Title: PROCESS FOR THE SYNTHESIS OF APIXABAN

Abstract: The present invention relates to the Process for the preparation of Apixaban and novel intermediates useful in the synthesis of Apixaban (I).
— as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))
— of inventorship (Rule 4.17(iv))

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— with international search report (Art. 21(3))
TITLE - PROCESS FOR THE SYNTHESIS OF APIXABAN

FIELD OF THE INVENTION
The present invention relates to the Process for the preparation of Apixaban and novel intermediates useful in the synthesis of Apixaban (I)

![Chemical Structure of Apixaban](image)

BACKGROUND OF THE INVENTION

Apixaban (BMS-562247-01, tradename Eliquis) is an anticoagulant for the prevention of venous thromboembolism and venous thromboembolic events. It is a direct factor Xa inhibitor.

US6967208B2 discloses a series of coagulation factor Xa inhibitors 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-l-yl)phenyl]-4,5-dihydropyrazolo[5,4-c]pyridine-3-carboxamide (also known as Apixaban). US7396932 discloses process for the preparation of Apixaban by condensing compound of formula II and compound of formula III in the presence of base.

![Chemical Structures II and III](image)

The published methodology involves diazotization species of compound of formula II and 1,3-dipolar
addition of compound of formula II with compound of formula III to achieve Apixaban. A safer approach which is free form diazotization species and simple in operation is still needed. The present invention addresses these issues and provides novel process for making Apixaban. The present invention also provides novel intermediates for the synthesis of Apixaban.

OBJECT OF THE INVENTION

Accordingly, it is an object of the present invention to provide novel process for the preparation of Apixaban comprising a step of reacting compound of formula IV with compound of formula X or salt thereof in the presence or absence of base and aprotic solvent to obtain compound of formula V.

![Diagram](image)

Wherein R¹ is selected from OR⁴, NR⁵R⁶, Cl, Br, I, SR⁴;
R² is H, Ci-C₆ alkyl, aryl, aryl substituted with alkyl group;
R³ and R⁴ are selected from Ci-C₆, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;
alternatively N R⁵ R⁶ is a 3-8 membered ring consisting of: carbon atoms, N and 0-1 O atoms
Y is selected from phenyl, pyridyl or pyrimidyl;
Z is selected from Cl, Br, I, CN, N02, NH2 or 5-10 membered heterocycle ring containing from 1-4 heteroatoms selected from the group consisting of N,0 and S substituted with 0-2 R⁷;
R⁸ at each occurance, is selected from H, =0, CHO, Cl, Br, I, CH₃, CH2-CH₃, CH2-CH2-CH₃, CH2-CH2-CH2-CH₃, CH (CH₃)2, CH2- CH (CH₃)2, CN, N02;
R⁹ is selected from ester, amide, nitrile, carboxylic acid;
R² is selected from halogen, mesylate, tosylate, 0-S0₂Ph, OR⁴, where in R⁴ is H, Ci-C₆ alkyl, aryl, aryl substituted with alkyl group.

Another object of the present invention to provide process for the preparation of compound of formula V where in
R¹ is preferably selected from NR²R³;
NR²R³ is preferably selected from morpholino, pyrolidino, pipieridino;
Y is preferably selected from phenyl;
Z is preferably selected from pyridine 2-one;
R² is preferably selected from halogen, tosylate and mesylate;
R³ is preferably selected from ester, carboxylic acid.

Base that used for the preparation of compound of formula V is selected from the group comprising of organic base such as pyridine, dimethyl amine and trimethyl amine and Inorganic base such as KOH, NaOH, K₂C₀₃, Na₂C₀₃, CaC₀₃, NH₄ and the like.

Aprotic solvent may be selected from the group consisting of chlorinated and ether solvent. Chlorinated solvent is selected from methyl chloride, dichloride methane, and chloroform; ether solvent is selected from tetrahydrofuran, dimethyl ether, polyethylene glycol, dioxin, diethyl ether.

Further object of the present invention is to provide a novel process for the preparation of Apixaban comprising a step of reacting compound of formula V with compound of formula VI or salt thereof in the presence of aq. alcoholic solvent to obtain compound of formula VII.

