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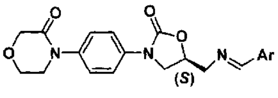
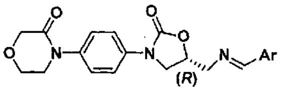
(54) Title: A PROCESS FOR THE PREPARATION OF RIVAROXABAN BASED ON THE USE OF (S)-EPICHLOROHYDRIN



(S)-(9)



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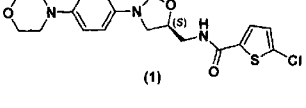
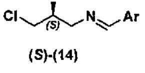


(1)



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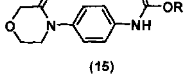

(15)

(57) Abstract: The invention relates to the stereoisomers of 4-{4-[(S/R)-5-[(((aryl)methylene)- amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-ones described by the chemical formulae (S)-(9) and (R)-(9). The optical isomer of compound (9) with the (S)- configuration is industrially applicable for the manufacture of the antithrombotic drug rivaroxaban (1). The new preparation process of rivaroxaban comprises a reaction of (S)-1- chloro-3-(((aryl)methylene)amino)propan-2-ols (S)-(14) with alkyl 4-(3-oxomorpholine-4- yl)phenylcarbamates (15) providing the key intermediate (S)-(9), which is further subjected to hydrolytic deprotection and subsequent acylation, producing rivaroxaban. The commercially available (S)-epichlorohydrin has been conveniently used as the chiral building block for the production of the key intermediate.

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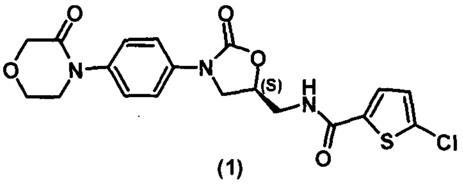
A process for the preparation of rivaroxaban based on the use of (*S*)-epichlorohydrin.

Technical Field

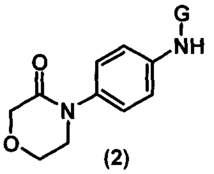
The invention relates to the stereoisomers of new chiral compounds of formulae (*S*)-**(9)** a (R)-**(9)**, the (*S*)-**(9)** compounds serving as intermediates for preparation of rivaroxaban of formula **(1)**, which is a chemical substance used for preparation of a drug from the therapeutic group of 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 (WO 01/47919, 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).

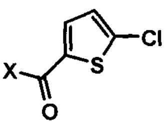


(1)



(2)

G = -H, alkyl, $-\underset{O}{\underset{\|}{C}}-$Oalkyl

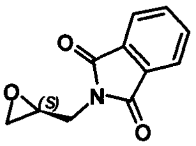


(3)

X = -OH, -Cl, -NH$_2$

For the preparation of rivaroxaban several key structures, referred to as building blocks, can be used as advanced intermediates. Virtually all the so far described syntheses are using two such building blocks. The first one are derivatives of 4-(4-aminophenyl)morpholin-3-one, where it may be the case of an unsubstituted amine (**2**, G means hydrogen), or a derivative alkylated on nitrogen, or a carbamate derived from this compound (**2**, G means an alkyl or COOalkyl group). The other general and commonly used building block for the rivaroxaban molecule are derivatives of 5-chlorothiophene-2-carboxylic acid (**3**, X means -OH), or its functional derivatives such as the chloride and amide (**3**, X means -Cl or -NH$_2$).

Various synthetic approaches used for synthesis of rivaroxaban differ from each other mainly as regards the chiral building block, which is the source for the construction of the central heterocycle, i.e., 2-oxo-1,3-oxazolidine, wherein the chirality centre is also located. For pharmaceutical purposes one optical isomer derived from rivaroxaban is only used, in particular the target molecule with the absolute configuration (*S*)-. The selection of a suitable chiral building block must be subjected to this fact.



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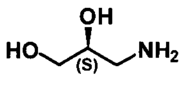

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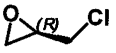

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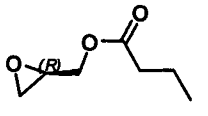

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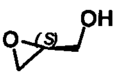
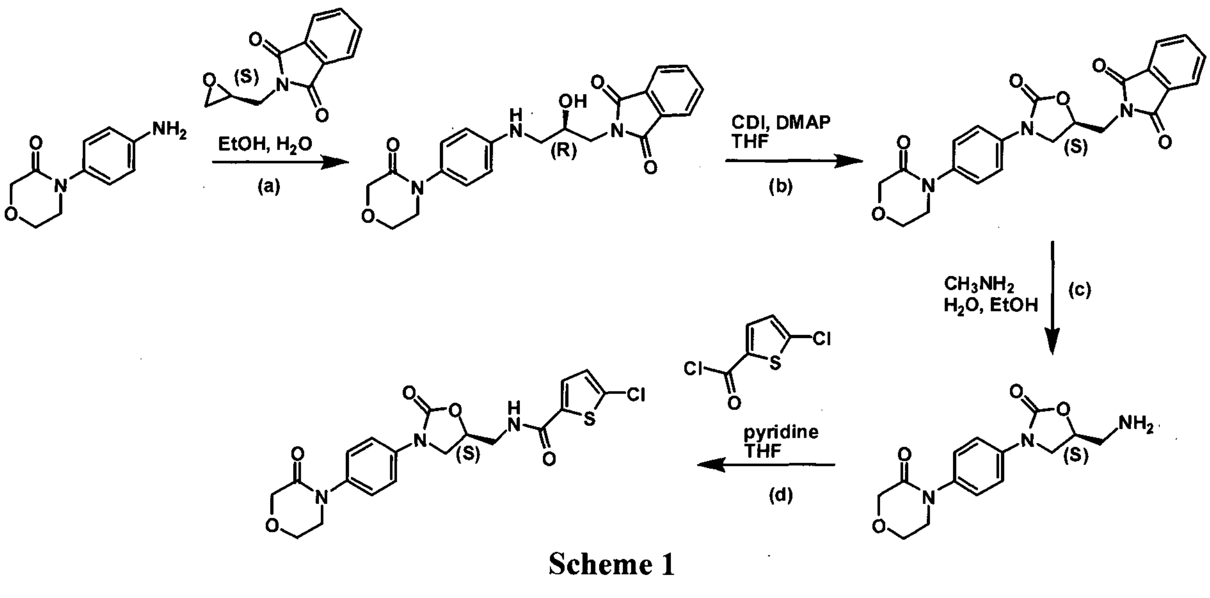


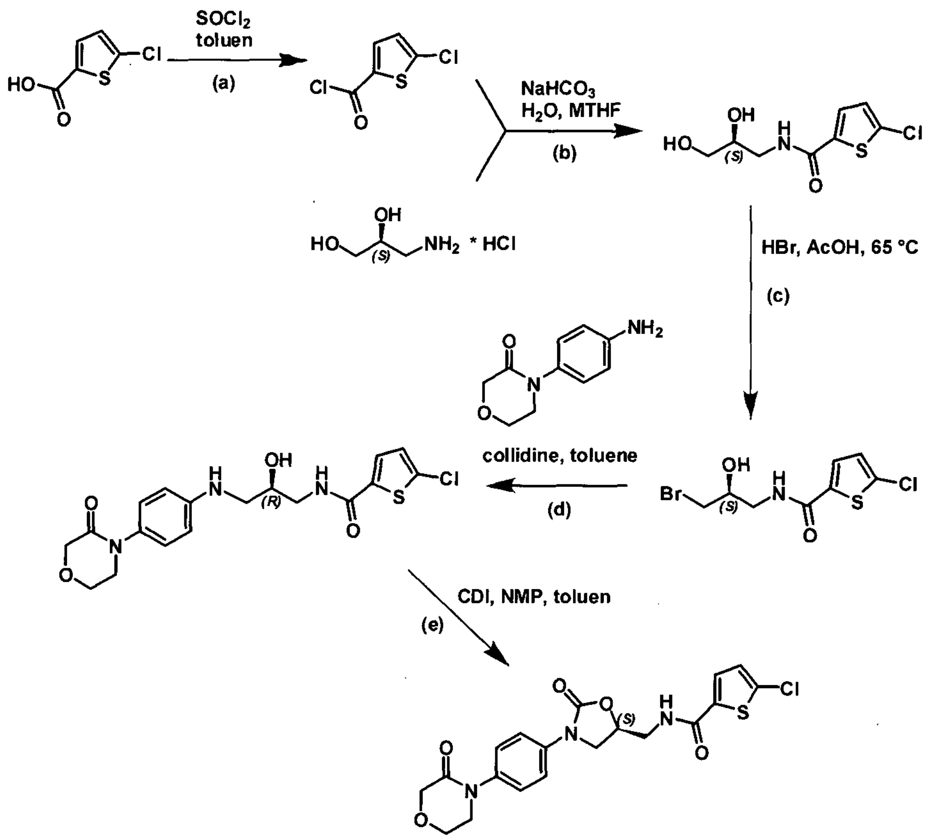
(8)

Chiral building blocks that have been successfully used for synthesis of rivaroxaban include (*S*)-glycidyl phthalimide **(4)**, (S)-3-aminopropane-1,2-diol **(5)**, (*R*)-epichlorohydrin **(6)** and (*R*)-glycidyl butyrate **(7)**. (*S*)-glycidol **(8)** was used as a starting material for the preparation of (*S*)-glycidyl phthalimide **(4)** (*Tetrahedron: Asymmetry,* Vol. 7, No. 6, pp. 1641-1648, 1996).

The known methods of chemical synthesis of rivaroxaban **(1)** are described in Schemes 1 to 7. The first one is the process according to Scheme 1 (WO 01/47919 Bayer, US 7 157 456 B2, *J.Med.Chem.* (2005), 48(19), 5900-5908), which starts from 4-(4-aminophenyl)morpholin-3-one and (*S*)-glycidyl phthalimide **(4)**. The second synthetic process follows Scheme 2 (WO 2004/060887, Bayer) and starts from 5-chlorothiophene-2-carboxylic acid (**3**, X means –OH) and (*S*)-3-aminopropane-1,2-diol **(5)**. 4-(4-aminophenyl)morpholin-3-one only engages in the synthesis in the penultimate stage in case of the process according to Scheme 2.

