



(51) International Patent Classification:

C07D 471/04 (2006.01) C07D 231/00 (2006.01)

C07D 201/08 (2006.01) C07D 471/02 (2006.01)

(21) International Application Number:

PCT/IB2017/053183

(22) International Filing Date:

30 May 2017 (30.05.2017)

(25) Filing Language:

English

(26) Publication Language:

English

(30) Priority Data:

201711007134 28 February 2017 (28.02.2017) IN

(71) Applicant: SUN PHARMACEUTICAL INDUSTRIES

LIMITED [IN/IN]; Sun House, Plot No. 201 B/1, Western Express Highway, Goregaon (E), Mumbai, Maharashtra 400 063 (IN).

(72) Inventors: SINGH, Pankaj Kumar; 35/FF, Street F4,

Vatika Road, Gurgaon, Haryana 122004 (IN). MADHRA, Mukesh Kumar; House No. 1036, Sector-06, Urban Estates, Karnal, Haryana 132001 (IN). PRASAD, Mohan; D-50, Green Woods City, Sector 46, Gurgaon, Haryana 122003 (IN).

(81) Designated States (unless otherwise indicated, for every

kind of national protection available): AE, AG, AL, AM, AO, AT, AU, AZ, BA, BB, BG, BH, BN, BR, BW, BY, BZ, CA, CH, CL, CN, CO, CR, CU, CZ, DE, DJ, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IR, IS, JP, KE, KG, KH, KN, KP, KR, KW, KZ, LA, LC, LK, LR, LS, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PA, PE, PG, PH, PL, PT, QA, RO, RS, RU, RW, SA, SC, SD, SE, SG, SK, SL, SM, ST, SV, SY, TH, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every

kind of regional protection available): ARIPO (BW, GH, GM, KE, LR, LS, MW, MZ, NA, RW, SD, SL, ST, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, RU, TJ, TM), European (AL, AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HR, HU, IE, IS, IT, LT, LU, LV, MC, MK, MT, NL, NO, PL, PT, RO, RS, SE, SI, SK, SM, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, KM, ML, MR, NE, SN, TD, TG).

Published:

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

(54) Title: PREPARATION OF ACTIVE PHARMACEUTICAL INGREDIENTS AND INTERMEDIATES THEREOF

(57) Abstract: The present invention provides processes for the preparation of active pharmaceutical ingredients and intermediates thereof in an aqueous designer smart surfactant solution.



PREPARATION OF ACTIVE PHARMACEUTICAL INGREDIENTS AND INTERMEDIATES THEREOF

Field of the Invention

The present invention provides processes for the preparation of active
5 pharmaceutical ingredients and intermediates thereof in an aqueous designer smart
surfactant solution.

Background of the Invention

Most pharmaceutical compounds are synthesized using organic solvents as the
reaction medium and as extraction solvents. This is due to the solubility of most of the
10 organic substrates, reagents, and catalysts in organic solvents. Thus, organic solvents
make up most of the organic waste created during synthesis. In view of growing concerns
over Environmental Health and Safety (EHS) and stringent rules regulating the use and
disposal of organic solvents, there is a need for developing non-hazardous alternatives for
synthesizing pharmaceutical compounds. A way forward in this regard is to use water as a
15 solvent instead of organic solvents, as this will radically reduce the use of organic
solvents. However, the use of water as a solvent is in itself limited due to the insolubility
of most of the organic substrates in water, and in most of the cases, either the reaction does
not take place at all, or the reaction yield is low. The use of conventional surfactants such
as sodium dodecylsulfate, cetyltrimethylammonium chloride, dodecyltrimethylammonium
20 chloride, and sodium dodecyl benzene sulphonate for increasing the solubility of organic
substrates in water is described in *Green Chem.*, 2015, 17, 644–683. Although the use of
such conventional surfactants increases the solubility of organic substrates in water by
lowering the interfacial tension between the substrate and water, they often disperse the
reactants resulting in slow reaction rates. Thus, there exists a need in the art for
25 developing faster and high yielding processes for the synthesis of active pharmaceutical
ingredients and intermediates thereof using water as the solvent. U.S. Patent No.
8,785,665; *Green Chem.*, 2016, 18, 14–19; and *Green Chem.*, 2015, 17, 644–683, in
general, describe the use of specifically designed aqueous, designer smart surfactant
solutions developed by Lipshutz and coworkers for carrying out various chemical
30 reactions, without providing specific examples of any active pharmaceutical ingredients.

The present invention provides the use of an aqueous designer smart surfactant
solution for synthesizing active pharmaceutical ingredients and intermediates thereof.

Summary of the Invention

The present invention provides ecofriendly, cost-effective, and industrially advantageous process for the preparation of active pharmaceutical ingredients and intermediates thereof using an aqueous designer smart surfactant solution. The designer smart surfactants used in the processes of the present invention differ from conventional surfactants in that the former have specifically engineered functional groups that generate micelles of appropriate size and shape so as to enhance the reaction rate.

Specifically, the present invention provides the use of an aqueous designer smart surfactant solution for carrying out a wide range of organic reactions selected from carbon-carbon coupling, amide synthesis, nitro reduction, Knoevenagel reaction, ester hydrolysis, amination of alcohols, oxidation of alcohols, aza lactone formation, Suzuki-Miyaura coupling, silylation, C-H activation, Negishi coupling, Buchwald-Hartwig amination, benzylic couplings, Pd-catalyzed couplings, Zn-mediated coupling, Heck coupling, CuH-catalyzed asymmetric hydrosilylation, Sonogashira coupling, borylation of aryl halides, aerobic oxidation in nanomicelles of aryl alkynes, asymmetric 1,4-additions, aldol condensation, nucleophilic aromatic substitution reactions, olefin metathesis, allylic aminations, transition metal catalyzed organic reactions, N-arylation and N-alkylation, O-alkylation of aromatic and aliphatic alcohols, reductive amination, asymmetric reduction of ketones, Diels-Alder reaction, and ring-closing metathesis.

More specifically, the present invention provides the use of an aqueous designer smart surfactant solution for preparing active pharmaceutical ingredients selected from those used as antidiabetics; antibiotics; antimicrobials; analgesics; anti-allergics; anti-asthmatics; anticancer drugs; CNS drugs such as antidepressants, anti-anxiety drugs, anti-Parkinson's drugs, antiepileptics and neuroleptic drugs; cardiovascular drugs such as diuretics, hypolipidemics, antiarrhythmics, vasodilators, anti-anginals, and antihypertensives; sympathomimetics; antiemetics; anti-inflammatory drugs; anti-histaminic drugs; antitussives; antivirals; antimigraine drugs; immunosuppressants; cholinomimetic drugs; adrenergic drugs; antimuscarinic drugs; antispasmodic drugs; skeletal muscle relaxants; expectorants, dermatological drugs; drugs for treating attention deficit hyperactive disorders (ADHD); and drugs for treating gastrointestinal disorders.

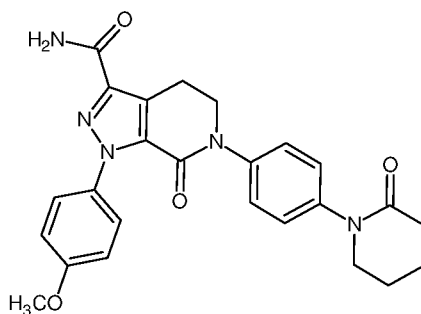
Most specifically, the present invention provides the use of an aqueous designer smart surfactant solution for preparing apixaban and intermediates thereof.

Detailed Description of the Invention

A first aspect of the present invention provides the use of an aqueous designer smart surfactant solution for carrying out organic reactions selected from C-C coupling, amide synthesis, ester hydrolysis, amination of alcohols, oxidation of alcohols, aza lactone formation, Suzuki–Miyaura coupling, silylation, C-H activation, Negishi coupling, 5 Buchwald-Hartwig amination, benzylic couplings, Pd-catalyzed couplings, Zn-mediated coupling, Heck coupling, CuH-catalyzed asymmetric hydrosilylation, Sonogashira coupling, borylation of aryl halides, aerobic oxidation in nanomicelles of aryl alkynes, asymmetric 1,4-additions, aldol condensation, nucleophilic aromatic substitution reactions, 10 olefin metathesis, allylic aminations, transition metal catalyzed organic reactions, N-arylation and N-alkylation, O-alkylation of aromatic and aliphatic alcohols, reductive amination, asymmetric reduction of ketones, Diels-Alder reaction, and ring-closing metathesis.

A second aspect of the present invention provides the use of an aqueous designer 15 smart surfactant solution for preparing active pharmaceutical ingredients selected from those used as antidiabetics; antibiotics; antimicrobials; analgesics; anti-allergics; anti-asthmatics; anticancer drugs; CNS drugs such as antidepressants, antianxiety drugs, anti-Parkinson's drugs, antiepileptics and neuroleptic drugs; cardiovascular drugs such as diuretics, hypolipidemics, antiarrhythmics, vasodilators, anti-anginals, and 20 antihypertensives; sympathomimetics; antiemetics; anti-inflammatory drugs; anti-histaminic drugs; antitussives; antivirals; antimigraine drugs; immunosuppressants; cholinomimetic drugs; adrenergic drugs; antimuscarinic drugs; antispasmodic drugs; skeletal muscle relaxants; expectorants; dermatological drugs; drugs for treating attention deficit hyperactive disorders (ADHD); and drugs for treating gastrointestinal disorders.

