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(54) **Title:** PROCESS FOR THE PREPARATION OF RIVAROXABAN

(57) **Abstract:** The present invention provides processes for the preparation of rivaroxaban. The present invention also provides processes for the preparation of a rivaroxaban intermediate.



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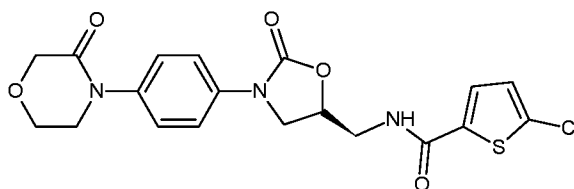
PROCESS FOR THE PREPARATION OF RIVAROXABAN

Field of the Invention

The present invention provides processes for the preparation of rivaroxaban. The present invention also provides processes for the preparation of a rivaroxaban intermediate.

Background of the Invention

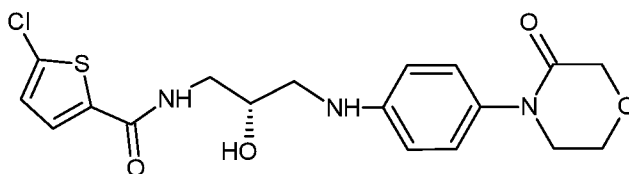
Rivaroxaban is chemically 5-chloro-N-({(5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl}methyl)-2-thiophenecarboxamide of Formula I.



Formula I

Rivaroxaban is used as an anti-thrombotic agent.

U.S. Publication No. 2007/0066615 provides a process for the preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide of Formula II



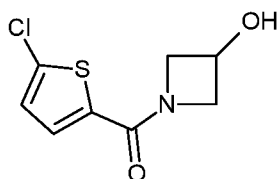
Formula II

which is an intermediate for the preparation of rivaroxaban, wherein a solution of 4-(4-aminophenyl)morpholin-3-one and 5-chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide in tetrahydrofuran is stirred overnight at 60°C in the presence of ytterbium(III) trifluoromethanesulfonate to give a precipitate, which is filtered off to provide the product (54% yield). The remaining filtrate is concentrated and the residue obtained is purified by preparative HPLC to provide a further 38% yield of the product.

U.S. Patent No. 8,106,192 provides a process for the preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-

thiophenecarboxamide of Formula II (named as N-{(R)-2-Hydroxy-3-[4-(3-oxomorpholin-4-yl)phenylamino]propyl}-5-chloro-thiophene-2-carboxamide), wherein a mixture of N-((S)-3-bromo-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide and 4-(4-aminophenyl)-3-morpholinone in toluene is admixed with collidine and ethanol and the reaction mixture is heated at 103°C to 105°C for 6 hours. The reaction mixture is admixed with 1-butanol and the product is isolated in 61.8% yield.

The process provided in the U.S. Publication No. 2007/0066615 makes use of an expensive rare earth metal catalyst, *i.e.*, ytterbium (III) trifluoromethanesulfonate, for the preparation of the intermediate of Formula II. Also, this process is carried out at an elevated temperature (60°C). This process provides the intermediate of Formula II in low yield which is attributed to the formation of impurities such as 11.22% of the azetidinol impurity of Formula III appearing at a relative retention time (RRT) of 0.83 and 11.33% of an unknown impurity appearing at a relative retention time (RRT) of 1.45 (Reference Example 1).



Formula III

The process provided in U.S. Patent No. 8,106,192 is carried out at an elevated temperature, involves the generation of corrosive hydrobromic acid as a by-product, and provides the product in low yield.

The prior art processes are not suitable on an industrial scale. Therefore, there is still a need to develop simple, safe, efficient, economical, eco-friendly, industrially feasible processes that provide the intermediate of Formula II in good yield and purity, and are convenient to operate on a commercial scale.

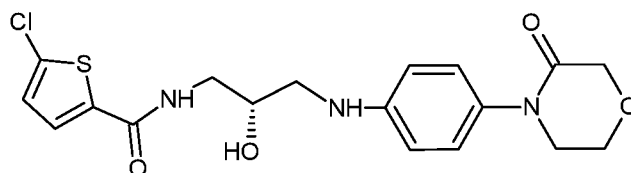
Summary of the Invention

The present invention provides industrially feasible processes for the preparation of rivaroxaban. The present invention also provides processes for the preparation of a rivaroxaban intermediate in good yield and purity.