Wherein R¹ is selected from OR², NR²R³, Cl, Br, I, SR³;
R² is H, C₁-C₆ alkyl, aryl, aryl substituted with alkyl group;
R^b and R^c are selected from Ci-C^6 alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzy1;
Alternatively, N R^b R^c is a 3-8 membered ring consisting of: C atoms, N and 0-1 O atoms;
Y is selected from phenyl, pyridyl or pyrimidyl;
Z is selected from Cl, Br, I, CN, N02, NH2 or 5-10 membered heterocycle ring containing 1-4 heteroatoms selected from the group consisting of N,0 and S substituted with 0-2 R^d;
R^d at each occurrence, is selected from H, =0, CHO, Cl, Br, I, CH3, CH2-CH3, CH2-CH2-CH3, CH2-CH2-CH2-CH3, CH (CH3)2, CH2-CH (CH3)2, CN, N02;
R is selected from halogen, OR^a, mesylate, tosylate, 0-SO_2-Ph;
R^3 is selected from from ester, amide, nitrile, carboxylic acid;
R is selected from OR^a where in H, Ci-C^6 alkyl, aryl, aryl substituted with alkyl group;

Further object of present invention is to provide process for the preparation of compound of formula VII where in,
R^1 is preferably selected from NR^b R^c;
NR^b R^c is preferably selected from morpholino, pyrolidino, pipieridino;
Y is preferably selected from phenyl;
Z is preferably selected from pyridine 2-one;
R^2 is preferably selected from halogen, tosylate and mesylate;
R^3 is preferably selected from ester, carboxylic acid.

Aq. alcoholic solvent that used in the preparation of compound of formula VII is mixture of alcohol and water. Alcoholic solvent is selected from the group consisting of C_1 to C_6 carbon. The preferred one is ethanol, methanol and isopropyl alcohol.

Yet another object of the present invention is to provide a process for the synthesis of Apixaban (I) from the compound of formula VII wherein R^3 is ester or carboxylic acid is reacted with ammonia.

Further object of present invention is to provide a novel compound of formula V and its use in the synthesis of Apixaban.
Wherein R is selected from OR, NR\textsubscript{2}, SR; R is H, Ci-C\textsubscript{6} alkyl, aryl, aryl substituted with alkyl group; R\textsubscript{b} and R\textsubscript{c} are selected from C1-6, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl, and benzyl; alternatively N R\textsubscript{b} R\textsubscript{c} is a 3-8 membered ring consisting of carbon atoms, N and 0-1 O atoms; Y is selected from phenyl, pyridyl or pyrimidyl; Z is selected from Cl, Br, I, CN, NO\textsubscript{2}, NH\textsubscript{2} or 5-10 membered heterocyclic ring containing from 1-4 heteroatoms selected from the group consisting of N, O and S substituted with 0-2 R\textsubscript{d}; R\textsubscript{d} at each occurrence, is selected from H, =O, CHO, Cl, Br, I, CH\textsubscript{3}, CH\textsubscript{2}-CH\textsubscript{3}, CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{2}-CH\textsubscript{3}, CH (CH\textsubscript{3})\textsubscript{2}, CH\textsubscript{2}-CH (CH\textsubscript{3})\textsubscript{2}, CN, NO\textsubscript{2}; R\textsubscript{3} is selected from ester, amide, nitrile, carboxylic acid.

Further object of present invention is to provide compound of formula V where in R\textsuperscript{1} is preferably selected from NR\textsubscript{b} R\textsubscript{c}; NR\textsubscript{b} R\textsubscript{c} is preferably selected from morpholino, pyrolidino, pipieridino; Y is preferably selected from phenyl; Z is preferably selected from pyridine 2-one; R\textsubscript{3} is preferably selected from ester, carboxylic acid.