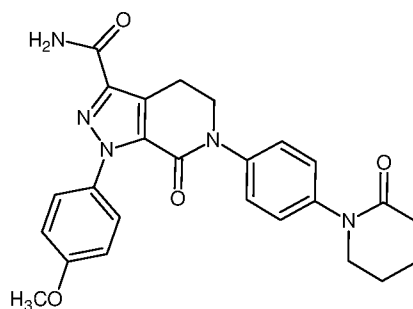
25 A third aspect of the present invention provides the use of an aqueous designer smart surfactant solution for preparing apixaban of Formula I



Formula I

and intermediates thereof.

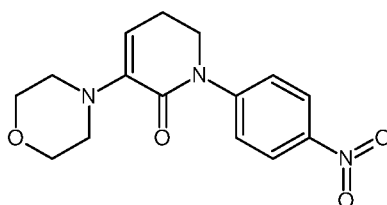
A fourth aspect of the present invention provides a process for preparing apixaban of Formula I



Formula I

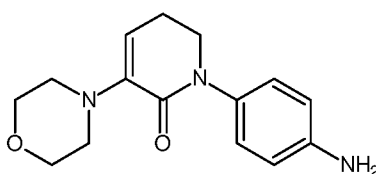
comprising:

- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II



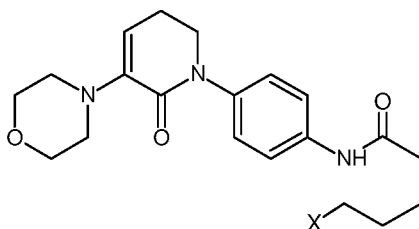
Formula II

to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;

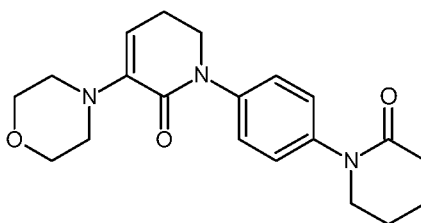


Formula III

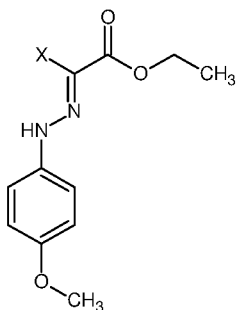
- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;

**Formula IV** (wherein X = halogen)

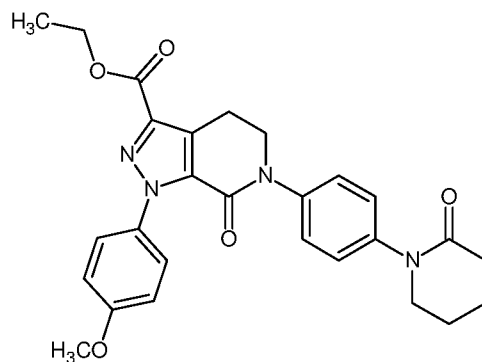
- iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;

**Formula V**

- iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI

**Formula VI** (wherein X = halogen)

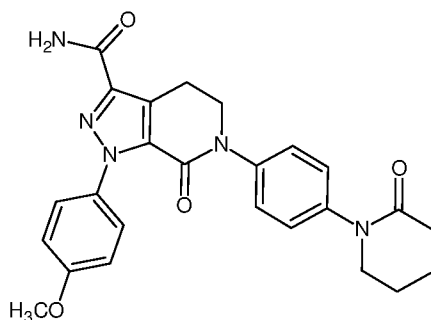
to obtain ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII; and

**Formula VII**

v) amidating 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 of
 5 Formula VII to obtain apixaban of Formula I,

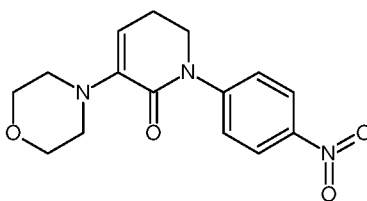
wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

A fifth aspect of the present invention provides a process for preparing apixaban of
 Formula I

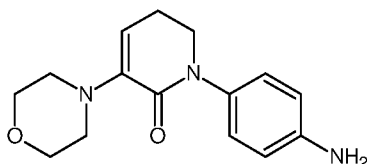
**Formula I**

comprising:

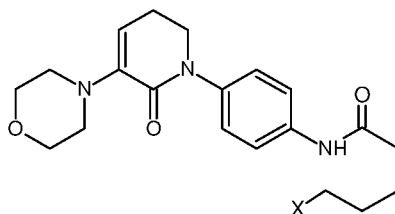
i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

**Formula II**

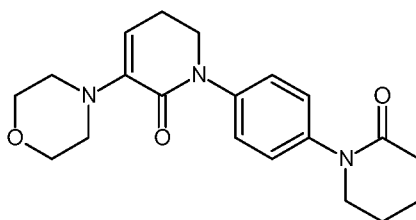
to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of
 Formula III;

**Formula III**

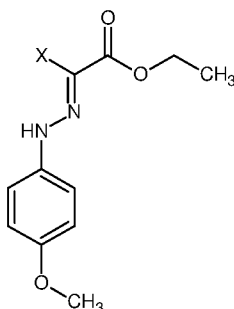
ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;

**Formula IV** (wherein X = halogen)

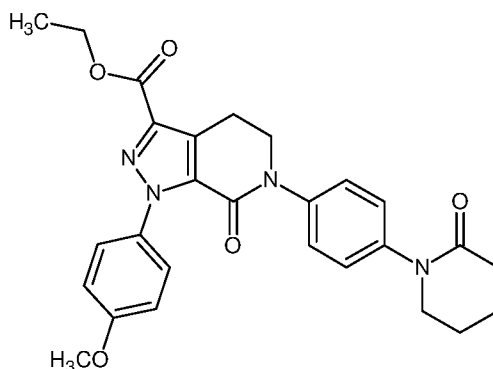
iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl} pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;

**Formula V**

iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl) hydrazinylidene]ethanoate of Formula VI

**Formula VI** (wherein X = halogen)

to obtain 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 of Formula VII; and

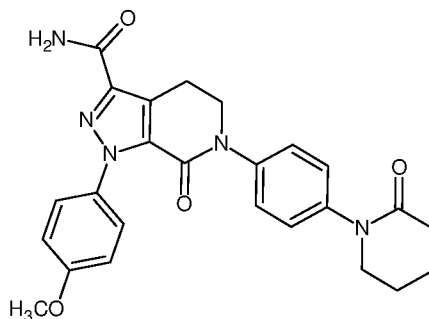


Formula VII

- 5 v) amidating 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 of Formula VII to obtain apixaban of Formula I,

wherein steps i) to iv) are carried out in an aqueous designer smart surfactant solution.

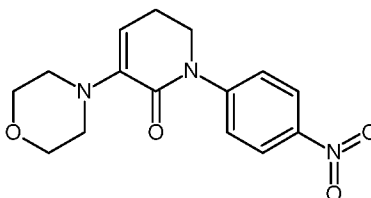
A sixth aspect of the present invention provides a process for preparing apixaban
10 of Formula I



Formula I

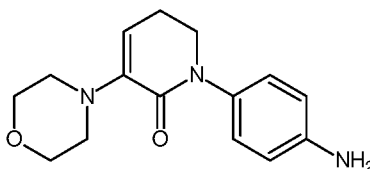
comprising:

- 15 i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II



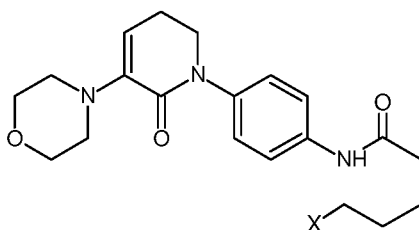
Formula II

to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;



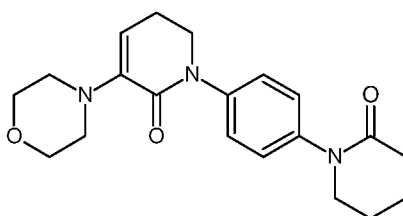
Formula III

- 5 ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;



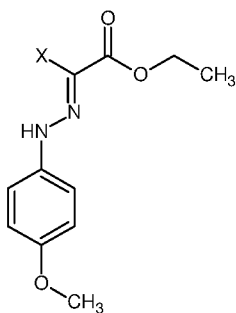
Formula IV (wherein X = halogen)

- 10 iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl} pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;

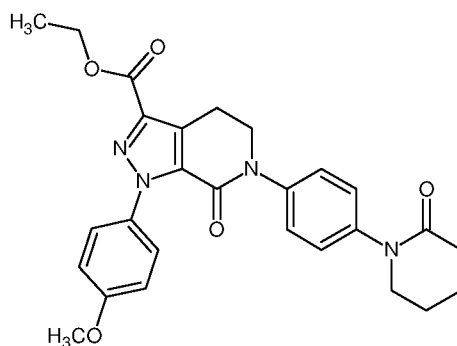


Formula V

- 15 iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl) hydrazinylidene]ethanoate of Formula VI

**Formula VI** (wherein X = halogen)

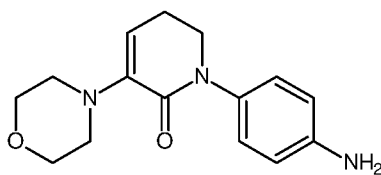
to obtain ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII; and

**Formula VII**

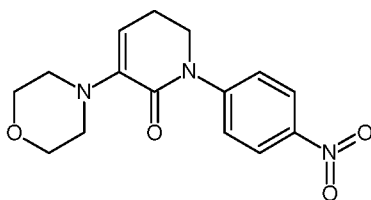
v) amidating ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII to obtain apixaban of Formula I,

wherein steps i) to v) are carried out in an aqueous designer smart surfactant solution.