The present inventors have found that the formation of the azetidinol impurity of Formula III appearing at a relative retention time (RRT) of 0.83, and the impurity appearing at a relative retention time (RRT) of 1.45 is controlled to be at a minimum level when the reaction between 4-(4-aminophenyl)morpholin-3-one and 5-chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide is carried out in the presence of inexpensive and readily available acid catalysts containing an alkali metal, an alkaline earth metal, or zinc metal. As a result, the overall yield is increased. This reaction also avoids the use of chromatography and the generation of corrosive by-products.

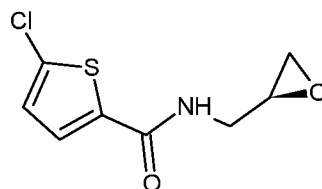
Detailed Description of the Invention

A first aspect of the present invention provides a process for the preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide intermediate of Formula II



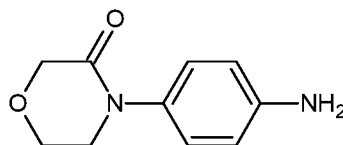
Formula II

wherein the process comprises reacting a compound of Formula IV



Formula IV

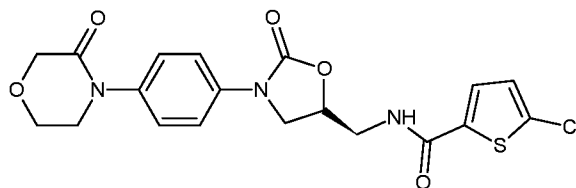
with a compound of Formula V



Formula V

in the presence of an acid catalyst containing an alkali metal, an alkaline earth metal, or zinc metal to obtain the intermediate of Formula II.

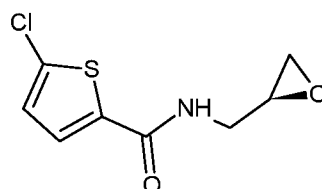
A second aspect of the present invention provides a process for the preparation of rivaroxaban of Formula I



Formula I

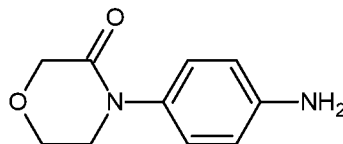
wherein the process comprises the steps of:

- a) reacting a compound of Formula IV



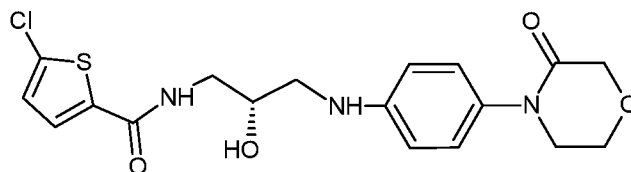
Formula IV

with a compound of Formula V



Formula V

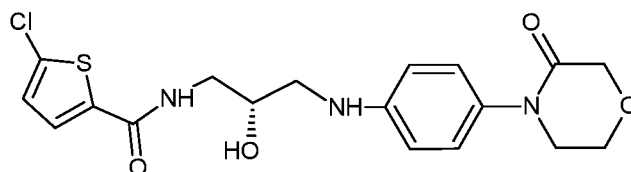
in the presence of an acid catalyst containing an alkali metal, an alkaline earth metal, or zinc metal to obtain an intermediate of Formula II; and



Formula II

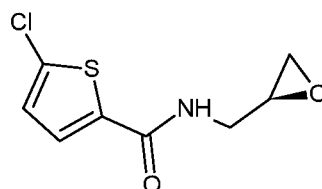
- b) converting the intermediate of Formula II into rivaroxaban of Formula I.

