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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
22 August 2013 (22.08.2013)

WIPO | PCT

(10) International Publication Number
WO 2013/120464 A1

(51) International Patent Classification:
C07D 409/14 (2006.01)

(21) International Application Number:
PCT/CZ2013/000014

(22) International Filing Date:
12 February 2013 (12.02.2013)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PV 2012-114 17 February 2012 (17.02.2012) CZ

(71) Applicant: **ZENTIVA, K.S.** [CZ/CZ]; U Kabelovny 130, 102 37 Praha 10 (CZ).

(72) Inventors: **HALAMA, Ales**; K Olsine 329, 530 09 Pardubice (CZ). **KRULIS, Radim**; Primeticka 6, 140 00 Praha 4 (CZ). **BRICHAC, Jiri**; V Pruceli 1653, 149 00 Praha 4 (CZ).

(74) Agents: **JIROTKOVA, Ivana** et al.; ROTT, RUZICKA & GUTTMANN, P.O. Box 44, 120 00 Praha 2 (CZ).

(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).

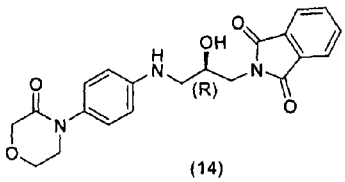
Declarations under Rule 4.17:

— *as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii))*

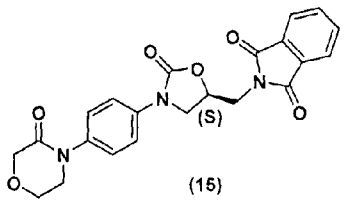
Published:

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

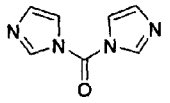
(54) Title: A PROCESS FOR THE PREPARATION OF RIVAROXABAN BASED ON SAVING OF 1,1'-CARBONYL DIIMIDAZOLE.



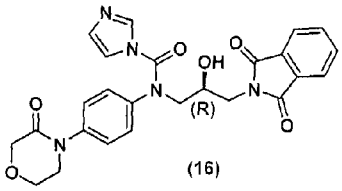
(14)



(15)



(8)



(16)

R–O–M

(17)

(57) Abstract: The invention provides a method of carrying out the cyclization of the compound of formula (14) to the compound (15), wherein first a non-cyclic intermediate (16) is prepared by the treatment with 1 to 1.5 equivalents of 1,1'-carbonyldiimidazole of formula (8), which further converts into the cyclic product (15) by treatment with heat or a base. The present method of cyclization of the compound (14) to the compound (15) is preferred and distinguished from the prior methods by the use of a lower amount of the expensive carbonylation agent, which is compensated by use of a cheap base (17), wherein R means an alkyl and M means an alkali metal.

WO 2013/120464 A1

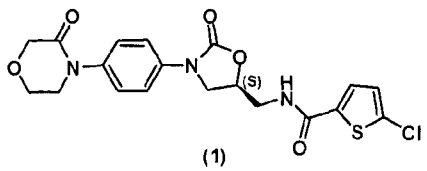
A process for the preparation of rivaroxaban based on saving of 1,1'-carbonyl diimidazole.

Technical Field

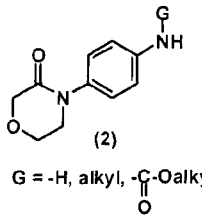
The invention relates a new method of performing of the cyclization reaction providing the 2-oxo-1,3-oxazolidine heterocycle during the chemical synthesis of rivaroxaban, which is an active pharmaceutical substance used for preparation of a drug from the therapeutic group of anticoagulants.

Background Art

Rivaroxaban, chemically (*S*)-5-chloro-N-({2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene-2-carboxamide, described by formula (**1**), was developed by the company Bayer Healthcare (WO01/47919, 2001). Rivaroxaban is applied in the clinical practice as the active ingredient of an orally available anticoagulant that is commercially marketed as Xarelto and is used in the prevention and treatment of arterial or venous thromboembolic disorders. In its effect, rivaroxaban is characterized by direct selective inhibition of the FXa coagulation enzyme (*Drugs of the Future* 2006, 31(6): 484-493).

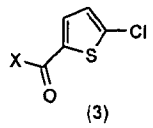


(1)



(2)

G = -H, alkyl, -C(=O)-Oalkyl



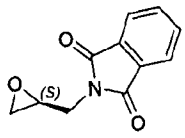
(3)

X = -OH, -Cl, -NH_2

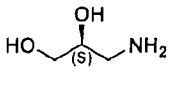
For the preparation of rivaroxaban (**1**) four key structures referred to as building blocks can be used as advanced intermediates. All the so far described syntheses are using two virtually equal building blocks. The first one are derivatives of 4-(4-aminophenyl)morpholin-3-one (**2**, G=H), where it may be the case of an unsubstituted amine or a derivative alkylated on nitrogen or a carbamate derived from this compound. The other general and commonly used building block for the rivaroxaban molecule are derivatives of 5-chlorothiophene-2-carboxylic acid (**3**, X=OH), or its functional derivatives such as the chloride or amide. Two more types of starting compounds are specific for either process. They include chiral building blocks, e.g. (*S*)-glycidyl phtalimide (**4**), (*S*)-3-aminopropane-1,2-diol (**5**), (*R*)-epichlorohydrin (**6**) and

(*R*)-glycidyl butyrate (**7**), as well as carbonylation agents, e.g. 1,1'-carbonyldiimidazole (**8**, abbreviated CDI), alkyl chloroformates (**9**) and phosgene (**10**).

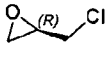
chiral building blocks:



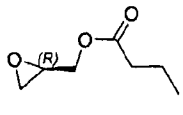
(4)



(5)

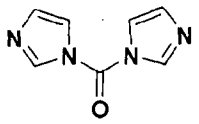


(6)

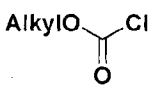


(7)

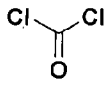
carbonylation agents:



(8)



(9)



(10)

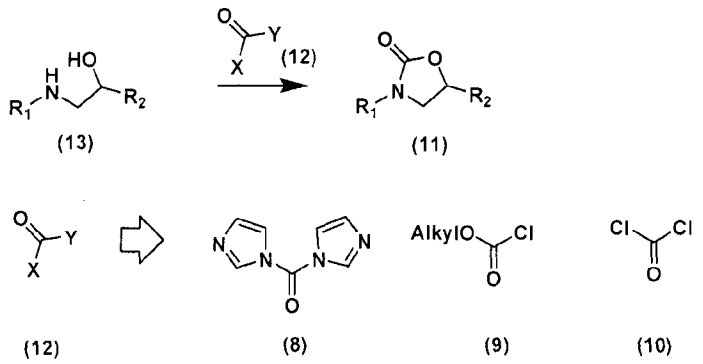
Up to now three synthetic methods have been described for chemical synthesis of rivaroxaban (**1**) based on the use of CDI as the carbonylation agent, which are distinguished from each other especially in the chiral building blocks used. The individual methods are described in a more detailed way in the following sources (reference source, chiral block):

(a) WO 01/47919, US 7 157 456B2, *J.Med.Chem.* (2005), 48(19), 5900-5908, (*S*)-glycidyl phthalimide,