A seventh aspect of the present invention provides a process for preparing 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III

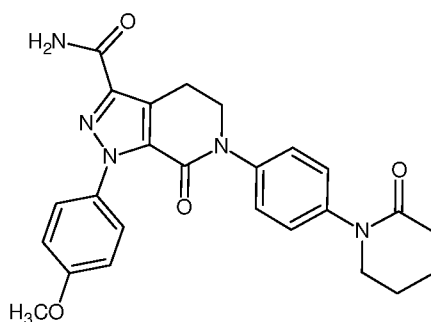
**Formula III**

comprising reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

**Formula II**

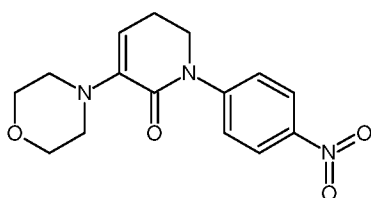
in the presence of a reducing agent in an aqueous designer smart surfactant solution.

An eighth aspect of the present invention provides a process for preparing
 5 apixaban of Formula I

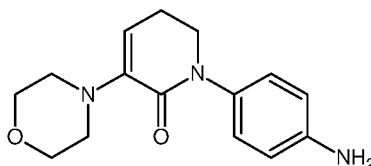
**Formula I**

comprising:

- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-
 10 one of Formula II

**Formula II**

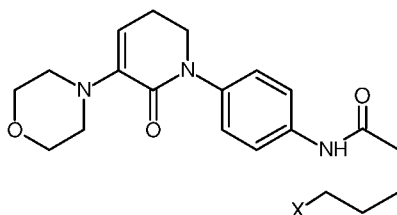
- in the presence of a reducing agent in an aqueous designer smart surfactant
 solution to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-
 15 2(1H)-one of Formula III; and

**Formula III**

- ii) converting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III into apixaban of Formula I.

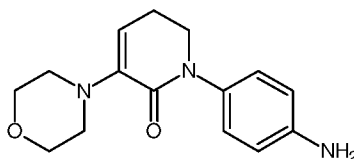
A ninth aspect of the present invention provides a process for preparing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of

5 Formula IV



Formula IV (wherein X = halogen)

comprising reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III

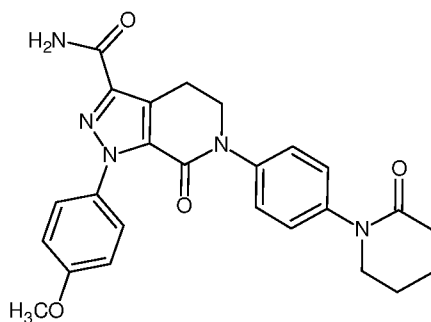


10

Formula III

with 5-halovaleryl halide in an aqueous designer smart surfactant solution.

A tenth aspect of the present invention provides a process for preparing apixaban of Formula I

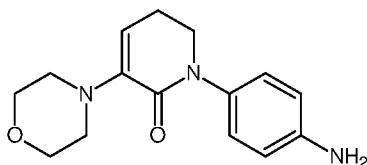


15

Formula I

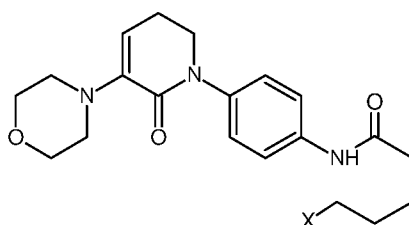
comprising:

- i) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III



Formula III

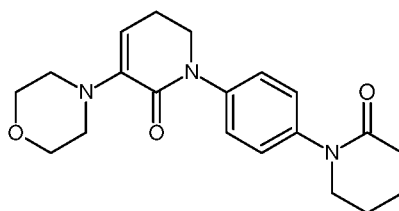
- 5 with 5-halovaleryl halide in an aqueous designer smart surfactant solution to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and



Formula IV (wherein X = halogen)

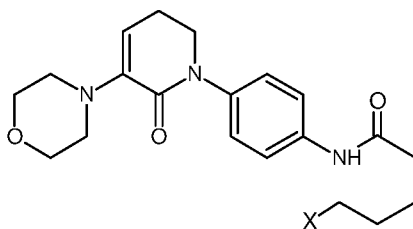
- 10 ii) converting 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV into apixaban of Formula I.

An eleventh aspect of the present invention provides a process for the preparation of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V



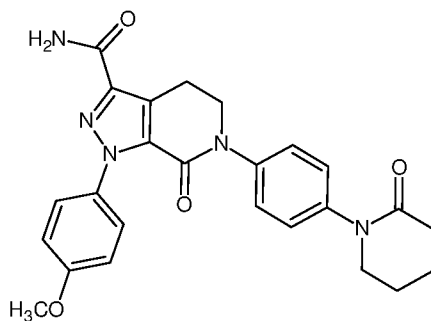
Formula V

comprising cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl} pentanamide of Formula IV

**Formula IV** (wherein X = halogen)

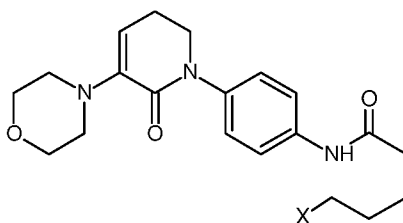
in an aqueous designer smart surfactant solution.

A twelfth aspect of the present invention provides a process for preparing apixaban
5 of Formula I

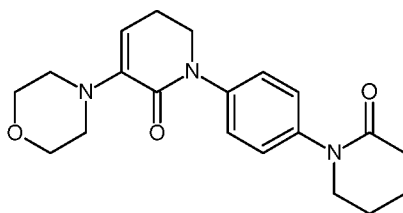
**Formula I**

comprising:

- i) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-
10 1(2H)-yl]phenyl} pentanamide of Formula IV

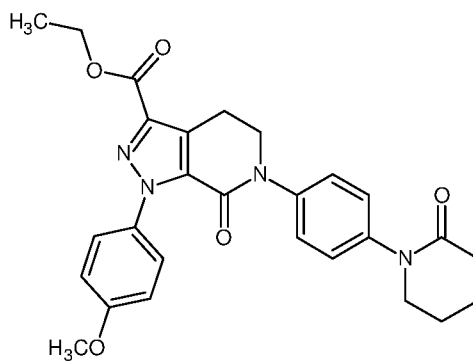
**Formula IV** (wherein X = halogen)

in an aqueous designer smart surfactant solution to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V; and

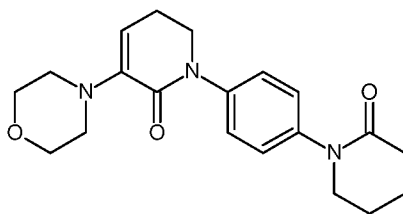
**Formula V**

- ii) converting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V into apixaban of Formula I.

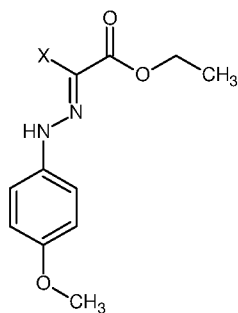
5 A thirteenth aspect of the present invention provides a process for the preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII

**Formula VII**

- 10 comprising reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V

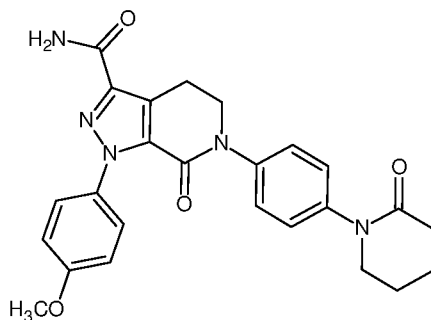
**Formula V**

with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI

**Formula VI** (wherein X = halogen)

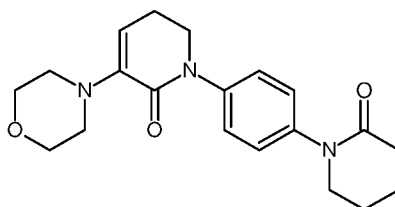
in an aqueous designer smart surfactant solution.

A fourteenth aspect of the present invention provides a process for preparing
 5 apixaban of Formula I

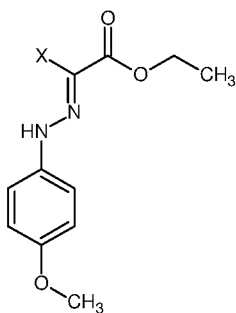
**Formula I**

comprising:

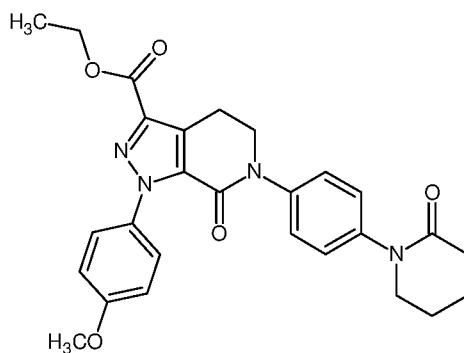
i) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-
 10 dihydropyridin-2(1H)-one of Formula V

**Formula V**

with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula
 VI

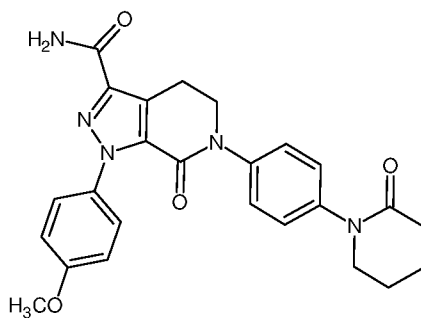
**Formula VI** (wherein X = halogen)

in an aqueous designer smart surfactant solution to obtain 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 of Formula VII; and

**Formula VII**

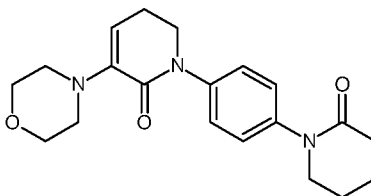
ii) converting ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII into apixaban of Formula I.

