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(54) Title: A PROCESS FOR PREPARING RIVAROXABAN OR A PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

(57) Abstract: The present invention relates to a process for the preparation of Rivaroxaban and its novel intermediates, or pharmaceutically acceptable salts thereof. The present invention provides novel intermediates, which may be useful for the preparation of Rivaroxaban or its pharmaceutically acceptable salts thereof. The process of preparation by using novel intermediate is very simple cost effective and may be employed at commercial scale. The product obtained by using novel intermediate yield the Rivaroxaban of purity 99% or more, when measured by HPLC. The present invention especially relates to a process for the preparation of Rivaroxaban from thioester of formula II, or a pharmaceutically acceptable salt thereof, wherein R is leaving group.

Formula II


Published:  
with international search report (Art. 21(3))
A PROCESS FOR PREPARING RIVAROXABAN OR A
PHARMACEUTICALLY ACCEPTABLE SALT THEREOF

Field of Invention

The present invention relates to a process for the preparation of Rivaroxaban and its novel intermediates, or pharmaceutically acceptable salts thereof. The present invention provides novel intermediates, which may be useful for the preparation of Rivaroxaban or its pharmaceutically acceptable salts thereof. The process of preparation by using novel intermediate is very simple cost effective and may be employed at commercial scale. The product obtained by using novel intermediate yield the Rivaroxaban of purity 99% or more, when measured by HPLC. The novel thioester intermediate represented by formula II

![Formula II](image1)

or a pharmaceutically acceptable salt thereof, wherein R is leaving group.

Background of the invention

The drug compound having the adopted name "Rivaroxaban" has chemical name, 5-chloro-N-((5S)-2-oxo-3-[4-(3-oxo-4-morpholinyl)phenyl]-1,3-oxazolidin-5-yl)methyl)-2-thiophenecarboxamide; and has the structural formula I.

![Formula I](image2)
The commercial pharmaceutical product XARELTO® tablets, contains rivaroxaban as active ingredient. Rivaroxaban is a factor Xa inhibitor useful as oral anticoagulant. Rivaroxaban can be used for the prevention and treatment of various thromboembolic diseases, in particular of deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarct, angina pectoris and restenoses after angioplasty or aortocoronary bypass, cerebral stroke, transitory ischemic attacks, and peripheral arterial occlusive diseases.

U.S. Patent No. 7,157,456 describes Rivaroxaban and process for the preparation thereof. The process of US '456 for rivaroxaban involves reaction of 2-[(2S)-2-oxiranylmethyl]-1H-isooindole-1,3(2H)-dione with 4-(4-aminophenyl)-3-morpholinone to provide 2-[(2R)-2-hydroxy-3-{4-(3-oxo-4-morpholiny)phenyl]amino Jpropyl]-1H-isooindole-1,3(2H)-dione, which on cyclization using N,N-carboxy diimidazole to afford 2-((5S)-2-Oxo-3-[4-(3-oxo-4-morpholiny)phenyl]-1,3-oxazolidin-5-yl)methyl]-1H-isooindole-1,3(2H)-dione, which on reacted with methylamine followed by reaction with 5-chlorothiophene-2-carbonyl chloride to provide Rivaroxamine.


The reported processes suffers one or the other problems like lower yield, use of carcinogenic reagents like hydrobromic acid at elevated temperature, longer reaction time, and the like.

Therefore, there is a need to develop a simple and industrially feasible process for Rivaroxaban and its intermediates or a pharmaceutically acceptable salt thereof.
**Summary of the Invention**

The present invention provides a process for the preparation of Rivaroxaban intermediates, or pharmaceutically acceptable salt thereof.

In an aspect, the present invention is to provide thioester of Formula II,

![Formula II](image)

or a pharmaceutically acceptable salt thereof, wherein R is leaving group selected from the alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole, benzisoxazole.

In another aspect, the present invention is to provide thioester of Formula IIA,

![Formula IIA](image)

Formula IIA

or a pharmaceutically acceptable salt thereof.

In another aspect, the present invention is to provide a process for the preparation of Rivaroxaban of Formula I,

![Formula I](image)

Formula I

or a pharmaceutically acceptable salt thereof, the process involves the reacting thioester of formula II,
or a pharmaceutically acceptable salt thereof, wherein R is leaving group selected from
the alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole, benzisoxazole, with the 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one of formula III,

or a pharmaceutically acceptable salt thereof and isolating the Rivaroxaban and pharmaceutically acceptable salt thereof.

