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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
15 August 2013 (15.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/119328 A1

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

(21) International Application Number:
PCT/US2012/071985

(22) International Filing Date:
28 December 2012 (28.12.2012)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
61/595,799 7 February 2012 (07.02.2012) US
61/604,757 29 February 2012 (29.02.2012) US

(71) Applicant *(for all designated States except BB, US)*: **ASSIA CHEMICAL INDUSTRIES LTD.** [IL/IL]; 2 Denmark Street, 49517 Petach Tikva (IL).

(71) Applicant *(for BB only)*: **TEVA PHARMACEUTICALS USA, INC.** [US/US]; 1090 Horsham Road, P.O. Box 1090, North Wales, PA 19454-1090 (US).

(72) Inventors; and
(71) Applicants : **COHEN, Meital** [IL/IL]; Hanna Robina 28, Petah-tikva (IL). **YEORI, Adi** [IL/IL]; Pilichovski 5 St., 69341 Tel Aviv (IL). **MITTELMAN, Ariel** [IL/IL]; 13 Shimon Hatzadik St., 40800 Elad (IL). **ERHLICH, Motti** [IL/IL]; 3 Rabi Yehuda Hanasi St., Petach-tikva (IL).

(74) Agents: **BIRDE, Patrick, J.** et al.; Kenyon & Kenyon LLP, One Broadway, New York, NY 10004-1050 (US).

(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, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, 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, 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, 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, ML, MR, NE, SN, TD, TG).

Declarations under Rule 4.17:

— *as to the applicant's entitlement to claim the priority of the earlier application (Rule 4.17(iii))*

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 2013/119328 A1

(54) Title: SOLID STATE FORMS OF APIXABAN

(57) Abstract: The present invention is directed to solid state forms of Apixaban, processes for preparing the solid state forms, and pharmaceutical compositions thereof.

SOLID STATE FORMS OF APIXABAN

CROSS REFERENCE TO RELATED APPLICATIONS

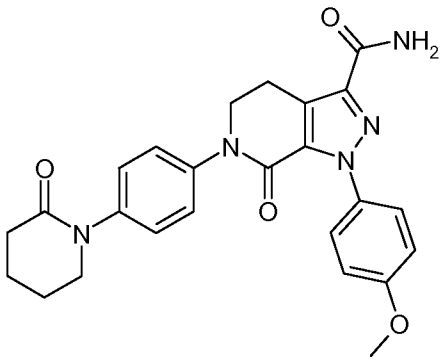
[0001] This application claims the benefit of U.S. Provisional Application Nos. 61/595,799, filed February 7, 2012, and 61/604,757, filed February 29, 2012, the contents of which are incorporated herein by reference.

FIELD OF THE INVENTION

[0002] The invention relates to solid state forms of Apixaban, processes for preparing the solid state forms, and pharmaceutical compositions thereof.

BACKGROUND OF THE INVENTION

[0003] Apixaban, 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl]-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, has the following chemical structure:



459.51
459
$C_{25}H_{25}N_5O_4$

[0004] It is being evaluated in phase III trials for the prevention of stroke in patients with atrial fibrillation.

[0005] The following PCT Publications describe the synthesis of Apixaban: WO03/026652, WO03/049681, WO2007/001385, and WO2010/030980.

[0006] Crystalline forms of Apixaban, Form H2-2 and Form N-1 are described in the PCT Publication No. WO2007/001385.

[0007] Polymorphism, the occurrence of different crystal forms, is a property of some molecules and molecular complexes. A single molecule may give rise to a variety of

polymorphs having distinct crystal structures and physical properties like melting point, thermal behaviors (e.g., measured by thermogravimetric analysis – "TGA", or differential scanning calorimetry – "DSC"), powder X-ray diffraction (XRD) pattern, infrared absorption fingerprint, and solid state NMR spectrum. One or more of these techniques may be used to distinguish different polymorphic forms of a compound.

[0008] Discovering new polymorphic forms and solvates of a pharmaceutical product can provide materials having desirable processing properties, such as ease of handling, ease of processing, storage stability, and ease of purification or as desirable intermediate crystal forms that facilitate conversion to other polymorphic forms. New polymorphic forms and solvates of a pharmaceutically useful compound thereof can also provide opportunities to improve the performance characteristics of a pharmaceutical product. They can also enlarge the repertoire of materials available to a formulation scientist for formulation optimization, for example by providing a product with different properties, e.g., better processing or handling characteristics, improved dissolution profile, or improved shelf-life. For at least these reasons, there is a need for additional polymorphs of Apixaban.