**DETAILED DESCRIPTION OF THE INVENTION**

An embodiment of the present invention provides a process for the preparation of Apixaba comprising a step of reacting compound of formula IV with a compound of formula X in the presence or absence of base and aprotic solvent to obtain compound of formula V
Wherein $R^1$ is selected from OR, $NR^bR^c$, Cl, Br, I, SR;
$R^a$ is H, Ci-C$_6$ alkyl, aryl, aryl substituted with alkyl group;
$R^b$ and $R^c$ are selected from Cl-6, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;
alternatively N $R^b$ $R^c$ is a 3-8 membered ring consisting of: carbon atoms, N and 0-1 O atoms
$Y$ is selected from phenyl, pyridyl or pyrimidyl;
$Z$ is selected from Cl, Br, I, CN, N02, NH2 or 5-10 membered heterocycle ring containing from 1-4 heteroatoms selected from the group consisting of N,0 and S substituted with 0-2 $R^d$;
$R^d$ at each occurrence, is selected from H, =0, CHO, Cl, Br, I, CH3, CH2-CH3, CH2-CH2-CH3, CH2-CH2-CH2-CH3, CH (CH3)2, CH2-CH (CH3)2, CN, N02;
$R^3$ is selected from ester, amide, nitrile, carboxylic acid;
$R^2$ is selected from halogen, mesylate, tosylate, 0-SO$_2$ Ph, OR.

Another embodiment of present invention is to provide process for the preparation of compound of formula V where in
$R^1$ is preferably selected from $NR^bR^c$;
$NR^bR^c$ is preferably selected from morpholino, pyrolidino, pipieridino;
$Y$ is preferably selected from phenyl;
$Z$ is preferably selected from pyridine 2-one;
$R^2$ is preferably selected from halogen, tosylate and mesylate;
$R^3$ is preferably selected from ester, carboxylic acid.

Base that used for the preparation of compound of formula V is selected from the group comprising of organic base such as pyridine, diethyl amine and trimethyl amine and Inorganic base such as KOH, NaOH, $K_2$CO$_3$, $Na_2$CO$_3$, CaCO$_3$, NH$_4$ and the like. More Preferable inorganic base is $K_2$CO$_3$ and organic base is pyridine.
The quantity of base used in this step may range from about 1 to about 3 molar equivalents, per mole of compound (IV).

Aprotic solvent may be selected from the group consisting of chlorinated and ether solvent. Chlorinated solvent is selected from methyl chloride, dichloride methane, and chloroform; ether solvent is selected from tetrahydrofuran, dimethyl ether, polyethylene glycol, dioxin, diethyl ether.

The amount of solvent that preferably used in this step may range from about 5 to 30 volumes to compound of formula (IV).

The residue obtain after the completion of reaction is treated with 5 to 30 % HCl and solid is filtered off to obtain compound of formula V.

Further embodiment of present invention is to provide Process for the preparation of Apixaban comprising a step of reacting compound of formula V with a compound of formula VI or salt thereof in the presence of aq. alcoholic solvent.

Wherein R^1 is selected from OR^a, NR^bR^c, Cl, Br, I, SR^a;
R^a is H, C_1-C_6 alkyl, aryl, aryl substituted with alkyl group;
R^b and R^c are selected from Cl-6, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;
Alternatively, N R R i s a 3-8 membered ring consisting of: carboan atoms, N and 0-1 O atoms
Y is selected from phenyl, pyridyl or pyrimidyl;
Z is selected from CI, Br , I, CN, N02, NH2 or 5-10 membered heterocyclic ring containing from 1-4 heteroatoms selected from the group consisting of N,0 and S substituted with 0-2 R4;
R4 at each occurrence, is selected from H, =0, CHO, CI, Br, I, CH3, CH2-CH3, CH2-CH2-CH3, CH2-CH2-CH2-CH3, CH (CH3)2, CH2- CH (CH3)2, CN, N02;
R is halogen, OR, mesylate, tosylate, 0-S0 2-Ph;
R3 is selected from ester, amide, nitrile, carboxylic acid.

Aq alcoholic solvent that used in the preparation of compound of formula VII is mixture of alcohol and water. Alcoholic solvent is selected from the group consisting of C1 to C8 carbon. The preferred one is ethanol, methanol and isopropyl alcohol.

The amount of solvent that preferably used in this step may range from about 5 to 30 volumes to compound of formula (V).

The salt of compound of formula VI is hydrochloride, hydrobromide or hydroiodide salt.

Yet another object of the present invention is to provide a process for the synthesis of Apixaban (I) from the compound of formula VII wherein R3 is ester or carboxylic acid is reacted with ammonia.

Further embodiment of present invention is to provide a process for the synthesis of Apixaban (I) from the compound of formula VII wherein the compound of formula VII is treated with ammonia when R3 is ester or carboxylic acid.