A third aspect of the present invention provides a process for the preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide intermediate of Formula II



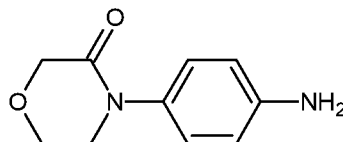
Formula II

wherein the process comprises reacting a compound of Formula IV



Formula IV

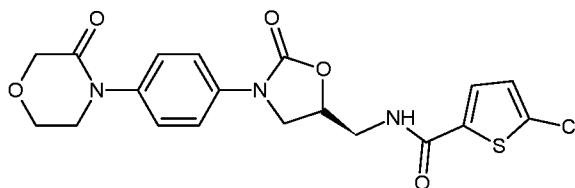
with a compound of Formula V



Formula V

in the presence of an acid catalyst selected from lithium perchlorate, magnesium perchlorate, magnesium trifluoromethanesulfonate, zinc perchlorate, or zinc trifluoromethanesulfonate to obtain the intermediate of Formula II.

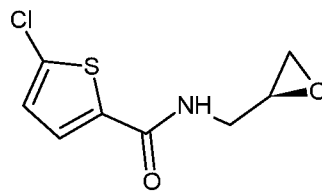
A fourth aspect of the present invention provides a process for the preparation of rivaroxaban of Formula I



Formula I

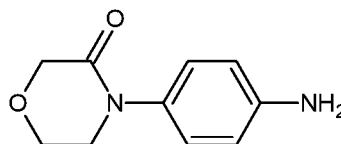
wherein, the process comprises the steps of:

- a) reacting a compound of Formula IV



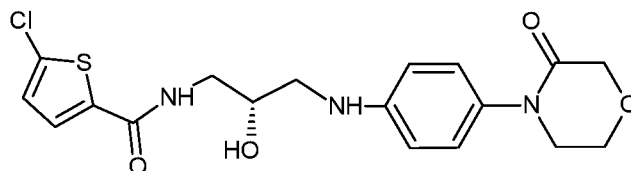
Formula IV

with a compound of Formula V



Formula V

in the presence of an acid catalyst selected from lithium perchlorate, magnesium perchlorate, magnesium trifluoromethanesulfonate, zinc perchlorate, or zinc trifluoromethanesulfonate to obtain an intermediate of Formula II; and



Formula II

- b) converting the intermediate of Formula II into rivaroxaban of Formula I.

The compounds of Formula IV and Formula V may be prepared by the processes known in the literature, such as those described in U.S. Patent No. 7,157,456 or U.S. Publication No. 2007/0066615, or by the processes described herein. The compound of Formula IV is reacted with the compound of Formula V in the presence of an acid catalyst containing an alkali metal, an alkaline earth metal, or zinc metal in a solvent. Examples of acid catalysts containing an alkali metal, an alkaline earth metal, or zinc metal include lithium perchlorate, magnesium perchlorate, magnesium trifluoromethanesulfonate, zinc perchlorate, or zinc trifluoromethanesulfonate. Examples of solvents to be used for the

reaction of the compound of Formula IV with the compound of Formula V include alcohols such as methanol, ethanol, and iso-propanol; ethers such as tetrahydrofuran, 2-methyltetrahydrofuran, cyclopentylmethyl ether, and tertiary butyl ether; alkyl acetates such as ethyl acetate; ketones such as acetone; chlorinated hydrocarbons such as dichloromethane; acetonitrile; dimethylformamide; dimethylsulfoxide; sulfolane; or mixtures thereof.

The compound of Formula IV is reacted with the compound of Formula V at about 10°C to about 35°C.

The intermediate of Formula II may be isolated from the reaction mixture by methods such as cooling, decantation, filtration, concentration, distillation, evaporation, centrifugation, or a combination thereof, followed by drying. The intermediate of Formula II may be purified using an alcohol solvent such as methanol, ethanol, isopropanol, or denatured spirit; water; or mixtures thereof, followed by further drying.

The term “about”, as used herein, when used along with values assigned to certain measurements and parameters means a variation of up to $\pm 10\%$ from such values, or in case of a range of values, means a variation of up to $\pm 10\%$ from both the lower and upper limits of such ranges.

The intermediate of Formula II prepared by the processes of the present invention may be converted into rivaroxaban of Formula I by following the processes known in the literature, such as by the process described in U.S. Patent No. 8,106,192, or by the process described herein.

Methods

The X-ray Powder Diffraction (XRPD) pattern of rivaroxaban of Formula I was recorded using a PANalytical[®] X'Pert Pro X-Ray Powder Diffractometer in the range 3 to 40 degree 2 theta under a tube voltage of 45 kV and a current of 40 mA. The copper radiation of wavelength 1.54 angstrom and an X'celerator[®] detector were used.