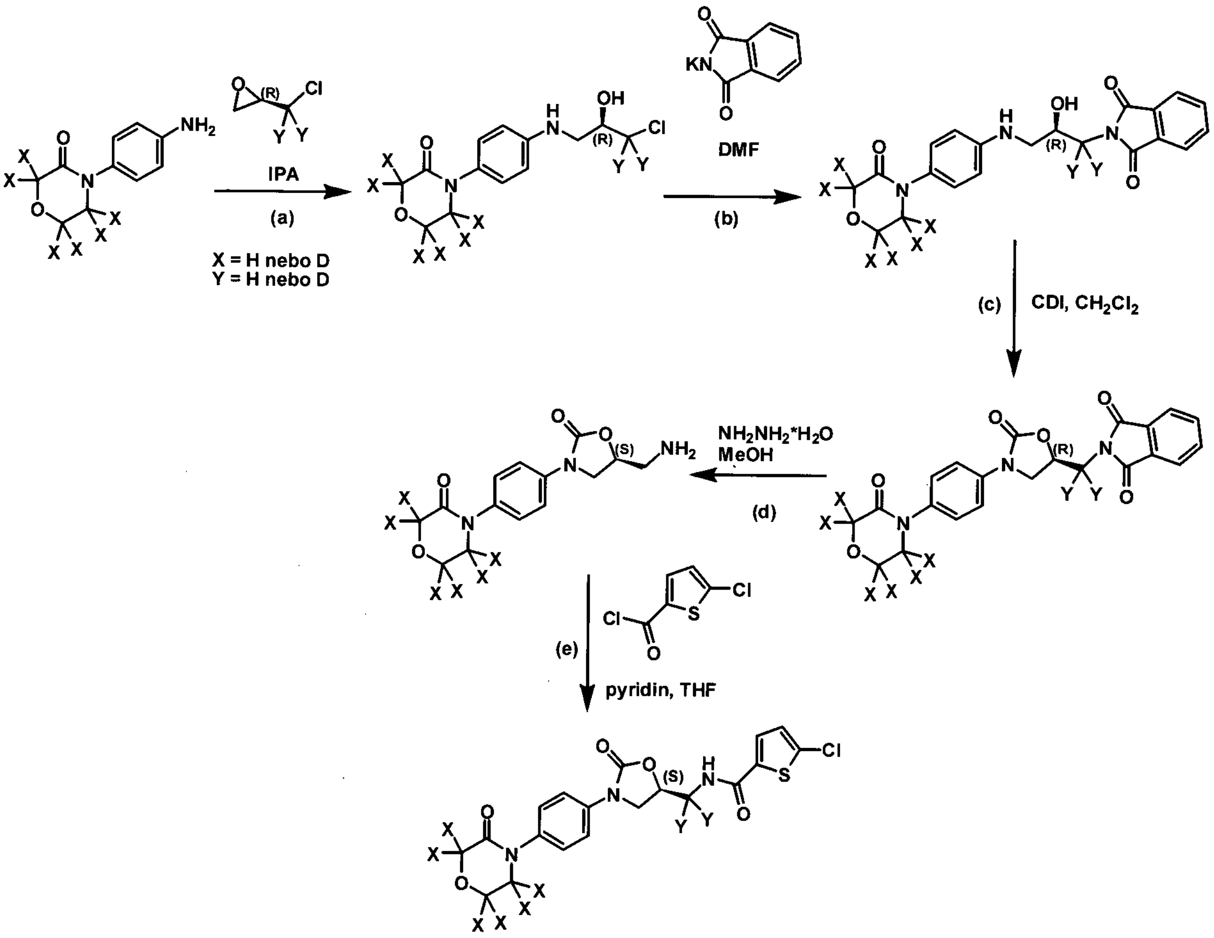


Scheme 1

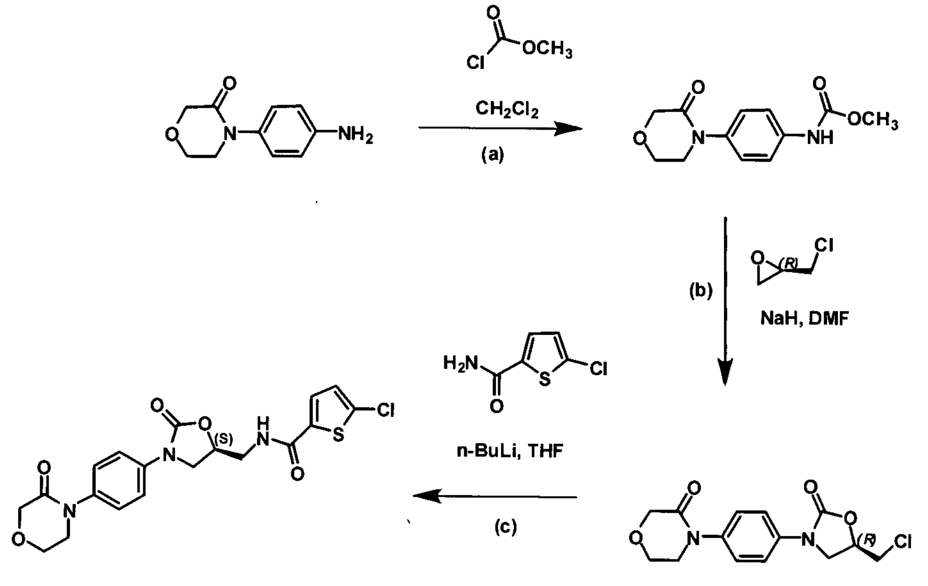


Scheme 2

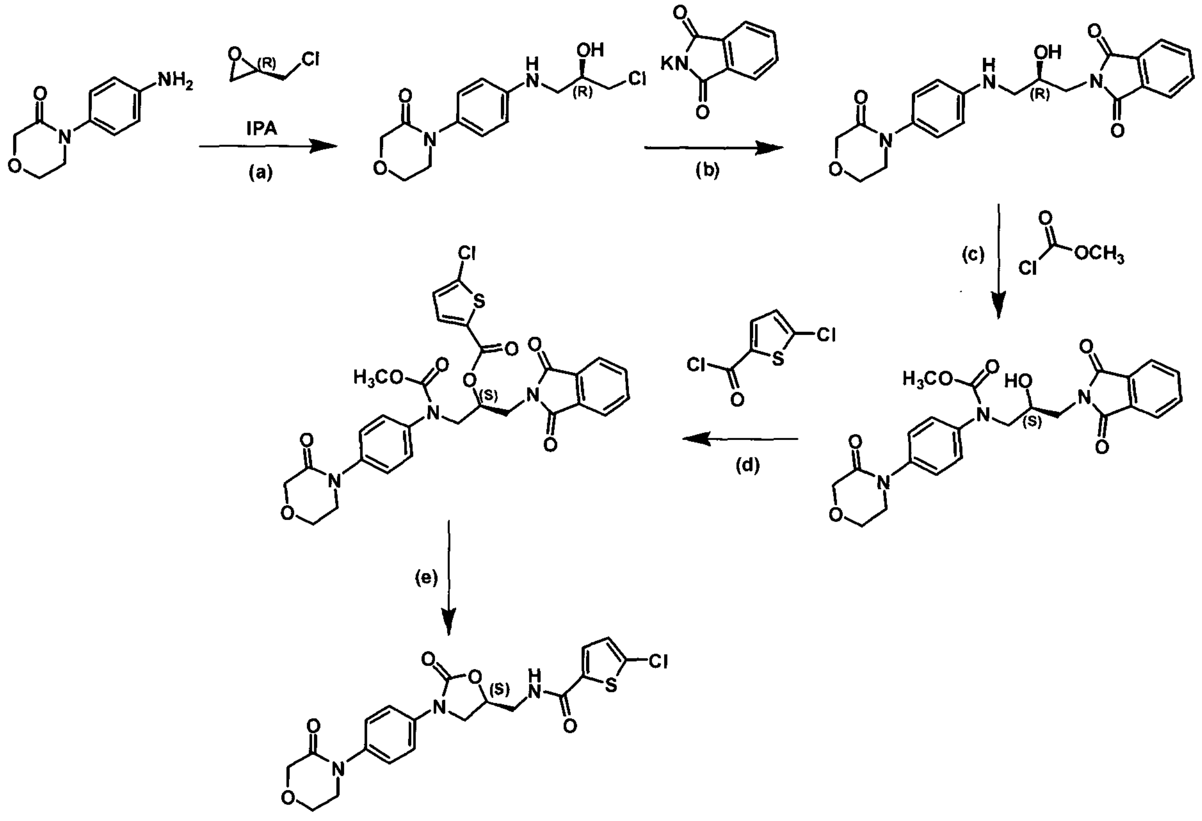
The third synthetic process, which proceeds according to Scheme 3, was mainly used for preparation of deuterated analogs of rivaroxaban (WO 2009/023233 A1, Concert Pharm.). It also represents the first synthetic process in which (*R*)-epichlorohydrin **(6)** was used as the chiral building block. The other key starting material for the third process was 4-(4-aminophenyl)morpholin-3-one. The fourth synthetic process, which proceeds according to Scheme 4 (WO 2010/124835 A1, Apotex), again uses (*R*)-epichlorohydrin as the chiral building block, which reacts with the alkyl carbamate derived from 4-(4-aminophenyl)morpholin-3-one in the key stage. The fifth synthetic process, which proceeds according to Scheme 5 (US 20110034465 A1), also uses (*R*)-epichlorohydrin as the chiral building block, which directly reacts with 4-(4-aminophenyl)morpholin-3-one in the key stage, which is the same reaction as in the third process. The differences between the third and fifth processes consist in the preparation method of the 2-oxo-1,3-oxazolidine cycle and in the carbonylation agent used. While the third process uses 1,1'-carbonyldiimidazol (CDI) as the carbonylation agent, the fifth process uses more available and cheaper alkyl chloroformates.