In another aspect, the present invention is to provide a process for the preparation of Rivaroxaban of Formula I,

or a pharmaceutically acceptable salt thereof, the process includes the step of, reacting thioester of formula IIA or pharmaceutically acceptable salt thereof
with the 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one of formula III,

![Formula III](image)

or a pharmaceutically acceptable salt thereof and isolating the Rivaroxaban or its pharmaceutically acceptable salt thereof.

**Description of the Invention**

The term "alkyl" as used herein, unless otherwise defined, refers to methyl, ethyl, n-propyl, isopropyl and butyl.

The term "aryl" as used herein, unless otherwise defined, refers to phenyl, naphthyl or substituted phenyl and naphthyl. The substitution can be with alkyl, halo, nitro, amine and the like.

The intermediates and starting materials of the present invention may be used as free bases or its salts.

The salt or pharmaceutically acceptable salt as used herein, unless otherwise defined, refers to inorganic or organic salt. Inorganic salt may include hydrochloride, hydrobromide and the like; organic slat may include acetate, mesylate, tosylate and the like.

In an aspect, the present invention is to provide thioesters of Formula II,
Formula II

or a pharmaceutically acceptable salt thereof, wherein R is leaving group selected from the alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole and benzisoxazole.

In an embodiment, the compound of formula II of the present invention is selected from the compounds of,

![Chemical structures](image)

or a pharmaceutically acceptable salt thereof.

The process for the preparation of compound of Formula II, which includes the step of reacting 5-chlorothiophene-2-carboxylic acid with the sulfide compound (R'-S-R or R'-S-S-R), wherein R' is benzothiazolyl, acetyl, substituted or unsubstituted benzoyl or benzopyridyl.

The reaction may be performed in presence of a tri-(lower alkyl)- or tri(aryl) phosphine or phosphite, such as triphenylphosphine.
The reaction may be performed in presence of a base includes but are not limited to organic base such as dimethylamine, diethylamine or triethylamine and inorganic base such as ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide, potassium t-butoxide.

The reaction may be performed at the temperature range of between -30°C to 100°C, such as the temperature range of between -30°C to 60°C, or -5 °C to 5°C.

The reaction may be performed in an inert, non-hydroxy-containing, organic solvent, for example a chlorinated hydrocarbon, such as methylene chloride; an ester solvent, such as ethyl acetate and optionally in the presence of water.

Isolation of compound of formula-II carried out by means of filtration and followed by washing with methylene chloride solvent. The compound dried under vacuum at temperature range between 50°C to 60°C.

In another aspect, the present invention is to provides, thioester of Formula IIA,

![Formula IIA](image)

or a pharmaceutically acceptable salt thereof.

In another aspect of the present invention provides a process for the preparation of compound of Formula IIA,
or pharmaceutically acceptable salt thereof, the process includes the step of, esterifying 5-chlorothiophene-2-carboxylic acid of formula IV,

with 1,2-bis(2-benzothiazolyl) disulfide of Formula V,

in the presence of triphenylphosphine and base to obtain the compound of Formula IIA.

The esterification reaction is performed in presence of solvent and base. The solvent includes but are not limited to a chlorinated solvent such as dichloromethane, dichloroethane, chloroform, chlorobenzene and the like; an ester such as ethyl acetate, and the like; a nitrile such as acetonitrile, propionitrile, and the like.

The reaction is performed in presence of base includes but are not limited to organic base such as dimethylamine, diethylamine or triethylamine and inorganic base such as ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide, potassium t-butoxide preferably triethylamine.

The temperature for performing the esterification is in between -30°C to 40°C more preferably at -5°C to 5°C. The reaction may be maintained for a period of 30 minutes to 2 hours to complete at -5°C to 5°C for the completion.
Isolation of compound of formula IIA carried out by means of filtration and washed with methylene chloride. The compound dried under vacuum at temperature range between 50°C to 60°C.

In another aspect, the present invention is to provide a process for the preparation of Rivaroxaban of Formula I,

![Formula I](Image)

or a pharmaceutically acceptable salt thereof, the process includes the step of reacting thioester of formula II or pharmaceutically acceptable salt thereof

![Formula II](Image)

wherein R is leaving group selected from the alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole, benzisoxazole, or a pharmaceutically acceptable salt thereof with the 4-{4-{(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl}phenyl}morpholine-3-one of formula III,

![Formula III](Image)

or a pharmaceutically acceptable salt thereof and isolating the Rivaroxaban and pharmaceutically acceptable salt thereof

The reaction may be carried out in the presence of an organic solvent and a base and optionally in the presence of water.
The reaction may be carried out at a temperature ranging from -5°C to about ambient temperature. The organic solvent used is selected from tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide (DMF), chlorinated hydrocarbons, ketones, esters or a mixture thereof.