The High Performance Liquid Chromatography (HPLC) was performed using a Waters[®] Alliance[®] 2695 HPLC Separations Module. An Agilent[®] Extend-C18 (250 x 4.6) mm, 5 μ m HPLC column was used for rivaroxaban of Formula I and an Inertsil[®] ODS-4 (150 x 4.6) mm, 5 μ m HPLC column was used for the intermediate of Formula II. The

gradients made from ammonium acetate buffer (in water) and acetonitrile were used as eluants, and the HPLC chromatogram was run at a flow rate of 1 mL/minute.

While the present invention has been described in terms of its specific embodiments, certain modifications and equivalents will be apparent to those skilled in the art and are intended to be included within the scope of the present invention.

EXAMPLES

Reference Example 1: Preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II) according to stage a) of Example 1 of U.S. Publication 2007/0066615

4-(4-Aminophenyl)morpholin-3-one (Formula V; 5 g) was dissolved in tetrahydrofuran (100 mL). 5-Chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (Formula IV; 6.79 g) and ytterbium(III) trifluoromethanesulfonate (1.61 g) were added to the reaction mixture at 25°C to 30°C. The reaction mixture was stirred at 60°C for 14 hours. The precipitated white product was filtered, washed with tetrahydrofuran (10 mL), and dried under vacuum to obtain 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide.

Yield: 43.8%

Reaction monitoring by HPLC:

Product Formation: 66.10%

Formation of azetidinol impurity at RRT 0.83: 11.22%

Formation of the impurity at RRT 1.45: 11.33%

Example 1: Preparation of (2S)-1-amino-3-chloropropan-2-ol hydrochloride

A solution of benzaldehyde (595 g) in methanol (2000 mL) was cooled to 15°C to 20°C and aqueous ammonia (25%; 540 g) was added over 45 minutes at 15°C to 20°C. The reaction mixture was stirred for 30 minutes at the same temperature and (S)-epichlorohydrin (500 g) was added to it. The reaction mixture was warmed to 35°C to 40°C, stirred for 6 hours at the same temperature, and then cooled to 25°C to 30°C. It was further stirred for 12 hours at the same temperature. The solvent was recovered completely from the reaction mixture at 50°C to 55°C. Toluene (1500 mL) was added to the resulting mass. Dilute hydrochloric acid (800 mL of concentrated hydrochloric acid

diluted in 1370 mL of water) was added to the reaction mixture over 15 minutes to 20 minutes at 25°C to 40°C, and the reaction mixture was stirred for 3 hours at the same temperature. The reaction mixture was cooled to 25°C to 30°C. The aqueous layer was separated and washed with toluene (1000 mL). The aqueous layer was recovered completely at 60°C to 70°C. Methanol (300 mL) was added to the resulting mass, and the solvent was recovered completely. Methanol (2000 mL) was added to the resulting mass, and it was heated to 70°C to 80°C. The reaction mixture was cooled to 25°C to 30°C over 30 minutes, followed by further cooling to -20°C to -25°C and stirring for 6 hours at this temperature. The solid was filtered under nitrogen and suck dried. The solid was washed with cold methanol (500 mL) and dried at 50°C to 55°C overnight under vacuum and unloaded under nitrogen atmosphere to obtain (2S)-1-amino-3-chloropropan-2-ol hydrochloride.

Yield: 66.11%

Example 2: Preparation of 5-chlorothiophene-2-carbonylchloride

5-Chlorothiophene-2-carboxylic acid (500 g) was added to toluene (2500 mL) and the reaction mixture was heated to 70°C to 80°C. Thionyl chloride (275 mL) was added to the reaction mixture over 90 minutes, and the reaction mixture was stirred for 1 hour at 70°C to 80°C. The reaction mixture was heated at 100°C to 105°C for 4 hours to 5 hours. The reaction mixture was cooled to 60°C to 65°C, and the solvent was completely recovered at 60°C to 65°C under vacuum to obtain 5-chlorothiophene-2-carbonylchloride.