(b) WO 2004060887,
(*S*)-3-aminopropane-1,2-diol,

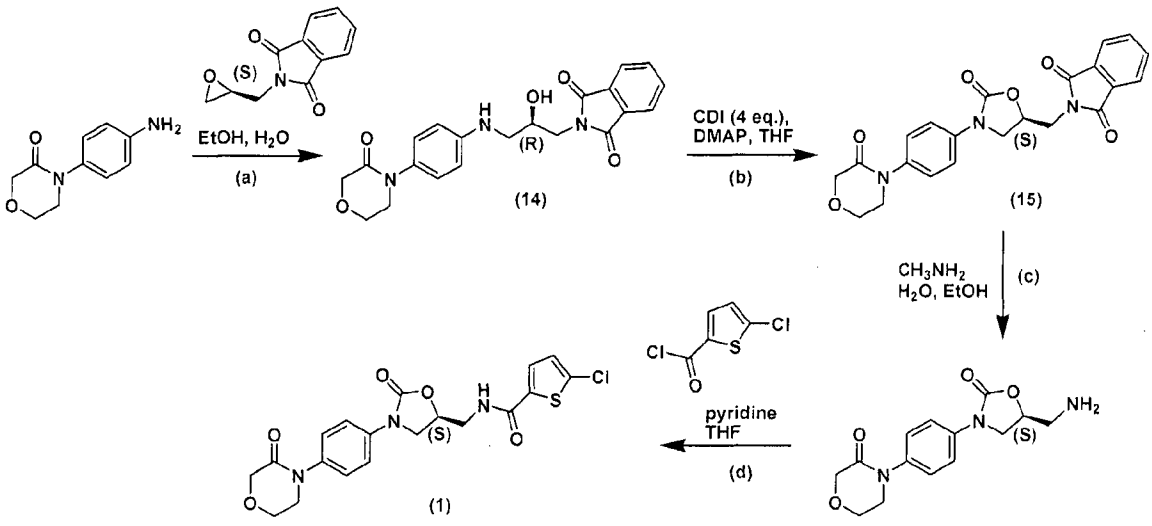
(c) WO 2009/023233 A1,
(*R*)-epichlorohydrin.

A substantial structural feature of rivaroxaban (**1**) is represented by the 3,5-substituted 2-oxo-1,3-oxazolidine heterocycle described by the general chemical formula (**11**), wherein R_1 means a substituted aryl and R_2 means a substituted alkyl. In the chemical synthesis of 3,5-substituted 2-oxo-1,3-oxazolidines (**11**) carbonylation agents of general formula (**12**) are used, wherein both X and Y mean a suitable leaving group, e.g. a halogen, alcoxy group or 1*H*-imidazol-1-yl. The carboxylation agents, which may be e.g. CDI (**8**), alkyl chloroformates (**9**) or phosgene (**10**), are the source of the carbonyl group in the target heterocycle. The starting compounds for the preparation of 3,5-substituted 2-oxo-1,3-oxazolidines include variously substituted 1-alkyl-2-(arylamino)ethanols of formula (**13**), wherein R_1 means a substituted aryl and R_2 means a substituted alkyl; see Scheme 1.



Scheme 1

In the case of cyclization performed in the synthesis of rivaroxaban (according to Scheme 2, stage (b)) four equivalents of CDI are consumed per one equivalent of the starting compound (WO 01/47919, *J.Med.Chem.* (2005), 48(19), 5900-5908). The consumption of CDI in case of this synthesis of rivaroxaban is unusually high. Compared to other carbonylation agents (phosgene, alkylchloroformates) the use of CDI brings a number of advantages as alternative agents are toxic, harmful for the environment and release highly corrosive hydrogen chloride during the reaction. On the other hand, CDI is considerably more expensive than the alternative agents. Thus, from the economical point of view it is convenient to minimize the amount of CDI used for the commercial production of rivaroxaban.



Scheme 2

The present invention relates to a new and industrially applicable method of carrying out the carbonylation reaction in the preparation of intermediates of rivaroxaban, which is characterized by saving of the expensive carboxylation agent (CDI), which makes it possible to reduce costs of commercial production of rivaroxaban.

Disclosure of Invention

The invention provides a convenient method of performing the cyclization reaction in the preparation of rivaroxaban intermediates that is characterized by a reduced consumption of the expensive carboxylation agent CDI.

The invention consists in a method of cyclizing 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**14**) to 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**15**), characterized by a process consisting of the following steps:

(a) reaction of compound (**14**) carried out in a suitable solvent with 1 to 1.5 equivalents of 1,1'-carbonyldiimidazole of formula (**8**), yielding a mixture of the non-cyclic intermediate 2-((2*R*)-2-hydroxy-3-(*N*-(4-(3-oxomorpholin-4-yl)phenyl)-1*H*-imidazol-1-yl-carbox-amido)propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**16**) and the cyclic product of formula (**15**), which contains more than 50% of compound (**16**);

(b) cyclization of the mixture of the compounds obtained in step (a) in a solvent or a mixture of solvents suitable for cyclization in the presence of a suitable base as the catalyst;

(c) isolation of the cyclic compound (**15**).

A C_4 to C_8 ether, polyethylene glycol, a C_1 to C_6 chlorinated solvent or their mixtures in any proportions can be used as a suitable solvent for the preparation of the compound (**15**) in step (a), preferably a solvent selected from the group of tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, di*tert*-butylether, polyethylene glycol PEG-200 to PEG-800, dichloromethane, chloroform, 1,1,2-trichloroethylene, chlorobenzene or their mixtures in any proportions.

A metal alkoxide of formula (**17**), wherein R means a linear or branched C_1 to C_8 alkyl and M means an alkali metal, can be used as a suitable base for preparation of the compound (**15**) in step (b).

R–O–M

(17)

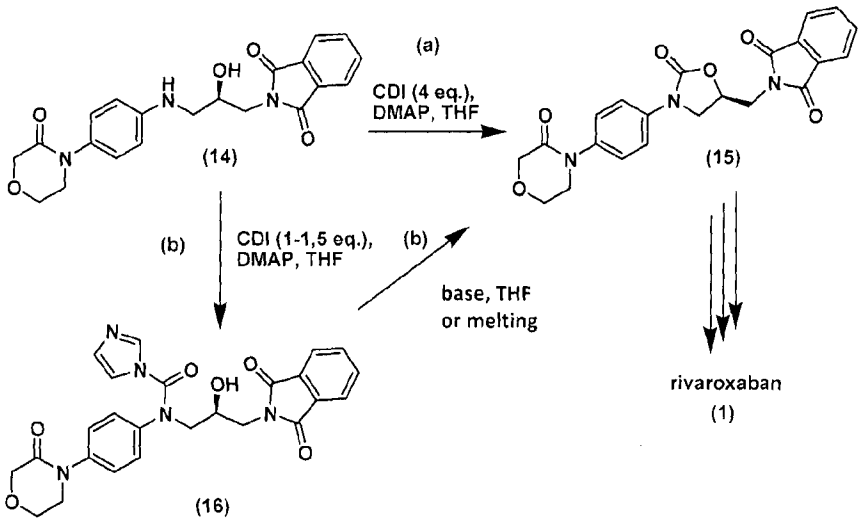
An alkoxide selected from the group of sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, sodium isopropoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, lithium *tert*-butoxide can be used as a suitable metal alkoxide in step (b). Besides a metal alkoxide, a suitable base can also be used in step (b), selected from the group of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, methyllithium, n-butyllithium, lithium diisopropylamide or lithium hexamethyldisilazide. Potassium *tert*-butoxide or its solution in an organic solvent, e.g. a solution in tetrahydrofuran, is preferably used as the base in step (b).

A solvent selected from the group of a C4 to C8 ether, polyethylene glycol, a C1 to C6 chlorinated solvent or their mixtures in any proportions can be used as suitable solvents for the preparation of the compound (**15**) in step (b). The preparation of the compound (**15**) is also characterized in that the cyclization in step (b) is carried out at a temperature in the range of from 40°C to the boiling point of the solvent.

The process of preparation of the compound (**15**) is finalized by its isolation from the reaction mixture, which is characterized in that the isolation in step (c) is carried out in such a way that the separated product is filtered off from the reaction mixture, washed with a C_1 to C_5 alcohol and/or water and the isolated product is dried.

The present invention relates to a method of carrying out the cyclization of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**14**) to 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**15**), see Scheme 3. The method according to the invention is characterized by making use of the possibility of cyclization of the reaction intermediate, 2-((2*R*)-2-hydroxy-3-(*N*-(4-(3-oxomorpholin-4-yl)phenyl)-1*H*-imidazol-yl-1-carboxamido)propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**16**), by treatment with bases or with heat during its melting, see path (b) in Scheme 4. Compared to the prior process, see path

(a) in Scheme 3, the consumption of the expensive carbonylation agent is saved. When the cyclization method according to the invention is used, only 1 to 1.5 equivalents of CDI per 1 equivalent of the starting compound (**14**) are consumed, while 4 CDI equivalents were consumed in the original method.