The reaction is carried out in the presence of bases such as inorganic base or organic base.

The organic base is selected from group of triethylamine, methyl amine, diisopropyl amine, N-methylpiperidine, pyridine, 1,8-diazabicycloundecene, 4-dimethylamino pyridine, or a mixture thereof; inorganic base is selected from group of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or mixtures thereof.

The compound of formula III may be prepared from the known processes, for example, US 7,157,456.

In another aspect, the present invention is to provide a process for the preparation of Rivaroxaban of Formula I,

![Formula I](image)

or a pharmaceutically acceptable salt thereof, the process includes the step of, reacting thioester of formula IIA or pharmaceutically acceptable salt thereof.
Formula IIA

with 4-\{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl\}morpholine-3-one of formula III,

or a pharmaceutically acceptable salt thereof and isolating the Rivaroxaban and pharmaceutically acceptable salt thereof.

The reaction may be carried out in the presence of an organic solvent and a base as herein described and optionally in the presence of water.

The reaction may be carried out at a temperature ranging from -5°C to about ambient temperature for about 2 to 12 hours.

The organic solvent used is selected from tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, chlorinated hydrocarbons, ketones, esters or a mixture thereof.

The reaction is carried out in the presence of bases such as inorganic base or organic base. The organic base is selected from group of triethylamine, methyl amine, diisopropyl amine, N-methylpiperidine, pyridine, 1,8-diazabicycloundecene, 4-dimethylamino pyridine, or a mixture thereof; inorganic base is selected from group of sodium hydroxide, potassium hydroxide, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate or mixtures thereof.

In another aspect, the present invention is to provide a process for the preparation of Rivaroxaban of Formula I,
or a pharmaceutically acceptable salt thereof, the process includes the steps of:

a) esterification of 5-chlorothiophene-2-carboxylic acid with 1,2-bis(2-benzothiazolyl) disulfide in the presence of triphenylphosphine to obtain the S-benzo[d]thiazol-2-yl 5-chlorothiophene-2-carbothioate in the solvent

(b) reacting S-benzo[d]thiazol-2-yl 5-chlorothiophene-2-carbothioate with 4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl)morpholine-3-one or a pharmaceutically acceptable salt thereof.

c) isolating from reaction mixture Rivaroxaban its salts thereof.

Isolation of Rivaroxaban carried out by means of quenching of reaction after completion with water, followed by repeated extraction in methylene chloride. The pH of methylene chloride layer is adjusted in the range of 6 to 7 with 2N hydrochloric acid. Finally distillation of solvent yields Rivaroxaban.

In another aspect, the present invention provides a Rivaroxaban, has purity more than 99.9 %.

The solvent is selected from the group of one or more chlorinated solvent, ester solvent, and nitrile solvent. The chlorinated solvent is selected from the group of one or more dichloromethane, dichloroethane, chloroform, chlorobenzene and the like; an ester is selected from the group of one or more ethyl acetate, and the like; a nitrile is selected from the group of one or more acetonitrile, propionitrile.
The resultant Rivaroxaban or a pharmaceutically acceptable salt thereof obtained from the present invention is useful for pharmaceutical composition.

In another aspect, the present invention relates to pharmaceutical composition comprising rivaroxaban or a pharmaceutically acceptable salt obtained from the present invention and pharmaceutically acceptable carriers and/or diluents thereof, and if desired, other active ingredients, which may be administered orally, intravascularly, subcutaneously, intramuscularly or topically for the use as anticoagulant in a mammal in need thereof.

The present invention may further be illustrated by the following examples which may be provided merely to be exemplary of the invention and do not limit the scope of the invention. Certain modifications and equivalents may be apparent to those skilled in the art and may be intended within the scope of the present invention.

**EXAMPLES**

**EXAMPLE 1**: A process for the preparation of Rivaroxaban

To the mixture of thioester (as referred as compound IIA, 10.7g), 4-{4-{(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl}phenyl}morpholine-3-one (10g) in tetrahydrofuran (30 ml), water (30 ml) under stirring triethylamine (3.8g) was added. The reaction mixture was further stirred at 5-10°C for 4-6 hours. After completion of the reaction, it was quenched with water & extracted in methylene chloride (250 ml x 2). The aqueous layer was back extracted using methylene chloride and methylene chloride layers were combined and its pH was adjusted to 6-7 with 2 N hydrochloric acid. Finally, the organic layer was concentrated to get desired product. The product obtained was dried to yield Rivaroxaban.