A fifteenth aspect of the present invention provides a one pot process for the preparation of apixaban of Formula I

**Formula I**

using aqueous designer smart surfactant solution.

A sixteenth aspect of the present invention provides a process for preparing 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V

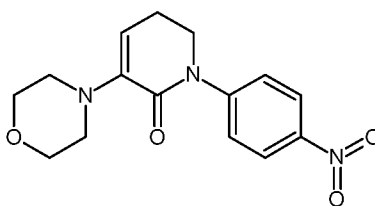


5

Formula V

comprising:

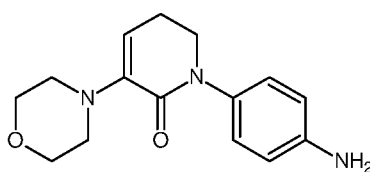
- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II



10

Formula II

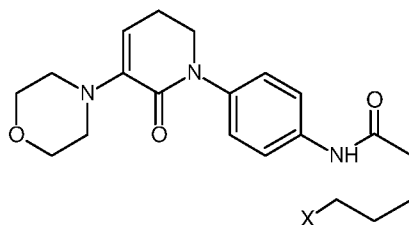
to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;



15

Formula III

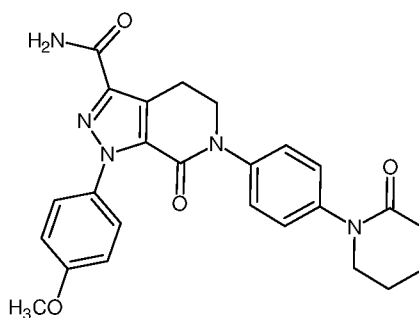
- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and

**Formula IV** (wherein X = halogen)

- iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V,

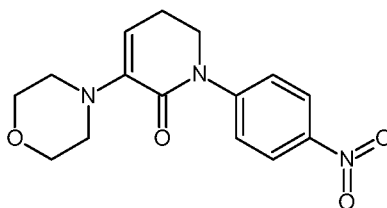
wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

A seventeenth aspect of the present invention provides a process for apixaban of Formula I

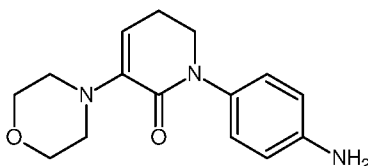
**Formula I**

comprising:

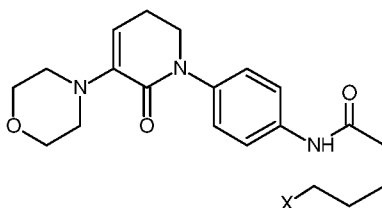
- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

**Formula II**

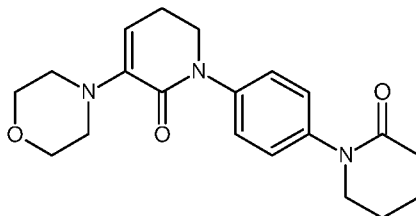
to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;

**Formula III**

- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and

**Formula IV** (wherein X = halogen)

- iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V; and

**Formula V**

- iv) converting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V into apixaban of Formula I, wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

The term “about,” as used herein, refers to any value which lies within the range defined by a number up to $\pm 10\%$ of the value.

The term “ambient temperature,” as used herein, refers to the temperature in the range of about 20°C to about 35°C .

- The term “halogen”, as used herein, refers to fluorine, chlorine, bromine, or iodine.

The term “pure,” as used herein, refers to an active pharmaceutical ingredient or an intermediate thereof having a high performance liquid chromatographic (HPLC) purity of greater than or equal to about 80%. In an embodiment of the present invention, the HPLC purity is greater than or equal to about 90%. In another embodiment of the present
5 invention, the HPLC purity is greater than or equal to about 99%.

The term “surfactant,” as used herein, refers to a surface active agent or a mixture of agents that lower the interfacial tension between a solid and a liquid, or two liquids.

The term “designer smart surfactant,” as used herein, refers to specially designed nonionic surfactants such as those disclosed in U.S. Patent No. 8,785,665; *Green Chem.*,
10 2016, 18, 14–19; and *Green Chem.*, 2015, 17, 644–683.

Examples of aqueous designer smart surfactant solutions include PTS, TPGS-750M, SPGS-550M (Nok), Triton® X-100, Tergitol® TMN-6, Tergitol® 15S40, Tergitol® 15S7, Brij®-35, Tween® 80, and PTS-7.

Examples of organic reactions include C-C coupling, amide synthesis, ester
15 hydrolysis, amination of alcohols, oxidation of alcohols, aza lactone formation, Suzuki–Miyaura coupling, silylation, C-H activation, Negishi coupling, Buchwald-Hartwig amination, benzylic couplings, Pd-catalyzed couplings, Zn-mediated coupling, Heck coupling, CuH-catalyzed asymmetric hydrosilylation, Sonogashira coupling, borylation of aryl halides, aerobic oxidation in nanomicelles of aryl alkynes, asymmetric 1,4-additions,
20 aldol condensation, nucleophilic aromatic substitution reactions, olefin metathesis, allylic aminations, transition metal catalyzed organic reactions, N-arylation and N-alkylation, O-alkylation of aromatic and aliphatic alcohols, reductive amination, asymmetric reduction of ketones, Diels-Alder reaction, and ring-closing metathesis.

The term “active pharmaceutical ingredient,” as used herein, refers to a substance
25 used in a finished pharmaceutical product (FPP) intended to furnish pharmacological activity or to otherwise have direct effect in the diagnosis, cure, mitigation, treatment, or prevention of a disease, or to have direct effect in restoring, correcting or modifying physiological functions in human beings. The active pharmaceutical ingredient may be present in the form of a free base or a pharmaceutically acceptable salt thereof.
30 Polymorphs and solvates of the active pharmaceutical ingredient(s) are also included within the scope of the present invention.

Examples of active pharmaceutical ingredient(s) include those used as antidiabetics; antibiotics; antimicrobials; analgesics; anti-allergics; anti-asthmatics; anticancer drugs; CNS drugs such as antidepressants, anti-anxiety drugs, anti-Parkinson's drugs, antiepileptics and neuroleptic drugs; cardiovascular drugs such as diuretics, hypolipidemics, antiarrhythmics, vasodilators, anti-anginals, and antihypertensives; 5 sympathomimetics; antiemetics; anti-inflammatory drugs; anti-histaminic drugs; antitussives; antivirals; antimigraine drugs; immunosuppressants; cholinomimetic drugs; adrenergic drugs; antimuscarinic drugs; antispasmodic drugs; skeletal muscle relaxants; expectorants, dermatological drugs; drugs for treating attention deficit hyperactive disorders; and drugs for treating gastrointestinal disorders. 10

Some specific examples of active pharmaceutical ingredient include apixaban, rivaroxaban, edoxaban, dabigatran etexilate, eluxadoline, canagliflozin, dapagliflozin, empagliflozin, pazopanib, fexofenadine, febuxostat, ciprofloxacin, amoxicillin, moxifloxacin, valacyclovir, valganciclovir, acyclovir, ganciclovir, asenapine, abiraterone, 15 ambrisentan, palbociclib, linagliptin, vildagliptin, sitagliptin, alogliptin, saxagliptin, omarigliptin, liraglutide, losartan, irbesartan, eprosartan, valsartan, amantadine, sertraline, sevelamer, gabapentin, atorvastatin, mesalamine, orlistat, lansoprazole, pantoprazole, esomeprazole, sodium oxybate, loratadine, desloratadine, isotretinoin, tretinoin, acetretin, doxycycline, allantoin, pimavanserin, ivacaftor, venetoclax, ribociclib, masitinib, 20 baricitinib, sunitinib, sorafenib, ibrutinib, apremilast, ixazomib, tofacitinib, dolutegravir, sofosbuvir, rifaximin, and LCZ696.

The term "intermediate," as used herein, refers to an organic compound that is formed at any stage during the preparation of an active pharmaceutical ingredient.

The term "substrate," as used herein, refers to a material on which a process is 25 conducted. The term "substrate," may also be used interchangeably with the term "reagent" or "reactant".

The present invention provides processes for the preparation of apixaban of Formula I and intermediates thereof in an aqueous designer smart surfactant solution, without using any organic solvent.

30 The reduction of 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-

2(1H)-one of Formula III is carried out in the presence of a reducing agent in an aqueous designer smart surfactant solution.

Examples of reducing agents include sodium sulphide, sodium hydrosulphite, iron, ammonium chloride, zinc, tin (II) chloride, platinum oxide, Fe/NH₄Cl, Zn/NH₄Cl, formic acid in presence of a metal catalyst, pyridinium zinc complex, and trihalosilanes.

The reduction of 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II is carried out at ambient temperature to a temperature of about 70°C, for example, at a temperature of about 40°C to about 60°C.

The reduction of 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II is carried out for about 30 minutes to about 8 hours, for example, for about 1 hour to about 6 hours.

1-(4-Aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III may be isolated from the reaction mixture, or the reaction mixture may be carried out as such to the next step.

Isolation of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III may be accomplished by filtration, decantation, extraction, distillation, evaporation, precipitation, centrifugation, concentration, or a combination thereof, followed by optional washing with de-ionized water, and optional drying.

Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying.

The reaction of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide is carried out in the presence of a base in an aqueous designer smart surfactant solution.