Scheme 3

The invention is based on the surprising finding that in the reaction of the compound (**14**) with CDI, the reaction intermediate (**16**) is formed very quickly, which is unexpectedly stable and can even be isolated from the reaction mixture in the solid state. Due to relatively high stability of the reaction intermediate (**16**) the conversion of the compound (**14**) to the target cyclic product (**15**) only proceeds very slowly and under treatment with an unusually big excess of the carbonylation agent (CDI). The observed phenomenon is surprising as very similar reactions of related compounds run easily and with the use of just one CDI equivalent per one equivalent of the compound cyclized (US2007032472). A high consumption of CDI (ca. 4 equivalents) during cyclization of the compound (**14**) to the cyclic product (**15**) was also confirmed by a comparative experiment, see Example 1. Conversely, when 2 to 3 equivalents of CDI were used (Examples 2, 5 and 6), a mixture of the compounds (**16**) and (**15**) was obtained where the compound (**16**) predominated with contents over 60%. When 1 CDI equivalent was used, the non-cyclic intermediate (**16**) was obtained, see Example 4 and Fig. 3.

It has been found out in investigating the properties of the isolated intermediate (**16**) that it could be cyclized without the need of using an excessive amount of CDI. Two principally

different methods of conversion of the compound (**16**) to the compound (**15**) have been found. The first method consists in heat-induced cyclization that occurs spontaneously during melting of the isolated compound. This way, the target product was prepared with in a 77% yield, see Example 3. The cyclization method based on melting of the compound (**16**) features high energy demands and is not suitable for application in the production scale. Melting of the compound (**16**) and its conversion to the compound (**15**) only occurs at temperatures over 150°C, which precludes the use of common solvents. The use of a suitable base that can, moreover, be used in significantly lower amounts than the equivalent of the cyclized compound (e.g. 0.2 eq. according to Example 8) has turned out to be more convenient for cyclization of the compound (**16**). Using this method the target product (**15**) was obtained from the isolated compound (**16**) by the action of a suitable base with the yield of 78% (calculated on the starting compound (**14**)), see Example 7. The method, wherein first a mixture of the compounds (**16**) and (**15**) is prepared from the compound (**14**) by treatment with 1 to 1.5 equivalents of CDI and subsequently a suitable base is added to the mixture to finalize the cyclization of the compound (**16**) to the cyclic product (**15**), has proved to be still more convenient. Using this approach to the cyclization reaction there is no need to isolate the compound (**16**) from the reaction environment, which saves the solvents used and time required for production of the compound (**15**). The method of cyclization without isolation of the compound (**16**) and with the use of a suitable base provided the cyclic product (**15**) with the yield of 84% (calculated on the starting compound (**14**)); see Example 8.

The process of cyclization of the compound (**14**) makes it possible to reproducibly obtain the cyclic product (**15**), characterized by the chemical purity of 99.8% and higher. The compound (**15**) prepared by the method of the invention can be further used for synthesis of rivaroxaban (**1**), which is the active substance in an anticoagulant drug. A convenient and distinguishing feature from the former method of cyclization of the compound (**14**) to the compound (**15**) consists in the use of a lower amount of the expensive carbonylation agent. The reduced amount of the carbonylation agent used is compensated by use of a cheap base.

Brief Description of Drawings

Fig. 1 presents the record of an LC MS analysis of the product (mixture of (**15**) and (**16**)) in accordance with Example 2.

Fig. 2 presents the record of an LC MS analysis of the product (mixture of (**15**) and (**16**)) in accordance with Example 6.

Fig. 3 presents the record of an LC MS analysis of the product (**16**) in accordance with Example 4.

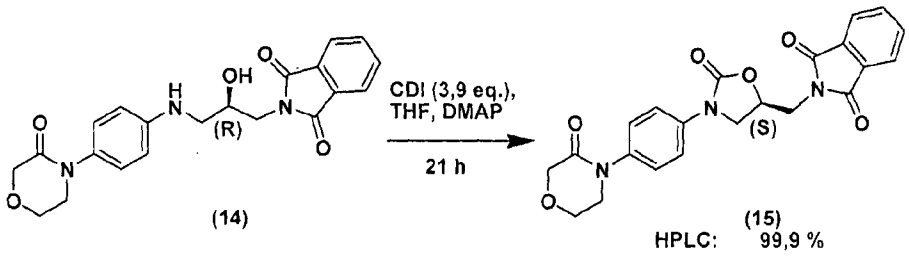
Fig. 4 presents the record of an LC MS analysis of the product (**15**) in accordance with Example 7.

Fig. 5 presents the MS spectrum of the compound (**16**) prepared by the process in accordance with Example 4.

Examples

The subject of the invention will be clarified in more detail by the examples below, which, however, do not affect the scope of the invention defined in the claims in any way.

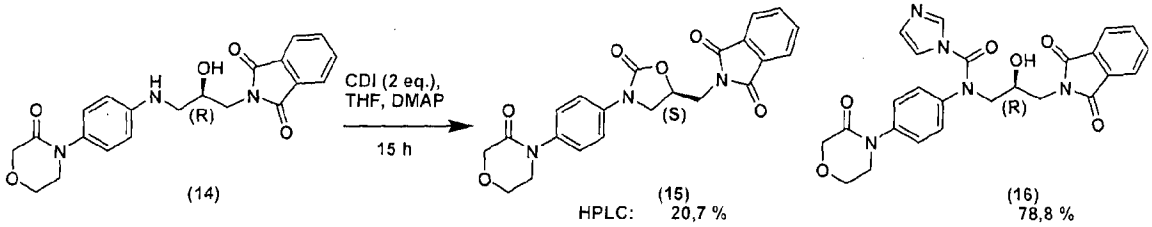
EXAMPLE 1 (preparation of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione (**15**))



300 ml of THF were added to 20 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0506 mol), 16 g of 1,1'-carbonyldiimidazole (0.09869 mol) and 0.1 g of 4-dimethylamino)pyridine. The suspension was stirred and heated to boiling for 7 hours, then slightly cooled and another portion of 1,1'-carbonyldiimidazole (0,09869 mol) was added. Then, the suspension was stirred under boiling for 14 hours. After that the mixture was cooled to 25°C, which was followed by filtration, washing of the cake with THF, with an ethanol/water mixture (9:1) and drying. 15.6

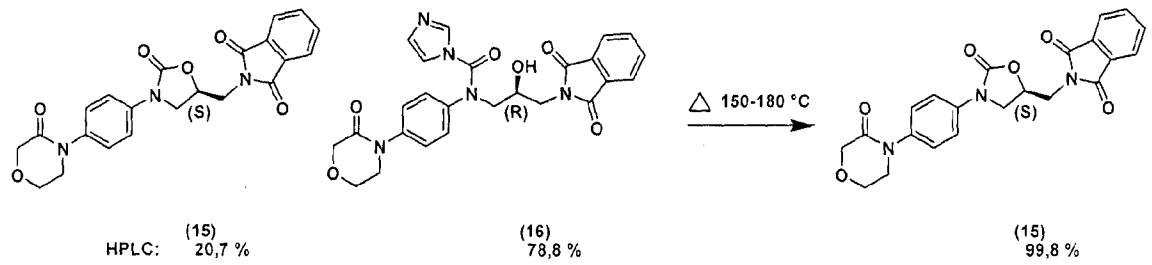
kg of an off-white powder was obtained that melted at the temperature of 216 to 217°C; HPLC 99.9%, content of the (R)- isomer below 0.03%, yield 73%.

EXAMPLE 2 (preparation of a mixture of the compounds (**15**) and (**16**))



400 ml of THF were added to 30 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0759 mol), 25 g of 1,1'-karbonyldiimidazole (0.1542 mol) and 0.1 g of 4-dimethylamino)pyridine. The obtained suspension was stirred and heated to boiling. After ca. 15 minutes from the beginning of boiling the suspension got dissolved, and conversely, after another 15 minutes of boiling a solid substance was formed. Then the suspension was stirred under boiling for 15 hours. After that the mixture was cooled to 25°C, which was followed by filtration, washing of the cake with THF (2x50 ml), with ethanol (2x50 ml) and drying. 32 g of an off-white powder was obtained. The measurement of the melting point showed that this powder first melts at 170-175°C, then re-crystallizes and melts again at 215 to 216 °C; according to HPLC the isolated product was a mixture of 20.7% of the compound (**15**) and 78.8% of the compound (**16**), see Fig. 1.

