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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
29 October 2015 (29.10.2015)

WIPO | PCT

(10) International Publication Number
WO 2015/162551 Al

(51) **International Patent Classification:**
C07D 471/04 (2006.01)

(21) **International Application Number:**
PCT/IB20 15/052894

(22) **International Filing Date:**
2 1 April 2015 (21 .04.2015)

(25) **Filing Language:** English

(26) **Publication Language:** English

(30) **Priority Data:**
2035/CHE/2014 2 1 April 2014 (21.04.2014) IN
4367/CHE/2014 5 September 2014 (05.09.2014) IN

(71) **Applicant: MYLAN LABORATORIES LTD** [IN/IN]; Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(72) **Inventors: JAYACHANDRA, Sureshbabu;** Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **KAUSHIK, Vipin Kumar;** Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **ACHANTA, Surya Nageswara Rao;** Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **DORASALA, Siva Prasad Reddy;** Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN). **DANDALA, Subramanyam;** Mylan Laboratories Ltd, Plot No 564/A/22, Road No 92, Jubilee Hills, Hyderabad 500033 (IN).

(74) **Agent: NAIR, Manisha Singh;** LEX ORBIS, 709-710, Tolstoy House, 15-17, Tolstoy Marg, New Delhi 110 001 (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, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KN, KP, KR, 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, 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).

Declarations under Rule 4.17 :

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.1 7(H))*

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.1 7(in))*

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))*

WO 2015/162551 A1

(54) Title: PROCESS FOR THE PREPARATION OF APIXABAN

(57) Abstract: The present disclosure provides processes and intermediates for the preparation of apixaban.

PROCESS FOR THE PREPARATION OF APIXABAN

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims the benefit of earlier Indian provisional patent application nos. 2035/CHE/2014 filed on April 21, 2014 and 4367/CHE/2014 filed on September 5, 2014.

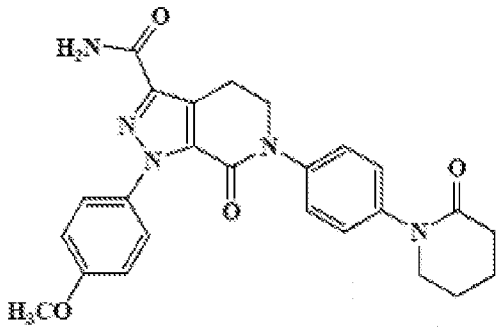
BACKGROUND OF THE INVENTION

FIELD OF THE INVENTION

The present invention relates generally to pharmaceutical compositions and more particularly to a process for the preparation of apixaban using novel intermediates.

BACKGROUND OF THE INVENTION

Apixaban is chemically known as l-(4-methoxy-phenyl)-7-oxo-6-[4-(2-oxopiperidin-l-yl)-phenyl]-4,5,6,7-tetrahydro-lH-pyrazolo[3,4c]-pyridine-3-carboxamide and has the following structural formula:



Apixaban is a direct factor Xa (FXa) inhibitor, and is used as an anticoagulant for the treatment of venous thromboembolic events. Apixaban is marketed by Bristol-Myers Squibb under the brand name ELIQUIS®.

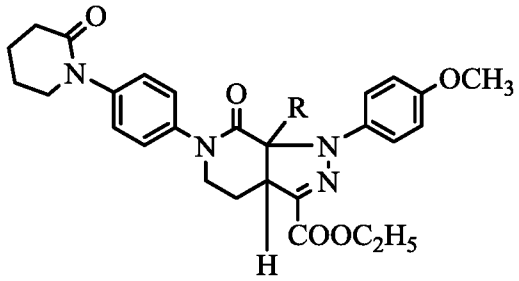
U.S. Patent Nos. 6,413,980 and 6,673,810, which are hereby incorporated by reference, broadly disclose nitrogen-containing heterobicyclic compounds, derivatives thereof, and pharmaceutically acceptable salts thereof, as inhibitors of factor Xa. U.S. Patent Nos. 6,967,208; 6,989,391; and 6,919,451, which are all hereby incorporated by reference, disclose processes for the preparation of apixaban.

There is a need to provide an improved process for the preparation of apixaban which avoids the use of expensive chemicals and formation of impurities. The present

invention provides a process for the preparation of apixaban and its intermediates which is efficient and industrially viable.

SUMMARY OF THE INVENTION

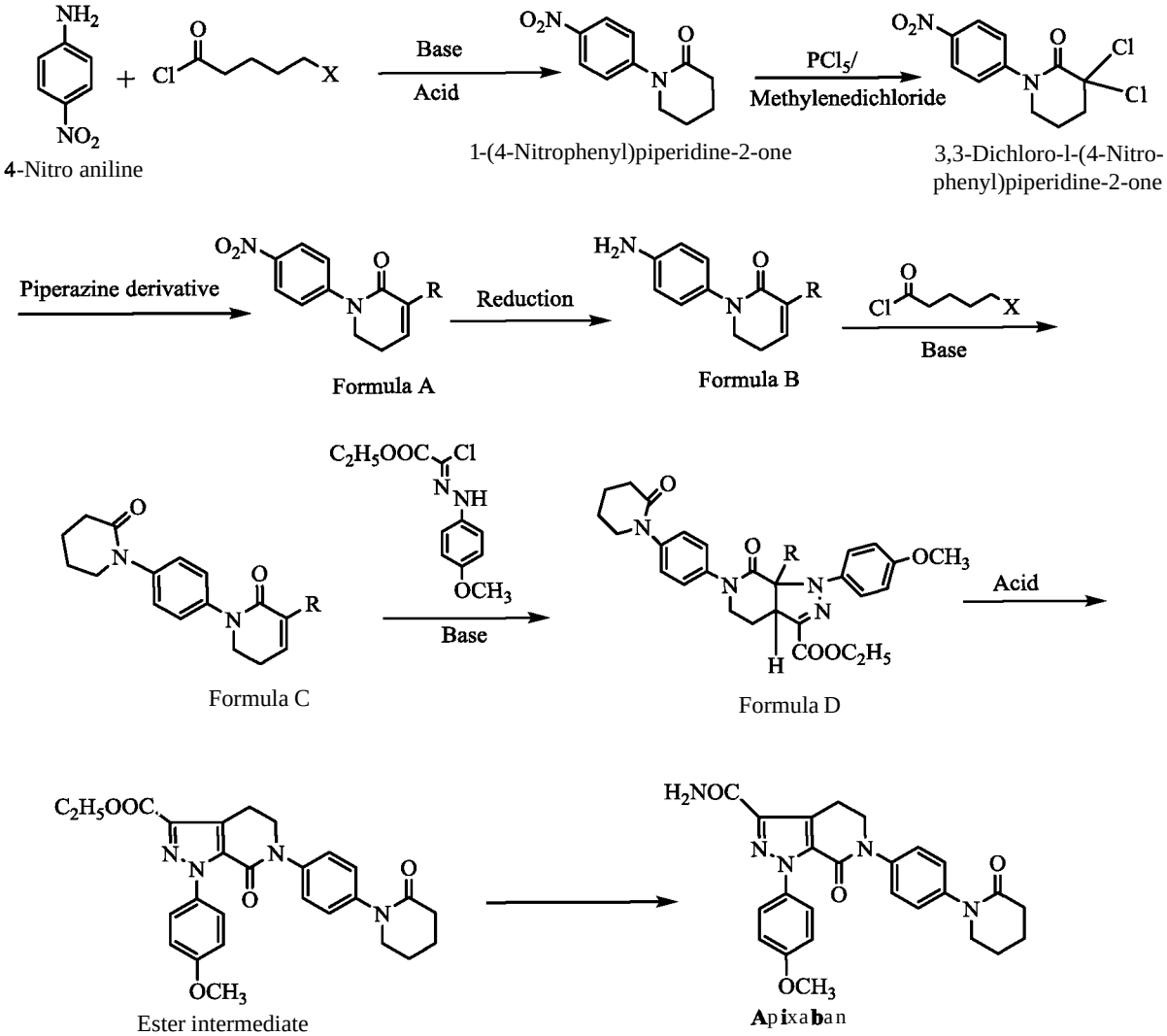
One aspect of the present invention provides a compound of Formula D shown below:



Formula D

where R may be N-methyl piperazine, N-ethyl piperazine, l-(2-pyrimidinyl)piperazine, 1-(2-pyridyl)piperazine, or benzyl piperazine. Within the context of the present invention, Formula D may be employed as a novel intermediate in the synthesis of apixaban.

Another aspect of the present invention provides a process to produce apixaban, which may be prepared by the following Scheme-I, shown below:



4-Nitro aniline

1-(4-Nitrophenyl)piperidine-2-one

3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one

Formula A

Formula B

Formula C

Formula D

Ester intermediate

Apixaban

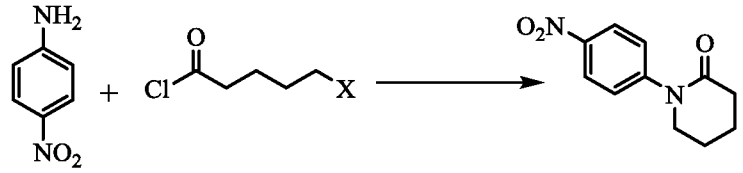
R is a Piperazine derivative such as
N-methyl piperazine,
N-ethyl piperazine,
1-(2-pyramidinyl)piperazine,
l-(2-pyridyl)piperazine, or benzyl piperazine;

X is chlorine or bromine.

Scheme-I

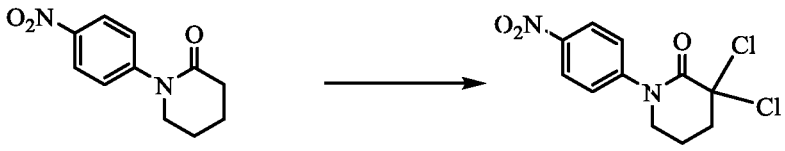
One embodiment of the present invention provides a process for the preparation of apixaban which may include the following steps (which shares some attributes of the procession of Formula B to apixaban disclosed in Scheme-I above):

a) treating 4-nitroaniline with 5-chloro-pentanoyl chloride in the presence of a base to obtain 1-(4-nitrophenyl)piperdin-2-one



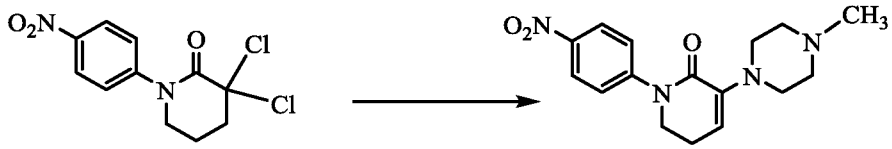
4-Nitro aniline **l-(4-Nitrophenyl)piperidine-2-one**

b) converting l-(4-nitrophenyl)piperdin-2-one to 3,3-dichloro-l-(4-nitrophenyl)piperidin-2-one



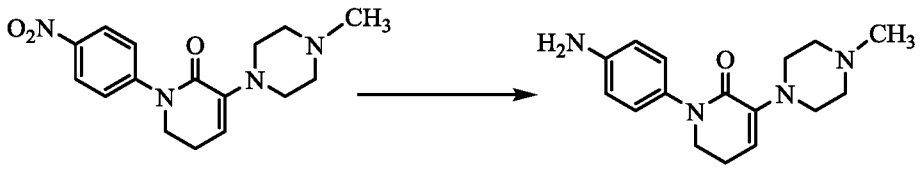
l-(4-Nitrophenyl)piperidine-2-one **3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one**

c) treating 3,3-dichloro-l-(4-nitrophenyl)piperidin-2-one with N-methyl piperazine to obtain a N-methyl piperazine nitro compound ("NMP Nitro compound", an example of Formula A from Scheme-I)



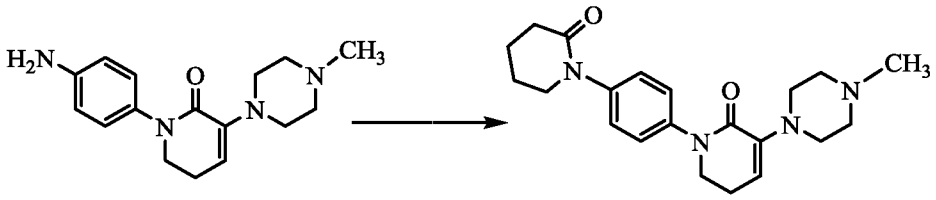
3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one **NMP Nitro compound**

d) reducing the N-methyl piperazine nitro compound to obtain an N-methyl piperazine amino compound ("NMP Amino compound", an example of Formula B from Scheme-I)



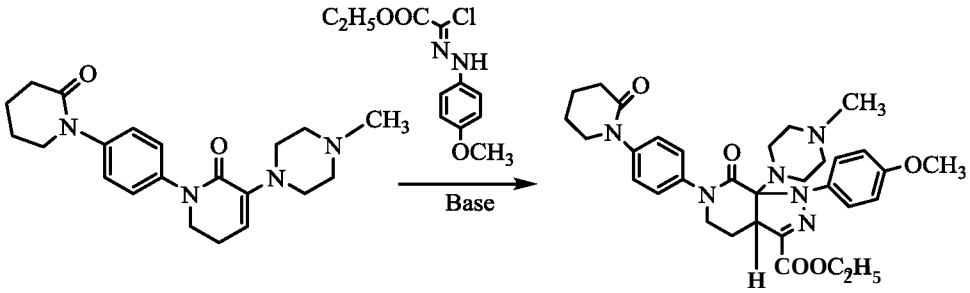
NMP Nitro compound **NMP Amino compound**

e) converting the N-methyl piperazine amino compound ("NMP Amino Compound") to an N-methyl piperazine cyclic intermediate ("NMP Cyclic Intermediate", an example of Formula C from Scheme-I)