Yield: 89.78%

Example 3: Preparation of N-((S)-3-chloro-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide

Sodium bicarbonate (230 g) was added to de-ionized water (1000 mL) at 25°C to 30°C and the reaction mixture was stirred for 10 minutes at this temperature. (2S)-1-Amino-3-chloropropan-2-ol hydrochloride (200 g) was added to the reaction mixture at 25°C to 30°C, and the reaction mixture was stirred for 30 minutes at this temperature. A solution of 5-chlorothiophene-2-carbonylchloride (from Example 2; 247.9 g) in toluene (1000 mL) was added to the reaction mixture over 1 hour at 25°C to 30°C, and the reaction mixture was stirred for 4 hours at this temperature. The solid was filtered and suck dried. The solid was washed with toluene (200 mL) and suck dried. The solid was

dried at 50°C to 55°C under vacuum for 15 hours to obtain N-((S)-3-chloro-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide.

Yield: 86.22%

Example 4: Preparation of 5-chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (Formula IV)

N-((S)-3-Chloro-2-hydroxypropyl)-5-chlorothiophene-2-carboxamide (from Example 3; 100 g) was dissolved in dichloromethane (300 mL) and dimethylformamide (200 mL). Pulverized potassium carbonate (98 g) was added to the reaction mixture at 25°C to 30°C, and the reaction mixture was stirred for 15 hours at this temperature. Dichloromethane (1000 mL) and de-ionized water (1000 mL) were added to the reaction mixture, and the reaction mixture was stirred for 10 minutes. The reaction mixture was allowed to settle for 10 minutes, and the aqueous and organic layers were separated. The aqueous layer was extracted with dichloromethane (200 mL) and the aqueous and organic layers were separated. The organic layers were combined and washed with de-ionized water (2 x 500 mL). The solvent from the organic layer was recovered at 30°C to 35°C. De-ionized water (1000 mL) was added to the resulting mass, and it was stirred for 1 hour at 25°C to 30°C. The solid was filtered and suck dried. The solid was washed with de-ionized water (200 mL), suck dried, and then further dried at 35°C to 40°C under vacuum to obtain 5-chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide.

Yield: 87.3%

Example 5: Preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II)

4-(4-Aminophenyl)morpholin-3-one (Formula V; 50 g) was dissolved in acetonitrile (500 mL) at 25°C to 30°C. 5-Chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (from Example 4; Formula IV; 58 g) and magnesium perchlorate (12.5 g) were added to the reaction mixture, and the reaction mixture was stirred at 25°C to 30°C for 3 hours. Toluene (500 mL) and aqueous sodium chloride solution (20%, 500 mL) were added slowly to the reaction mixture, and the reaction mixture was stirred for 2 hours. The solid was filtered, washed with water (100 mL), and suck dried. The solid was dried at 55°C to 60°C under vacuum for 5 hours to obtain crude 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (90 g, 84.5%). The crude material (50 g) was stirred with denatured spirit (500 mL) at

50°C to 55°C for 45 minutes. The reaction mixture was cooled to 25°C to 30°C, filtered, and washed with denatured spirit (100 mL). The solid obtained was suck dried, and then further dried at 55°C to 60°C for 12 hours to obtain 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide.

Yield: 86%

HPLC Purity: 99.88%

Example 6: Preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II)

4-(4-Aminophenyl)morpholin-3-one (Formula V; 3 g) was dissolved in acetonitrile (45 mL) at 25°C to 30°C. 5-Chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (from Example 4; Formula IV; 3.5 g) and magnesium perchlorate (0.8 g) were added to the reaction mixture, and the reaction mixture was stirred at 25°C to 30°C for 3 hours. Toluene (150 mL) and aqueous sodium chloride solution (20%, 30 mL) were added slowly to the reaction mixture, and the reaction mixture was stirred for 2 hours. The solid was filtered, washed with water (10 mL), suck dried, and then further dried at 55°C to 60°C under vacuum for 12 hours to obtain crude 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (5.3 g; 93.97%). The crude material was stirred with de-ionized water (53 mL) at 25°C to 30°C for 15 minutes. The solid was filtered, washed with water (10 mL), suck dried, and then further dried at 55°C to 60°C for 2 hours to obtain 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide.