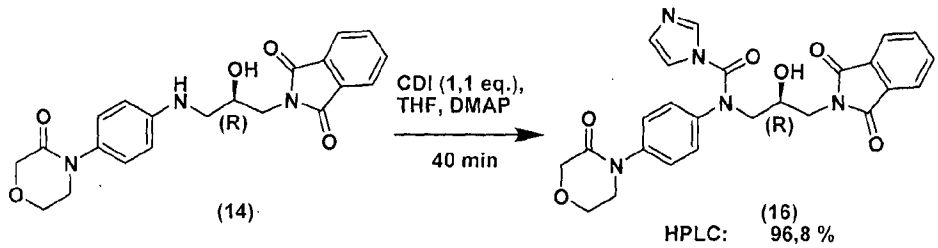
EXAMPLE 3 (preparation of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione (**15**) by melting of the compound (**16**))



The mixture of the compounds (**15**) and (**16**), prepared by the process of Example 2 was heated in a sand bath. The solid substance started to melt when the bath temperature exceeded

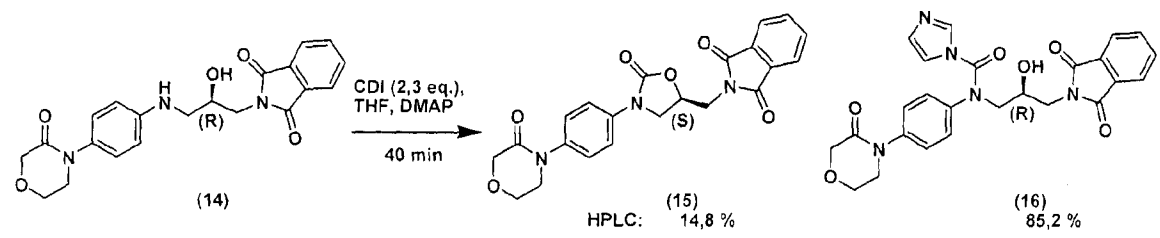
150°C; the temperature was gradually increased to 180°C and the mixture was heated at this temperature for 30 minutes. After cooling the re-melted material was suspended in 75 ml of ethanol and the suspension was thoroughly stirred up. This was followed by filtration, washing of the cake with 25 ml of ethanol and vacuum drying at 120°C. 25.6 g of a white powder with the melt. point of 216 to 218°C was obtained; HPLC 99.8%; the yield, calculated on to starting material (**14**) from Example 2 was 77%.

EXAMPLE 4 (2-((2*R*)-2-hydroxy-3-(*N*-(4-(3-oxomorpholin-4-yl)phenyl)-1*H*-imidazol-yl-1-carboxamido)propyl)-1*H*-isoindol-1,3(2*H*)-dione (**16**))



400 ml of THF were added to 31.2 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0789 mol), 14.5 g of 1,1'-carbonyldiimidazole (0.0894 mol) and 0.1 g of 4-dimethylamino)pyridine. The suspension was stirred and heated to boiling. After ca. 20 minutes from the beginning of boiling the suspension got dissolved, and conversely, after another 5 minutes of boiling a solid substance was formed. Then, the mixture was boiled for another 15 minutes and after that cooled to ca. 40 °C, which was followed by filtration, washing of the cake with THF (2x25 ml) and drying. 35.8 g of white powder that melted at 191 to 193°C was obtained; HPLC 96.8 %, MS (M+1) 490.1, yield 92 %, see Fig. 3 (LC MS) and Fig. 5 (MS).

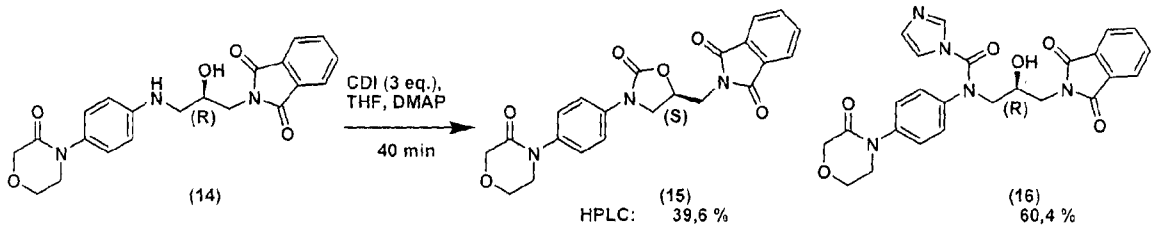
EXAMPLE 5 (preparation of a mixture of the compounds (**15**) and (**16**))



200 ml of THF were added to 15.5 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0392 mol), 14.5 g of 1,1'-

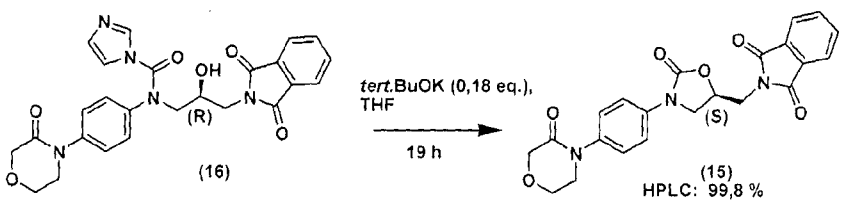
carbonyldiimidazole (0.0894 mol) and 0.05 g of 4-dimethylamino)pyridine. The suspension was stirred and heated to boiling. After ca. 20 minutes from the beginning of boiling the suspension got dissolved, and conversely, after another 5 minutes of boiling a solid substance was formed. Then, the mixture was boiled for another 15 minutes and after that cooled to ca. 40°C, which was followed by filtration, washing of the cake with THF (25 ml) and drying. 18.3 g of an off-white powder that melted at 185-188°C was obtained; according to HPLC the isolated product was a mixture of 14.8% of the compound (**15**) and 85.2% of the compound (**16**).

EXAMPLE 6 (preparation of a mixture of the compounds of (**15**) and (**16**))



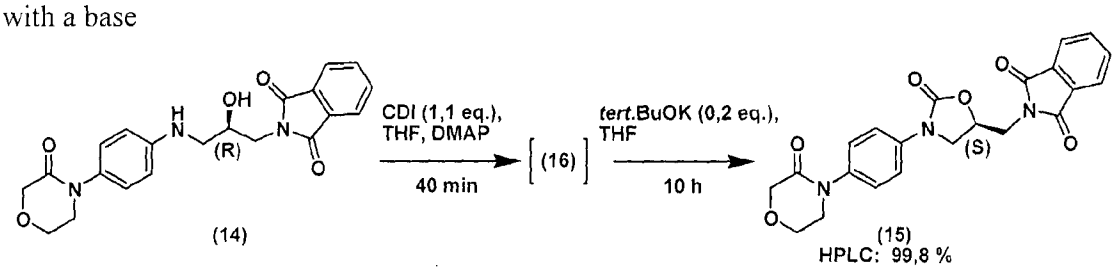
200 ml of THF were added to 15.5 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0392 mol), 19.0 g of 1,1'-carbonyldiimidazole (0.1176 mol) and 0.05 g of 4-dimethylamino)pyridine. The suspension was stirred and heated to boiling. After ca. 20 minutes from the beginning of boiling the suspension got dissolved, and conversely, after another 5 minutes of boiling a solid substance was formed. Then, the mixture was boiled for another 15 minutes and after that cooled to ca. 40°C, which was followed by filtration, washing of the cake with THF (25 ml) and drying. 17.8 of an off-white powder that first melts at 165-175°C, then re-crystallizes and melts again at 215 to 217°C was obtained. According to HPLC the isolated product was a mixture of 39.6% of the compound (**15**) and 60.4% of the compound (**16**), see Fig. 2.