SUMMARY OF THE INVENTION

[0009] The present invention provides new solid state forms of Apixaban. These solid state forms can be used to prepare salts and/or formulations thereof.

[0010] The invention further provides the use of the solid state forms described below for the manufacture of a medicament for the prevention and treatment of thrombosis and pulmonary embolism, and provides a method of preventing and treating of thrombosis and pulmonary embolism comprising administering a therapeutically effective dose of the solid state forms described herein.

BRIEF DESCRIPTION OF THE FIGURES

[0011] Figure 1 provides a powder XRD pattern of crystalline Form I of Apixaban.

[0012] Figure 2 provides a powder XRD pattern of crystalline Form II of Apixaban.

[0013] Figure 3 provides a powder XRD pattern of crystalline Form III of Apixaban.

DETAILED DESCRIPTION OF THE INVENTION

[0014] The present invention provides new solid state forms of Apixaban. These solid state forms can be used to prepare salts and/or formulations thereof.

[0015] The salts and solid state forms of the present invention have advantageous properties selected from at least one of: chemical purity, flowability, solubility, morphology or crystal habit, stability – such as storage stability, stability to dehydration, stability to polymorphic conversion, low hygroscopicity, and low content of residual solvents.

[0016] A crystal form (or polymorph) may be referred to herein as substantially free of any other solid forms. As used herein in this context, the expression "substantially free" will be understood to mean that the crystalline form contains 20% or less, 10% or less, 5% or less, 2% or less, or 1% or less of any other solid form of the subject compound as measured, for example, by powder X-ray diffraction (PXRD). Thus, polymorphs of Apixaban described herein as substantially free of any other solid forms would be understood to contain greater than 80% (w/w), greater than 90% (w/w), greater than 95% (w/w), greater than 98% (w/w), or greater than 99% (w/w) of the subject form of Apixaban. Accordingly, in some embodiments of the invention, the described polymorphs of Apixaban may contain from 1% to 20% (w/w), from 5% to 20% (w/w), or from 5% to 10% (w/w) of one or more other solid forms of Apixaban.

[0017] A solid state form may be referred to herein as being characterized by graphical data "as shown in" a Figure. Such data include, for example, powder X-ray diffractograms and solid state NMR spectra. The skilled person will understand that such graphical representations of data may be subject to small variations, *e.g.*, in peak relative intensities and peak positions due to factors such as variations in instrument response and variations in sample concentration and purity, which factors are well known to the skilled person. Nonetheless, the skilled person would readily be capable of comparing the graphical data in the Figures herein with graphical data generated for an unknown crystal form and confirming whether the two sets of graphical data characterize the same solid state form or two different solid state forms. The skilled person would understand that a solid state form referred to herein as being characterized by graphical data "as shown in" a Figure would include any solid state form of the same chemical characterized by graphical data substantially similar to the Figure except for such small variations, the potential occurrence of which is well known to the skilled person.

[0018] Unless indicated otherwise, the solid state forms of the present invention can be dried. Drying may be carried out, for example, at elevated temperature under reduced pressure. The crystalline form can be dried, for example, at a temperature from about 40°C to about 80°C, or about 40°C to about 50°C, for example, about 40°C. The drying can be carried out under reduced pressure (i.e., less than 1 atmosphere, for example, about 10 mbar to about 100 mbar, or about 10 mbar to about 25 mbar). The drying can be carried out over a suitable period, for example, of about 8 hours to about 36 hours, or about 10 hours to about 24 hours, for example, about 16 hours. Drying can be carried out overnight.

[0019] As used herein, and unless stated otherwise, the term "anhydrous" in relation to crystalline Apixaban relates to a crystalline Apixaban which contains not more than 1% (w/w), more preferably not more than 0.5% (w/w) of either water or organic solvents as measured by TGA.

[0020] As used herein, Form DF-1 is a crystalline form characterized by a powder XRD pattern with peaks at 6.0, 7.1, 17.6, 19.1 and 22.8 ± 0.2 degrees 2θ. Alternatively, Form DF-1 can be characterized by a powder XRD pattern having peaks at 6.0, 7.1, 17.6, 19.1 and 22.8 ± 0.2 degrees 2θ, and also having one, two, three, four or five peaks selected from 26.1, 27.3, 28.8, 30.1 and 31.0 ± 0.2 degrees 2θ.

[0021] The present invention provides Apixaban propylene glycol solvate.

[0022] The present invention provides a crystalline Apixaban, designated Form I. Form I can be characterized by data selected from: a powder XRD pattern with peaks at 5.5, 11.0, 15.9, 16.3, and 20.3 ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 1; and any combinations thereof.