Examples of 5-halovaleryl halides include 5-chlorovaleryl chloride, 5-bromovaleryl chloride, and 5-chlorovaleryl bromide.

Examples of bases include organic and inorganic bases selected from ethyl amine, ammonia, triethyl amine, N-methylmorpholine, isobutylamine, tributyl amine, diisopropyl amine, diisopropylethylamine, triisopropylamine, pyridine, 4-dimethylaminopyridine (DMAP), potassium tert-butoxide, 4-ethylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane, 2,6-di-tert-butyl-4-dimethylaminopyridine, lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate,

potassium carbonate, barium carbonate, sodium bicarbonate, magnesium bicarbonate, and potassium bicarbonate.

The reaction of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide is carried out at a temperature of about 0°C to about 50°C, for example, at a temperature of about 15°C to about 40°C.

The reaction of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide is carried out for about 15 minutes to about 4 hours, for example, for about 30 minutes to about 3 hours.

5-Halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV may be isolated from the reaction mixture, or the reaction mixture may be carried out as such to the next step.

Isolation of 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV may be accomplished by filtration, decantation, extraction, distillation, evaporation, precipitation, centrifugation, concentration, or a combination thereof, followed by optional washing with de-ionized water, and optional drying.

Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying.

The cyclization of 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V is carried out in the presence of a base and a catalyst in an aqueous designer smart surfactant solution.

Examples of bases include organic and inorganic bases selected from ethyl amine, ammonia, triethyl amine, N-methylmorpholine, isobutylamine, tributyl amine, diisopropyl amine, diisopropylethylamine, triisopropylamine, pyridine, 4-dimethylaminopyridine (DMAP), potassium tert-butoxide, 4-ethylmorpholine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane, 2,6-di-tert-butyl-4-dimethylaminopyridine, lithium hydroxide, sodium hydroxide, potassium hydroxide, barium hydroxide, sodium carbonate, potassium carbonate, barium carbonate, sodium bicarbonate, magnesium bicarbonate, and potassium bicarbonate.

Examples of catalysts include tetra butylammonium iodide, tetra butylammonium bromide, potassium iodide, and potassium bromide.

The cyclization of 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV is carried out at a temperature of about 15°C to about 60°C, for example, at about 20°C to about 40°C.

The cyclization of 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV is carried out for about 5 hours to about 15 hours, for example, for about 7 hours to about 12 hours.

3-(Morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V may be isolated from the reaction mixture, or the reaction mixture may be carried out as such to the next step.

Isolation of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V may be accomplished by filtration, decantation, extraction, distillation, evaporation, precipitation, centrifugation, concentration, or a combination thereof, followed by optional washing with de-ionized water, and optional drying.

Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying.

The reaction of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI to obtain 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 of Formula VII may be carried out in an aqueous designer smart surfactant solution.

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 of Formula VII may be isolated from the reaction mixture, or it may be carried out as such to the next step without isolation.

Isolation 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 of Formula VII may be accomplished by filtration, decantation, extraction, distillation, evaporation, precipitation,

centrifugation, concentration, or a combination thereof, followed by optional washing with de-ionized water, and optional drying.

Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying.

5 The amidation 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 of Formula VII to obtain apixaban of Formula I may be carried out in an aqueous designer smart surfactant solution.

10 The conversion of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V into apixaban of Formula I may be carried out by processes known in the art such as by the process disclosed in U.S. Patent No. 7,396,932, which is incorporated herein by reference at least for the disclosure of such a process.

15 Isolation of apixaban of Formula I may be accomplished by filtration, decantation, extraction, distillation, evaporation, precipitation, centrifugation, concentration, or a combination thereof, followed by optional washing with de-ionized water, and drying.

Drying may be carried out using any suitable method such as drying under reduced pressure, air drying, or vacuum tray drying.

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

Method

Chromatographic purity of the samples were determined by HPLC using an Agilent® 1200 Series HPLC system with G1322A Degasser, G1311A Quaternary pump, G1329A Autosampler and G1314B Detector.

25 The following examples are for illustrative purposes only and should not be construed as limiting the scope of the invention in any way.

EXAMPLES

Comparative Examples:

Example 1: Preparation of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one (Formula III) using an organic solvent

5 3-(Morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (100 g; Formula II) was added into a reaction vessel containing methanol (1500 mL) and water 1000 (mL). Sodium sulphide (120 g) was added. The reaction mixture was stirred at 45°C to 50°C. On completion, de-ionized water (100 mL) was added into the reaction mixture. The reaction mixture was cooled to 10°C to 15°C, and stirred for 1 hour. Dichloromethane
10 (700 mL) was added, and the reaction mixture was stirred for 10 minutes. The reaction mixture was allowed to settle for 10 minutes. Layers were separated and dichloromethane (500 mL) was added to the aqueous layer at 10°C to 20°C. The contents were stirred for 10 minutes, and then allowed to settle for 10 minutes. Layers were separated and dichloromethane (300 mL) was again added to the aqueous layer at 10°C to 20°C. The
15 contents were stirred for 10 minutes, and then allowed to settle for 10 minutes. Layers were separated. De-ionized water (300 mL) was added to the combined organic layers. The contents were stirred for 5 minutes and then allowed to settle for 10 minutes. The organic layer was evaporated under reduced pressure at a temperature not exceeding 40°C to obtain a residue. Dichloromethane (1000 mL) was added to the residue. The contents
20 were stirred for 15 minutes, and taken as such to the next step (water content at this stage should not be more than 0.15 % w/w).

Example 2: Preparation of 5-bromo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide (Formula IV; when X = Br) using an organic solvent

 The organic layer containing 1-(4-Aminophenyl)-3-(morpholin-4-yl)-5,6-
25 dihydropyridin-2(1H)-one (Formula III) obtained from Example 1 was cooled to -10°C to -5°C. Triethylamine (70 g) and 5-bromo valeryl chloride (72.6 g) were added at -10°C to 0°C over a period of 30 minutes. The reaction mixture was stirred for 30 minutes. After completion, de-ionized water (500 mL) was added at a temperature of not more than 30°C. The reaction mixture was stirred for 10 minutes, and then allowed to settle for 20 minutes.
30 The layers were separated and the organic layer was taken as such to the next step.

Example 3: Preparation of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one (Formula V) using an organic solvent

- The organic layer containing 5-bromo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide (Formula IV; when X = Br) obtained from
- 5 Example 2 was cooled to 0°C to 10°C. Aqueous potassium hydroxide solution (40 g potassium hydroxide in 100 mL water) was added. The reaction mixture was refluxed for 8 hours to 12 hours. On completion, the reaction mixture was cooled to 25°C to 30°C. De-ionized water (500 mL) was added. The reaction mixture was stirred for 15 minutes. The layers were separated. De-ionized water (500 mL) was added to the organic layer.
- 10 The reaction mixture was stirred for 15 minutes. The layers again were separated. The organic layer was dried under reduced pressure at a temperature of not more than 40°C to obtain the title compound.

HPLC Purity: 85.58%

15 Working Examples

Example 1: Preparation of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one (Formula III) in an aqueous designer smart surfactant solution

- 3-(Morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (10 g; Formula II) was added to a reaction vessel containing an aqueous solution of SPGS-550M
- 20 (20 mL, 2 wt. % in water) at ambient temperature. Sodium sulphide (20 g) was added. The reaction mixture was heated to 50°C to 55°C and stirred for 3 hours to 4 hours. The reaction mixture was cooled to ambient temperature. The reaction mixture was filtered, washed with de-ionized water (30 mL), and then dried in an air oven at 45°C to 50°C to obtain the title compound.

- 25 Yield: 94%

Example 2: Preparation of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one (Formula III) in an aqueous designer smart surfactant solution

- 3-(Morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (5 g; Formula II) was added to a reaction vessel containing an aqueous solution of Triton X 100 (2.5 g in
- 30 50 mL water) at ambient temperature. Sodium sulphide (10 g) was added. The reaction mixture was heated to 50°C to 55°C and stirred for 3 hours to 4 hours. The reaction

mixture was cooled to ambient temperature. The reaction mixture was filtered, washed with de-ionized water (30 mL), and then dried in an air oven at 45°C to 50°C to obtain the title compound.

Yield: 77%

5 Example 3: Preparation of 5-bromo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide (Formula IV; when X = Br) in an aqueous designer smart surfactant solution

1-(4-Aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one (4 g; Formula III) was added to a reaction vessel containing an aqueous solution of TPGS-750-M (2 wt. % in 40 mL water) at ambient temperature. The reaction mixture was cooled to 5°C to 10°C. N-methyl morpholine (4 g) was added followed by the slow addition of 5-bromovaleryl chloride (6 g) to the reaction mixture. The reaction mixture was stirred at ambient temperature for 1 hour to 2 hours. The reaction mixture was filtered, washed with de-ionized water (30 mL), and then dried in an air oven at 45°C to 50°C to obtain the title compound.

Yield: 80%

Example 4: Preparation of 5-bromo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide (Formula IV; when X = Br) in an aqueous designer smart surfactant solution

1-(4-Aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one (1 g; Formula III) was added to a reaction vessel containing an aqueous solution of TPGS-750-M (2 wt. % in 10 mL water) at ambient temperature. The reaction mixture was cooled to 5°C to 10°C. Triethylamine (0.923 g) was added into the reaction mixture followed by the slow addition of 5-bromovaleryl chloride (1.5 g). The reaction mixture was stirred at ambient temperature for 1 hour to 2 hours. The reaction mixture was filtered, washed with de-ionized water (30 mL), and then dried in an air oven at 45°C to 50°C to obtain the title compound.