EXAMPLE 7 (preparation of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione (**15**) by treatment of the compound (**16**)) with a base



25 g of 2-((2*R*)-2-hydroxy-3-(*N*-(4-(3-oxomorpholin-4-yl)phenyl)-1*H*-imidazol-yl-1-carboxamido)propyl)-1*H*-isoindol-1,3(2*H*)-dione (**16,** 51 mmol) prepared according to Example 4 were suspended in 350 ml of THF, 5.5 ml of a solution of *tert*-BuOK (20% by weight, 9.1 mmol) was added dropwise under stirring, which was diluted with 20 ml of THF before adding. The suspension was stirred and heated to boiling for 19 hours, then 400 ml of ethanol were added and the boiling continued for 2 hours. Cooling of the mixture to 35°C was followed by filtration, washing of the cake with ethanol, water and ethanol again. After drying, 16.8 g of an off-white powder that melted at 215-217°C was obtained; HPLC 99.8%, content of the (R)- isomer below 0.03%, yield 78%, see Fig. 4.

EXAMPLE 8 (preparation of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione (**15**) by treatment of the compound (**16**)) with a base



400 ml of THF were added to 30 g of 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione (**14**, 0.0759 mol), 13.5 g of 1,1'-carbonyldiimidazole (0.0832 mol) and 0.1 g of 4-dimethylamino)pyridine. The suspension was stirred and heated to boiling. After ca. 20 minutes from the beginning of boiling the suspension got dissolved, and conversely, after another 5 minutes of boiling a solid substance was formed. Then the mixture was boiled for another 15 minutes and after that 9.6 ml of a solution of *tert*-BuOK in THF (20% by weight, 9.1 mmol) diluted with 35 ml of THF were added dropwise. The suspension was stirred and heated to boiling for 10 hours, then 600 ml of ethanol were added and boiling continued for 2 hours. Cooling of the mixture to 35°C was followed by filtration, washing of the cake with ethanol, water and ethanol again. After vacuum drying, 18.2 g of an off-white powder that melted at 216-217°C was obtained; HPLC 99.8%, content of the (R)- isomer below 0.03%, yield 84%.

ANALYTIC METHODS (A-C): Below, the analytic methods used for characterization of the compounds prepared in accordance with the invention are described.

A Mass spectroscopy combined with liquid chromatography (LC-MS)

The mass spectra were obtained with the use of an API 3000 mass spectrometer based on triple quadrupole (AB Sciex, USA), which was connected to an HPLC 200 series liquid chromatograph (Perkin-Elmer, USA). 10 μL of the sample was sprayed onto a Kinetex column, 150 x 4.6 mm; 2.6μ (Phenomenex, USA). The mobile phase consisted of a mixture of ACN – 10 mM ammonium formate, pH 6.3. The gradient program was as follows: isocratically 30% ACN up to 4 min, then gradient to 100% ACN up to 18 min. The flow rate of the mobile phase was 600 μl/min. An APCI ion source in the positive full scan mode was used for detection in the mass spectrometer. The temperature of the ion source was 300°C, the scanning range was from m/z 50 to m/z 1000 and nitrogen with the flow of 12 arbitrary units was used as the nebulization gas. The wavelength of 230 nm was used for detection in the PDA detector. The Analyst 1.4.1. software (AB Sciex, USA) was used for data acquisition.

B Melting point

Melting points of the prepared substances were measured on a Kofler block with the sample heating rate of 10°C/min (up to 120°C) and 4°C/min (over 120°C). The measured values of melting points or melting intervals, respectively, are given in the respective Examples.

C High-Performance Liquid Chromatography (HPLC)

Related substances and optical purity of substances were measured in a Waters Alliance 2695/2695XC liquid chromatograph with a W2996/W2998 PDA detector.

For determination of related substances of the products (**15**) and (**16**), a Discovery RP Amide C16 column, 150 x 4.0 mm, 5 μm was used at 10°C. Gradient elution with a three-component mobile phase (component A: 10 mM aqueous solution of ammonium acetate, pH = 5.0; component B: acetonitrile; component C: methanol) in accordance with the table below was used:

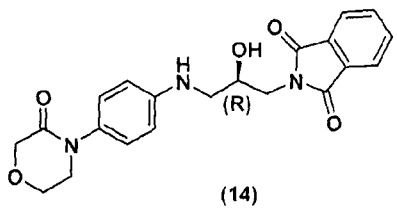
Time (min)	Flow (ml/min)	Component A (%)	Component B (%)	Component C (%)
0	1.0	90	10	0
1	1.0	90	10	0
11	1.0	65	20	15
16	1.0	65	20	15
25	1.0	40	60	0
35	1.0	40	60	0
36	1.0	90	10	0
40	1.0	90	10	0

The wavelength used for the detection was 260 nm

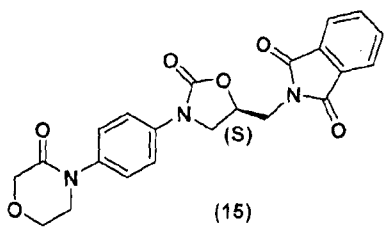
For determination of the optical purity of the product (**15**), a Chiralpak AD-RH column, 150 x 4.6 mm, 5 μm was used at 35°C. Isocratic elution with a two-component mobile phase with the following composition: component A: 0.01 M aqueous solution of potassium hydrogen phosphate pH = 7.5; component B: acetonitrile was used. The analysis was performed at the flow rate of 1.0 ml/min and the proportion of the A:B components = 40:60 *(V/V)*; the substances were detected at the wavelength of 240 nm.

CLAIMS

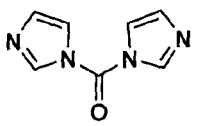
1. A process for the preparation of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**15**), characterized in that 2-((2*R*)-2-hydroxy-3-{[4-(3-oxomorpholin-4-yl)phenyl]amino}propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**14**) is cyclized by a process, which consists of the following steps:
   (a) reaction of the compound (**14**) performed in a suitable solvent with 1 to 1.5 equivalents of 1,1'-carbonyldiimidazole of formula (**8**), producing a mixture of the non-cyclic intermediate 2-((2*R*)-2-hydroxy-3-(*N*-(4-(3-oxomorpholin-4-yl)phenyl)-1*H*-imidazol-1-yl-carboxamido)propyl)-1*H*-isoindol-1,3(2*H*)-dione of formula (**16**) and the cyclic product of formula (**15**) that contains more than 50% of the compound (**16**);
   (b) cyclization of the mixture of compounds from step (a) in a solvent or a mixture of solvents suitable for cyclization in the presence of a suitable base as the catalyst;
   (c) isolation of the cyclic compound (**15**).



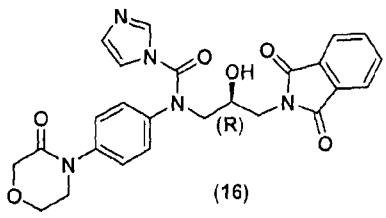
(14)



(15)



(8)



(16)

2. A process for the preparation of the compound (**15**) according to claim 1, characterized in that said suitable solvent in step (a) is selected from the group comprising a C_4 to C_8 ether, polyethylene glycol, a C_1 to C_6 chlorinated solvent or their mixtures in any proportion.

3. A process for the preparation of the compound (**15**) according to claims 1 and 2, characterized in that said suitable solvent in step (a) is selected from the group comprising tetrahydrofuran, 2-methyltetrahydrofuran, 1,4-dioxane, *tert*-butylmethylether, di*tert*-butylether, polyethylene glycol PEG-200 to PEG-800, dichloromethane, chloroform, 1,1,2-trichloroethylene, chlorobenzene or their mixtures in any proportion.

4. A process for the preparation of the compound (**15**) according to claim 1, characterized in that said suitable base in step (b) is a metal alkoxide of formula (**17**),

R-O-M

(17)

wherein R means a linear or branched C_1 to C_8 alkyl and M means an alkali metal.

5. A process for the preparation of the compound (**15**) according to claim 4, characterized in that said suitable base in step (b) is a metal alkoxide selected from the group of sodium methoxide, potassium methoxide, sodium ethoxide, potassium ethoxide, sodium isopropoxide, sodium *tert*-butoxide, potassium *tert*-butoxide, lithium *tert*-butoxide.