[0023] Alternatively, Form I can be characterized by a powder XRD pattern having peaks at 5.5, 11.0, 15.9, 16.3, and 20.3 ± 0.2 degrees 2θ, and also having any one, two, three, four or five peaks selected from 21.2, 22.6, 24.6, 25.1, and 31.2 ± 0.2 degrees 2θ.

[0024] The present invention also provides a crystalline Apixaban, designated Form II. Form II can be characterized by data selected from: a powder XRD pattern having peaks at 7.6, 12.7, 15.2, 16.3, and 16.9± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 1; and any combinations thereof.

[0025] Alternatively, Form II can be characterized by a powder XRD pattern having peaks at 7.6, 12.7, 15.2, 16.3, and 16.9± 0.2 degrees 2θ, and also having any one, two, three, four or five peaks selected from 18.1, 19.6, 20.1, 21.5, and 22.9± 0.2 degrees 2θ.

[0026] The present invention also provides a crystalline Apixaban, designated Form III. Form III can be anhydrous.

[0027] Form III can be characterized by data selected from: a powder XRD pattern having peaks at 7.8, 9.5, 10.9, 11.7, and 18.0± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 3; and any combinations thereof.

[0028] Alternatively, Form III can be characterized by a powder XRD pattern having peaks at 7.8, 9.5, 10.9, 11.7, and 18.0± 0.2 degrees 2θ, and also having any one, two, three, four or five peaks selected from 15.6, 18.8, 19.5, 20.6, and 22.2± 0.2 degrees 2θ.

[0029] The present invention provides a process for preparing another solid state form of Apixaban, for example, Form H2-2 or Form N-1, comprising preparing the above described solid state form of Apixaban by the process of the present invention, and converting it to another solid state form of Apixaban.

[0030] The present invention further encompasses 1) a pharmaceutical composition comprising any one or combination of solid state Forms, as described above, and at least one pharmaceutically acceptable excipient and 2) the use of any one or combination of the above-described solid state Forms, in the manufacture of a pharmaceutical composition. The pharmaceutical composition can be useful for the prevention and treatment of thrombosis and pulmonary embolism.

[0031] Having described the invention with reference to certain preferred embodiments, other embodiments will become apparent to one skilled in the art from consideration of the specification. The invention is further defined by reference to the following examples describing in detail the preparation of the composition and methods of use of the invention. It will be apparent to those skilled in the art that many modifications, both to materials and methods, may be practiced without departing from the scope of the invention.

X-Ray Power Diffraction:

[0032] The analysis was performed on ARL (SCINTAG) powder X-Ray diffractometer model X'TRA equipped with a solid state detector. Copper radiation of 1.5418 Å was used. Scanning parameters: range: 2-40 degrees two-theta; scan mode: continuous scan; step size: 0.05°, and a rate of 3 deg/min.

EXAMPLES

Example 1a: 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:

[0033] Dry tetrahydrofuran (THF) (5 L) was loaded to the reactor followed by Ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(5-bromovaleroylamino)phenyl]-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate. The wall of the vessel was washed with additional THF (1 L). The reactor was purged with nitrogen. Ethoxide solution in ethanol was slowly added using cannula during 30 min. Reaction temperature did not exceed 25 °C. Reaction was monitored with HPLC. Additional amount of reagent was added if needed. Reaction was quenched with glacial acetic acid (12 mL), water (24 L) was added.

[0034] Off-white solid separated, mixture was agitated for additional 12 hrs. Solids were filtered off using nutsche filter, washed with water (5 L) and pre-dried using infra red – drier. Crude product was dissolved in refluxing 2-butanone (8.7 mL per gram of the starting compound), resulting solution was cooled to 55 °C, methyl tert-butyl ether (MTBE) (4.35 mL per gram of the starting compound was added and resulting mixture was cooled to room temperature. Separated solids were filtered off, washed with MTBE and dried in vacuo to give 550 g (64 %) off-white solid.

[0035] Second crop was obtained by processing of the mother liquor.

Example 1b: Preparation of Apixaban:

3-Chloro-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one

[0036] 3,3-dichloro-1-(4-nitrophenyl)piperidin-2-one (379.7 g, 1.31 mol) was dissolved in dry dimethyl formamide (1900 mL). Lithium carbonate (193.6 g, 2.62 mol) was added, and the resulting mixture was heated to 100-105 °C for 5 hrs under nitrogen. After cooling to room temperature, a dark brown solution was decanted from crystalline inorganic

salts and evaporated to dryness. Ethyl acetate (500 mL) was added to the crystalline residue. Free flowing crystals were filtered off and washed with water (3x 300 mL).