Scheme 3

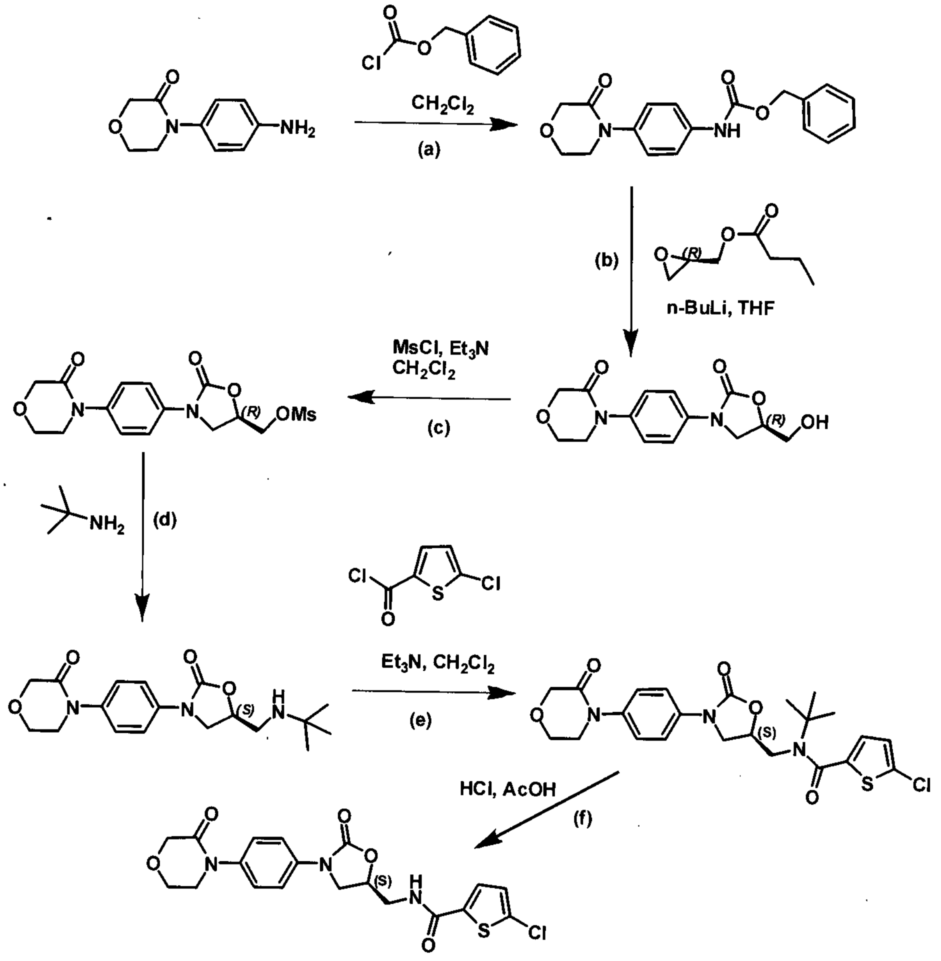


Scheme 4

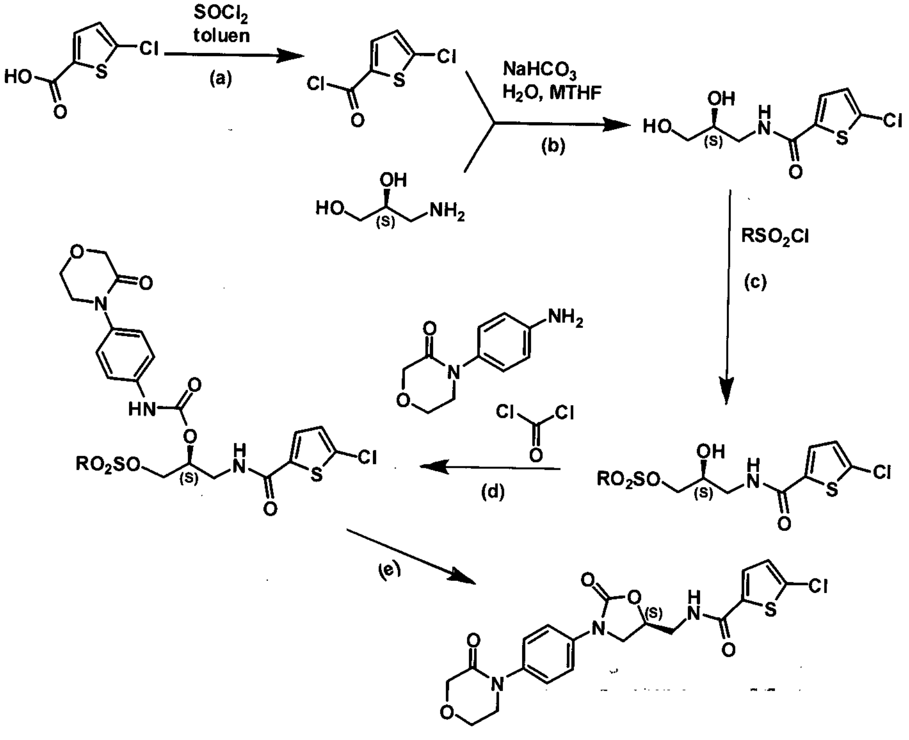


Scheme 5

The sixths synthetic process, which proceeds according to Scheme 6 (WO 2011/080341 A1), uses (*R*)-glycidyl butyrate **(7)** as the chiral building block, which in the key stage reacts with the alkyl carbamate derived from 4-(4-aminophenyl)morpholin-3-one. The last, seventh synthetic process leading to rivaroxaban proceeds according to Scheme 7 (WO 2011/098501 A1) and, like process 2, uses (*S*)-3-aminopropane-1,2-diol **(5)** as the chiral building block. The differences between the second and seventh processes consist in the preparation process of the 2-oxo-1,3-oxazolidine cycle and the carbonylation agent used. While the second process uses 1,1'-carbonyldiimidazol (CDI) as the carbonylation agent, the fifth process uses the cheaper, but very toxic phosgene.

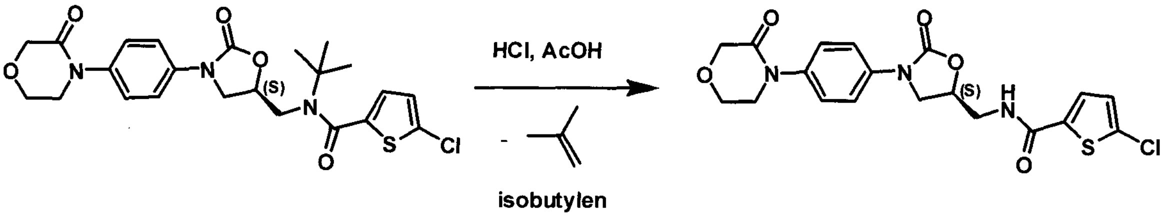


Scheme 6



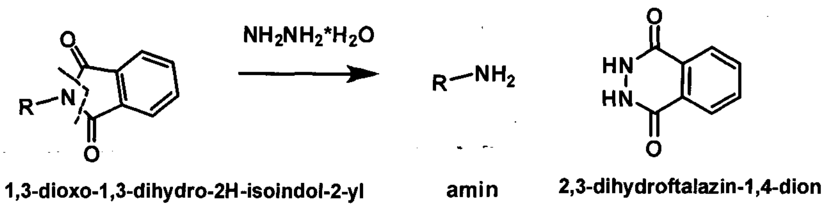
Scheme 7

The processes used for the synthesis of rivaroxaban differ from each other especially in the chiral building block (compounds 4 to 7) and in the carbonylation agents (CDI, alkyl chloroformates, phosgene) used. Another difference can be found in the method of performing deprotection reactions, i.e. such reactions that lead to elimination of the protecting groups, initially bound to the nitrogen atom of the advanced intermediates and which had the initial purpose of protecting these intermediates from undesired chemical transformations. No deprotection reactions were necessary in the case of the processes according to Schemes 2, 4 and 7, as the protecting groups bound to the nitrogen atom eventually became part of the final product. In the case of process 6 it was necessary to deprotect the *tert*-butyl group bound to the nitrogen. The reaction used was an acid catalyzed reaction of the *tert*-butyl group, releasing isobutylene according to Scheme 8. In normal conditions isobutylene is a gas and thus can be very easily separated from the final product.



Scheme 8

In the case of the processes according to Schemes 1, 3 and 5 it was necessary to perform deprotection of the 1,3-dioxo-1,3-dihydro-2*H*-isoindol-2-yl protecting group according to Scheme 9. In these cases it consisted either in hydrazinolysis or aminolysis of this protecting group, which resulted in release of the desired amine. Simultaneous formation of hard-to-separate impurities, e.g. 2,3-dihydrophthalazine-1,4-dione, was an undesired side effect, which rendered isolation of the chemically pure amine impossible without using special separation techniques. In these cases, a mixture of the amine with side products of the deprotection was used in the final synthetic step, which represents acylation of the amine (*J.Med.Chem.* (2005), 48(19), 5900-5908, and WO 2009/023233 A1).



Scheme 9

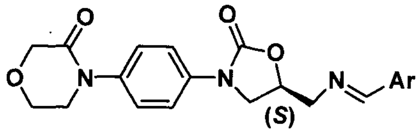
The present invention relates to new optically active precursors of rivaroxaban and to a simple, efficient and industrially applicable method of using these precursors for synthesis of rivaroxaban. With regard to the use of the widely available and cheap raw material as the chiral building block, the invented process can potentially significantly reduce the costs of commercial production of rivaroxaban.

Disclosure of Invention

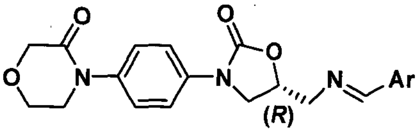
The invention provides the stereoisomers of 4-{4-[(*S*/*R*)-5-[(((aryl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one described by the chemical formulae (*S*)-**(9)** and (*R*)-**(9)**. The invention also encompasses a new process for the preparation of the antithrombotic drug rivaroxaban **(1)**, which comprises reaction of (*S*)-1-chloro-3-(((aryl)methylene)amino)propan-2-ol of formula (*S*)-**(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate **(2,** G = **COOalkyl)** providing the key intermediate of formula (*S*)-**(9)**, which is further subjected to hydrolytic deprotection and acylation producing rivaroxaban **(1)**. The commercially available (*S*)-epichlorohydrin was preferably used as the chiral building block for preparation of the key intermediate (*S*)-**(9)**.

Detailed description of the invention

The present invention relates to the stereoisomers of the compounds with the chemical name 4-{4-[(*S*/*R*)-5-[(((aryl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-ones, which are described by the chemical formulae (*S*)-**(9)** and (*R*)-**(9)**, wherein (*S*)- and (*R*)- stand for the absolute configuration of the optical isomer, Ar means an aryl, preferably an aryl selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl.



