formed in step ii is in crystalline form.

7. 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5.

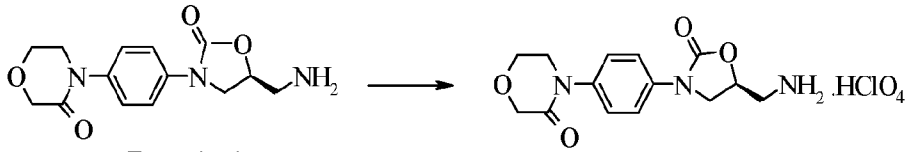
8. A process to prepare 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5) wherein the process comprises;

i. reacting 2-{(5S)-2-oxo-3-[(4-(3-oxo-4-morpholynyl)phenyl]-1,3-oxazolidine-5-yl}methyl-1H-isoindole-1,3(2H)-dione of Formula-4 with methylamine to obtain amine of Formula-4a *in-situ*;



Formula-4 Formula-4a

ii. converting *in-situ* prepared amine of Formula-4a in step i to 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 by reacting it with Perchloric acid;



Formula-4a Formula-5

9. The process as claimed in claim 8, wherein a solvent in step i and ii is selected from methanol, ethanol, IPA water or mixture thereof.

10. A crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate.

11. The Crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate as claimed in claim 10, wherein crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is

characterized by XRPD pattern with 2θ values at 10.26, 13.70, 19.27, 19.67, 20.24, 20.37, 20.58, 23.08, 24.04, 24.76, 31.09 +/- 0.2θ.

12. The Crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate as claimed in claim 10, wherein crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is characterized by DSC peak at 206.84°C.

13. A process to prepare highly pure, crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate (Formula-5), wherein the process comprises the steps of:

i. crystallizing 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate in a crystallizing solvent at a temperature of 30°C to 82°C;

ii. Separating crystals of 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate from the crystallizing solvent.

14. The process as claimed in claim 13, wherein in step i crystallizing solvent is selected form Acetic acid methanol, IPA, ethanol, dichloromethane and mixture thereof, preferably mixture of Dichloromethane and methanol in the ratio of 1:3 to 3:1, preferred being 4:2.

15. The process as claimed in claim 13, wherein preferred temperature of crystallization in step i is 30°C to 40°C.

16. The process as claimed in claim 13, wherein 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate in step i is prepared by the process as claimed in claim 8.

17. The Crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate as claimed in claim 10, wherein crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is characterized by XRPD pattern with 2θ values at 10.26, 19.27, 20.24, 20.58, 24.04 and 31.09 +/- 0.2θ.

18. The Crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate as claimed in claim 10, wherein crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is characterized by XRPD pattern with 2θ values at 10.26, 13.70, 19.67, 20.37, 23.08, 24.76 +/- 0.2θ.