[0037] Crystalline material was finally dried in vacuo at 45 °C. 257.2 g of yellow to brown solid were obtained.

3-Morpholin-4-yl-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one

[0038] 3-Chloro-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (11.1 g, 43.9 mmol) was suspended in dry Tetrahydrofuran (45 mL). Morpholine (3.8 g, 43.9 mmol, 1 eq.) and triethylamine (8.9 g, 87.9 mmol) were added successively. Resulting mixture was heated to reflux under nitrogen atmosphere. Additional Morpholine (1.5 mol%) and triethylamine (3 mol%) were added after 22 h. After next 6 h, reaction mixture still contained 0.5% of the starting compound. Morpholine (0.5 mol%) and triethylamine (1 mol%) were added and resulting mixture was further heated to reflux for 18 h. THF was evaporated and the solid residue was mixed with water (25 mL) and Ethyl acetate (25 mL). Solid material was collected, washed with water (2×15 mL) and Ethyl acetate (2×15 mL) to give 11.2 g of yellow solid.

Ethyl 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate

[0039] Mixture of (Z)-ethyl 2-chloro-2-(2-(4-methoxyphenyl)hydrazono)acetate (10.0 g, 38.77 mmol 1.05 eq.) and 3-morpholin-4-yl-1-(4-nitrophenyl)-5,6-dihydropyridin-2(1H)-one (11.2 g, 36.93 mmol, 1 eq.) in dry toluene (225 mL) was heated to 90°C under nitrogen atmosphere. Triethylamine (7.47 g, 73.85 mmol, 2 eq.) was added dropwise and the resulting mixture was heated for 5 h. Precipitated solid was filtered off after cooling to room temperature. Solid material was washed with Toluene (40 mL), water (5× 40 mL) and dried at 50°C. 17.0 g of yellow powder was obtained.

[0040] The resulting solid was dissolved in CH_2Cl_2 (170 mL). Trichloroacetic acid (15.9 g, 97.41 mmol, 3 eq.) was added dropwise. The obtained solution was stirred for 1.5 h at room temperature. The mixture was diluted with Dichloromethane (170 mL) and washed with water (2× 250 mL), saturated $NaHCO_3$ (3× 250 mL) and water (1× 250 mL), dried over Na_2SO_4 and evaporated to give 14.0 g of pale yellow solid.

Ethyl 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate

[0041] Pd/C 5% (Aldrich, 5.7 g) was added to the solution of ethyl 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (29.0 g, 66.45 mmol) in NMP (185 mL) in 2 L stainless steel autoclave. The autoclave was flushed with nitrogen and pressurized to 6 bar with hydrogen. The reaction mixture was stirred at room temperature for 23 h. The reactor was depressurized and the content was filtered over sintered glass filter with Celite pad. Reactor was washed with Ethyl acetate (500 mL) and the filter cake was washed with additional Ethyl acetate (200 mL). The solvent was evaporated from the N-methylpyrrolidone solution and diluted brine was added (1:1, 530 mL), Precipitated product was filtered off and washed well with water (1.7 L). Pale yellow solid (25.1 g) was obtained after drying at 50 °C.

6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

[0042] Mixture of Ethyl 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (24.8 g, 61.0 mmol) and saturated solution of ammonia in Methanol (620 mL) was heated to 100°C in 2 L stainless steel autoclave for 18 h. Reactor was depressurized and the content was concentrated in vacuo, separated solid was filtered off, washed with Methanol and dried at 50°C to afford 20.9 g of beige solid.

6-(4-(5-bromopentanamido)phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

[0043] 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (20.5 g, 54.32 mmol) was suspended in THF. Aqueous solution of potassium carbonate (40%, 20.7 g, 1.1 eq.) was added. 5-Bromovaleroyl chloride (13.0 g, 65.19 mmol, 1.2 eq.) was added dropwise while cooling in water bath. Reaction mixture was vigorously stirred for 1 h. Additional 5-bromovaleroyl chloride (0.83 g, 4.16 mmol) was added. HPLC showed reaction completion after 20 min. Tetrahydrofuran phase was separated and evaporated in vacuo to give brown solid. Water (120 mL) was added and the obtained solid was collected and washed with water (3× 200 mL). Drying in vacuo afforded 29.2 g of brownish crystalline solid.