(*S*)-(9)



(*R*)-(9)

The stereoisomers of the compounds that are described by the formulae (*S*)-**(9)** and (*R*)-**(9)** can preferably be isolated in a crystalline form, which can be characterized by means of the X-ray powder diffraction method. For the crystalline derivatives (*S*)-**(9)** and (*R*)-**(9)**, wherein Ar means 4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl, XRPD patterns have been measured by means of copper emitted radiation with the wavelength of 0.15418 nm. The crystalline derivatives described by the formulae (*S*)-**(9)** and (*R*)-**(9)**, wherein Ar stands for 4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl, are characterized by the following reflections in the X-ray powder diffraction:

(a) 2.2; 6.5; 8.7; 13.1; 17.5; 20.6 and 26.6 ± 0.2° (2θ) for the derivative wherein Ar stands for 4-fluorophenyl,

(b) 6.6; 8.7; 13.0; 17.6; 20.9; 27.0 and 28.5 ± 0.2° (2θ) for the derivative wherein Ar stands for 4-chlorophenyl,

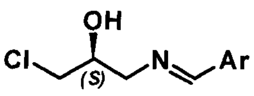
(c) 4.2; 6.3; 8.4; 12.5; 14.6; 20.8; 27.2 and 33.7 ± 0.2° (2θ) for the derivative wherein Ar stands for 4-bromophenyl,

The experimentally obtained data are summarized in Tables 2 to 4, the XRPD patterns are illustrated in Figures 1 to 3 and selected values of characteristic reflections are given in the examples that describe the preparation method of these crystalline substances.

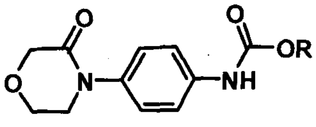
Another aspect of this invention provides a method for the preparation of the compound of formula (*S*)-**(9)** which consists of the following steps:

(a) reaction of (*S*)-epichlorohydrin with ammonia and an aromatic aldehyde of formula **(13)**, wherein Ar means an aryl, preferably an aryl selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl, producing (*S*)-1-chloro-3-(((aryl)methylene)amino)propan-2-ol of formula (*S*)-**(14)**, wherein Ar corresponds to the Ar of the aldehyde **(13)** used,

ArCHO
(13)



(S)-(14)



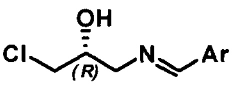
(15)

(b) reaction of (*S*)-**(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate of formula **(15)**, wherein R means an alkyl, preferably benzyl, under catalysis by bases.

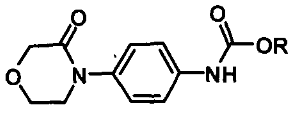
Analogously, the compound (*R*)-**(9)** can be prepared by a process that consists of:

(a) reaction of (*R*)-epichlorohydrin with ammonia and an aromatic aldehyde of formula **(13)**, wherein Ar means an aryl, preferably an aryl selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl, producing (*R*)-1-chloro-3-(((aryl)methylene)amino)propan-2-ol of formula (*R*)-**(14)**, wherein Ar corresponds to the Ar of the aldehyde **(13)** used,

ArCHO
(13)



(R)-(14)



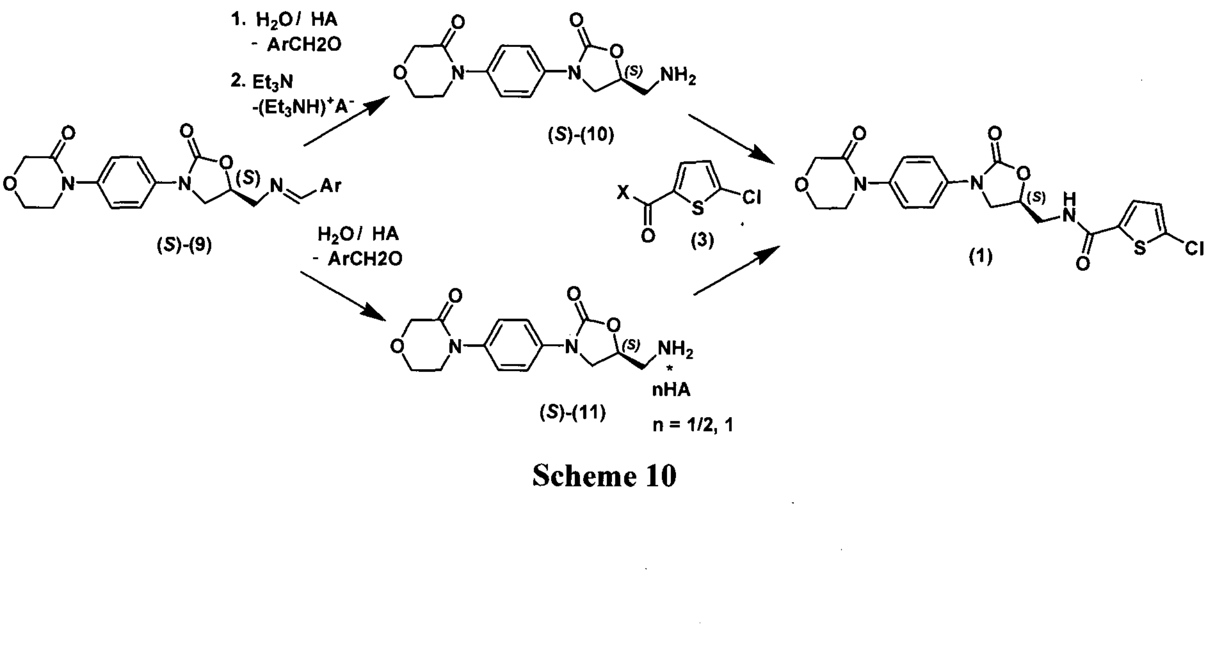
(15)

(b) reaction of (*R*)-**(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate described by formula **(15)**, wherein R stands for an alkyl, preferably benzyl, under catalysis by bases.

The (*S*)-isomer of the compound **(9)** can preferably be used for the preparation of rivaroxaban **(1)**. For example, by the process according to Scheme 10 consisting of the following steps:

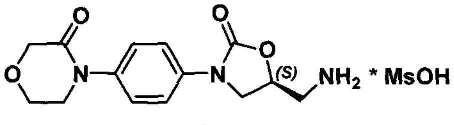
(a) hydrolysis of (*S*)-**(9)**, producing 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one described by formula (*S*)-**(10)** or its salts with acids described by formula (*S*)-**(11)**, wherein HA stands for an acid selected from the group of methanesulfonic, benzenesulfonic, p-toluenesulfonic, (*R*)- and (*S*)- camphorsulfonic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, D- and L- tartaric, benzoic, oxalic and trifluoroacetic acid,

(b) reaction of the product of the previous stage with an acylation agent of formula **(3)**, wherein X stands for a halogen, producing rivaroxaban.



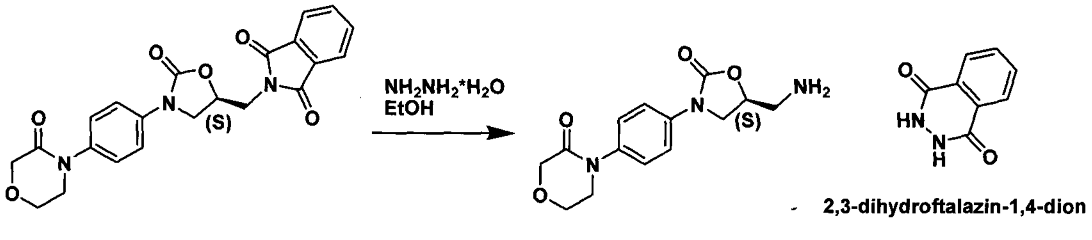
Scheme 10

This method is especially preferred wherein, after the deprotection of (*S*)-**(9)** according to Scheme 10 the well-crystallizing and low-solubility salt of (*S*)-**(10)** with methanesulfonic acid, described by formula (*S*)-**(12)** is isolated, which can be obtained reproducibly in yields over 95% and which is characterized by the following reflection values in the X-ray powder diffraction (Table 5, Fig. 4): 2.6; 7.7; 10.3; 15.4; 17.7; 19.9; 22.0 and 25.4 ± 0.2° (2θ), the said reflection values corresponding to an XRPD pattern obtained using copper-emitted radiation with the wavelength of 0.15418 nm.



(S)-(12)

A preferred modification of the deprotection reaction, differing from the previously described solutions, results in the amine (*S*)-**(10)** or its salts (*S*)-**(11)**, see Scheme 10. In the process according to the invention deprotection reactions are performed hydrolytically, under mild conditions and with high yields. During the deprotection according to the invention an aromatic aldehyde is released besides the desired amine, which is very well soluble in the solvents used for the deprotection reaction unlike the desired amine. This way a chemically pure amine or its salts with acids are obtained (HPLC purity more than 98%). Thus, the desired products are not contained in mixtures with a significant proportion of the side product of the deprotection, as was the case of hydrazinolyses proceeding according to Scheme 9 (*J.Med.Chem.* (2005), 48(19), 5900-5908 and WO 2009/023233 A1). For comparison to prior deprotection methods a comparative experiment (see Example 31) was carried out according to the following chemical equation.

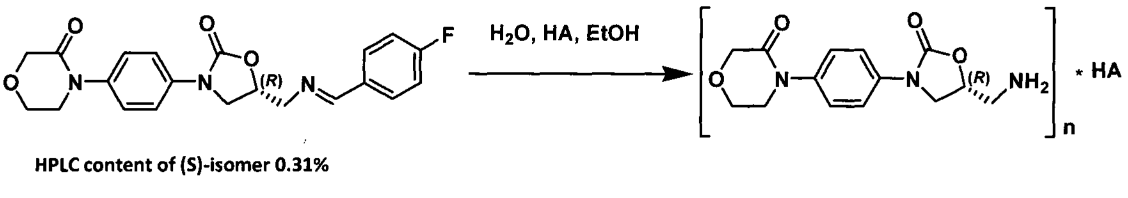


The experiment resulted in an isolated mixture containing 86.7% of the desired product, 12.7% of the ballast 2,3-dihydrophthalazine-1,4-dione (the rest up to 100% is represented by unidentifiable impurities) according to HPLC. The yield of the isolated amine recalculated to the pure substance was approximately 73%, which is considerably less compared to yields achieved with hydrolytic deprotections of the compounds (*S*)-**(9)** and (*R*)-**(9)**; in addition, the obtained substance was not chemically pure in this case.

The hydrolytic reactions according to the invention are preferably acid catalyzed, the primary product being salts of the amine with acids, see Scheme 10. The free base of the amine can be released from these salts by treatment with suitable bases, e.g. tertiary amines, see Scheme 10. Both the amine (*S*)-**(10)** and its salts with acids (*S*)-**(11)** are useful for the preparation of rivaroxaban. The deprotection method has turned out to be unexpectedly convenient in terms of the achieved optical purity of the product, especially depending on the acid used. The results of several comparative experiments for the tested reaction are summarized in Table 1. In all the cases a considerable reduction of the content of undesired enantiomer was observed after the deprotection completed. The best results were achieved with hydrochloric and oxalic acid. In both the cases the optical contamination was considerably reduced, namely from the content level of the undesired enantiomer of 0.31% in the input raw material to the level of 0.08 and 0.05% in the isolated salts, while nearly quantitative yields of the corresponding salts (98 and 96%) were achieved at the same time. An interesting result was also registered in the case of L- and D- dibenzoyltartaric acids, which are commonly used for resolution of racemic mixtures. It is true that in both the cases the content of the minority enantiomer was considerably reduced but to the same level of the content of the (*S*)-enantiomer of the corresponding amine, 0.09%. This means that neither of these acids provided a significantly optically purer product as expected in advance.