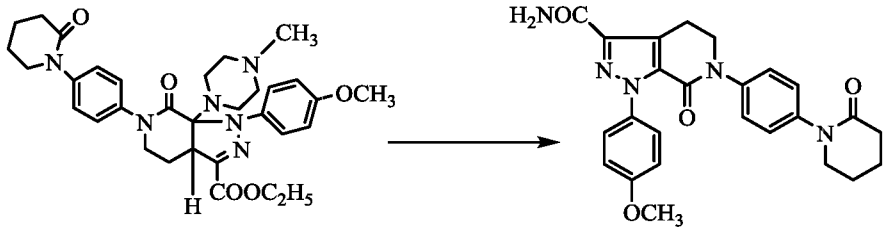
NMP Amino compound **NMP Cyclic Intermediate**

f) treating the N-methyl piperazine cyclic intermediate with a hydrazine intermediate to obtain an apixaban ester intermediate ("NMP Ester Intermediate", an example of Formula D in Scheme-I), and



NMP Cyclic Intermediate **NMP Ester Intermediate**

g) converting the NMP Ester intermediate to apixaban.



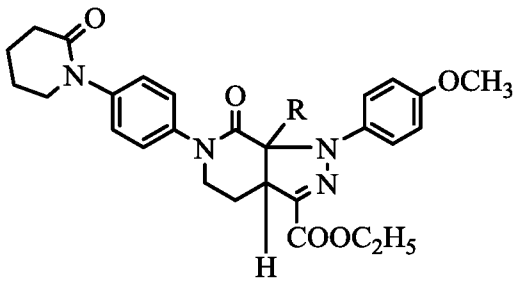
NMP Ester Intermediate **Apixaban**

h) optionally purifying the obtained apixaban.

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to a process for the preparation of apixaban using novel intermediates.

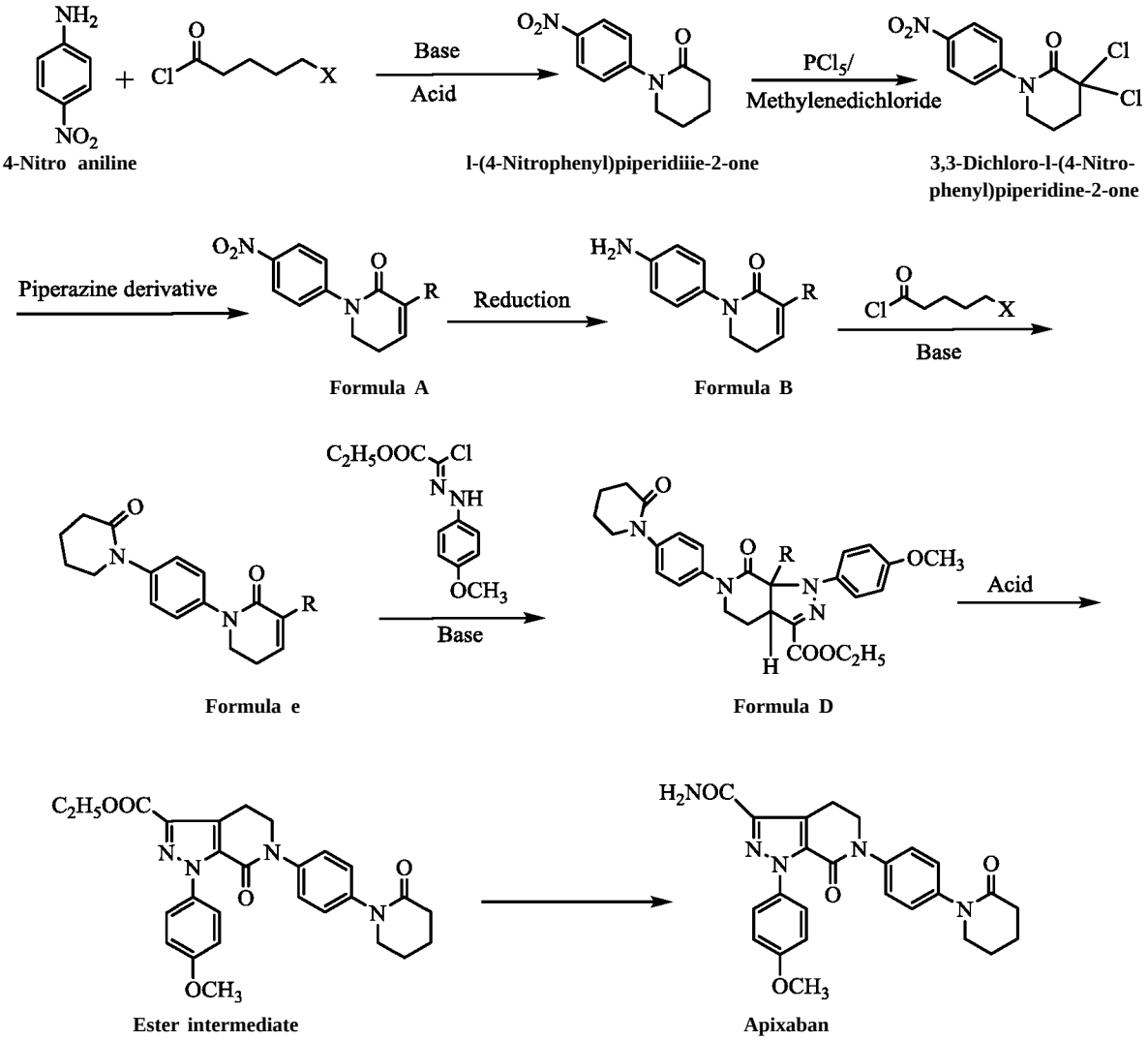
In one aspect, the present invention provides a compound of Formula D shown below:



Formula D

where R may be N-methyl piperazine, N-ethyl piperazine, l-(2-pyrimidinyl)piperazine, 1-(2-pyridyl)piperazine, or benzyl piperazine. Within the context of the present invention, Formula D may be employed as a novel intermediate in the synthesis of apixaban.

In another aspect, the present invention provides a process to produce apixaban, which may be prepared by the following Scheme-I, shown below:



4-Nitro aniline

l-(4-Nitrophenyl)piperidiiie-2-one

3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one

Formula A

Formula B

Formula e

Formula D

Ester intermediate

Apixaban

R is a Piperazine derivative such as
N-methyl piperazine,
N-ethyl piperazine,
1-(2-pyramidiny l)piperazine,
l-(2-pyridyl)piperazine, or benzyl piperazine;

X is chlorine or bromine.