**Yield**: 11.5

**Purity**: 99.3%

**EXAMPLE 2**: A process for the preparation of rivaroxaban
Exemplified procedure in example 1 with the replacement thioester of compound IIA with S-methyl 5-chlorothiophene-2-carbothioate in N,N-dimethylacetamide and water with potassium carbonate were used in place of triethylamine, during workup methylene chloride was used in mixture of N,N dimethyl acetamide and water to extract the Rivaroxaban.

EXAMPLE 3: A process for the preparation of Rivaroxaban

Exemplified procedure in example 1 with the replacement thioester of compound IIA with S-benzo[d]thiazol-2-yl 5-chlorothiophene-2-carbothioate in N,N-dimethylformamide with sodium carbonate were used and followed similar process of example 2 to isolate the Rivaroxaban.

EXAMPLE 4: A process for the preparation of rivaroxaban

Exemplified procedure in example 1 with the replacement thioester of compound IIA with S-3H-1,2,3-triazol-4-yl 5-chlorothiophene-2-carbothioate in dichloromethane with N-methylpiperidine were used to get the Rivaroxaban.

EXAMPLE 5: A process for the preparation of Rivaroxaban

Exemplified procedure in example 1 with the replacement thioester of compound IIA with S-benzo[d]isoxazol-3-yl 5-chlorothiophene-2-carbothioate in acetone with potassium hydroxide were used and similar workup process of example 2 was followed to get the Rivaroxaban.

EXAMPLE 6: A process for intermediate of Formula IIA:

The mixture of triphenylphosphine (161.32 gm) and mercaptobenzothiazole disulphide (214.72 gm) in methylene chloride was stirred at 25-30°C for 1 hr. 5-chlorothiophene-2-
carboxylic acid (100g) and triethyl amine (52.8g) were added at 10°C in the above mixture and reaction mixture was stirred at 10-20°C for 2 hrs. After completion of the reaction, reaction mixture was filtered washed with methylene chloride (200 ml), followed by removed of methylene chloride and drying yields title compound.

Yield: 150 gm
Purity: < 98.40 %

EXAMPLE 7: One pot process for Rivaroxaban

The triphenylphosphine (11.5g) and mercaptobenzothiazole disulphide (15.31g) were taken in methylene chloride and reaction mixture was stirred at 28°C -30°C for 1 hr. The 5-chlorothiophene-2-carboxylic acid (7.2g) and triethylamine (3.8 g) were added to the above reaction mixture. The reaction mixture is stirred at 0°C -25°C for 1 hr. after 1 hr 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one (10g) and triethylamine (3.8g) were added. The resulting reaction mixture further stirred for 2 hrs. After completion of the reaction, water was added and stirred for 10 min. aqueous layer was separated and washed with methylene chloride. The organic layer was acidified to pH 6-7 with 2N hydrochloric acid and finally the organic layer was concentrated to get desired product. The product was purified and dried to yield Rivaroxaban.

Yield: 10.0 gm
Purity: 99.3 %

EXAMPLE 8: One pot process for Rivaroxaban

Exemplified procedure in example 7 with the replacement of solvent ethyl acetate and base potassium hydroxide were used to get the rivaroxaban.

EXAMPLE 9: One pot process for Rivaroxaban

Exemplified procedure in example 7 with the replacement of solvent acetonitile and base potassium carbonate were used, methylene chloride was added in the reaction mixture to extract the Rivaroxaban.
We Claim:

1. A process for the preparation of Rivaroxaban of formula I,

   ![Formula I](image)

   or a pharmaceutically acceptable salt thereof, the process comprises the step of reacting of thioester of formula II or pharmaceutically acceptable salts thereof,

   ![Formula II](image)

   wherein R is leaving group with 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one of formula III,

   ![Formula III](image)

   or a pharmaceutically acceptable salt thereof.

2. The process of claim 1, wherein leaving group is selected from alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole and benzisoxazole.

3. The process of claim 1, wherein Rivaroxaban has a purity of more than 99 %, when measured by HPLC
4. The process of claim 1, wherein the compound of Formula II is thioester of formula IIA,

![Formula IIA]

5. The process of claim 1, wherein the reaction is performed in presence of base and solvent.

6. A thioester of compound of Formula II or a pharmaceutically acceptable salt thereof.

![Formula II]

wherein R is leaving group.