Table 1 Comparison of some acids used for the deprotection reaction and their influence on the yield, chemical and optical purity of the isolated salts according to the reaction presented under the Table

Example	Acid (HA)	n	Yield (%)	HPLC (%)	(S)-isomer (%)
21	L-dibenzoyltartaric	2	80	99.6	0.09
22	D-dibenzoyltartaric	2	82	99.5	0.09
23	**hydrochloric**	**1**	**98**	**99.7**	**0.08**
24	**oxalic**	**2**	**96**	**99.7**	**0.05**
25	p-TsOH	1	60	99.3	0.14
26	TFA	1	76	99.6	0.06



The hydrolytic method of deprotection of the compounds (*S*)-**(9)** and (*R*)-**(9)**, proceeding according to Scheme 10 combines a number of the following advantages:

(a) it is a selective process that leads to chemically pure products without any content of ballast substances;

(b) it is a quick process with low energy demands and easily applicable in the production scale;

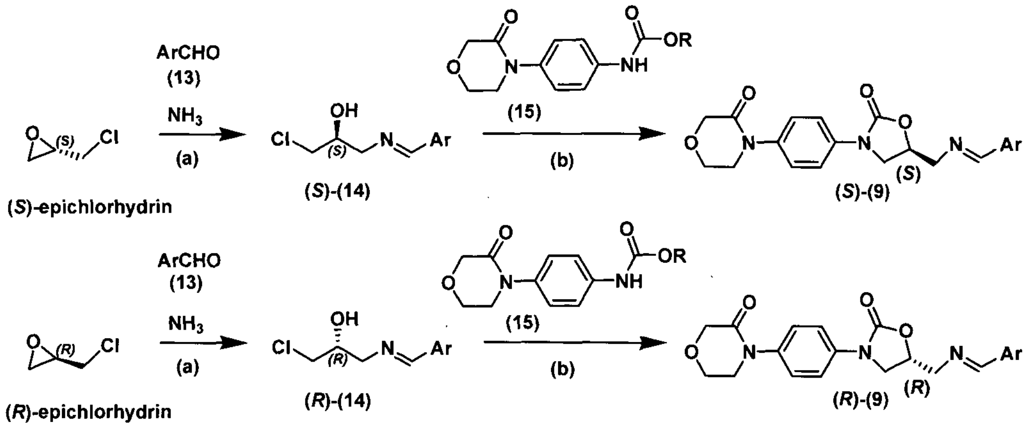
(c) it is a process that provides the product in a high yield, especially as compared to the previously known deprotection processes;

(d) it is a process that enables efficient performance of optical purification, which has a principal impact on the quality of the subsequently prepared rivaroxaban.

The compounds of formulae (*S*)-**(9)** and (*R*)-**(9)**, which are subject of the invention, can be prepared by the process which is described by Scheme 11 and which consists of the following steps:

(a) reaction of (*S*)- or (*R*)- epichlorohydrin with ammonia and an aromatic aldehyde of formula **(13)**, wherein Ar stands for an aryl, preferably an aryl selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl, producing (*S*)- or (*R*)- 1-chloro-3-(((aryl)methylene)amino)propan-2-ol described by formula **(14)**, wherein Ar stands for an aryl, preferably an aryl selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl,

(b) reaction of (*S*)- or (*R*)- 1-chloro-3-(((aryl)methylene)amino)propan-2-ol **(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate of formula **(15)**, wherein R means an alkyl, preferably benzyl.

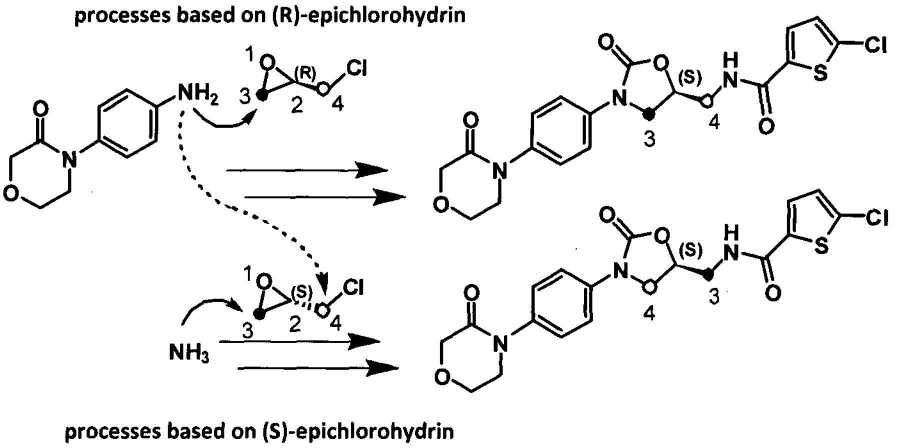


Scheme 11

Step (b) according to Scheme 11 is best carried out under basic catalysis, wherein a base selected from the group of n-butyllithium, lithium *tert*-butoxide, lithium hydroxide, lithium diisopropylamide or lithium hexamethyldisilazide is used as the catalyst. Commercially available optical isomers of epichlorohydrin that exhibited contents of the undesired antipode below 1% were used for the process according to the invention. The compounds (*S*)-**(14)** and (*R*)-**(14)**, as well as methods of their preparation already belong to known state of the art (WO2007116284A1) and, as such, are not subject of the invention, except for derivatives of 4-fluorobenzaldehyde, which have not been described so far.

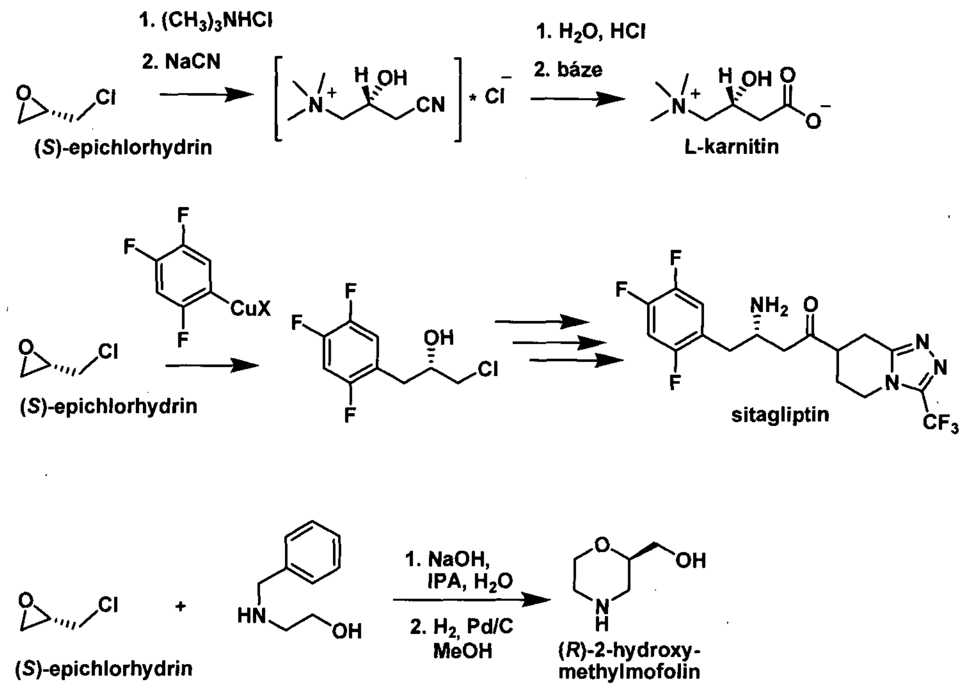
The capacity of compounds of formula (*S*)-**(9)** and (*R*)-**(9)** to form crystalline structures is a convenient and unexpected property, which has a positive impact on the achieved chemical (99-100%) and optical (99-100%) purity of these substances. This property in turn also influences quality of the prepared rivaroxaban or its (*R*)-isomer. Common purifying methods of rivaroxaban by means of crystallization have proved to be able to reduce the content of possible chemical impurities below the limits accepted for pharmaceutical substances (usual limit 0.10%), but they are not able to also reduce the content of the undesired enantiomer (usual limit 0.15%), i.e. these methods cannot be used to obtain a qualitatively acceptable substance from excessively optically contaminated rivaroxaban (see Example 32). Thus, crystalline compounds of the general formula (*S*)-**(9)**, which have already significantly better optical purity than required for pharmaceutical purposes, can be conveniently used in the preparation of rivaroxaban. No substantial changes of optical purity, e.g. due to partial racemization, occur during further transformations and rivaroxaban prepared this way is characterized by nearly the identical optical purity as those of compounds (*S*)-**(9)** used for its preparation.

It is further characteristic, unique and convenient for the present invention to use of (*S*)-epichlorohydrin as the chiral starting material for the preparation of both the compound (*S*)-**(9)** and rivaroxaban, which can be easily and conveniently prepared from (*S*)-**(9)**. The prior processes either use other chiral building blocks, e.g. (*S*)-glycidyl phthalimide **(4)**, (*S*)-3-aminopropane-1,2-diol **(5)** or (*R*)-epichlorohydrin. What is an interesting circumstance is the fact that rivaroxaban, which is characterized by the (*S*)- configuration of the chiral centre, can be prepared from both optical isomers of epichlorohydrin. This surprising possibility results from the fact that epichlorohydrin contains two reactive centres that are capable of reacting with a nucleophilic agent, e.g. an amine. The resulting absolute configuration of the product is not only controlled by the configuration of the starting material, but also by the sequence of steps, as indicated in Scheme 12. Prior processes starting from (*R*)-epichlorohydrin are characteristic by forming a bond between the carbon no. 3 in the skeleton of epichlorohydrin and the amino group coming from 4-(4-aminophenyl)morpholin-3-one in the initial stage of the synthesis. It is only then that a bond between carbon no. 4 in the epichlorohydrin skeleton and the nitrogen of the other agent is formed. However, according to the present invention the sequence of these events is just opposite, which surprisingly makes it possible to obtain the final product of the same configuration even using (S)-epichlorohydrin. Conversely, the use of (*R*)-epichlorohydrin in processes according to the invention results in formation of isomeric rivaroxaban with the (*R*)- configuration, which is further useful as an analytic standard for setting analytic methods used to check the optical purity of rivaroxaban.