1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban)

[0044] Potassium ethoxide solution in Ethanol (24%, 46.9 g, 2.5 eq.) was added dropwise to the suspension of 6-(4-(5-bromopentanamido)phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (28.9 g, 53.48 mmol) in dry Tetrahydrofuran (460 mL). HPLC showed reaction completion after 30 min. Glacial acetic acid (0.9 mL) was added to quench the reaction. Reaction mixture was concentrated in vacuo to give off-white slurry. Water (700 mL) was added and the solid material was filtered off and washed with water (1 L) to afford 20 g of crude product.

Example 1c: Preparation of Apixaban:

[0045] Ethyl 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate was prepared as described in example 1b.

Ethyl 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate

[0046] 1 L glass reactor was charged with MeOH (200 ml) followed by 1-(4-methoxyphenyl)-6-(4-nitrophenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylateand (20 g, 46 mmol) and Pd/C 10% (0.5 g). The mixture was pressurized to 3 bar with hydrogen and the reaction was heated to 75°C . After 4 h reaction, the mixture was cooled down to 25°C and the reactor was washed with N_2. MeOH (150 ml) was added and the mixture was heated to reflux, the solution was filtrated hot over hyflo, and the MeOH was evaporated to give yellow powder.

6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

[0047] 1L glass reactor was charged with the ethyl 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxylate (30 g, 73.9 mmol) in MeOH (480 ml). Ammonia was bubbled and the yellow slurry was heated to 74°C. The reaction was mixed for overnight under pressure. Then, the reaction mixture was cooled to 25°C, and was washed with N_2. The slurry was concentrated to 150 ml of solvent

and the solid was filtrated and washed with MeOH (60 mL). The product was dried at the oven under reduced pressure at 50°C overnight.

6-(4-(5-chloropentanamido)phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide

[0048] 6-(4-aminophenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (5g, 13.25 mmol) and K_2CO_3 (2 g, 14.57 mmol) were suspended in NMP (50 ml) at room temperature. 5-Chlorovaleroyl chloride (2.4 ml, 18.55 mmol) was added dropwise. The reaction mixture was stirred for overnight. HPLC was monitored for reaction completion.

1-(4-methoxyphenyl)-7-oxo-6-(4-(2-oxopiperidin-1-yl)phenyl)-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide (Apixaban)

[0049] To NMP solution of 6-(4-6-(4-(5-chloropentanamido)phenyl)-1-(4-methoxyphenyl)-7-oxo-4,5,6,7-tetrahydro-1H-pyrazolo[3,4-c]pyridine-3-carboxamide, potassium ethoxide (8.23 ml, 18.5 mmol) was added dropwise at 5°C, the reaction was stirred for 6 h. Then, acetic acid (1 ml) followed by water (50 ml) were added and the mixture was stirred for overnight. The obtained slurry was filtered, washed with water (10 ml) and MTBE (2 X 10 ml) and dried at vacuum oven at 50°C.

Example 2: Preparation of Apixaban form I:

[0050] Ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (1 g) and a solution of 5% NH_3 in propylene glycol (8 mL, 11 equiv.) were added to a 25 mL head space vial equipped with a magnetic stirrer. The vial was sealed, heated to 100°C and stirred overnight. A white slurry was obtained and the reaction mixture subsequently became clear. The reaction mixture was then cooled to room temperature. A solid precipitated and was separated by filtration, washed with ethanol (10 vol.) and dried overnight in a vacuum oven at 40°C. The resulting product was analyzed by XRPD to give a pattern of Apixaban crystalline Form I.

Example 3: Preparation of Apixaban Form II:

[0051] Ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (1 g) and a solution of 5% NH_3 in

propylene glycol (8 mL, 11 equiv.) were added to a 25 mL head space vial equipped with a magnetic stirrer. The vial was sealed, heated to 100°C and stirred overnight. A white slurry was obtained and subsequently the reaction mixture became clear. The reaction mixture was then cooled to room temperature. A solid precipitate formed. Ethanol (20 vol.) was added to the mixture and the resulting slurry was stirred at room temperature for 3 h, then filtered, washed with ethanol (10 vol.) and dried overnight in a vacuum oven at 40°C. The resulting product was analyzed by XRPD to give a pattern of Apixaban crystalline Form II.