7. The compound of claim 6, wherein leaving group is selected from alkyl, aryl, 2-pyridyl, pyrimidinyl, triazolyl or thiazolyl, 2-benzothiazolyl, benzimidazole, or benzisoxazole;

8. The compound of claim 6, wherein alkyl group is methyl, ethyl, n-propyl, isopropyl, butyl and aryl group is phenyl, naphthyl or substituted phenyl and naphthyl.

9. The compound of claim 6, is selected from the compounds of
10. A thioester of compound of Formula IIA,

\[ \text{Formula IIA} \]

or a pharmaceutically acceptable salt thereof.

11. A process for the preparation of compound of Formula IIA,

\[ \text{Formula IIA} \]

or pharmaceutically acceptable salt thereof, the process comprises the step of esterification of 5-chlorothiophene-2-carboxylic acid of formula IV.
with 1,2-bis(2-benzothiazolyl) disulfide of Formula V

in the presence of triphenylphosphine and base.

12. The process of claim 11, wherein the reaction is performed in presence of chlorinated solvent selected from the group of one or more dichloromethane, dichloroethane, chloroform, chlorobenzene; an ester selected from the group of one or more ethyl acetate; a nitrile solvents selected from the group of one or more acetonitrile and propionitrile.

13. The process of claim 11, wherein the reaction is performed in dichloromethane solvent.

14. A process for the preparation of Rivaroxaban of Formula I,

or a pharmaceutically acceptable salt thereof, which comprises reaction of thioester of formula IIA or pharmaceutically acceptable salt thereof
with 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one of formula III,

or a pharmaceutically acceptable salt thereof.

15. The process of claim 14, wherein Rivaroxaban obtained has a purity of more than 99%, when measured by HPLC.

16. The process of claim 14, wherein the reaction is performed in the presence of solvent selected from the group of one or more tetrahydrofuran, N,N-dimethylacetamide, N,N-dimethylformamide, chlorinated hydrocarbons selected from the group of one or more dichloromethane, dichloroethane, chloroform, chlorobenzene, ketones such as acetone.

17. The process of claim 14, wherein the reaction is performed in tetrahydrofuran solvent.

18. The process of claim 11 and 14, wherein the reaction is performed in the presence of organic or inorganic base.

19. The process of claim 11 and 14, wherein organic base is selected from one or more dimethylamine, diethylamine or triethylamine.
20. The process of claim 11 and 14, wherein inorganic base is selected from ammonia, sodium carbonate, potassium carbonate, sodium bicarbonate, potassium bicarbonate, sodium hydroxide or potassium hydroxide, potassium t-butoxide.

21. The process of claim 11 and 14, wherein the reaction is performed in the presence of triethyl amine.

22. A process for the preparation of rivaroxaban of Formula I,

![Formula I](image)

or a pharmaceutically acceptable salt thereof, the process comprises the steps of,

a) esterification of 5-chlorothiophene-2-carboxylic acid with 1,2-bis(2-benzothiazolyl) disulfide in the presence of triphenylphosphine to obtain the S-benzo[d]thiazol-2-yl 5-chlorothiophene-2-carbothioate in the solvent

b) reacting S-benzo[d]thiazol-2-yl 5-chlorothiophene-2-carbothioate with 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholine-3-one or a pharmaceutically acceptable salt thereof.

c) isolating from reaction mixture Rivaroxaban its salts thereof.

23. The process of claim 22, wherein the solvents are chlorinated solvent such as dichloromethane, dichloroethane, chloroform and chlorobenzene.

24. The process of claim 22, wherein the solvents are an ester such as ethyl acetate.
25. The process of claim 22, wherein the solvents are nitrile solvent selected from acetonitrile and propionitrile.

26. The process of claim 22, wherein Rivaroxaban has purity of more than 99%, when measured by HPLC.
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/14
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 practical, search terms used)
EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

<table>
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<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
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<td>X</td>
<td>CN 104 098 556 A (ZHEJIANG JIUZHOU PHARMACEUTICAL TECHNOLOGY CO LTD) 15 October 2014 (2014-10-15) paragraph [0060]; cl aims 7,9</td>
<td>1-26</td>
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<td>X</td>
<td>FRIDMAN, M. ET AL.: &quot;Chemoenzymatic Formations of Novel Aminocoumarin Anti bi are observed by the Enzymes CouN and CouN\ BIOCHEMISTRY, vol. 46, 2007, pages 8462-8471, Scheme 1; example 23</td>
<td>6</td>
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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 that published on or after the international filing date
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- "S" document member of the same patent family

Date of the actual completion of the international search: 18 March 2015

Date of mailing of the international search report: 01/04/2015

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
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Baston, Eckhard

Form PCT/ISA/210 (second sheet) (April 2005)
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