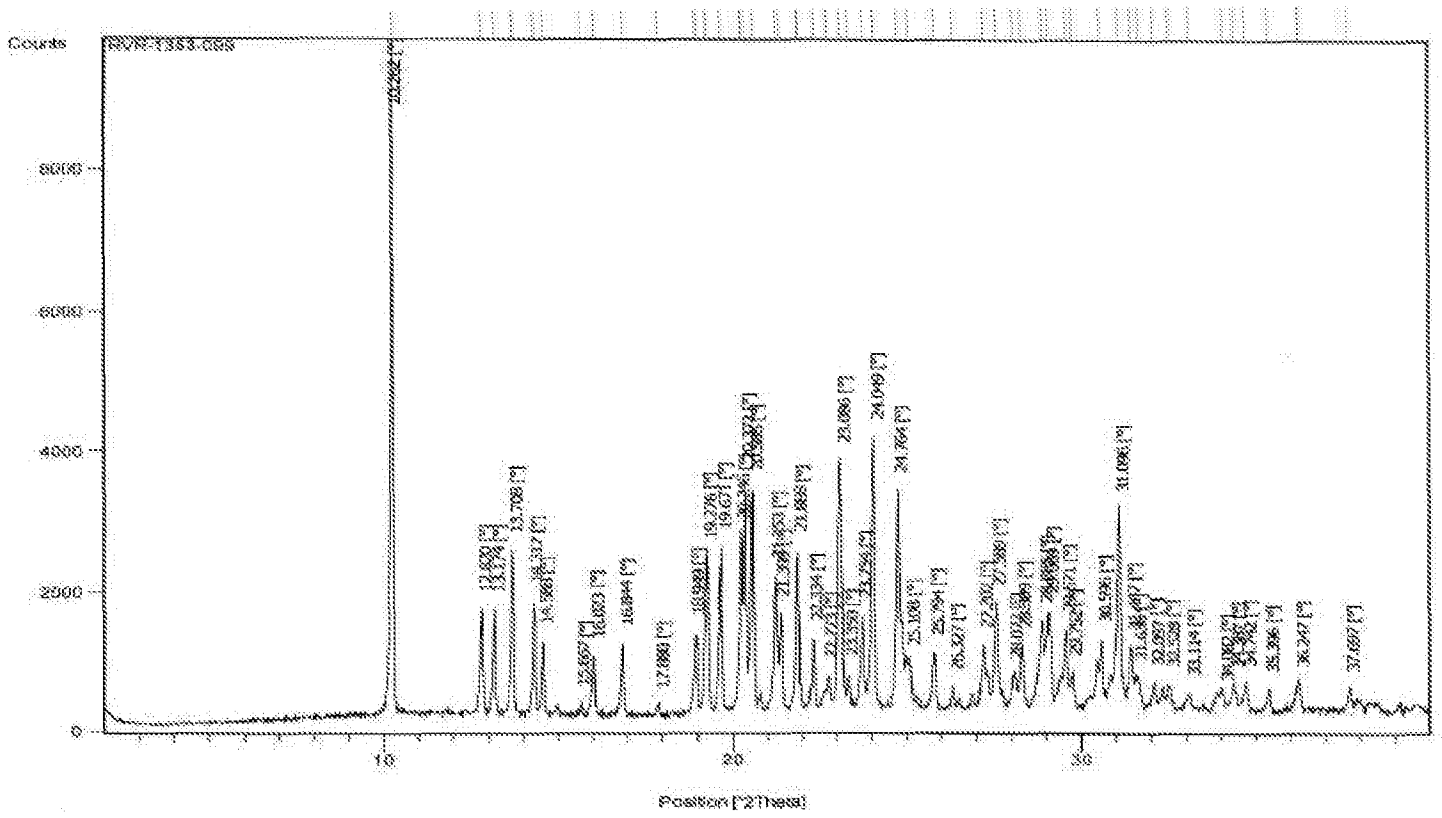
19. The Crystalline 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate as claimed in claim 10, wherein crystalline 4-{4-

[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate is characterized by XRPD pattern with 2θ values at 13.70, 19.27, 20.24, 20.37, 24.04 +/- 0.2θ.

20. Rivaroxaban as prepared by the process claimed in claim 1.

21. Rivaroxaban prepared by the process comprising 4-{4-[(5S)-(Aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]-phenyl}-morpholin-3-one perchlorate of Formula-5 as an intermediate.