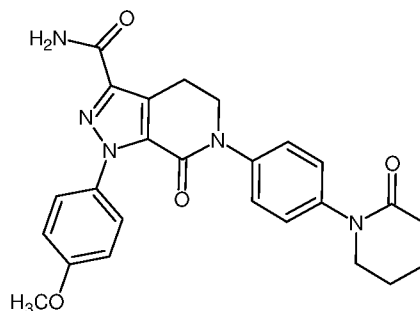
Yield: 64%

Example 5: Preparation of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one (Formula V) in an aqueous designer smart surfactant solution

- 5-Bromo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl} pentanamide (0.75 g; Formula IV when X = Br) was added to a reaction vessel containing
- 5 an aqueous solution of SPGS-550M (2 wt. % in 10 mL water) at ambient temperature. Potassium tert-butoxide (0.3 g) and potassium iodide (0.05 g) were added into the reaction mixture. The reaction mixture was stirred at 35°C to 40°C for 9 hours to 10 hours. The reaction mixture was filtered, washed with de-ionized water (10 mL), and then dried in an air oven at 45°C to 50°C to obtain the title compound.
- 10 Yield: 64%
- HPLC Purity: 94.12%

We claim:

- 1 1. Use of an aqueous designer smart surfactant solution for preparing apixaban of
- 2 Formula I

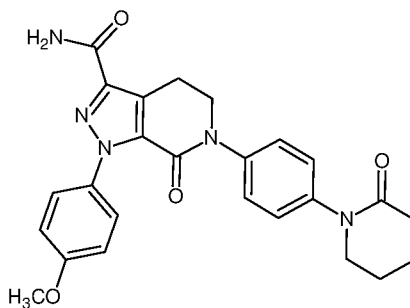


Formula I

and intermediates thereof.

- 1 2. The use according to the claim 1, wherein the aqueous designer smart surfactant
- 2 solution is selected from the group consisting of PTS, TPGS-750M, SPGS-550M (Nok),
- 3 Triton™ X-100, Tergitol® TMN-6, Tergitol® 15S40, Tergitol® 15S7, Brij®-35, Tween®
- 4 80, and PTS-7.

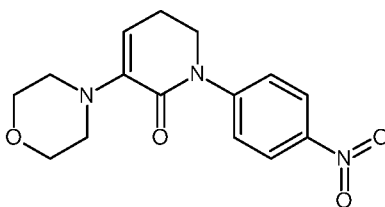
- 1 3. A process for preparing apixaban of Formula I



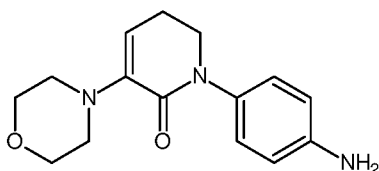
Formula I

comprising:

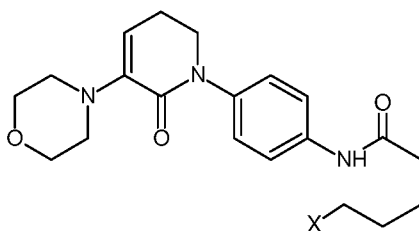
- 5 i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-
- 6 one of Formula II

**Formula II**

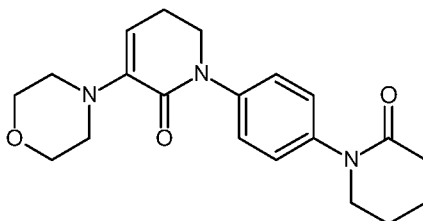
to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;

**Formula III**

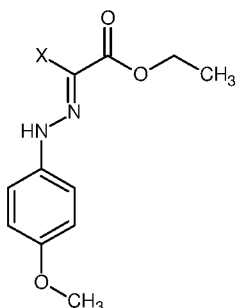
ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;

**Formula IV** (wherein X = halogen)

iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;

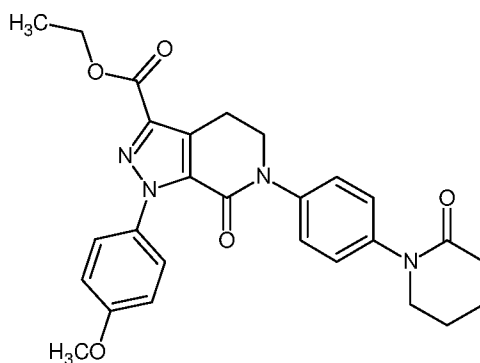
**Formula V**

iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI



Formula VI (wherein X = halogen)

to obtain 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 of Formula VII; and

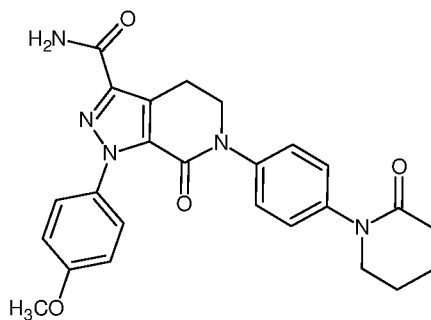


Formula VII

v) amidating 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 of Formula VII to obtain apixaban of Formula I,

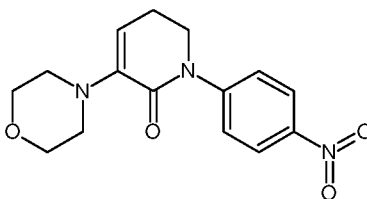
wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

4. A process for preparing apixaban of Formula I

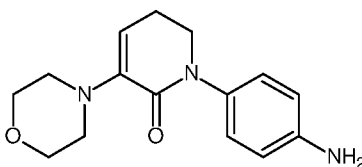
**Formula I**

comprising:

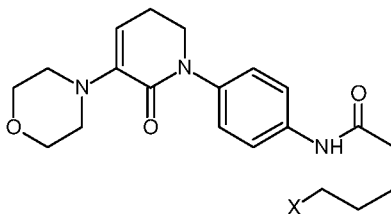
- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

**Formula II**

to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;

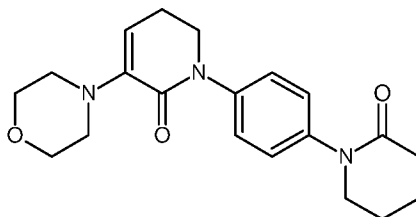
**Formula III**

- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;

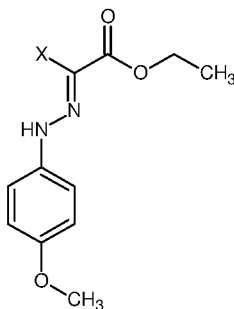


Formula IV (wherein X = halogen)

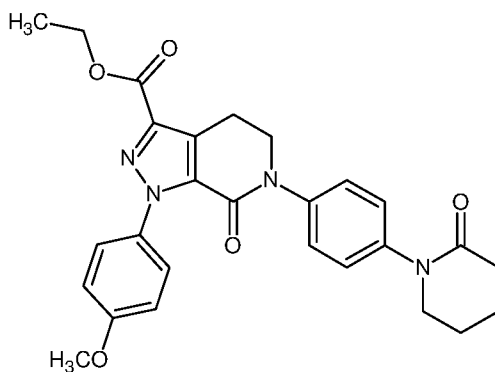
iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;

**Formula V**

iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI

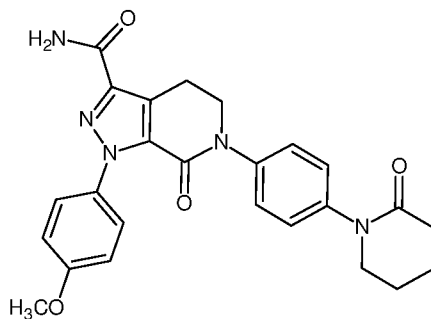
**Formula VI** (wherein X = halogen)

to obtain 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 of Formula VII; and

**Formula VII**

- 32 v) amidating ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-
 33 yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of
 34 Formula VII to obtain apixaban of Formula I,
 35 wherein steps i) to- iv) are carried out in an aqueous designer smart surfactant solution.

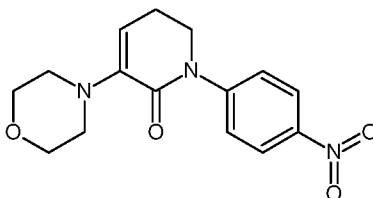
1 5. A process for preparing apixaban of Formula I



2
3 **Formula I**

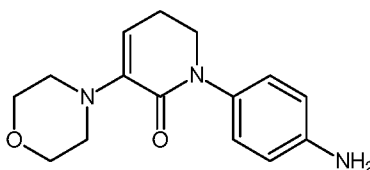
4 comprising:

- 5 i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-
 6 one of Formula II



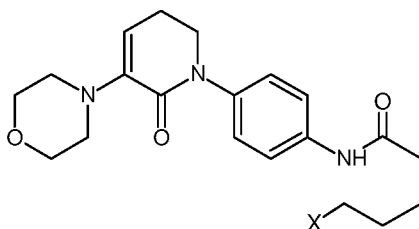
7
8 **Formula II**

9 to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of
 10 Formula III;



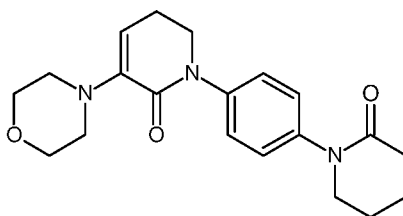
11
12 **Formula III**

- 13 ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-
 14 one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-
 15 4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV;



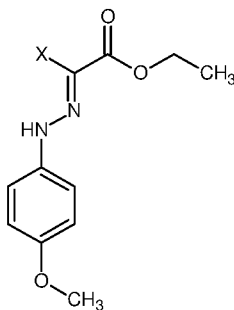
Formula IV (wherein X = halogen)

iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V;



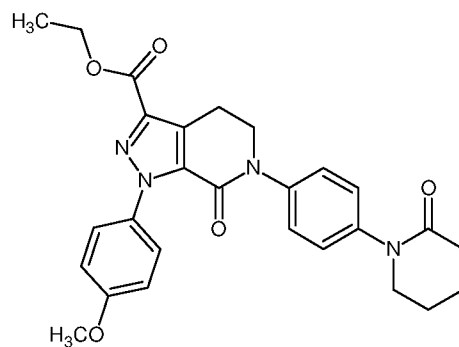
Formula V

iv) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI



Formula VI (wherein X = halogen)

to obtain 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 of Formula VII; and

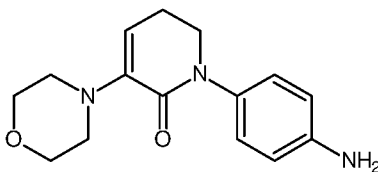


Formula VII

v) amidating 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 of Formula VII to obtain apixaban of Formula I,

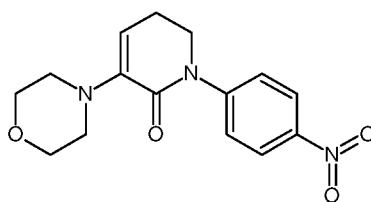
wherein steps i) to v) are carried out in an aqueous designer smart surfactant solution.