Scheme-I

According to the present disclosure, 4-nitroaniline is reacted with a 5-chloropentanoyl halide in the presence of a base and an acid to result in l-(4-nitrophenyl)piperidin-2-one. Within the context of the present invention, the 5-chloropentanoyl halide may be 5-chloropentanoyl chlorine or 5-chloropentanoyl bromine. Within the context of the present invention, the base may be, for example, methylamine, ethylamine, dimethylamine, triethylamine, trimethylamine, or isopropylethylamine. The

acid may be an inorganic acid, for example, hydrochloric acid, sulfuric acid, or phosphoric acid.

Next, l-(4-nitrophenyl)piperidin-2-one is reacted in the presence of phosphorous pentachloride and suitable solvent selected from chlorinated solvents (such as chloroform, dichloromethane, dichloroethane) or ether solvents (such as tetrahydrofuran), to result in 3,3-dichloro- 1-(4-nitrophenyl)piperidin-2-one. Next, 3,3-dichloro- 1-(4-nitrophenyl)piperidin-2-one without isolation is reacted with a piperazine derivative to get Formula A. Within the context of the present invention, the piperazine derivative may be, for example, N-methyl piperazine, N-ethylpiperazine, l-(2-pyramidyl)piperizine, l-(2-pyridyl)piperazine, or benzyl piperazine. Formula A may then be reduced to obtain Formula B. Within the context of the present invention, suitable reagents for reducing Formula A include, for example, sodium sulfide, and Raney nickel, though other well-known reducing agents from the art may also be employed.

Next, Formula B is converted to Formula C. This reaction may be carried out by treating Formula B with a 5-chloropentanoyl halide in the presence of suitable organic or inorganic base and a solvent. Within the context of the present invention, the 5-chloropentanoyl halide may be 5-chloropentanoyl chlorine or 5-chloropentanoyl bromine. Examples of suitable organic bases include methylamine, ethylamine, dimethylamine, triethylamine, trimethylamine, and isopropylethylamine. Examples of suitable inorganic base include sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Examples of suitable solvents include chlorinated solvents such as chloroform, dichloromethane, dichloroethane or ether solvents such as tetrahydrofuran.

Next, Formula C may be reacted with a hydrazine intermediate in presence of an organic or inorganic base and a solvent to yield Formula D. Within the context of the present invention, the hydrazine intermediate may be Z-ethyl-2-chloro-2-[2-(4-methoxyphenyl)hydrazono] acetate. The organic base may be, for example, pyridine, piperidine, N-methyl morpholine, N-methylpiperidine, N-phenylpiperidine, or an alkyl amine. Examples of suitable alkyl amines include diethylamine, triethyl amine, di-isopropylethylamine, and diphenylamine. Examples of suitable inorganic bases include potassium hydroxide, sodium hydroxide, potassium carbonate, and sodium carbonate. Examples of suitable solvents include ethyl acetate, butyl acetate, isopropyl acetate, methyl acetate, tetrahydrofuran, methylene dichloride, and mixtures thereof. Within the context of

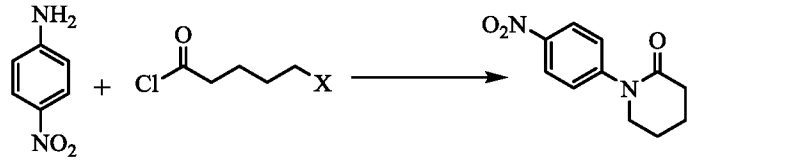
the present invention, an ester solvent was found to be particularly useful in carrying out this step of the reaction.

Formula D is then treated with a suitable acid to result in an ester intermediate. Suitable acids include, for example, hydrochloric acid, sulfuric acid, trifluoroacetic acid, nitric acid, and mixtures thereof.

The ester intermediate may then be treated with a suitable amine source in the presence of a suitable solvent to produce apixaban. Examples of suitable amine sources include ammonia gas, liquid ammonia, and ammonium formate. Generally, alcoholic solvents may be employed in this step of the reaction. Suitable alcoholic solvents include, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, tert-butanol, amyl alcohol, methylene chloride, ethylene chloride, tetrahydrofuran, or mixture thereof. Apixaban may be optionally purified by recrystallization in a suitable solvent, such as methanol, ethanol, isopropyl alcohol, water, or mixtures thereof. Apixaban may then be isolated, for example, through filtration, distillation, spray drying, or tray drying to obtain substantially pure apixaban.

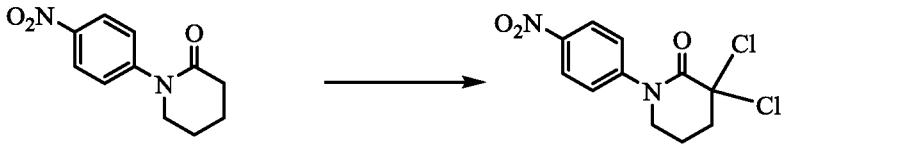
One embodiment of the present invention provides a process for the preparation of apixaban which may include the following steps (which shares some attributes of the procession of Formula B to apixaban disclosed in Scheme-I above):

a) treating 4-nitroaniline with a 5-chloropentanoyl halide in the presence of a base to obtain l-(4-nitrophenyl)piperdin-2-one. Within the context of the present invention, the 5-chloropentanoyl halide may be 5-chloropentanoyl chlorine or 5-chloropentanoyl bromine. The base may be, for example, methylamine, ethylamine, dimethylamine, triethylamine, trimethylamine, or isopropylethylamine. Examples of suitable acids include inorganic acids such as hydrochloric acid, sulfuric acid, and phosphoric acid.



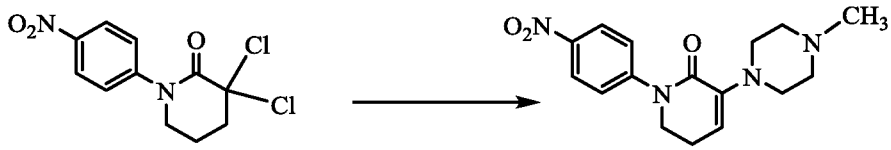
4-Nitro aniline **l-(4-Nitrophenyl)piperidine-2-one**

b) converting l-(4-nitrophenyl)piperdin-2-one to 3,3-dichloro-l-(4-nitrophenyl)piperidin-2-one. This reaction may be carried out in the presence of methylene dichloride.



l-(4-Nitrophenyl)piperidine-2-one **3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one**

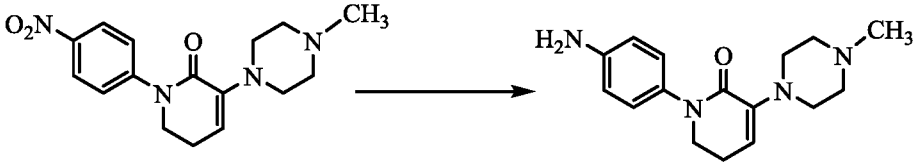
c) treating 3,3-dichlori-l-(4-nitrophenyl)piperidin-2-one with N-methyl piperazine to obtain an N-methyl piperazine nitro compound ("NMP Nitro compound", an example of Formula A from Scheme-I).