Scheme 12

The advantages of using (*S*)-epichlorohydrin for the production of rivaroxaban mainly consist in its availability and cost, as (*S*)-epichlorohydrin is already commercially used in a number of industrial production processes of biologically active compounds or their intermediates, e.g. in the production of L-carnitine (WO2010/043110), the antidiabetic sitagliptin (WO2011/102640) and (*R*)-2-hydroxymethyl-morpholine (WO 2010/082627 A1), see Scheme 13.



Scheme 13

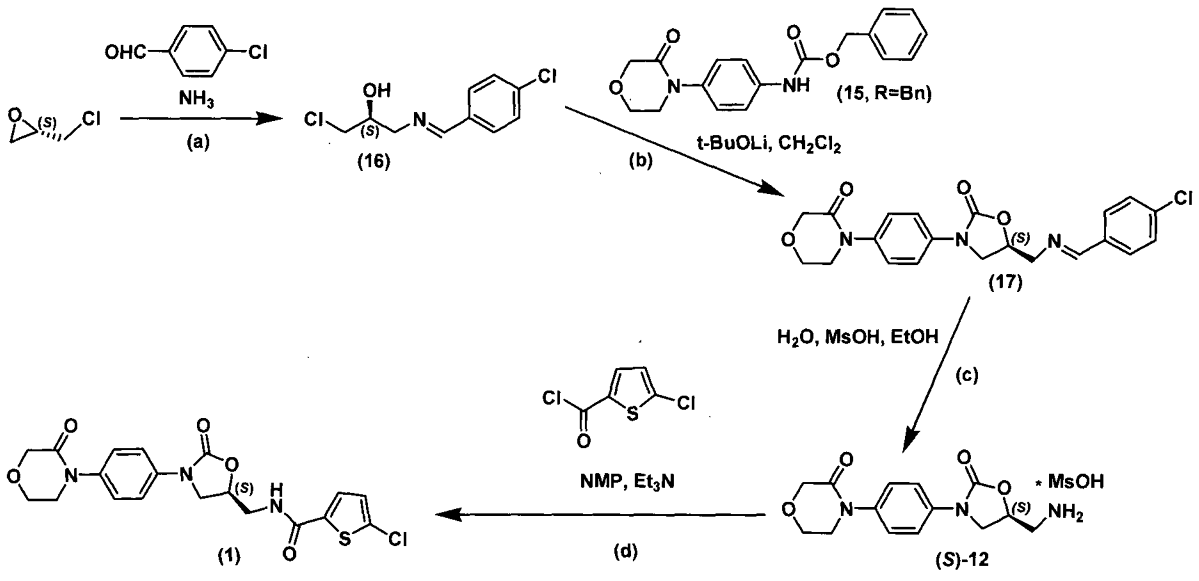
In a specific embodiment the invention relates to a method for the preparation of rivaroxaban **(1)**, which is described by Scheme 14 and which consists of the following steps:

(a) reaction of (*S*)-epichlorohydrin with ammonia and 4-chlorobenzaldehyde, producing (*S*)-1-chloro-3-[((4-chlorophenyl)methylene)amino]propan-2-ol **(16)**,

(b) reaction of the product of step (a) with benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate (**15**, R=Bn) and lithium *tert*-butoxide performed in dichloromethane, producing 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one **(17)**,

(c) reaction of the product of step (b) with water and methanesulfonic acid carried out in methanol, producing the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid (S)-**(12)**,

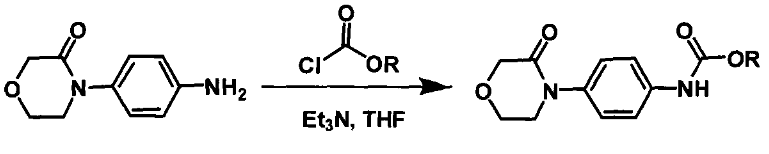
(d) reaction of the product of step (c) with 5-chlorothiophene-2-carbonyl chloride carried out in a solvent selected from the group of dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrolidone, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, dichloromethane, chloroform or a mixture of these solvents and in the presence of a base selected from the group of triethylamine, diisopropylethylamine, N-alkylpiperidine, N-alkylmorpholine, pyridine, sodium hydrogen carbonate.



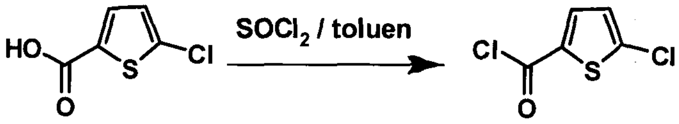
Scheme 14

The process according to Scheme 14 makes it possible to obtain, in a reproducible manner, rivaroxaban **(1)** exhibiting chemical purity higher than 99.8%, with contents of individual impurities below 0.1% (according to HPLC) and a content of the undesired (*R*)-isomer below 0.05% (according to HPLC). These quality parameters meet very strict quality requirements made on pharmaceutical substances, which means that rivaroxaban prepared by the above-described process, which starts with the available and inexpensive (*S*)-epichlorohydrin, can be used to prepare a drug with an anticoagulation effect.

Besides (*S*)-epichlorohydrin, which is the subject of the invention, other starting materials are necessary for the preparation of rivaroxaban by the process of the invention. In particular, this is the case of alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamates **(15)** prepared by the method according to Scheme 15, and 5-chlorothiophene-2-carbonyl chloride (**3**, X= -Cl) prepared by the method according to Scheme 16. These intermediates, as well as methods of their preparation, already belong to the state of the art.



Scheme 15



Scheme 16

The invention provides stereoisomeric 4-{4-[(*S*/*R*)-5-[(((aryl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-ones **(9)**. Rivaroxaban **(1)** can be prepared from the optical isomer (*S*)-**(9)** by a simple and efficient process with a number of advantages in a quality required for pharmaceutical substances. The use of (*S*)-epichlorohydrin as a new and convenient chiral building block is a principal feature of this process that is different from the prior solutions.

Brief Description of Drawings

Fig. 1 presents an X-Ray Powder Diffraction (XRPD) pattern of the crystalline form of 4-{4-[(*S*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one prepared according to Example 9. Particular axes: independently variable: reflection angle 2θ, dependently variable: intensity of detected radiation.

Fig. 2 presents an X-Ray Powder Diffraction (XRPD) pattern of the crystalline form of 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one prepared according to Example 11. Particular axes: independently variable: reflection angle 2θ, dependently variable: intensity of detected radiation.

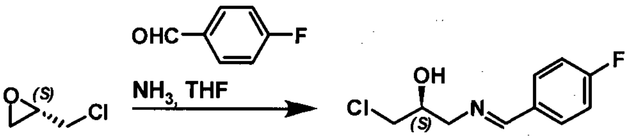
Fig. 3 presents an X-Ray Powder Diffraction (XRPD) pattern of the crystalline form of 4-{4-[(*S*)-5-[(((4-bromophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one prepared according to Example 13. Particular axes: independently variable: reflection angle 2θ, dependently variable: intensity of detected radiation.

Fig. 4 presents an X-Ray Powder Diffraction (XRPD) pattern of the crystalline form of the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid (1:1) prepared according to Example 16. Particular axes: independently variable: reflection angle 2θ, dependently variable: intensity of detected radiation.

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 (*S*)-1-chloro-3-{[(4-fluorophenyl)methylene]amino}propan-2-ol)



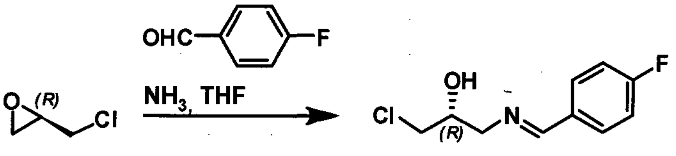
56 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-fluorobenzaldehyde (57 ml) in 200 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 15 minutes. Then, 41.5 ml of (*S*)-epichlorohydrin and 50 ml of tetrahydrofuran were added. The mixture was stirred at 25-30°C for 24 hours. Then 100 ml of dichloromethane was added. The separated organic layer was washed with water (2x50 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, dichloromethane (100 ml) and heptane (300 ml) were added to the residue and the mixture was again concentrated *in vacuo* in order to selectively evaporate the lower-boiling dichloromethane. 50 ml of dichloromethane were gradually added to the obtained emulsion until a solution was produced. The solution was stirred and slowly cooled to 15°C. The separated crystalline product was filtered, washed with heptane (2x25 ml) and dried. 55.4 g (yield 51%) of off-white crystals with the melt. point of 59-61°C were obtained, GC 99.4%, content of the (*R*)-isomer 0.55% according to GC.

^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm): 3.07 (bs, OH); 3.66 (m, 2H, CH_2); 3.78 (m, 2H, CH_2); 4.12 (pent, 1H, CH); 7.00-7.14 (m, 2H); 7.68-7.76 (m, 2H); 8.29 (s, 1H, CH).

^{13}C NMR (250 MHz, $CDCl_3$), δ (ppm): 47.1; 63.1; 70.9; 115.7; 130.1; 131.9; 162.2; 164.5.

MS (m/z): 216.0584 $(M+H)^+$.

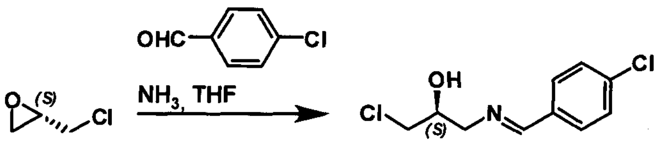
EXAMPLE 2 (preparation of (*R*)-1-chloro-3-{[(4-fluorophenyl)methylene]amino}propan-2-ol)



112 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-fluorobenzaldehyde (114 ml) in 300 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 15 minutes. Then, 83 ml of (*R*)-epichlorohydrin and 100 ml of tetrahydrofuran were added. The mixture was stirred at 22-25°C for 24 hours. Then 200 ml of dichloromethane was added. The separated organic layer was washed with water (2x50 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, dichloromethane (200 ml) and heptane (600 ml) were added to the residue and the mixture was again concentrated *in vacuo* in order to selectively evaporate the lower-boiling dichloromethane. 100 ml of dichloromethane were gradually added to the obtained emulsion until a solution was produced. The solution was stirred and slowly cooled to 10 to 15°C. The separated crystalline product was filtered, washed with heptane (2x25 ml) and dried. 128.4 g (yield 56%) of the product with the melt. point 55-58°C was obtained, GC 98,0%, content of the (*S*)- isomer 0.29% according to GC.