6. A process for the preparation of the compound (**15**) according to claim 1, characterized in that said suitable base in step (b) is a base selected from the group of sodium hydroxide, potassium hydroxide, lithium hydroxide, sodium hydride, methyllithium, n-butyllithium, lithium diisopropylamide or lithium hexamethyldisilazide.

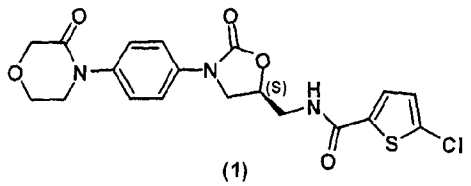
7. A process for the preparation of the compound (**15**) according to claim 5, characterized in that said suitable base is potassium *tert*-butoxide or its solution in an organic solvent, preferably a solution in tetrahydrofuran.

8. A process for the preparation of the compound (**15**) according to claim 1, characterized in that said suitable solvent for cyclization in step (b) is selected from the group comprising a C_4 to C_8 ether, polyethylene glycol, a C_1 to C_6 chlorinated solvent or their mixtures in any proportion.

9. A process for the preparation of the compound (**15**) according to claim 1, characterized in that the cyclization in step (b) is carried out at a temperature of from 40°C to the boiling point of the solvent.

10. A process for the preparation of the compound (**15**) according to claim 1, characterized in that the isolation in step (c) is carried out by filtering the product from the reaction mixture, washing with a C_1 to C_5 alcohol and/or water and drying the isolated product.

11. Use of the compound (**15**), prepared by a process according to any one of claims 1 to 10, for the preparation of rivaroxaban (**1**).



(1)