3,3-Dichloro-l-(4-Nitro-phenyl)piperidine-2-one **NMP Nitro compound**

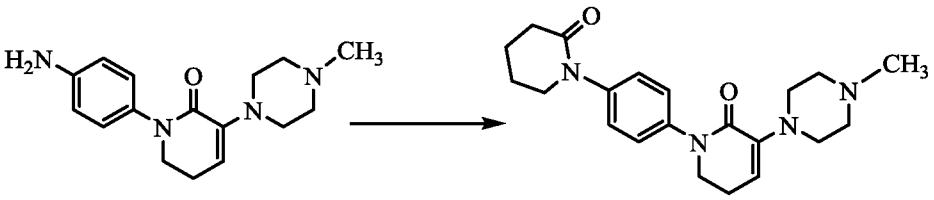
d) reducing the N-methyl piperazine nitro compound to obtain an N-methyl piperazine amino compound ("NMP Amino compound", an example of Formula B from Scheme-I). Within the context of the present invention, suitable reagents

for reducing N-methyl piperazine include, for example, sodium sulfide or Raney nickel.



NMP Nitro compound **NMP Amino compound**

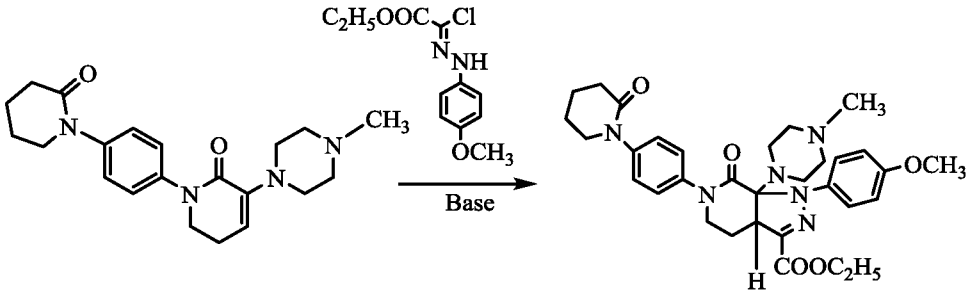
e) converting the N-methyl piperazine amino compound ("NMP Amino Compound") to an N-methyl piperazine cyclic intermediate ("NMP Cyclic Intermediate", an example of Formula C from Scheme-I).



NMP Amino compound **NMP Cyclic Intermediate**

This reaction may be carried out by treating the NMP Nitro compound with a 5-chloro-pentanoyl halide in the presence of suitable organic or inorganic base and a solvent. Within the context of the present invention, the 5-chloropentanoyl halide may be 5-chloropentanoyl chlorine or 5-chloropentanoyl bromine. Examples of suitable organic bases include methylamine, ethylamine, dimethylamine, triethylamine, trimethylamine, and isopropylethylamine. Examples of suitable inorganic base include sodium carbonate, potassium carbonate, sodium bicarbonate, and potassium bicarbonate. Examples of suitable solvents include chlorinated solvents such as chloroform, dichloromethane, dichloroethane or ether solvents such as tetrahydrofuran.

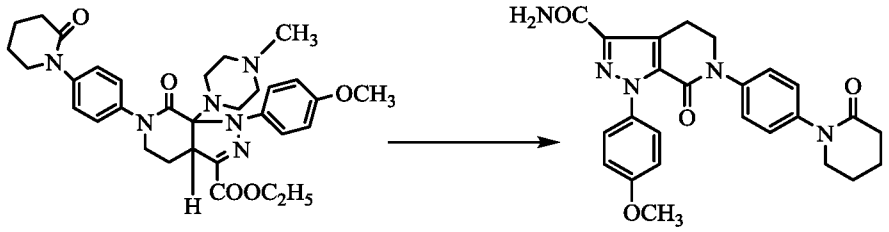
f) treating the N-methyl piperazine cyclic intermediate with a hydrazine intermediate to obtain an apixaban ester intermediate ("NMP Ester Intermediate", an example of Formula D in Scheme-I),



NMP Cyclic Intermediate **NMP Ester Intermediate**

This reaction may be carried out in the presence of an organic base and suitable solvent. Within the context of the present invention, the hydrazine intermediate may be Z-ethyl-2-chloro-2-[2-(4-methoxyphenyl)hydrazono] acetate. The organic base may be, for example, pyridine, piperidine, N-methyl morpholine, N-methylpiperidine, N-phenylpiperidine, or an alkyl amine. Examples of suitable alkyl amines include diethylamine, triethyl amine, di-isopropylethylamine, and diphenylamine. Examples of suitable inorganic bases include potassium hydroxide, sodium hydroxide, potassium carbonate, and sodium carbonate. Examples of suitable solvents include ethyl acetate, butyl acetate, isopropyl acetate, methyl acetate, tetrahydrofuran, methylene dichloride, and mixtures thereof.

g) converting the NMP Ester intermediate to apixaban.



NMP Ester Intermediate **Apixaban**

The NMP ester intermediate may be converted to apixaban by first treating with suitable acid to result in an ester intermediate, as well understood in the art (step not shown above, but represented in Scheme-I). Suitable acids may be, for example, hydrochloric acid, sulfuric acid, trifluoroacetic acid, nitric acid, and mixtures thereof. The ester intermediate may then be treated with a suitable amine source in the presence of a suitable solvent to result in apixaban. Examples of suitable amine sources include ammonia gas, liquid ammonia, and ammonium formate. Suitable solvents include, for example, methanol, ethanol, isopropanol, n-propanol, n-butanol, tert-butanol, amyl alcohol, methylene chloride,

ethylene chloride, tetrahydrofuran, or mixtures thereof. In some embodiments of the present invention, an alcoholic solvent was found to be particularly useful for execution of this step of the reaction.

h) optionally purifying the obtained apixaban.

Apixaban may be optionally purified by recrystallization in a suitable solvent. Suitable solvents include, for example, methanol, ethanol, isopropyl alcohol, water, or mixtures thereof. Apixaban may then be isolated, for example, through filtration, distillation, spray drying, or tray drying to obtain substantially pure apixaban.