The NMR and MS spectra are in accordance with Example 1.

EXAMPLE 3 (preparation of (*S*)-1-chloro-3-{[(4-chlorophenyl)methylene]amino}propan-2-ol)



55 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-chlorobenzaldehyde (75 g) in 200 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 20 minutes. Then, 41.5 ml of (*S*)-epichlorohydrin and 50 ml of tetrahydrofuran were added. The mixture was stirred at ca. 25°C for 19 hours and then at 40-45°C for 3 hours and then being slowly cooled to a temperature below 30°C for another 2 hours. After that 200 ml of toluene was added. The separated organic layer was washed with water (2x50 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, 50 ml of toluene added to the residue and the mixture was again concentrated *in vacuo*. 400 ml of heptane and 50 ml of toluene were added to the obtained oil, the emulsion was stirred and heated at 60-65°C until a solution was produced. The solution was stirred under very slow cooling from the temperature of ca. 60 °C to the target temperature of the suspension of ca. 27 °C for 1 hour. The separated crystalline product

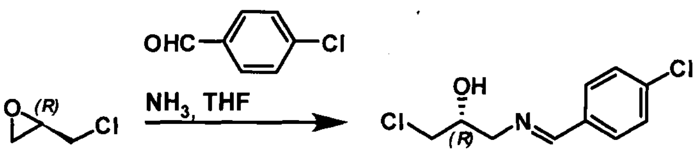
was filtered, washed with heptane (2x50 ml) and dried. 56.7 g (yield 46 %) of off-white crystals with the melt. point 70-71°C were obtained, GC 99.3 %, content of the (*R*)- isomer 0.10% according to GC.

^{1}H NMR (250 MHz, DMSO-D6), δ (ppm): 3.60 (m, 2H); 3.73 (m, 2H); 3.95 (m, 1H); 5.26 (m, 1H); 7.51 (m, 2H); 7.77 (m, 2H); 8.34 (m, 1H).

^{13}C NMR (250 MHz, DMSO-D6), δ (ppm): 47.9; 63.6; 69.9, 128.7; 129.5; 134.8; 135.2; 161.3.

MS (m/z): 232.0288 $(M+H)^+$.

EXAMPLE 4 (preparation of (*R*)-1-chloro-3-{[(4-chlorophenyl)methylene]amino}propan-2-ol)



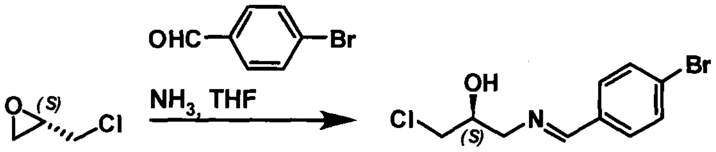
55 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-chlorobenzaldehyde (75 g) in 250 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 30 minutes. Then, 41.5 ml of (*R*)-epichlorohydrin and 50 ml of tetrahydrofuran were added. The mixture was stirred at ca. 20°C for 19 hours and then at 40-45°C for 4 hours and then being slowly cooled to a temperature below 30°C for another 1 hour. After that 200 ml of toluene was added. The separated organic layer was washed with water (2x50 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, 50 ml of toluene added to the residue and the mixture was again concentrated *in vacuo*. 400 ml of heptane and 40 ml of toluene were added to the obtained oil, the emulsion was stirred and heated at 60-65°C until a solution was produced. The solution was stirred under very slow cooling from the temperature of ca. 60°C to the target temperature of the suspension of ca. 25°C for 1.5 hours. The separated crystalline product was filtered, washed with heptane (2x50 ml) and dried. 64.2 g (yield 51%) of off-white crystals with the melt point of 69-70°C were obtained, GC 99.4%, content of the (*S*)-isomer 0.09% according to GC.

^{1}H NMR (250 MHz, DMSO-D6), δ (ppm): 3.61 (m, 2H); 3.73 (m, 2H); 3.95 (m, 1H); 5.26 (m, 1H); 7.51 (m, 2H); 7.77 (m, 2H); 8.34 (s, 1H).

^{13}C NMR (250 MHz, DMSO-D6), δ (ppm): 47.9; 63.5; 69.9, 128.7; 129.5; 134.8; 135.2; 161,3.

MS (m/z): 232.0289 $(M+H)^+$.

EXAMPLE 5 (preparation of (*S*)-1-chloro-3-{[(4-bromopfenyl)methylene]amino}propan-2-ol)



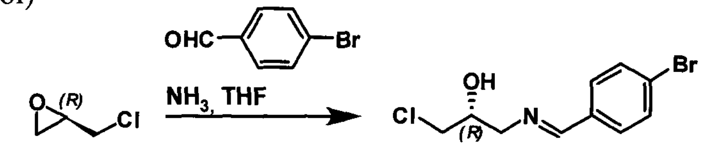
7.4 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-bromo benzaldehyde (12 g) in 30 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 15 minutes. Then, 5.6 ml of (*S*)-epichlorohydrin and 7 ml of tetrahydrofuran were added. The mixture was stirred at ca. 22° for 20 hours and then at 40-45°C for 1 hour and then being cooled to a temperature below 30°C for another 1/2 hour. After that 30 ml of toluene was added. The separated organic layer was washed with water (2 x 7 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, 10 ml of toluene added to the residue and the mixture was again concentrated *in vacuo*. 60 ml of heptane and 10 ml of toluene were added to the obtained oil, the emulsion was stirred and heated at 75 to 80°C until a solution was produced. The solution was stirred under very slow cooling from the temperature of ca. 75°C to the target temperature of the suspension of ca. 23°C for 2 hours. The separated crystalline product was filtered, washed with heptane (2 x 20 ml) and dried. 9.7 g (yield 54%) of off-white crystals with the melt. point of 81.5-83.5°C were obtained, GC 99.0%, content of the (*R*)- isomer 0.18% according to HPLC.

^{1}H NMR (250 MHz, $CDCl_3$), δ (ppm): 2.78 (bs, OH); 3.65 (m, 2H, CH_2); 3.75 (m, 2H, CH_2); 4.13 (pent, 1H, CH); 7.34-7.58 (m, 4H); 8.29 (s, 1H, CH).

^{13}C NMR (250 MHz, $CDCl_3$), δ (ppm): 47.1; 63.1; 70.8, 125.6; 129.6; 131.9; 134.6; 162.4,

MS (m/z): 277.9782$(M+H)^+$.

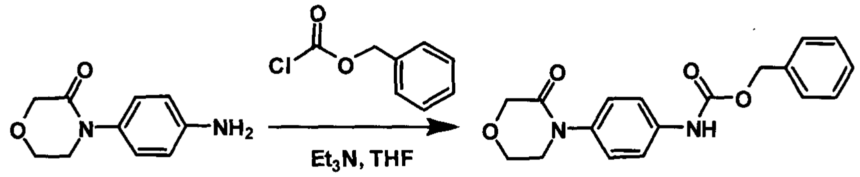
EXAMPLE 6 (preparation of (*R*)-1-chloro-3-{[(4-bromophenyl)methylene]amino}propan-2-ol)



7.4 ml of an aqueous solution of ammonia (25-28%) were added to a solution of 4-bromobenzaldehyde (12 g) in 30 ml of tetrahydrofuran. The mixture was stirred at the laboratory temperature for ca. 15 minutes. Then, 5.6 ml of (*R*)-epichlorohydrin and 7 ml of tetrahydrofuran were added. The mixture was stirred for 20 hours at ca. 22°C and then at 40-45°C for 1 hour and then being cooled to a temperature below 30°C for another 1/2 hour. After that 30 ml of toluene was added. The separated organic layer was washed with water (2 x 7 ml) and dried over sodium sulphate. After removal of the desiccant by filtration the filtrate was concentrated *in vacuo*, 10 ml of toluene added to the residue and the mixture was again concentrated *in vacuo*. 60 ml of heptane and 10 ml of toluene were added to the obtained oil, the emulsion was stirred and heated at 75 to 80°C until a solution was produced. The solution was stirred under very slow cooling from the temperature of ca. 75°C to the target temperature of the suspension of ca. 22°C for 2 hours. The separated crystalline product was filtered, washed with heptane (2 x 20 ml) and dried. 9.1 g (yield 51%) of off-white crystals with the melt. point of 82-84°C were obtained, GC 99.5%, content of the (*S*)- isomer 0.75% according to HPLC.

The NMR and MS spectra are in accordance with Example 5.

EXAMPLE 7 (preparation of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate)

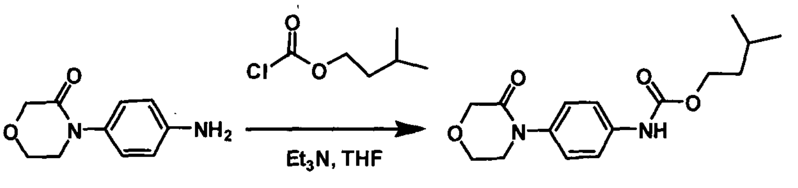


4-(4-aminophenyl)-3-morpholinone (38.5 g) was dissolved in a mixture of 400 ml of water and 400 ml of tetrahydrofuran at 45-50°C, then 32 ml of triethylamine were added and the obtained solution was maintained at 45°C. In parallel, a solution of benzylchloroformate (36 ml) in 100 ml of tetrahydrofuran was prepared under stirring and cooling to ca. 0°C. The solution of 4-(4-aminophenyl)-3-morpholinone was added dropwise to the cooled solution of benzylchloroformate during 15 minutes, the reaction mixture was stirred under cooling in an ice bath for 15 minutes, then heptane (200 ml) was added and the obtained suspension was thoroughly stirred up. The separated product was aspirated, washed with water (2 x 100 ml), heptane (2 x 100 ml) and dried *in vacuo*. 52.1 g of a white crystalline powder with the melt. point of 190-192°C was obtained.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 2.68 (m, 2H, CH$_2$); 3.97 (m, 2H, CH$_2$); 4.29 (s, 2H, CH$_2$); 5.18 (s, 2H, CH$_2$); 7.10-7.45 (m, 10H, 9xCH + NH).

^{13}C NMR (250 MHz, CDCl$_3$), δ (ppm): 49.8; 64.1; 66.9; 68.5; 119.4; 126.1; 128.2; 128.6; 136.1; 136.3; 137.0; 153.3; 166.9.