Yield: 74.28%

HPLC Purity: 98.93%

Example 7: Preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II)

4-(4-Aminophenyl)morpholin-3-one (Formula V; 3 g) was dissolved in acetonitrile (30 mL) at 25°C to 30°C. 5-Chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (from Example 4; Formula IV; 3.5 g) and zinc perchlorate hexahydrate (0.75 g) were added to the reaction mixture, and the reaction mixture was stirred at 25°C to 30°C for 3 hours. Toluene (30 mL) and aqueous sodium chloride solution (20%; 30 mL) were added slowly to the reaction mixture, and the reaction mixture was stirred for 2 hours. The solid

was filtered, washed with water (10 mL), suck dried, and then further dried at 55°C to 60°C under vacuum for 12 hours to obtain 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide.

Yield: 80.95%

HPLC Purity: 97.11%

Example 8: Preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II)

4-(4-Aminophenyl)morpholin-3-one (Formula V; 0.5 g) was dissolved in acetonitrile (10 mL) at 25°C to 30°C. 5-Chloro-N-[(2S)-2-oxiranylmethyl]-2-thiophenecarboxamide (from Example 4; Formula IV; 0.55 g) and magnesium trifluoromethanesulfonate (0.25 g) were added to the reaction mixture, and the reaction mixture was stirred overnight at 25°C to 30°C. The solid was filtered and washed with water to obtain 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide.

Reaction Monitoring by HPLC:

Product formation: 83.56%

Formation of azetidinol impurity at 0.83RRT: 1.88%

Formation of the impurity at 1.45 RRT: 3.88%

Example 9: Preparation of seed of crystalline modification I of rivaroxaban (Formula I)

A mixture of rivaroxaban (30 g) in dichloromethane (810 mL) and methanol (300 mL) was stirred at 35°C to 40°C to obtain a solution. Activated carbon (1.5 g) was added to the reaction mixture, and the reaction mixture was stirred for 30 minutes at 35°C to 40°C. The reaction mixture was filtered through a Hyflo[®] bed and the filtrate was concentrated to obtain a white solid compound. The white solid was suspended in methanol (300 mL) and dichloromethane (240 mL). The reaction mixture was heated to 50°C and then cooled to 25°C to 30°C. The slurry obtained was stirred for 1 hour at 25°C to 30°C. The precipitate was filtered and dried at 60°C to 65°C under vacuum to obtain the seed of crystalline modification I of rivaroxaban.

Yield: 75%

Example 10: Preparation of rivaroxaban (Formula I)

5-Chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide (Formula II; 100 g) was added to ethyl acetate (1500 mL) at 25°C to 30°C. The seed of crystalline modification I of rivaroxaban (from Example 9; 4 g) and 1,1-carbonyldiimidazole (71.1 g) were added to the reaction mixture, and the reaction mixture was stirred for 8 hours at 25°C to 30°C. The solid was filtered and suck dried. The solid was washed with ethyl acetate (200 mL), suck dried, and then further dried at 55°C to 60°C under vacuum to obtain rivaroxaban.

Yield: 85%

Example 11: Purification of rivaroxaban (Formula I)

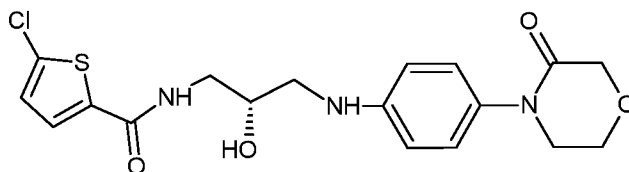
Rivaroxaban (100 g) was added to acetic acid (1800 mL) at 25°C to 30°C and the reaction mixture was heated to 75°C to 80°C to obtain a clear solution. Activated carbon (2.55 g) was added to the reaction mixture, and the reaction mixture was stirred for 30 minutes at 75°C to 80°C. The reaction mixture was filtered through a Hyflo[®] bed and the bed was washed with acetic acid (200 mL). Acetic acid was recovered up to 1500 mL under vacuum at 50°C to 55°C to obtain a white slurry. The mixture was cooled to 25°C to 30°C and it was stirred for 1 hour at 25°C to 30°C. The solid was filtered and suck dried. The solid was washed with de-ionized water (200 mL) and suck dried. De-ionized water (500 mL) was added to the wet solid. The pH of the reaction mixture was adjusted to 6.5 to 7.5 with aqueous sodium bicarbonate, and the reaction mixture was stirred for 1 hour at 25°C to 30°C. The solid was filtered and suck dried. The solid was washed with de-ionized water (200 mL) and dried at 55°C to 60°C under vacuum for 12 hours to obtain pure rivaroxaban.