In view of the above description and the examples below, one of ordinary skill in the art will be able to practice the invention as claimed without undue experimentation. The foregoing will be better understood with reference to the following examples that detail certain procedures for the preparation of molecules, compositions and formulations according to the present invention. All references made to these examples are for the purposes of illustration. The following examples should not be considered exhaustive, but merely illustrative of only a few of the many aspects and embodiments contemplated by the present disclosure.

Example 1: Preparation of l-(4-nitrophenyl) piperidin-2-one

5-chloropentanoyl chloride (140.3 g, 0.91 moles) was dissolved in methylene dichloride (2000 ml). 4-nitroaniline (100 g, 0.72 moles) and triethylamine (147.7 g, 1.46 moles) were added at 0-5 °C under nitrogen atmosphere. The reaction mass was stirred at room temperature. After completion of the reaction, the reaction mass was cooled to 0-5 °C and potassium tert-butoxide (223.5 g, 1.99 moles) was added at 0-5 °C over a period of about 3 hours. Thereafter, the reaction mass temperature was raised slowly to 25-35 °C. After completion of the reaction, the reaction mass was poured into ice water. The organic layer was separated and aqueous layer was extracted with methylene dichloride (300 ml). After washing with water (2000 ml), the combined organic layers were concentrated and crystallized from isopropyl alcohol to afford l-(4-nitrophenyl) piperidin-2-one.

Example la: Preparation of l-(4-nitrophenyl) piperidin-2-one

To a cooled mixture of 4-nitroaniline (100 g, 0.72 moles), methylene dichloride (1300 ml), tetrahydrofuran (100 ml), a solution of potassium carbonate (130.08 g (0.94 moles) potassium carbonate dissolved in 400 ml of water), and 5-chloropentanoyl chloride

solution (140.29 g (0.72 moles) 5-chloropentanoyl chloride mixed in 100 ml of methylene dichloride) was added at 5-10 °C, and the reaction mass was heated to 27 to 32 °C. The reaction mixture was stirred until the reaction was completed, as monitored by HPLC. The reaction mass was then cooled to 10 to 15 °C.

Tetrabutylammonium bromide (TBAB) (2.33 g) and a sodium hydroxide solution (202.72 g, 5.06 moles sodium hydroxide dissolved in 500 ml of water, cooled to 25-30 °C (Slight exothermic addition)) was added to this reaction mass at 10 to 15 °C, and the reaction mass was heated to 27 to 32 °C. The reaction mass was stirred until the reaction was completed as monitored by HPLC. The reaction mass was then cooled to 10 to 15 °C. After completion of the reaction, the organic layer was separated and aqueous layer was extracted with methylene dichloride (300 ml). After washing with water (500 ml), the combined organic layers were concentrated and crystallized from isopropyl alcohol to afford l-(4-nitrophenyl) piperidin-2-one.

Example 2: Preparation of 5, 6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-nitrophenyl) pyridin-2(lH)-one

l-(4-nitrophenyl) piperidin-2-one (100 g, 0.45 moles) was dissolved in methylene dichloride (1200 ml) and phosphorus pentachloride (288.3 g, 1.36 moles) was added slowly. The resulting mixture was heated to reflux. After completion of reaction, the reaction mass was poured into ice water. The organic layer was separated and the aqueous layer was extracted with methylene chloride (300 ml). The combined organic layers were washed with water (1000 ml), dried over anhydrous sodium sulfate, and concentrated in vacuum. The obtained residue was dissolved in N-methyl piperazine (500 ml) and the reaction temperature was raised slowly to 120-130 °C. After completion of the reaction, the reaction mixture was cooled to 100 °C, concentrated under reduced pressure, and water was added to precipitate the product. After filtration, the obtained product was recrystallized from isopropyl alcohol to afford 5, 6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-nitrophenyl) pyridin-2(lH)-one.

Example 3: Preparation of l-(4-aminophenyl)-5, 6-dihydro-3-(4-methylpiperazin-l-yl) pyridin-2(lH)-one (an example of Formula B)

5, 6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-nitrophenyl)pyridin-2(lH)-one (100 g, 0.32 moles) and sodium sulfide nonahydrate (151.7 g, 0.63 moles) were dissolved sequentially in water (400 ml). Thereafter, the reaction mass temperature was raised to 35-

40 °C and stirred. After completion of the reaction, the reaction mass was cooled to 15-20 °C and filtered to afford l-(4-aminophenyl)-5,6-dihydro-3-(4-methyl-piperazin-l-yl)pyridin-2(lH)-one.

Example 3A: Preparation of l-(4-aminophenyl)-5, 6-dihydro-3-(4-methylpiperazin-l-yl)pyridin-2(lH)-one (an example of Formula B)

5,6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-nitrophenyl)pyridin-2(lH)-one (100 g, 0.32 moles), methanol (1500 ml) and methanolic ammonia (50 ml) were stirred and Raney nickel (15 g) was added at 27 to 30° C. The autoclave/pressure vessel was filled with hydrogen gas to attain a pressure of 2-3 kg/cm^2. Thereafter, the reaction mass temperature was raised to 42 to 45 °C while stirring. After completion of the reaction, the reaction mass was cooled to 27 to 30 °C, filtered, and crystallized from isopropyl alcohol to afford l-(4-aminophenyl)-5,6-dihydro-3-(4-methyl-piperazin-l-yl)pyridin-2(lH)-one.

Example 4: Preparation of 5, 6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-(2-oxopiperidin-l-yl)phenyl)-pyridine-2(lH)-one (an example of Formula C)

5-chloropentanoyl chloride (67.67 g, 0.44 moles) and l-(4-aminophenyl)-5,6-dihydro-3-(4-methylpiperazin-l-yl)pyridin-2(lH)one (100 g, 0.35 moles) were dissolved in methylene dichloride (2000 ml). Triethylamine (70.0 g, 0.69 moles) was then added at 0-5 °C. The reaction mass temperature was raised to 25-35 °C and stirred. After completion of the reaction, the reaction mass was cooled to 0-5 °C and potassium tert-butoxide was added (116 g, 1.04 moles). Again, the reaction mass temperature was raised to 25-35 °C and stirred. After completion of the reaction, the reaction mass was poured into ice water. The organic layer was separated and aqueous layer was re-extracted with methylene dichloride. The combined organic phases were washed with saturated sodium chloride solution (800 ml), dried over anhydrous sodium sulfate, and concentrated under reduced pressure to obtain 5, 6-dihydro-3-(4-methyl-piperazin-l-yl)-l-(4-(2-oxopiperidin-l-yl) phenyl)pyridin-2(lH)-one.