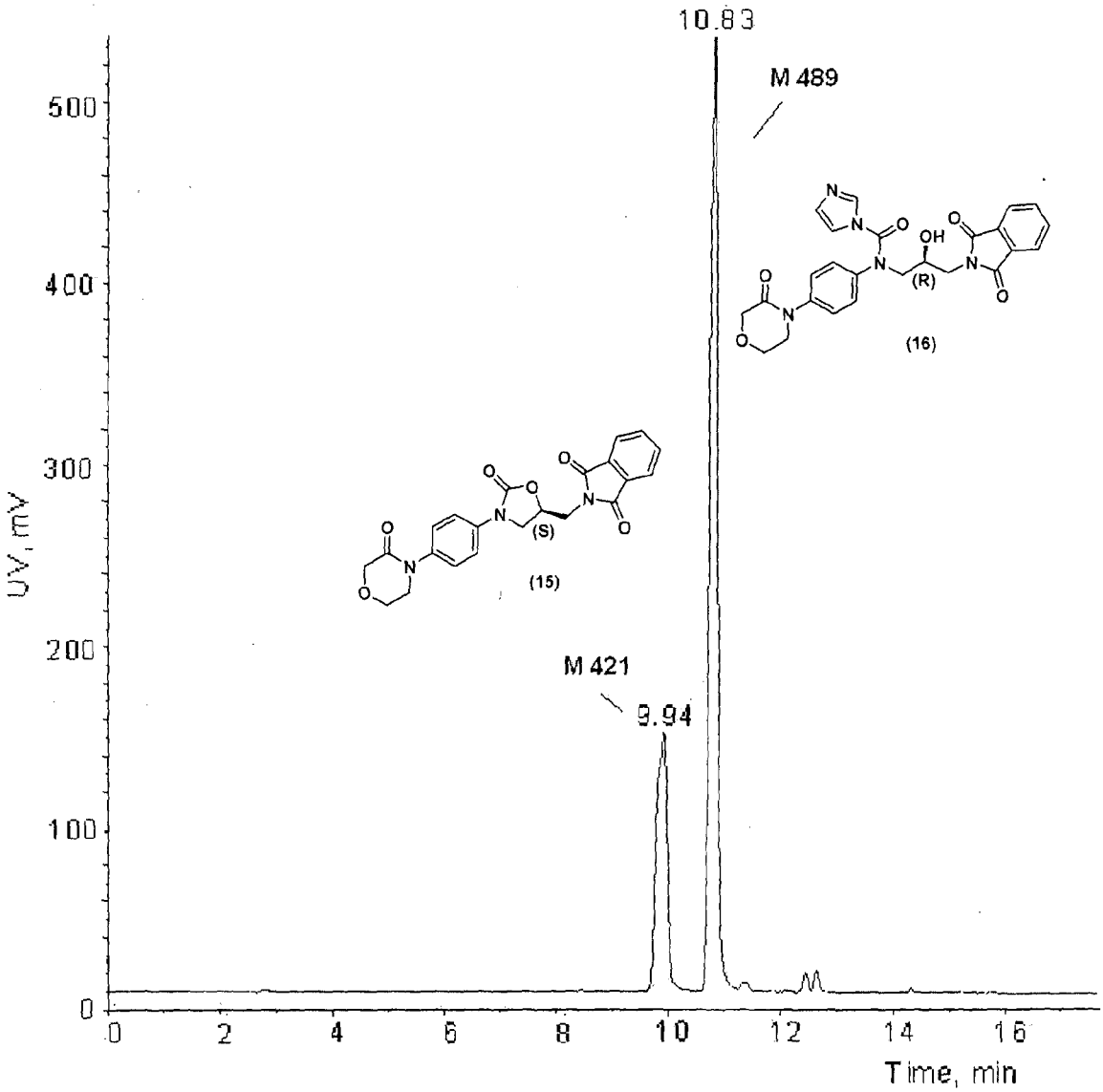

10.83
M 489
500
400
300
200
100
0
UV, mV
0
2
4
6
8
10
12
14
16
Time, min
M 421
9.94
(S)
(15)
(R)
(16)
OH

Fig. 1

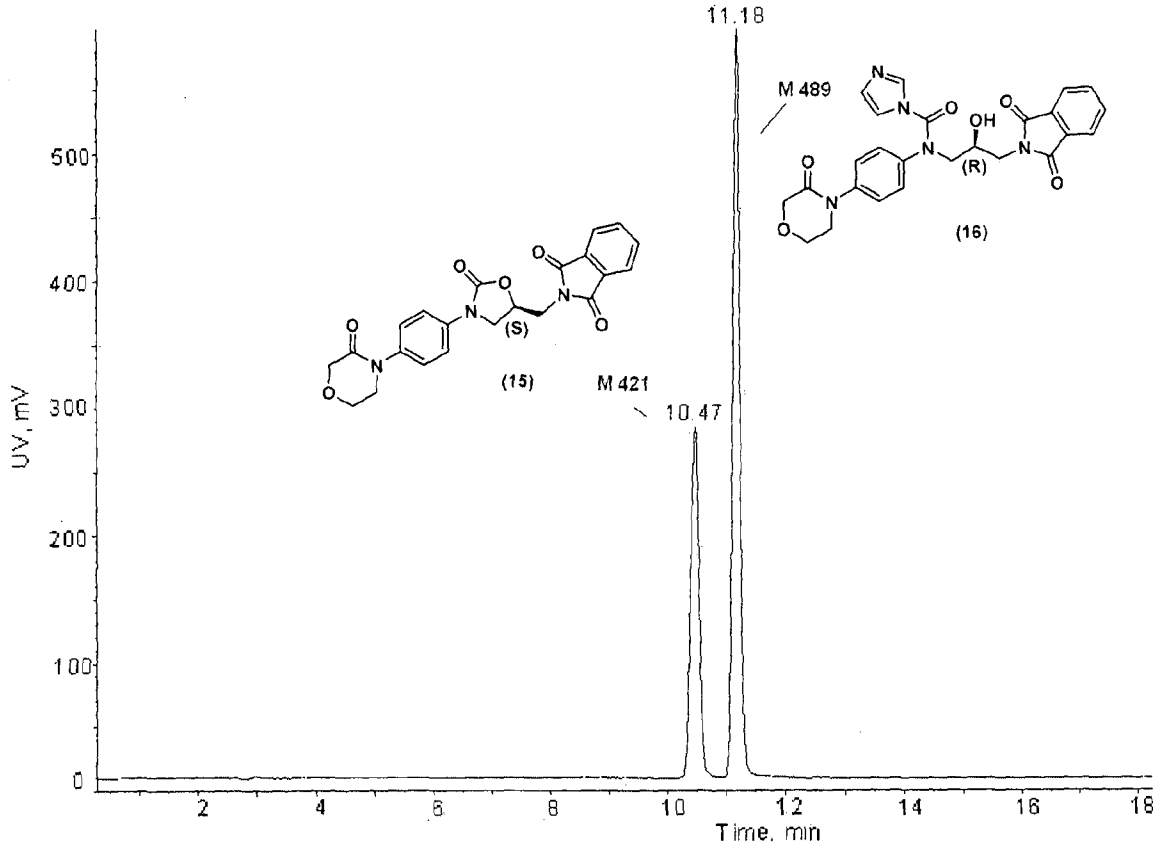

11.18
M 489
OH
(R)
(16)
(S)
(15)
M 421
10.47
UV, mV
500
400
300
200
100
0
2
4
6
8
10
12
14
16
18
Time, min

Fig. 2

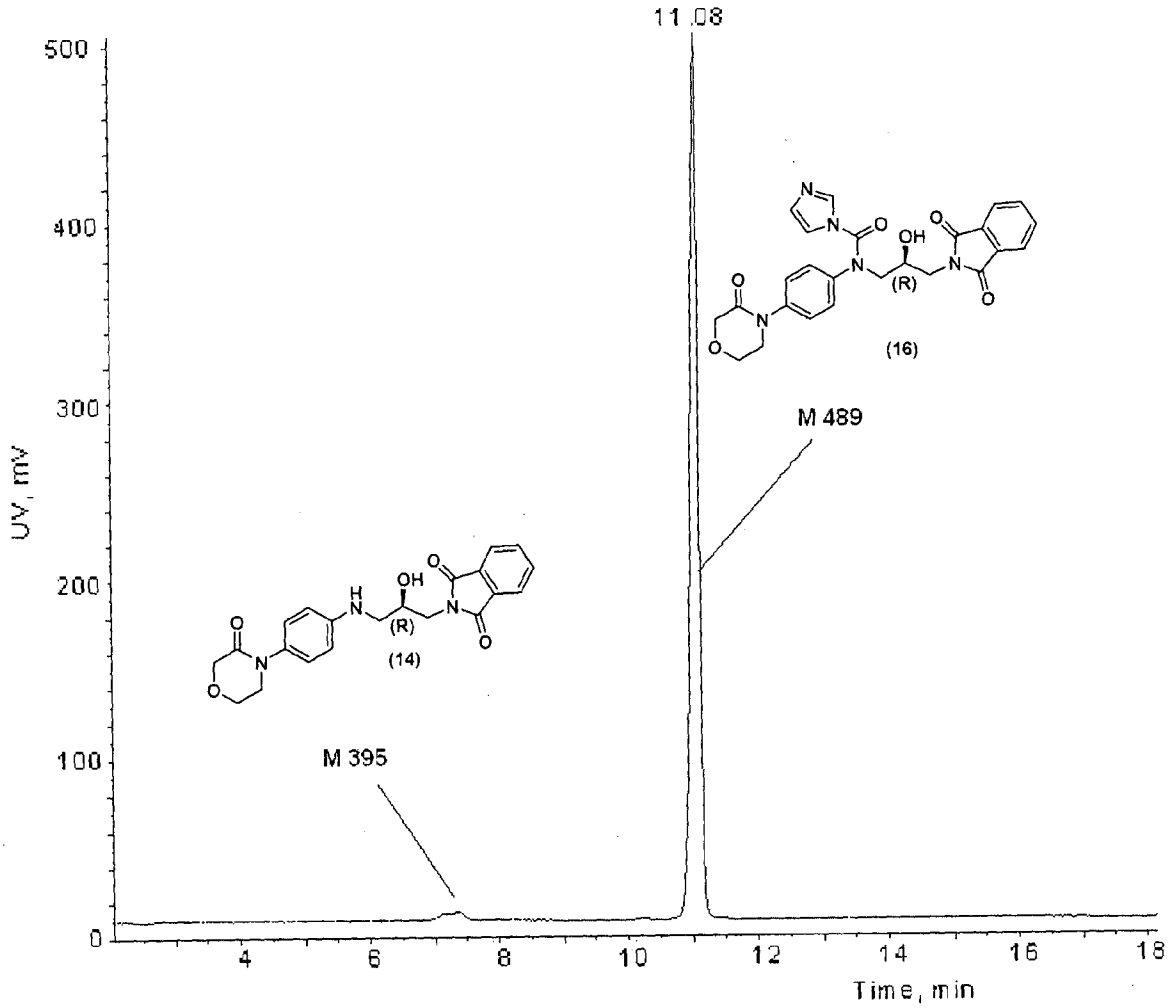

11.08
500
400
300
200
100
0
UV, mV
M 489
M 395
(14)
(16)
4
6
8
10
12
14
16
18
Time, min