Example 4: Preparation of Apixaban Form II:

[0052] Ethyl 1-(4-methoxyphenyl)-7-oxo-6-[4-(2-oxopiperidin-1-yl)phenyl-4,5,6,7-tetrahydro-1*H*-pyrazolo[3,4-*c*]pyridine-3-carboxylate (1 g) and a solution of 5% NH_3 in propylene glycol (8 mL, 11 equiv.) were added to 25 mL head space vial equipped with a magnetic stirrer. The vial was sealed, heated to 100°C and stirred overnight. A white slurry was obtained and subsequently the reaction mixture became clear. The reaction mixture was then cooled to room temperature and a solid precipitate formed. Water (20 vol.) was added to the mixture and the resulting slurry was stirred at room temperature for 3 h, then filtered, washed with water (10 vol.) and dried overnight in a vacuum oven at 40°C. The resulting product was analyzed by XRPD to give a pattern of Apixaban crystalline Form II.

Example 5: Preparation of Apixaban Form III:

[0053] A sample of Apixaban form DF-1 was heated up to 200°C for 2 minutes in a vacuum oven. The sample was analyzed by XRPD instrument to give a pattern of Apixaban crystalline Form III.

Example 6: Preparation of Apixaban Form DF-1

[0054] Form DF-1 was obtained by refluxing a suspension of Apixaban free base (0.25 g) in acetone (70 mL) for 2h. After cooling to room temperature the product is isolated by filtration and dried at 40°C / 70 mbar.

What is claimed is:

1. Crystalline Form I of Apixaban, characterized by data selected from: a powder XRD pattern with peaks at 5.5, 11.0, 15.9, 16.3, and 20.3 ± 0.2 degrees 2θ; a powder XRD pattern as shown in figure 1; and any combinations thereof.

2. Crystalline Form II of Apixaban, characterized by data selected from: a powder XRD pattern having peaks at 7.6, 12.7, 15.2, 16.3, and 16.9± 0.2 degrees 2 θ; a powder XRD pattern as shown in figure 2; and any combinations thereof.

3. Crystalline Form III of Apixaban, characterized by data selected from: a powder XRD pattern having peaks at 7.8, 9.5, 10.9, 11.7, and 18.0± 0.2 degrees 2 θ; a powder XRD pattern as shown in figure 3; and any combinations thereof.

4. A pharmaceutical composition comprising one or more solid state forms according to any one of claims 1 to 3, and at least one pharmaceutically acceptable excipient.

5. The use of one or more of the crystalline forms according to any one of claims 1 to 3 for the manufacture of a medicament.

6. A process for preparing a pharmaceutical composition comprising combining any one or more of the solid state forms according to any one of claims 1 to 3, and at least one pharmaceutically acceptable excipient.

Figure 1

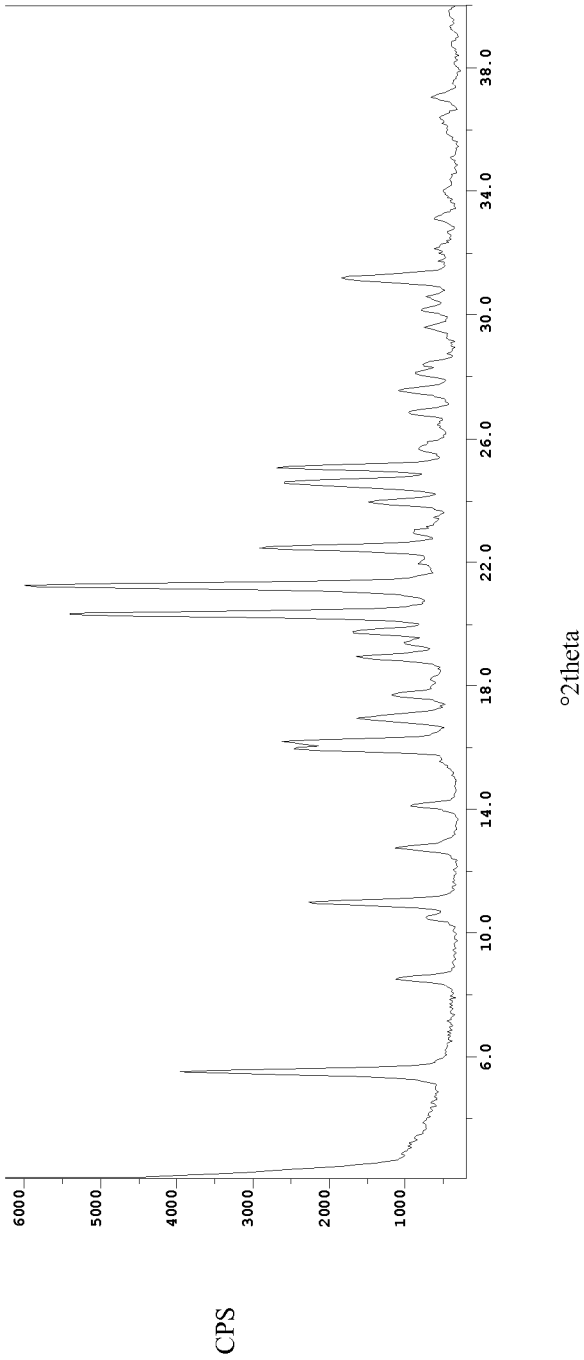

CPS
6000
5000
4000
3000
2000
1000
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