Example 4a: Preparation of 5, 6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-(2-oxopiperidin-l-yl)phenyl)-pyridine-2(lH)-one (an example of Formula C)

5-chloropentanoyl chloride (67.67 g, 0.44 moles) was added to a cooled mixture of l-(4-aminophenyl)-5,6-dihydro-3-(4-methylpiperazin-l-yl)pyridin-2(lH)one (100 g, 0.35 moles), methylene dichloride (2000 ml), and potassium carbonate solution (62.73 g K_2CO_3 dissolved in 125 mL water). The reaction mass temperature was raised to 27 to 32 °C and

stirred. After completion of the reaction, the reaction mass was cooled to 0 to 5 °C. Potassium tert-butoxide (117.52 g) was added to the reaction mass. The temperature of the reaction mass was raised to 27 to 32° C and stirred. Water (300 ml) was slowly added to this reaction mass and the mass was stirred until the product precipitate was obtained. The product was filtered and washed with water to obtain 5, 6-dihydro-3-(4-methyl-piperazin-l-yl)-l-(4-(2-oxopiperidin-l-yl) phenyl) pyridin-2(lH)-one.

Example 5: Preparation of ethyl l-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-l-yl) phenyl)-4, 5, 6, 7-tetrahydro-lH-pyrazolo [3, 4-c] pyridin-3-carboxylate (an example of Formula D)

5,6-dihydro-3-(4-methylpiperazin-l-yl)-l-(4-(2-oxopiperidin-l-yl)phenyl)pyridin-2(lH)-one (100 g, 0.27 moles), triethylamine (82.4 g, 0.81 moles), and potassium iodide (4.4 g, 0.026 moles) were added sequentially to a solution of (Z)-ethyl 2-chloro-2-(2-(4-methoxyphenyl)hydrazono acetate (83.6 g, 0.33 moles) in ethyl acetate (2000 ml) at 25-35 °C. The reaction mass temperature was raised to reflux. After completion of the reaction, mass was cooled to 0-5 °C and 6.0 N hydrochloric acid (180 ml) was added slowly. Stirring of reaction mass was continued at 25-35 °C. After completion of the reaction, the organic phase was separated and the aqueous phase was extracted with ethyl acetate (300 ml). The combined organic phase were washed with water (500 ml) followed by a saturated sodium chloride solution (500 ml). The organic layer was concentrated under vacuum and crystalized with ethanol to afford ethyl l-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-l-yl)phenyl)- 4,5,6,7-tetrahydro-lH-pyrazolo[3,4-c]pyridin-3-carboxylate.

Example 6: Preparation of l-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-l-yl) phenyl)-4,5,6,7- tetra-hydro-lH-pyrazolo [3, 4-c] pyridine-3-carboxamide (apixaban)

Ethyl l-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-l-yl)phenyl)-4, 5,6,7-tetrahydro-lH- pyrazolo[3,4-c]pyridine-3-carboxylate and methanol (1500 ml) were added to a autoclave vessel, and the vessel was flushed with nitrogen. After feeding anhydrous ammonia gas (8.0 kg/cm^2 99.99%), the reaction mass temperature was raised to 45 °C and stirred. After completion of the reaction, the ammonia was vented to a scrubber. Thereafter, the reaction mass was cooled to 35 °C and concentrated under reduced pressure to dryness. Methylene dichloride (2000 ml) and ethyl acetate (2000 ml) were added to the concentrated mas and the contents were heated to 50 °C. The resulting mixture was cooled

to 25-35 °C and filtered to afford l-(4-methoxy-phenyl)-7-oxo-6-(4-(2-oxopiperidin-l-yl)phenyl)- 4,5,6,7-tetrahydro-lH-pyrazolo-[3,4-c]pyridine-3-carboxamide.

The obtained solid was recrystallized in a mixture of methanol (800 ml) and water (2400 ml) to produce apixaban.

Example 7: Preparation of (Z)-ethyl 2-chloro-2-(2-(4-methoxyphenyl) hydrazono) acetate.

Part-A

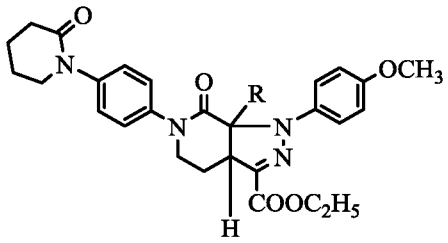
Hydrochloric acid (35% w/w, 229 g, 2.2 moles) was added to a solution of 4-methoxyaniline (100 g, 0.81 moles) in water (320 ml) at 0-5 °C. Sodium nitrite (67.6 g, 0.98 moles) was added slowly to the reaction mixture at -5 to 0 °C and stirred for -30 min at the same temperature.

Part-B

Water (320 ml) and sodium acetate (153.2 g 1.86 moles) were added sequentially to a solution of ethyl 2-chloroacetoacetate (134.26 g, 0.82 moles) in ethyl acetate (650 ml). The resulting mixture was cooled to 0-5 °C and stirred for 1 hour. The solution prepared in Part-A was added slowly over a period of 1 hour at 0-5 °C. Thereafter, reaction mass temperature was raised to 25-30 °C and stirred for 1 hour. The organic layer was separated and aqueous phase was extracted with ethyl acetate (350 ml). The combined organic layers were washed with water (500 ml) and concentrated. Finally, the obtained concentrated mass was crystalized in ethanol/water to afford (Z)-ethyl 2-chloro-2-(2-(4-methoxyphenyl) hydrazono) acetate.

CLAIMS:

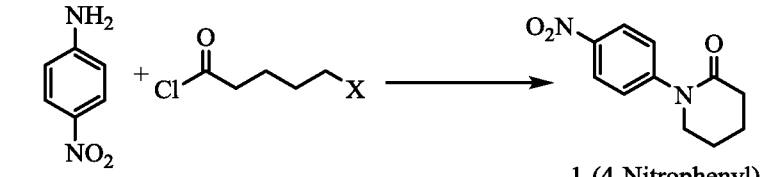
1. A compound of formula::



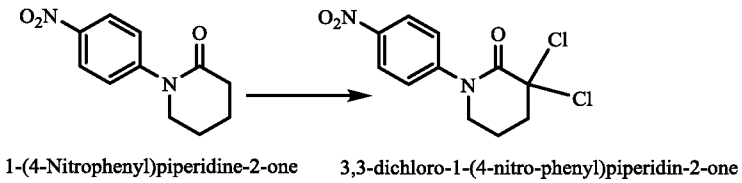
where R is selected from the group consisting of N-methyl piperazine, N-ethyl piperazine, l-(2-pyrimidinyl) piperazine, l-(2-pyridyl) piperazine, and benzyl piperazine.