Yield: 91%

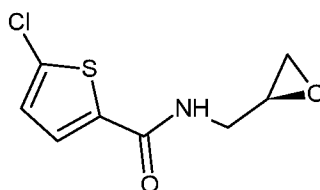
HPLC Purity: 99.96%

We Claim:

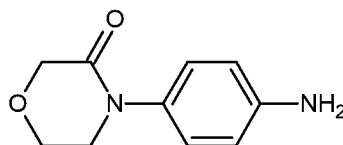
1. A process for the preparation of 5-chloro-N-((2R)-2-hydroxy-3-{[4-(3-oxo-4-morpholinyl)-phenyl]amino}propyl)-2-thiophenecarboxamide intermediate of Formula II

**Formula II**

wherein the process comprises reacting a compound of Formula IV

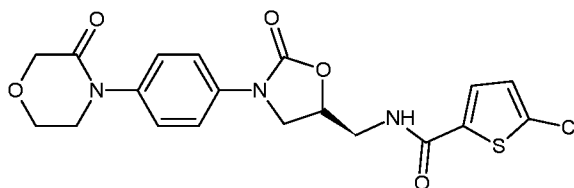
**Formula IV**

with a compound of Formula V

**Formula V**

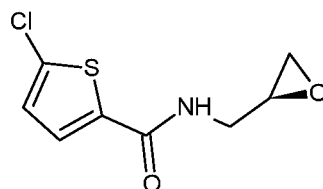
in the presence of an acid catalyst containing an alkali metal, an alkaline earth metal, or zinc metal to obtain the intermediate of Formula II.

2. A process for the preparation of rivaroxaban of Formula I

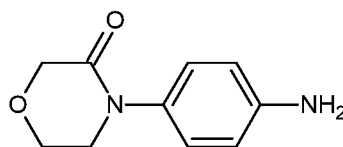
**Formula I**

wherein the process comprises the steps of:

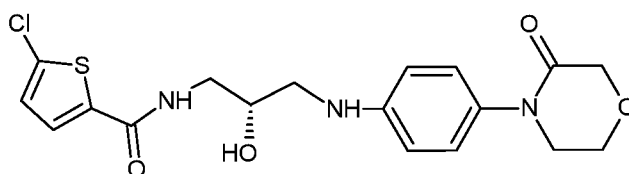
- a) reacting a compound of Formula IV

**Formula IV**

with a compound of Formula V

**Formula V**

in the presence of an acid catalyst containing an alkali metal, an alkaline earth metal, or zinc metal to obtain an intermediate of Formula II; and

**Formula II**

- b) converting the intermediate of Formula II into rivaroxaban of Formula I.
3. The process according to claim 1 or 2, wherein the acid catalyst is selected from the group consisting of lithium perchlorate, magnesium perchlorate, magnesium trifluoromethanesulfonate, zinc perchlorate, and zinc trifluoromethanesulfonate.
4. The process according to claim 1 or 2, wherein the compound of Formula IV is reacted with the compound of Formula V in a solvent.
5. The process according to claim 4, wherein the solvent is selected from the group consisting of alcohols, ethers, alkyl acetates, ketones, chlorinated hydrocarbons, acetonitrile, dimethylformamide, dimethylsulfoxide, sulfolane, and mixtures thereof.
6. The process according to claim 1 or 2, wherein the compound of Formula IV is reacted with the compound of Formula V at about 10°C to about 35°C.

INTERNATIONAL SEARCH REPORT

International application No

PCT/IB2014/063191

A. CLASSIFICATION OF SUBJECT MATTER

INV. C07D413/14 C07D413/12
ADD.

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)
C07D

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	DE 10 2007 032347 A1 (BAYER HEALTHCARE AG) 15 January 2009 (2009-01-15) claims; examples 4A, 7A, 8A -----	1-6
Y	WO 2004/101557 A1 (BAYER HEALTHCARE AG) 24 November 2004 (2004-11-24) cited in the application claims; example 1 -----	1-6

☐ 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

10 September 2014

Date of mailing of the international search report

17/09/2014

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Helps, Ian

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/IB2014/063191

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