Figure 2

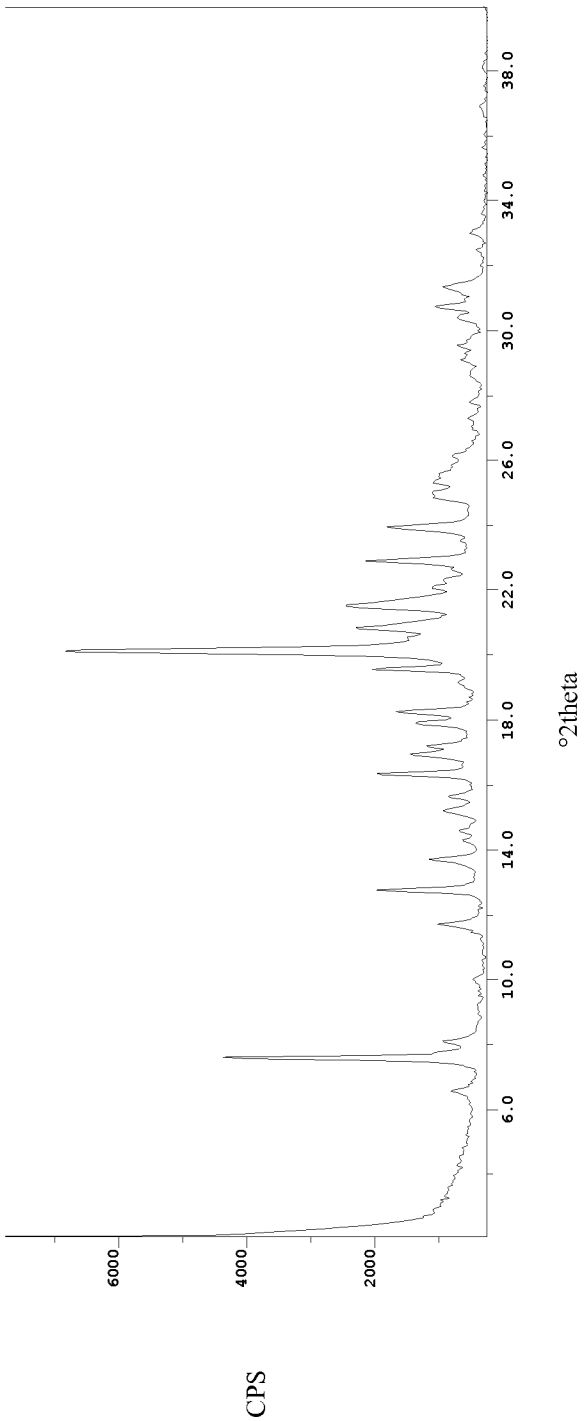
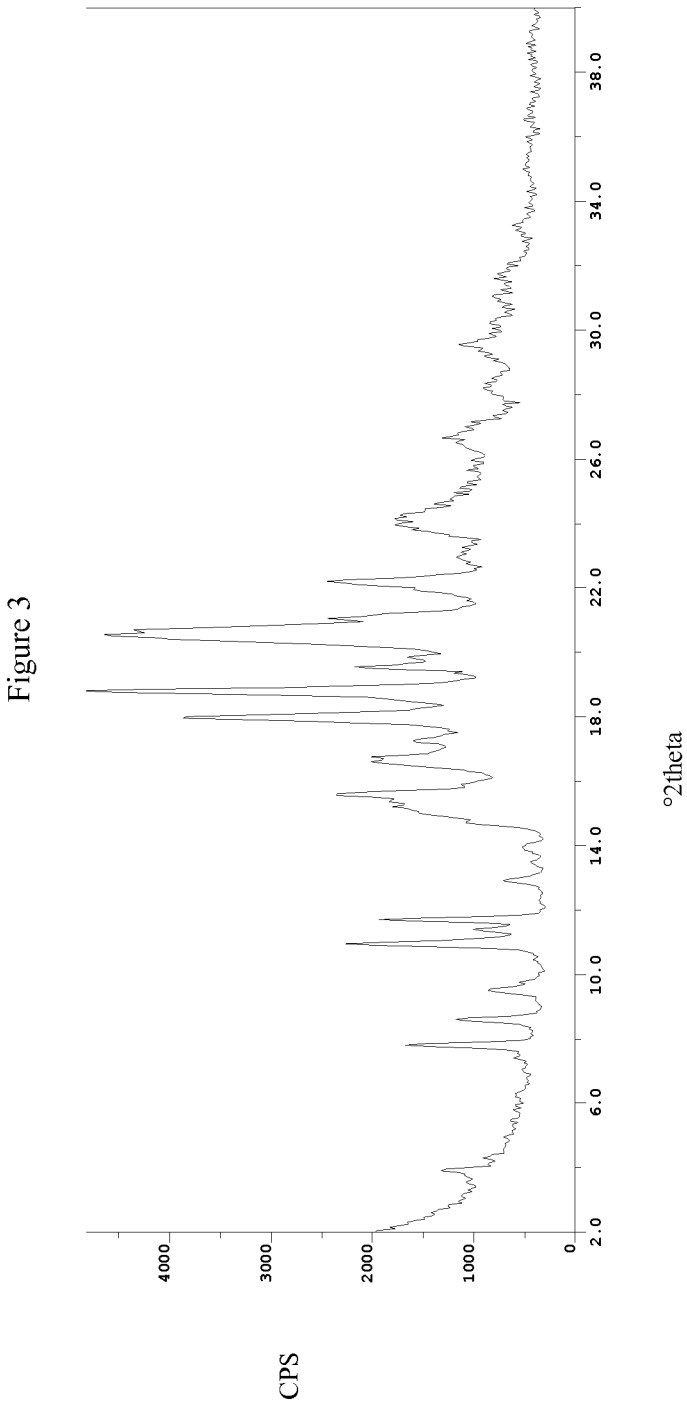