One of the embodiments of present invention provides novel compound of formula V.

And its use in the synthesis of Apixaban
Wherein $R^1$ is selected from OR$^a$, NR$^b$R$^c$, Cl, Br, I, SR$^a$;
$R^a$ is H, C$_1$-C$_6$ alkyl, aryl, aryl substituted with alkyl group;
$R^b$ and $R^c$ are selected from Cl-6, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;
Alternatively $N\ R^b\ R^c$ is a 3-8 member ring consisting of: carbon atoms, N and 0-1 O atoms
$Y$ is selected from phenyl, pyridyl or pyrimidyl;
$Z$ is selected from Cl, Br, I, CN, NO$_2$, NH$_2$ or 5-10 membered heterocyclic ring containing from 1-4 heteroatoms selected from the group consisting of N, O and S substituted with 0-2 $R^d$;
$R^d$ at each occurrence, is selected from H, =O, CHO, Cl, Br, I, CH$_3$, CH$_2$-CH$_3$, CH$_2$-CH$_2$-CH$_3$, CH$_2$-CH$_2$-CH$_2$-CH$_3$, CH (CH$_3$)$_2$, CH$_2$- CH (CH$_3$)$_2$, CN, NO$_2$;
$R^3$ is selected from ester, amide, nitrile, carboxylic acid;

Further embodiment of present invention provides compound of formula $V$ where in
$R^1$ is preferably selected from NR$^b$R$^c$;
$NR^bR^c$ is preferably selected from morpholino, pyrrolidino, pipieridino;
$Y$ is preferably selected from phenyl;
$Z$ is preferably selected from pyridine 2-one;
$R^3$ is preferably selected from ester, carboxylic acid.

The embodiments of present invention are shown schematically as below.

Scheme I

Scheme II
The process described in the present invention is illustrated in the following examples which should not be construed to limit the scope of the invention in any way.

**EXAMPLES**

**EXAMPLE 1**

Preparation of ethyl \([5\text{-hydroxy-6-oxo-1-[4-(2-oxopiperidin-1-yl)phenyl]}\cdot1,2,3,6\text{-tetrahydropyridin-4-yl}]\)(oxo)acetate.

5,6-Dihydro-3-(4-morpholinyl)-1-[4-(2-oxo-1-piperidinyl)phenyl]-2(1H)-pyridinone (100 gm) is stirred with Ethyl oxalyl chloride (42.24 gm) in dichloromethane (800 ml) in the presence of Pyridine (26.7 gm) at 25-30°C for 3 hrs. After the reaction completion dichloromethane is distilled completely and Ethyl acetate (100 ml) is added. To this 10% HCl solution (500 ml) is added and stirred for 1 hr. The solid is filtered and dried. Yield 90%

Example 2

Preparation of Ethyl 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo [3,4-c]pyridine-3-carboxylate.

Ethyl \([5\text{-hydroxy-6-oxo-1-[4-(2-oxopiperidin-1-yl)phenyl]}\cdot1,2,3,6\text{-tetrahydropyridin-4-yl}]\)(oxo)acetate (100 gm) is stirred with 4-Methoxy phenyl hydrazine hydrochloride (49.72 gm) in aqueous Isopropyl alcohol (2000 ml) at 50-55°C for 1 hr. After the reaction completion Isopropyl alcohol is distilled completely and the product is crystallized from mixture of Ethyl acetate and ethanol (1300 ml). The solid is filtered and dried. Yield 90%
Example 3
Preparation of 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-
1H-pyrazolo[3,4-c]pyridine-3-carboxamide.
Ethyl 1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7tetrahydro-1H-
pyrazolo[3,4-c]pyridine-3-carboxylate (100 gm) is heated with Ethylene glycol-NH₃ (5-6 % w/w)
(1000 ml) in pressure reactor at 115-120°C for 1.5 hrs. After the completion of reaction it is cooled
to 35-40°Cand the product is precipitated by addition of water (600 ml). The solid is filtered and dried.
Yield 75%.