Fig 1: XRPD pattern of Compound of Formula-5

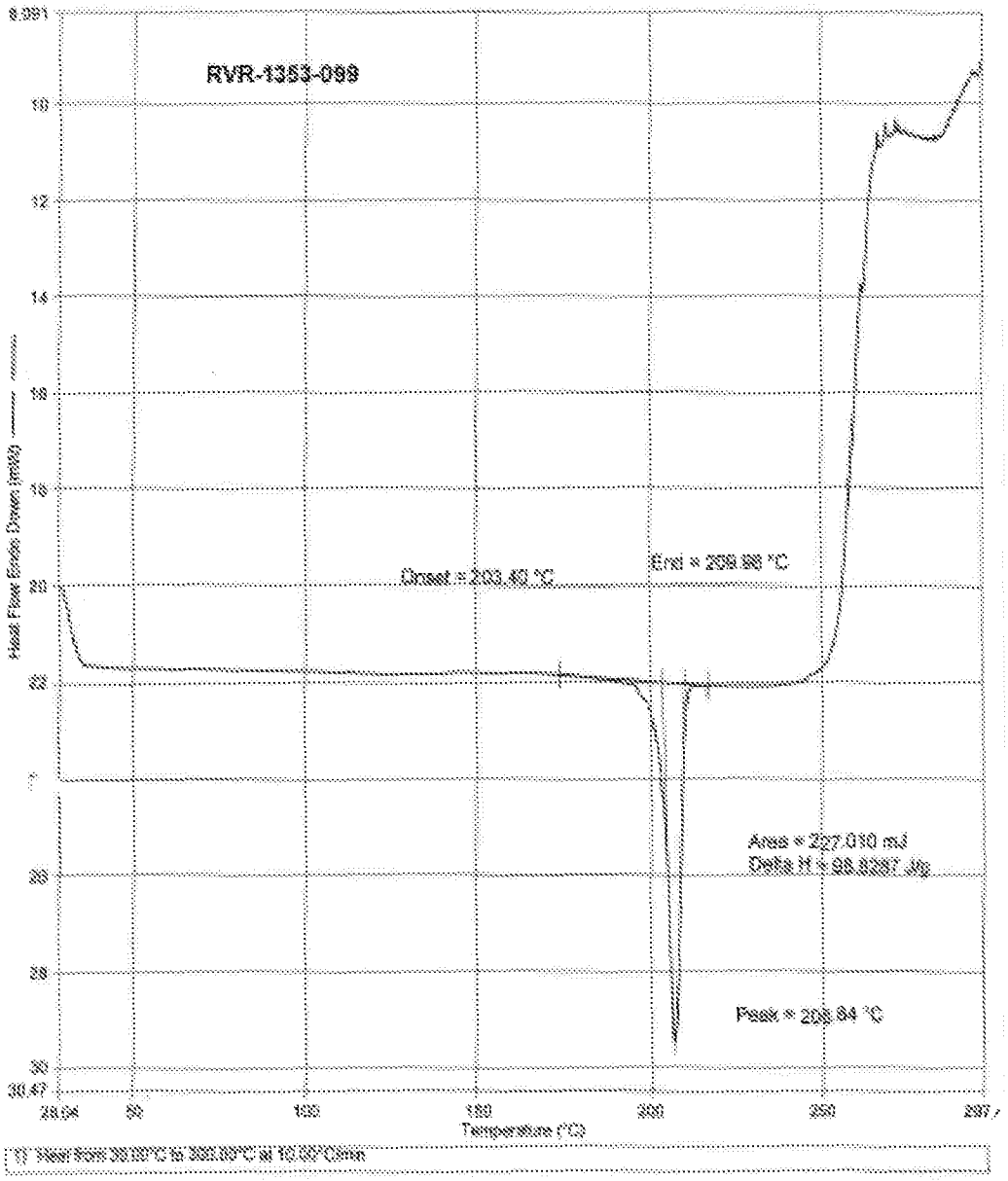


Peak List

Peak [°2Th.]	Height[cts]	FWHM[°2Th.]	d-spacing[Å]	Rel.Int.[%]
10.2815	9765.86	0.0802	8.61353	100.00
12.8196	1943.42	0.0802	6.89980	19.90
13.1736	1540.35	0.0802	6.71528	15.77
13.7080	2369.30	0.0802	6.45467	24.26
14.3169	1650.46	0.0802	6.18151	16.90
14.5883	1082.28	0.0802	6.06709	10.98
15.6872	171.04	0.1203	5.65163	1.75
16.0226	873.87	0.1003	5.52706	8.95
16.8456	1048.82	0.0802	5.25948	10.74
17.8787	148.05	0.1203	4.96095	1.52
18.9489	1164.13	0.0802	4.67861	11.92
19.2758	2251.80	0.0802	4.60097	23.06
19.6712	2378.66	0.0802	4.50936	24.36
20.2456	2498.56	0.0802	4.38272	25.58
20.3720	3345.11	0.0802	4.35581	34.26
20.5852	3193.60	0.0802	4.31117	32.70
21.2525	1925.99	0.0802	4.17728	19.72
21.3991	1389.38	0.0802	4.14900	14.23
21.8078	2285.73	0.0802	4.07249	23.40
22.1340	1019.89	0.1003	4.01346	10.44
22.7720	476.10	0.0802	3.90173	4.88
23.0860	3536.12	0.1604	3.84951	36.20
23.3497	506.84	0.0802	3.80665	5.19
23.7542	1341.12	0.1003	3.74276	13.73
24.0486	3882.36	0.1003	3.69755	39.75
24.7044	3126.07	0.0802	3.59238	32.01
25.1081	657.73	0.0802	3.54380	6.74
25.7944	796.33	0.0802	3.45113	8.17
26.3269	296.82	0.1203	3.38252	3.07
27.2020	898.71	0.1003	3.27565	9.20
27.5969	1501.40	0.1203	3.23059	15.37
28.0772	447.16	0.1203	3.17550	4.58
28.3094	898.64	0.1203	3.14998	9.20
28.8854	1271.97	0.0802	3.08886	13.03
29.0690	1396.85	0.1003	3.06937	14.30
29.5710	1125.02	0.0802	3.01860	11.52
29.7519	508.47	0.0802	3.00046	5.20
30.5959	995.85	0.0802	2.91959	10.20
31.0963	2847.15	0.0802	2.87373	29.15
31.4469	885.65	0.1003	2.84249	9.07
31.6355	845.06	0.1203	2.82597	8.66
32.0966	391.71	0.1003	2.78642	4.01
32.5280	360.32	0.1203	2.75068	3.69
33.1135	237.31	0.2406	2.70313	2.43
34.0818	182.78	0.4813	2.62852	1.87
34.3869	372.19	0.1203	2.60590	3.81
34.7422	399.24	0.1604	2.58005	4.09
35.3962	330.32	0.0802	2.53387	3.38
36.2869	391.27	0.1203	2.47633	4.01
37.6873	340.66	0.1203	2.38422	3.49

Peak List of the as depicted in XRPD pattern in Fig 1