6. A process for preparing 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III



Formula III

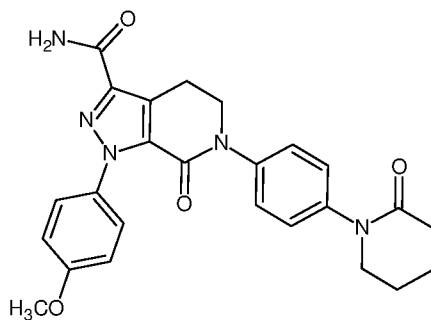
comprising reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II



Formula II

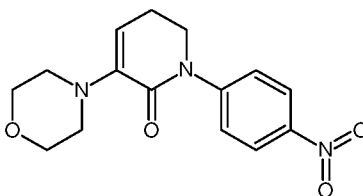
in the presence of a reducing agent in an aqueous designer smart surfactant solution.

7. A process for preparing apixaban of Formula I

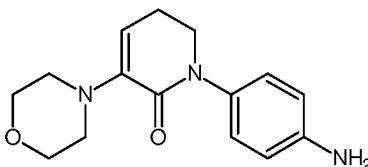
**Formula I**

comprising:

- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

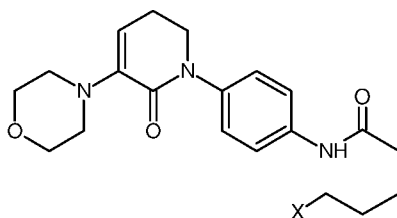
**Formula II**

in the presence of a reducing agent in an aqueous designer smart surfactant solution to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III; and

**Formula III**

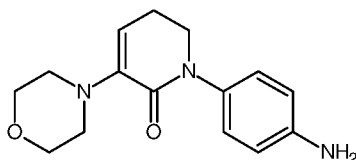
- ii) converting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III into apixaban of Formula I.

8. A process for preparing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV



Formula IV (wherein X = halogen)

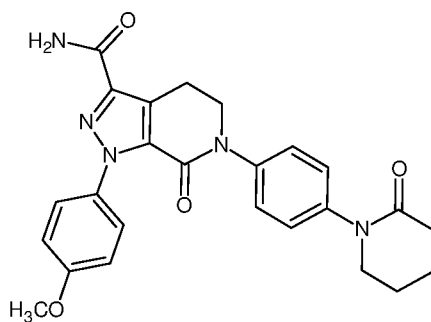
comprising reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III



Formula III

with 5-halovaleryl halide in an aqueous designer smart surfactant solution.

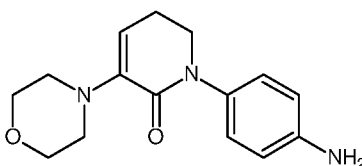
9. A process for preparing apixaban of Formula I



Formula I

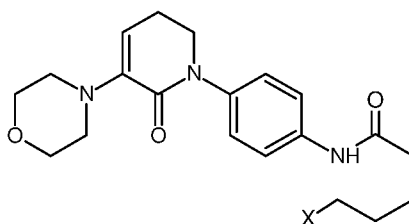
comprising:

i) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III



Formula III

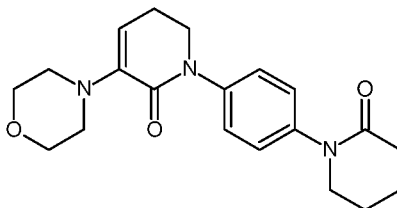
with 5-halovaleryl halide in an aqueous designer smart surfactant solution to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and



Formula IV (wherein X = halogen)

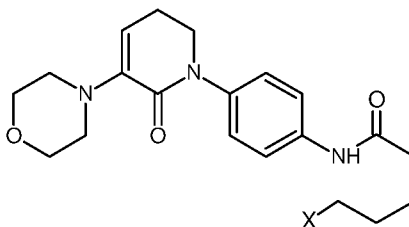
ii) converting 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV into apixaban of Formula I.

10. A process for the preparation of 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V



Formula V

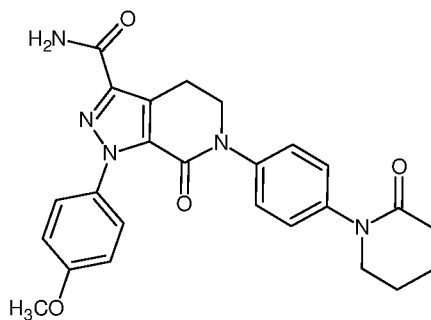
comprising cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV



Formula IV (wherein X = halogen)

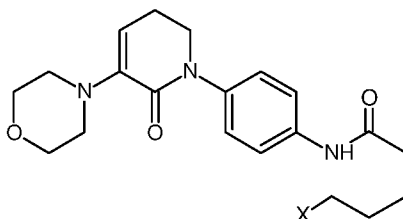
in an aqueous designer smart surfactant solution.

11. A process for preparing apixaban of Formula I

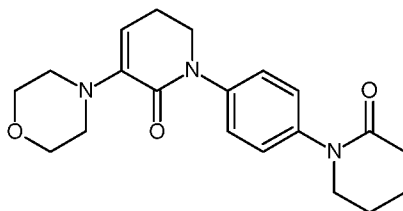
**Formula I**

comprising:

- i) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV

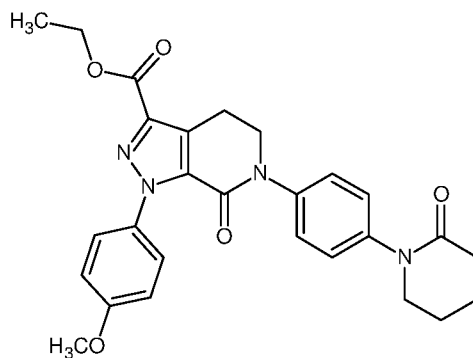
**Formula IV** (wherein X = halogen)

in an aqueous designer smart surfactant solution to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V; and

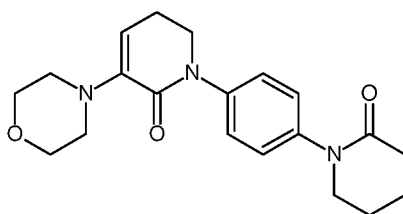
**Formula V**

- ii) converting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V into apixaban of Formula I.

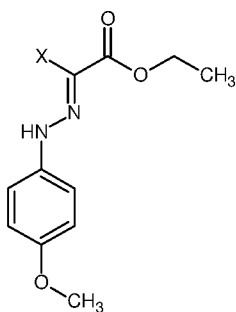
12. A process for the preparation of ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII

**Formula VII**

comprising reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V

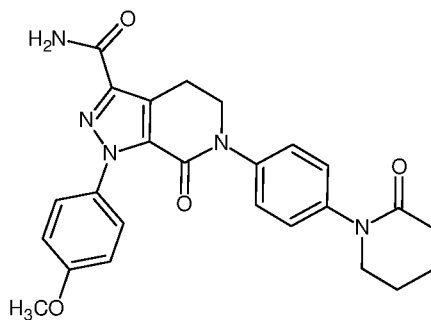
**Formula V**

with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI

**Formula VI** (wherein X = halogen)

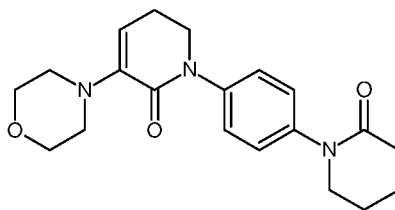
in an aqueous designer smart surfactant solution.