2. A process for the preparation of apixaban, comprising the steps of:

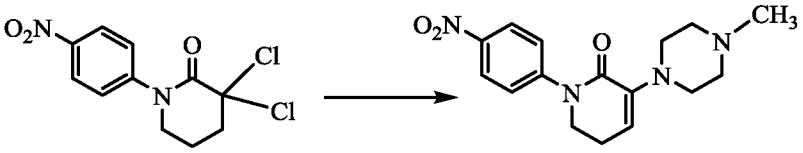
a. treating 4-nitroaniline with 5-chloropentanoyl halide in the presence of a first base to obtain l-(4-nitrophenyl)piperdin-2-one, wherein X is chlorine or bromine;



b. converting l-(4-nitrophenyl)piperdin-2-one to 3,3-dichloro010(4-nitro-phenyl)piperidin-2-one;

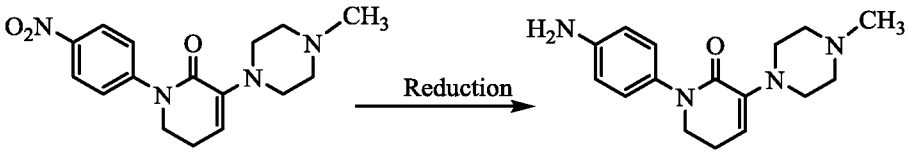


c. treating 3,3-dichloro-l-(4-nitro-phenyl)piperidin-2-one with a piperazine derivative to obtain Formula A;



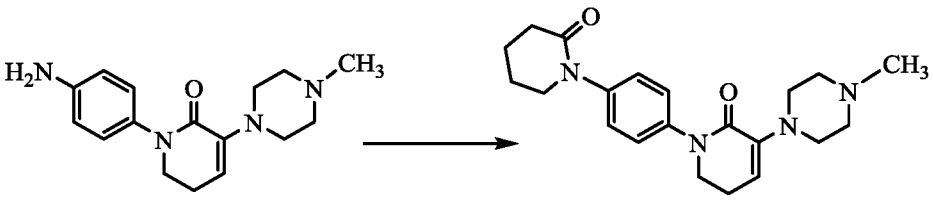
3,3-dichloro-l-(4-nitro-phenyl)piperidin-2-one **Formula A**

d. reducing Formula A to obtain Formula B with a reducing agent;



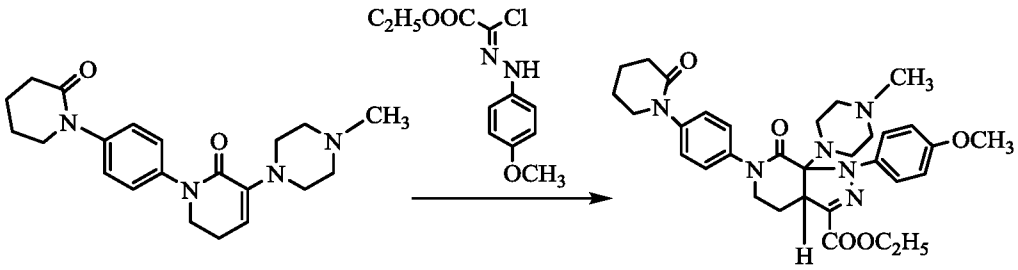
Formula A **Formula B**

e. converting Formula B to Formula C in the presence of a second base;



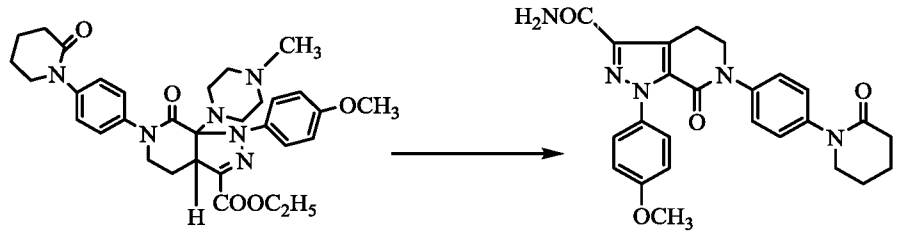
Formula B **Formula C**

f. treating Formula C with Z-ethyl-2-chloro-2-[2-(4-methoxyphenyl)hydrazono] acetate in the presence of a third base to obtain Formula D; and



Formula C **Formula D**

g. converting Formula D to apixaban



Formula D Apixaban

3. The process according to claim 2, further comprising purifying apixaban after converting the Formula D to apixaban.

4. The process according to claim 2, wherein the first base and the second base are independently selected from the group consisting of methylamine, ethylamine, dimethylamine, triethylamine, trimethylamine, and isopropylethylamine.

5. The process according to claim 2, wherein the piperazine derivative is N-methylpiperazine, N-ethylpiperazine, l-(2-pyramidyl)piperazine, l-(2-pyridyl)piperazine, or benzyl piperazine.

6. The process according to claim 2, wherein the reducing agent is selected from sodium sulfide or Raney nickel.

7. The process according to claim 2, wherein the third base is an organic base or an inorganic base.

8. The process according to claim 6, where the organic base is selected from the group consisting of pyridine, piperidine, N-methyl morpholine, N-methylpiperidine, N-phenylpiperidine, and an alkyl amine.

9. The process according to claim 8, wherein the alkyl amine is selected from the group consisting of diethylamine, triethyl amine, di-isopropylethylamine, and diphenylamine.

10. The process according to claim 7, where the inorganic base is selected from the group consisting of potassium hydroxide, sodium hydroxide, potassium carbonate, and sodium carbonate.

11. The process according to claim 2, wherein R is N-methylpiperazine.

12. The process according to claim 3, further comprising the steps of:

h. dissolving apixaban in a solvent; and

i. isolating substantially pure apixaban,

after step g.

13. The process according to claim 12, wherein the solvent is selected from the group consisting of methanol, ethanol, isopropyl alcohol, water, and mixtures thereof.

14. The process according to claim 12, where the isolation step is carried out by filtration, distillation, spray drying, or tray drying.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2015/052894

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/04
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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2014/044107 A1 (SHANGHAI HENGRUI PHARM CO LTD [CN] ; JIANGSU HENGRUI MEDICINE CO [CN]) 27 March 2014 (2014-03-27) page 11	1-14
X	XING, J. ET AL: "Synthesis and factor Xa inhibitory activity of apixaban derivatives", JOURNAL OF CHINA PHARMACEUTICAL UNIVERSITY, vol. 44, no. 4, 15 April 2013 (2013-04-15) , pages 289-295 , XP002740642 , page 291	1-14
X,P	CN 103 923 079 A (SHENYANG J & HEALTH PHARAMACEUTICAL CO LTD) 16 July 2014 (2014-07-16) page 8	1-14

☐ 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" documentwhich may throw doubts on priority claim(s) orwhich 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
9 June 2015	19/08/2015

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Baston , Eckhard

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2015/052894

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2014044107 A1	27-03-2014	CN 104039788 A	10-09-2014
		WO 2014044107 A1	27-03-2014
		WO 2014044113 A1	27-03-2014
CN 103923079 A	16-07-2014	NONE	