Example 4
Preparation of [5-hydroxy-6-oxo-l-[4-(2-oxopiperidin-1-yl)phenyl]-1,2,3,6-tetrahydropyridin-4-
yl](oxo)acetic acid.
5,6-Dihydro-3-(4-moΦ holinyl)-l-[4-(2-oxo-l-piperidinyl)phenyl]-2(IH)-pyridinone (100 gm) is
stirred with sodium monoethyl oxalate (45.3 gm) in Ethanol (800 ml). After the reaction completion
ethanol is distilled completely and Ethyl acetate (100 ml) is added. To this 10 % HCl solution (500 ml)
is added and stirred for 1 hr. The solid is filtered and dried.

Example 5
Preparation of ethyl [5-hydroxy-6-oxo-l-[4-(2-oxopiperidin-1-yl)phenyl]-1,2,3,6-tetrahydropyridin-4-
yl](oxo)acetate.
[5-hydroxy-6-oxo-l-[4-(2-oxopiperidin-1-yl)phenyl]-1,2,3,6-tetrahydropyridin-4-y]l(oxo)acetic acid
(10 gm) was refluxed with Ethanolic HCl (100ml). After completion of the reaction ethanol is
removed under reduced pressure. Ethyl acetate (15 ml) is added and the solid is filtered and dried.

Example 6
Preparation of ethyl [5-hydroxy-6-oxo-l-[4-(2-oxopiperidin-1-yl)phenyl]-1,2,3,6-
tetrahydropyridin-4-yl](oxo)acetate.
3-ethoxy-l-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(IH)-one (50 gm) is stirred with
Ethyl oxalyl chloride (20 gm) in dichloromethane (350 ml) in the presence of Pyridine (13.5 gm) at
25-30°C for 3 hrs. After the reaction completion dichloromethane is distilled completely and Ethyl
acetate (50ml) is added. To this 10 % HCl solution (250 ml) is added and stirred for 1 hr. The solid is
filtered and dried.
CLAIMS

1. Process for the preparation of Apixaban comprising a step of reacting compound of formula IV with a compound of formula X in the presence or absence of base and aprotic solvent to obtain compound of formula V

Wherein \( R^1 \) is selected from \( \text{OR}^2, \text{NR}^3 \text{R}^4, \text{Cl}, \text{Br}, \text{I}, \text{SR}^5; \)
\( R^4 \) is \( \text{H}, \text{C}_i-\text{C}_6 \text{ alkyl, aryl, aryl substituted with alkyl group;} \)
\( R^3 \) and \( R^5 \) are selected from \( \text{Cl}-6, \text{alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;} \)
alternatively \( N \text{ R}^2 \text{ R}^3 \) is a 3-8 member ring consisting of: carboan atoms, \( \text{N} \) and 0-1 \( \text{O} \) atoms
\( Y \) is selected from \( \text{Cl}, \text{Br}, \text{I}, \text{CN}, \text{NH}_2 \text{ or 5-10 member heterocyclic ring containing from 1-4 heteroatoms selected from the group consisting of N,0 and S substituted with 0-2 R}^4; \)
\( R^4 \) at each occurrence, is selected from \( \text{H}, =\text{0}, \text{CHO, Cl, Br, I, CH}_3, \text{CH2-CH}_3, \text{CH2-CH2-CH}_3, \text{CH2-CH2-CH2-CH}_3, \text{CH}_2(\text{CH}_3)_2, \text{CH2-CH(} \text{CH}_3)_2, \text{CN, N02;} \)
\( R^3 \) is selected from ester, amide, nitrile, carboxylic acid;
\( R^2 \) is selected from halogen, mesylate, tosylate, 0-S0, 0-CO-CO-OR \( x; \)
\( R^3 \) is selected from alkyl, substituted alkyl and cyclo alkyl;

2. Process for the preparation of Apixaban comprising a step of reacting compound of formula V with a compound of formula VI or salt there of in the presence of aq. alcoholic solvent.
Wherein $R^1$ is selected from OR, N$R^b$R$^c$, CI, Br, I, SR;
$R^2$ is H, C$_1$-C$_6$ alkyl, aryl, aryl substituted with alkyl group;
$R^b$ and $R^c$ are selected from CI-6, alkyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, phenyl and benzyl;
Alternatively, N $R^b$$R^c$ is a 3-8 member ring consisting of: carbon atoms, N and 0-1 O atoms;
$Y$ is selected from phenyl, pyridyl or pyrimidyl;
$Z$ is selected from CI, Br, I, CN, N02, NH2 or 5-10 member heterocycle ring containing from 1-4 heteroatom selected from the group consisting of N,0 and S substituted with 0-2 R$^d$;
$R^d$ at each occurrence, is selected from H, =0, CHO, CI, Br, I, CH3, CH2-CH3, CH2-CH2-CH3, CH2-CH2-CH2-CH3, CH2-CH2-CH2-CH2-CH3, CH (CH3)2, CH2- CH (CH3)2, CN, N02;
$R$ is halogen, OR, mesylate, tosylate, 0-S0$_2$Ph.
$R^3$ is selected from ester, amide, nitrile, carboxylic acid.