13. A process for preparing apixaban of Formula I

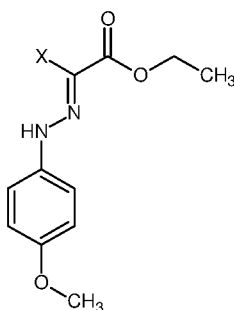
**Formula I**

comprising:

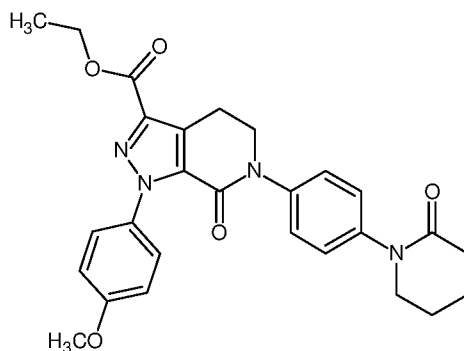
- i) reacting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V

**Formula V**

with ethyl (2Z)-halo[2-(4-methoxyphenyl)hydrazinylidene]ethanoate of Formula VI

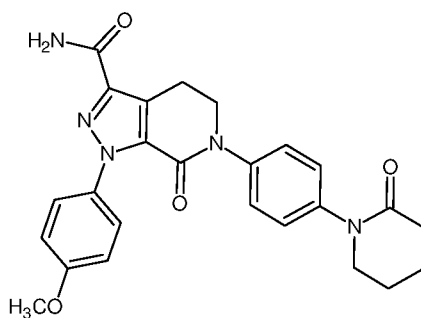
**Formula VI** (wherein X = halogen)

in an aqueous designer smart surfactant solution to obtain 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 of Formula VII; and

**Formula VII**

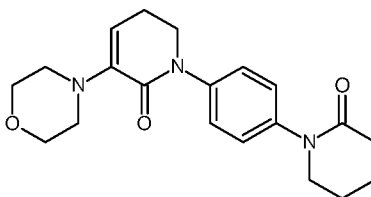
ii) converting ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate of Formula VII into apixaban of Formula I.

14. A one pot process for the preparation of apixaban of Formula I

**Formula I**

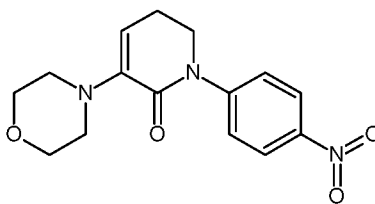
using aqueous designer smart surfactant solution.

15. A process for preparing 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V

**Formula V**

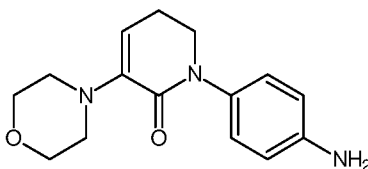
comprising:

- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II



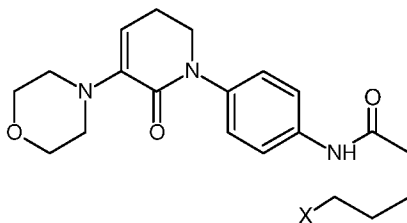
Formula II

- to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;



Formula III

- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and

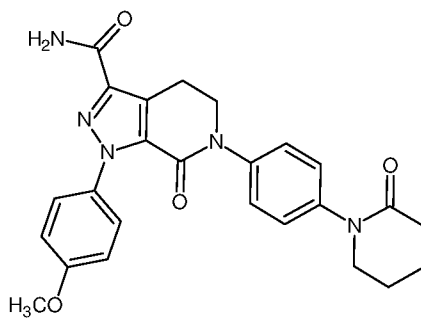


Formula IV (wherein X = halogen)

- iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V,

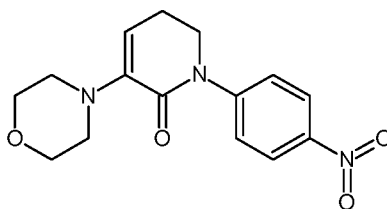
wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

16. A process for apixaban of Formula I

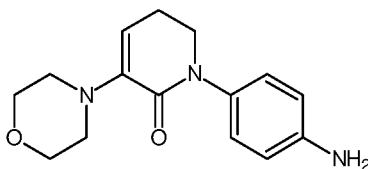
**Formula I**

comprising:

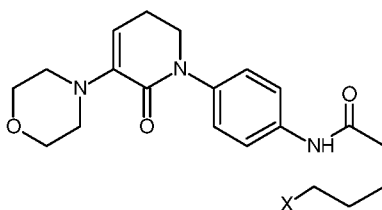
- i) reducing 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II

**Formula II**

to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III;

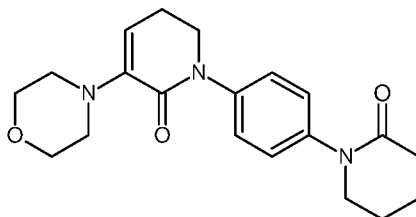
**Formula III**

- ii) reacting 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide to obtain 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV; and



Formula IV (wherein X = halogen)

iii) cyclizing 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V; and

**Formula V**

iv) converting 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V into apixaban of Formula I,

wherein steps i) to iii) are carried out in an aqueous designer smart surfactant solution.

17. The processes according to any one of claims 3-16, wherein the aqueous designer smart surfactant solution is selected from the group consisting of PTS, TPGS-750M, SPGS-550M (Nok), Triton X-100, Tergitol® TMN-6, Tergitol® 15S40, Tergitol® 15S7, Brij®-35, Tween® 80, and PTS-7.

18. The processes according to any one of claims 3, 4, 5, 15, or 16, wherein the reduction of 3-(morpholin-4-yl)-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one of Formula II to obtain 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III is carried out in the presence of a reducing agent.

19. The processes according to any one of claims 3-7, 15, or 16, wherein the reducing agent is selected from the group consisting of sodium sulphide, sodium hydrosulphite, iron, ammonium chloride, zinc, tin (II) chloride, platinum oxide, Fe/NH₄Cl, Zn/NH₄Cl, formic acid in presence of a metal catalyst, pyridinium zinc complex, and trihalosilanes.

20. The processes according to any one of claims 3, 4, 5, 8, 9, 15, or 16, wherein the reaction of 1-(4-aminophenyl)-3-(morpholin-4-yl)-5,6-dihydropyridin-2(1H)-one of Formula III with 5-halovaleryl halide is carried out in the presence of a base.

21. The processes according to claim 20, wherein the base is selected from the group consisting of ethyl amine, ammonia, triethyl amine, N-methylmorpholine, isobutylamine, tributyl amine, diisopropyl amine, diisopropylethylamine, triisopropylamine, pyridine, 4-

4 dimethylaminopyridine (DMAP), potassium tert-butoxide, 4-ethylmorpholine, 1,8-
5 diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane, 2,6-di-tert-butyl-4-
6 dimethylaminopyridine, lithium hydroxide, sodium hydroxide, potassium hydroxide,
7 barium hydroxide, sodium carbonate, potassium carbonate, barium carbonate, sodium
8 bicarbonate, magnesium bicarbonate, and potassium bicarbonate.

1 22. The processes according to any one of claims 3, 4, 5, 8, 9, 15, or 16, wherein the 5-
2 halovaleryl halide is selected from the group consisting of 5-chlorovaleryl chloride, 5-
3 bromovaleryl chloride, and 5-chlorovaleryl bromide.

1 23. The processes according to any one of claims 3, 4, 5, 10, 11, 15, or 16, wherein the
2 cyclization of 5-halo-N-{4-[5-(morpholin-4-yl)-6-oxo-3,6-dihydropyridin-1(2H)-
3 yl]phenyl}pentanamide of Formula IV to obtain 3-(morpholin-4-yl)-1-[4-(2-oxopiperidin-
4 1-yl)phenyl]-5,6-dihydropyridin-2(1H)-one of Formula V is carried out in the presence of
5 a base and a catalyst.

1 24. The processes according to claim 23, wherein the base is selected from the group
2 consisting of ethyl amine, ammonia, triethyl amine, N-methylmorpholine, isobutylamine,
3 tributyl amine, diisopropyl amine, diisopropylethylamine, triisopropylamine, pyridine, 4-
4 dimethylaminopyridine (DMAP), potassium tert-butoxide, 4-ethylmorpholine, 1,8-
5 diazabicyclo[5.4.0]undec-7-ene (DBU), 1,4-diazabicyclo[2.2.2]octane, 2,6-di-tert-butyl-4-
6 dimethylaminopyridine, lithium hydroxide, sodium hydroxide, potassium hydroxide,
7 barium hydroxide, sodium carbonate, potassium carbonate, barium carbonate, sodium
8 bicarbonate, magnesium bicarbonate, and potassium bicarbonate.

1 25. The processes according to claim 23, wherein the catalyst is selected from the
2 group consisting of tetra butylammonium iodide, tetra butylammonium bromide,
3 potassium iodide, and potassium bromide.

INTERNATIONAL SEARCH REPORT

International application No.

PCT/IB2017/053183

A. CLASSIFICATION OF SUBJECT MATTER

IPC(8) - C07D 471/04; C07D 201/08; C07D 231/00; C07D 471/02 (2017.01)

CPC - C07D 471/04; C07D 201/08; C07D 231/00; C07D 471/02 (2017.08)

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

See Search History document

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

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

See Search History document

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 2016/0244440 A1 (CHENGDU EASTON BIOPHARMACEUTICAL CO LTD) 25 August 2016 (25.08.2016) entire document	1-25
A	US 2016/0280646 A1 (SHANGHAI SYNCORES TECHNOLOGIES INC) 29 September 2016 (29.09.2016) entire document	1-25
A	US 2015/0353541 A1 (THIRUMALAI RAJAN et al) 10 December 2015 (10.12.2015) entire document	1-25
A	US 2017/0015663 A1 (UNICHEM LABORATORIES LIMITED) 19 January 2017 (19.01.2017) entire document	1-25

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

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier application or patent but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

10 September 2017

Date of mailing of the international search report

27 SEP 2017

Name and mailing address of the ISA/US

Mail Stop PCT, Attn: ISA/US, Commissioner for Patents
P.O. Box 1450, Alexandria, VA 22313-1450

Facsimile No. 571-273-8300

Authorized officer

Blaine R. Copenheaver

PCT Helpdesk: 571-272-4300
PCT OSP: 571-272-7774