Fig 2: DSC of compound of Formula-5



INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB17/58245

A. CLASSIFICATION OF SUBJECT MATTER

IPC - A61K 31/422, 31/5355, 31/5377; A61P 7/02; C07D 413/14 (2018.01)
CPC - A61K 31/422, 31/5355, 31/5377; C07D 413/10, 413/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
See Search History document

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched
See Search History document

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2015/0166568 A1 (BAYER INTELLECTUAL PROPERTY GMBH) 18 June 2015; paragraphs [0542], [0549]-[0550]	1-15, 17-21
A	WO 2015/198259 A1 (ERREGIERRE S.P.A.) 30 December 2015; page 2, paragraphs 3-5; page 3, paragraph 1; page 4, paragraphs 2-5; page 5, paragraph 1	1-15, 17-21
A	US 2015/0126733 A1 (DODDA, MR et al.) 07 May 2015; paragraphs [0029]-[0030], [0047]	1-15, 17-21
A	US 2007/0004712 A1 (SELVAKUMAR, N et al.) 04 January 2007; paragraphs [0009], [0027], [0043], [0280]	1-15, 17-21

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
"A" document defining the general state of the art which is not considered to be of particular relevance
"E" earlier application or patent but published on or after the international filing date
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
"O" document referring to an oral disclosure, use, exhibition or other means
"P" document published prior to the international filing date but later than the priority date claimed
"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 April 2018 (23.04.2018)	02 MAY 2018
Name and mailing address of the ISA/ Mail Stop PCT, Attn: ISA/US, Commissioner for Patents P.O. Box 1450, Alexandria, Virginia 22313-1450 Facsimile No. 571-273-8300	Authorized officer Shane Thomas PCT Helpdesk: 571-272-4300 PCT OSP: 571-272-7774

Form PCT/ISA/210 (second sheet) (January 2015)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB17/58245

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☒ Claims Nos.: 16
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.