3. Compound of formula V

And its use in the synthesis of Apixaban

$R^1$ is preferably selected from N$R^b$R$^c$ and OR$^a$;
N$R^b$R$^c$ is preferably selected from morpholino, pyrolidino, pipieridino;
OR$^a$ is preferably selected from H and 0-6 alkyl;
Y is preferably selected from phenyl;
Z is preferably selected from pyridine 2-one;
R\textsuperscript{3} is preferably selected from ester and carboxylic acid.

4. A process as claimed in claim 1 or claim 2 where in R\textsuperscript{1} is preferably selected from NR\textsuperscript{b}R\textsuperscript{c} and OR\textsuperscript{a}:
NR\textsuperscript{b}R\textsuperscript{c} is preferably selected from morpholino, pyrrolidino, pipieridino;
OR\textsuperscript{a} is preferably selected from H and 0-6 alkyl;
Y is preferably selected from phenyl;
Z is preferably selected from pyridine 2-one;
R\textsuperscript{2} is preferably selected from halogen, tosylate and mesylate;
R\textsuperscript{3} is preferably selected from ester, carboxylic acid;
R is preferably selected from OR\textsuperscript{a}.

5. A process as claimed in claim 1 where in base is selected from the group comprising of organic base such as pyridine, dimethyl amine and trimethyl amine and Inorganic base such as KOH, NaOH, K\textsubscript{2}C\textsubscript{0}\textsubscript{3}, Na\textsubscript{2}C\textsubscript{0}\textsubscript{3}, CaC\textsubscript{0}\textsubscript{3}, NH\textsubscript{4} and the like.

6. A process as claimed in claim 5 where in organic base is pyridine and inorganic base is K\textsubscript{2}C\textsubscript{0}\textsubscript{3}.

7. A process as claimed in claim 2 where in alcoholic solvent is selected from the group consisting of C1 to C8 carbon.

8. A process as claimed in claim 7 where in alcoholic solvent is ethanol, methanol and isopropyl alcohol.

9. A process according to claim 2 or 4 where in R\textsuperscript{3} is ester or carboxylic acid treated with ammonia to obtain apixaban of formula (I).
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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<th>INV.</th>
<th>C07D401/10</th>
<th>C07D471/Q4</th>
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**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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
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<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
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</table>

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

- **"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
- **"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
- **"Z"** document member of the same patent family

**Date of the actual completion of the international search**

6 February 2014

**Date of mailing of the international search report**

17/02/2014

Name and mailing address of the ISA/

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Authorized officer

Sarakinos, Georgios
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<td>PINTO D J P ET AL: &quot;1- [3-Ami nobenzi soxazol -5'-yl] -3-tri fluoro methyl -6- [2'- (3- (R) -hydroxy-N-pyrrol i di ny l )methyl - [l, l ']-bi phen-4-yl ] -1,4,5,6-tetrah ydopyrazolo-[3,4-c] -pyri din-7-one (BMS-740808) a hi ghly potent, sel e ctive, and oral ly bi oavail able inhibi tor of blood coagul ation factor Xa&quot;, BIOORGANIC &amp; MEDICINAL CHEMISTRY LETTERS, PERGAMON, AMSTERDAM, NL, vol . 16, no. 15, 1 August 2006 (2006-08-01) , pages 4141-4147 , XP027966517, ISSN : 0960-894X [retrieved on 2006-08-01] the whole document</td>
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<td>CN 101 967 145 B (UNIV EAST CHINA SCIENCE &amp; TECH; SHANDONG HAOYUAN INDUSTRY GROUP CO LTD) 4 July 2012 (2012-07-04) the whole document</td>
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