Fig. 3

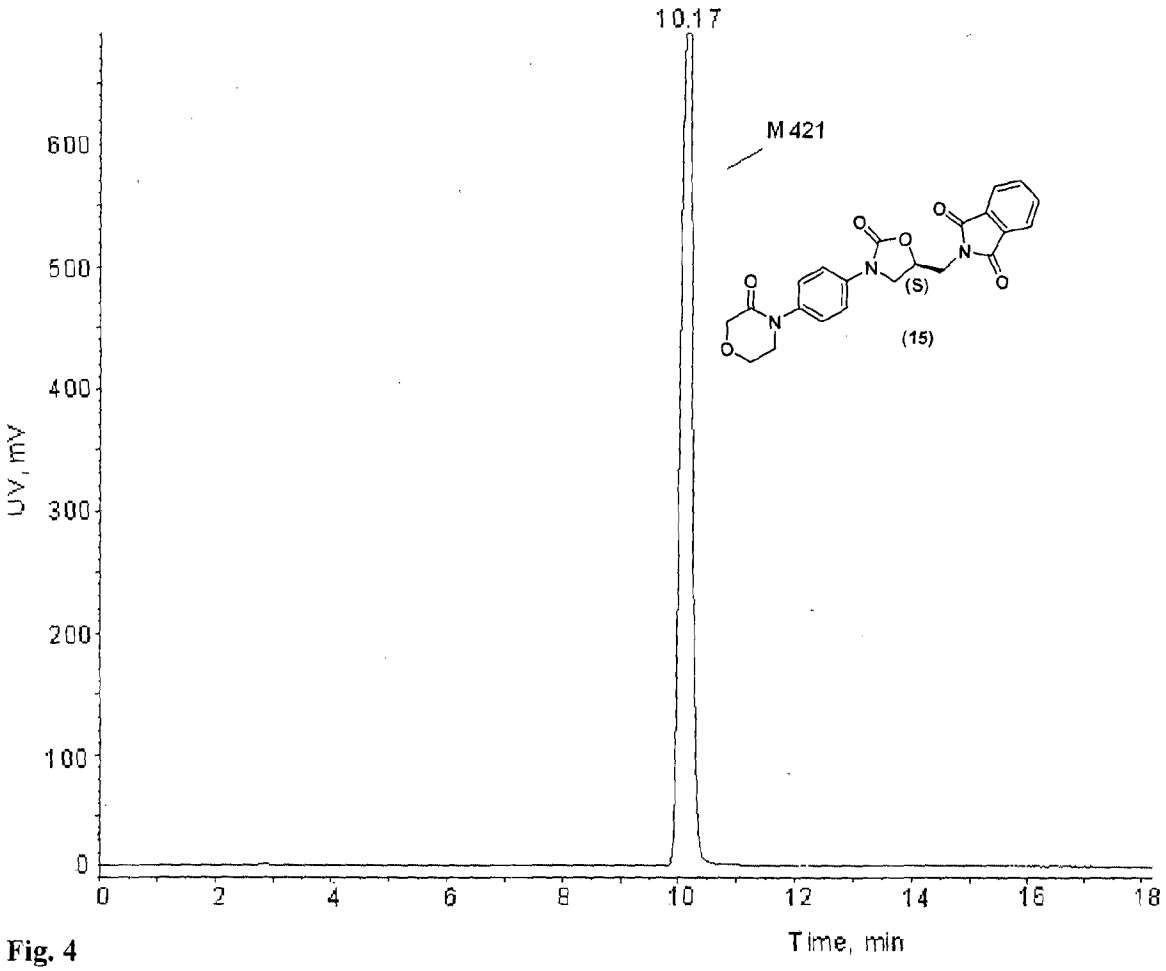

10.17
M421
600
500
400
300
200
100
0
UV, mV
0
2
4
6
8
10
12
14
16
18
Time, min
(S)
(15)

Fig. 4

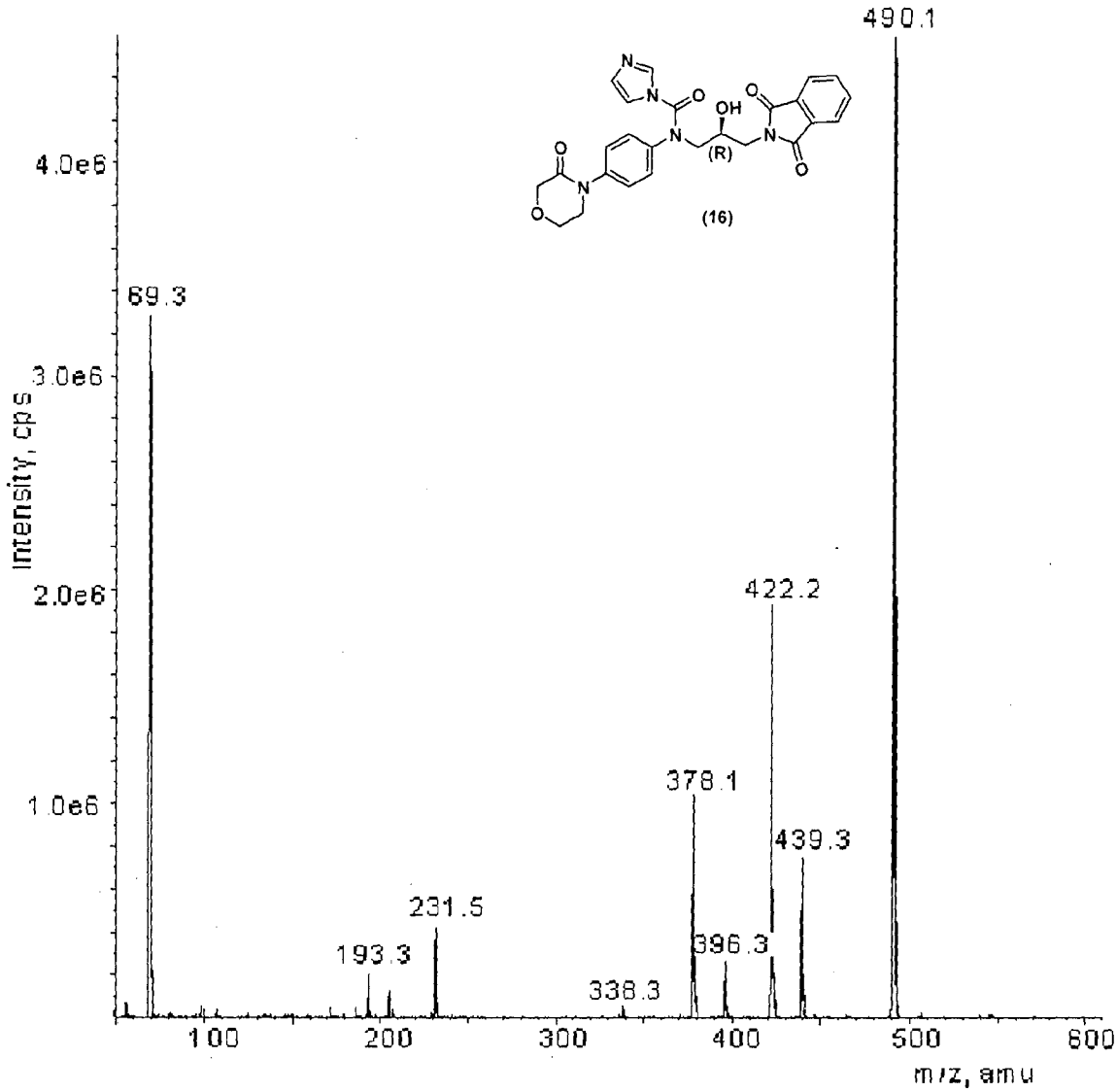

490.1
69.3
422.2
378.1
439.3
231.5
193.3
396.3
338.3
4.0e6
3.0e6
2.0e6
1.0e6
Intensity, cps
100
200
300
400
500
600
m/z, amu
(16)

Fig. 5

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000014

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D409/14
ADD.

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2008/155034 A1 (BAYER HEALTHCARE AG [DE]; ROEHRIG SUSANNE [DE]; HAERTER MICHAEL [DE];) 24 December 2008 (2008-12-24) page 75; example 61A -----	1-11
X	DE 10 2004 002044 A1 (BAYER HEALTHCARE AG [DE]) 4 August 2005 (2005-08-04) page 6 - paragraph 32 -----	1-11
	-/--	

[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
26 March 2013	08/04/2013

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	Bissmire, Stewart

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

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000014

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SUSANNE ROEHRIG ET AL: "Discovery of the Novel Antithrombotic Agent 5-Chloro-N-({(5S)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)thiophene2-carboxamide (BAY-59-7939): An Oral, Direct Factor Xa Inhibitor", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 48, no. 19, 22 September 2005 (2005-09-22), pages 5900-5908, XP002680548, ISSN: 0022-2623, DOI: 10.1021/JM050101D [retrieved on 2005-08-18] cited in the application the whole document -----	1-11

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2013/000014

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2008155034 A1	24-12-2008	AR 067058 A1	30-09-2009
		AU 2008266527 A1	24-12-2008
		CA 2692172 A1	24-12-2008
		CN 101772496 A	07-07-2010
		CO 6251282 A2	21-02-2011
		CR 11169 A	01-07-2010
		DE 102007028320 A1	24-12-2008
		DO P2009000287 A	31-01-2010
		EC SP099806 A	29-01-2010
		EP 2167495 A1	31-03-2010
		GT 200900318 A	04-10-2010
		JP 2010530385 A	09-09-2010
		KR 20100029213 A	16-03-2010
		MA 31570 B1	02-08-2010
		PA 8784101 A1	09-02-2009
		PE 03332009 A1	15-04-2009
		RU 2010101302 A	27-07-2011
		TW 200914447 A	01-04-2009
		US 2010184767 A1	22-07-2010
		UY 31136 A1	30-01-2009
		WO 2008155034 A1	24-12-2008
DE 102004002044 A1	04-08-2005	AR 047389 A1	18-01-2006
		AT 518856 T	15-08-2011
		AU 2004313694 A1	28-07-2005
		BR PI0418405 A	15-05-2007
		CA 2553237 A1	28-07-2005
		CN 1906191 A	31-01-2007
		DE 102004002044 A1	04-08-2005
		DK 1720866 T3	21-11-2011
		EC SP066703 A	31-10-2006
		EP 1720866 A1	15-11-2006
		ES 2369140 T3	25-11-2011
		GT 200400277 A	18-08-2005
		HK 1103722 A1	14-01-2011
		HN 2005000016 A	01-06-2009
		HR P20110796 T1	31-12-2011
		IL 176767 A	28-04-2011
		JP 2007517816 A	05-07-2007
		JP 2012097106 A	24-05-2012
		KR 20130004257 A	09-01-2013
		MA 28290 A1	01-11-2006
		MY 138944 A	28-08-2009
		NZ 548506 A	26-06-2009
		PE 07632005 A1	02-12-2005
		PL 1720866 T3	31-01-2012
		PT 1720866 E	12-10-2011
		RU 2383540 C2	10-03-2010
		SI 1720866 T1	31-01-2012
		US 2005182055 A1	18-08-2005
		UY 28718 A1	31-08-2005
		WO 2005068456 A1	28-07-2005
		ZA 200605747 A	31-10-2007