Figure 3


CPS
4000
3000
2000
1000
0
2.0
6.0
10.0
14.0
18.0
22.0
26.0
30.0
34.0
38.0
°2theta

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/071985

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, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2007/001385 A2 (SQUIBB BRISTOL MYERS CO [US]; SHAPIRO RAFAEL [US]; ROSSANO LUCIUS T [U) 4 January 2007 (2007-01-04) page 1, paragraph 1 page 40 - page 41; example 9; table 1	1,4-6
A	US 2006/160841 A1 (WEI CHENKOU [US] ET AL) 20 July 2006 (2006-07-20) page 3 - page 4; claim 13; examples 1-3	1,4-6
A	US 2007/203178 A1 (MALLEY MARY F [US] ET AL) 30 August 2007 (2007-08-30) page 6; claims 1, 5	1,4-6

-/--

[X] Further documents are listed in the continuation of Box C.

[X] 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	Date of mailing of the international search report
28 February 2013	26/07/2013

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	Jeanjean, Fabien

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2012/071985

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fees, this Authority did not invite payment of additional fees.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☒ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

1(completely); 4-6(partially)

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.

☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

☐ No protest accompanied the payment of additional search fees.

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1(completely); 4-6(partially)

   Form I of Apixaban

   ---

2. claims: 2(completely); 4-6(partially)

   Form II of Apixaban

   ---

3. claims: 3(completely); 4-6(partially)

   Form III of Apixaban

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2012/071985

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	CAIRA M R: "CRYSTALLINE POLYMORPHISM OF ORGANIC COMPOUNDS", TOPICS IN CURRENT CHEMISTRY, SPRINGER, BERLIN, DE, vol. 198, 1 January 1998 (1998-01-01), pages 163-208, XP001156954, ISSN: 0340-1022, DOI: 10.1007/3-540-69178-2_5 ISBN: 978-3-540-36760-4 page 165, paragraph 2.1 -----	1,4-6

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/US2012/071985

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2007001385 A2	04-01-2007	AR 051304 A1	03-01-2007
		AU 2005333566 A1	04-01-2007
		BR PI0516187 A	26-08-2008
		CA 2582233 A1	04-01-2007
		EP 1805178 A2	11-07-2007
		JP 2008514712 A	08-05-2008
		KR 20070067177 A	27-06-2007
		US 2006069258 A1	30-03-2006
		WO 2007001385 A2	04-01-2007
US 2006160841 A1	20-07-2006	US 2006160841 A1	20-07-2006
		WO 2006078331 A2	27-07-2006
US 2007203178 A1	30-08-2007	NONE	