EXAMPLE 8 (preparation of isobutyl 4-(3-oxomorpholin-4-yl)phenylcarbamate)

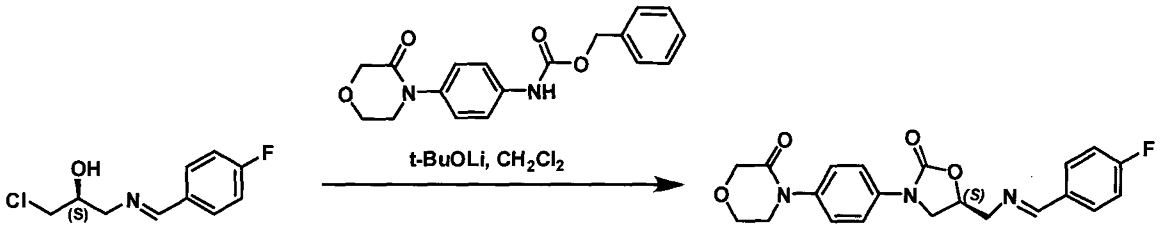


4-(4-aminophenyl)-3-morpholinone (9.6 g) was dissolved in a mixture of 100 ml of water and 100 ml of tetrahydrofuran at 45-50°C, then 8 ml of triethylamine were added and the obtained solution was maintained at 45°C. In parallel, a solution of isobutylchloroformate (7.5 ml) in 25 ml of tetrahydrofuran was prepared under stirring and cooling to ca. 0°C. The solution of 4-(4-aminophenyl)-3-morpholinone was added dropwise to the cooled solution of isobutylchloroformate during 5 minutes, the reaction mixture was stirred under cooling in an ice bath for 30 minutes, then heptane (50 ml) was added and the obtained suspension was thoroughly stirred up. The separated product was aspirated, washed with water (25 ml), heptane (2 x 100 ml) and dried *in vacuo*. 10.9 g of a white crystalline powder with the melt. point of 221-223°C was obtained.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 0.97 (d, 6H, 2xCH$_3$); 1.97 (sept, 1H, CH); 3.72 (m, 2H, CH$_2$); 3.94 (d, 2H, CH$_2$); 4.02 (m, 2H, CH$_2$); 4.33 (s, 2H, CH$_2$); 7.02 (bs, 1H, NH); 7.21 (m, 2H, 2xCH); 7.36 (m, 2H, 2xCH).

^{13}C NMR (250 MHz, CDCl$_3$), δ (ppm): 19.0; 27.9; 49.8; 64.1; 68.5; 71.3; 119.4; 126.1; 136.2; 137.2; 153.7; 166.9.

EXAMPLE 9 (preparation of 4-{4-[(*S*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



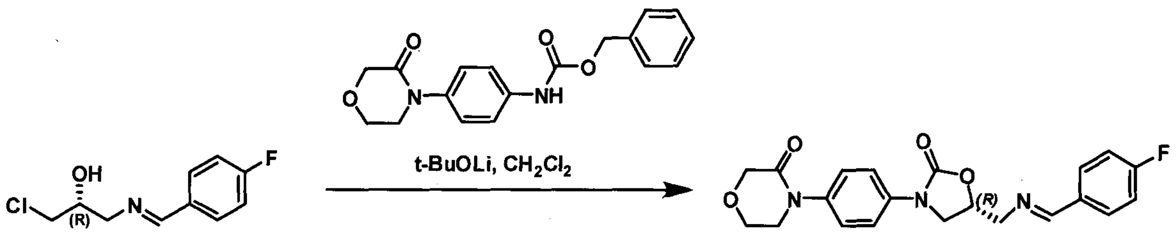
Lithium *tert*-butoxide (16 g) and 50 ml of dichloromethane were added to a mixture of 32.6 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 150 ml of dichloromethane. The mixture was stirred and heated to 40°C for ca. 10 minutes, subsequently cooled below 30°C and 26 g of (*S*)-1-chloro-3-{[(4-fluorophenyl)methylene]amino}propan-2-ol and 50 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 19 hours, then cooled below 30°C and 50 ml of water and 150 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 50 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 150 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 150 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 30 ml) and dried *in vacuo*. 31.1 g (yield 78%) of an off-white powder with the melt. point of 156-157°C was obtained, HPLC 99.3%, optical purity 99.6%, $[\alpha]_D^{25} = -95.7°$ (CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.75 (m, 2H, CH_2); 3.88-3.99 (m, 2H, CH_2); 4.03 (m, 2H, CH_2); 4.09-4.19 (m, 2H, CH_2); 4.34 (s, 2H, CH_2); 4.97 (m, 1H, CH); 7.08 (m, 2H); 7.34 (m, 2H); 7.59 (m, 2H); 7.70 (m, 2H); 8.35 (m, 1H, CH).

^{13}C NMR (500 MHz, $CDCl_3$), δ (ppm): 48.1; 49.7; 63.1; 64.1; 68.5; 71.8; 115.7; 119.0; 126.1; 130.3; 131.8; 137.0; 154.5; 163.3; 163.6; 165.6; 166.7.

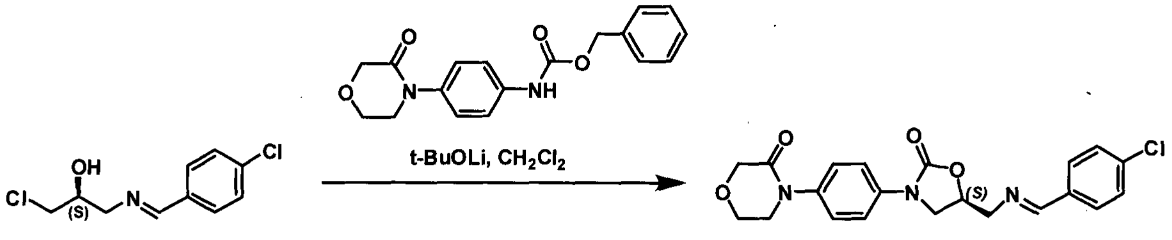
XRPD: 2.2; 6.5; 8.7; 13.1; 17.5; 20.6 and 26.6 ± 0,2° (2θ).

EXAMPLE 10 (preparation of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



Lithium *tert*-butoxide (16 g) and 50 ml of dichloromethane were added to a mixture of 32.6 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 150 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 26 g of (*R*)-1-chloro-3-{[(4-fluorophenyl)methylene]amino}propan-2-ol and 50 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 18 hours, then cooled below 30°C and 50 ml of water and 150 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 50 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 150 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 150 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 50 ml) and dried. 27.3 g (yield 68%) of an off-white power with the melt. point of 156.5-157.5°C was obtained, HPLC 99.7%, optical purity 100.0%, $[\alpha]_D^{25}$ = +95.2° (CH_2Cl_2). The NMR spectra and XRPD record are in accordance with Example 9.

EXAMPLE 11 (preparation of 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



Lithium *tert*-butoxide (20 g) and 50 ml of dichloromethane were added to a mixture of 32.6 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 150 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 29 g of (*S*)-1-chloro-3-{[(4-chlorophenyl)methylene]amino}propan-2-ol and 50 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 21 hours, then cooled below 30°C and 50 ml of water and 150 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 50 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 100 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 150 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 25 ml) and dried. 28.3 g (yield 68%) of an off-white powder with the melt. point of 143-144°C was obtained, HPLC 99.3%, optical purity 100.0%, $[\alpha]_D^{25}$ = -101.9° (CH_2Cl_2).

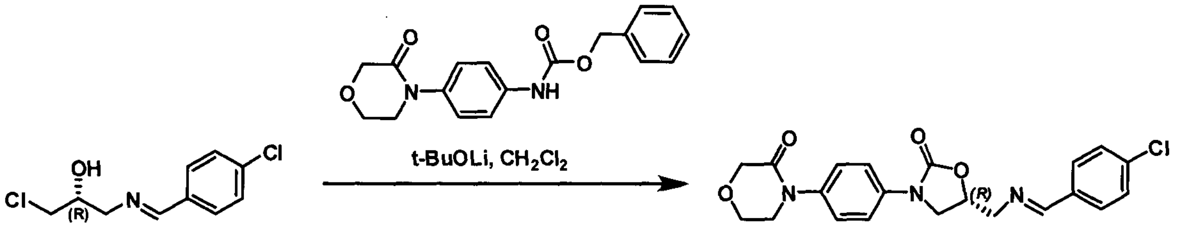
^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.75 (m, 2H, CH_2); 3.88-3.99 (m, 2H, CH_2); 4.00-4.09 (m, 2H, CH_2); 4.09-4.21 (m, 2H, CH_2); 4.34 (s, 2H, CH_2); 4.97 (m, 1H, CH); 7.30-7.40 (m, 4H); 7.54-7.68 (m, 4H); 8.35 (m, 1H, CH).

^{13}C NMR (500 MHz, $CDCl_3$), δ (ppm): 48.2; 49.7; 63.2; 64.1; 68.6; 71.8; 119.0; 126.1; 128.9; 129.5; 134.0; 137; 137.1; 137.3; 154.5;163.5; 166.7.

MS (m/z): 414.1219 $(M+H)^+$.

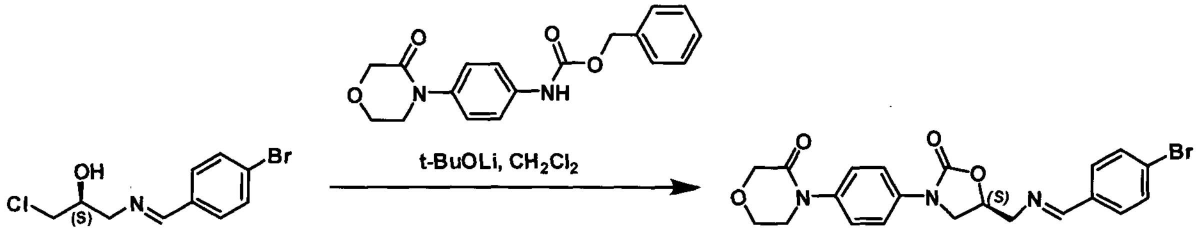
XRPD: 6.6; 8.7; 13.0; 17.6; 20.9; 27.0 and 28.5 ± 0.2° (2θ).

EXAMPLE 12 (preparation of 4-{4-[(*R*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



Lithium *tert*-butoxide (4.0 g) and 10 ml of dichloromethane were added to a mixture of 6.5 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 30 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 5.8 g of (*R*)-1-chloro-3-{[(4-chlorophenyl)methylene]amino}propan-2-ol and 10 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 21 hours, then cooled below 35°C and 10 ml of water and 30 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 10 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 50 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 50 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 25 ml) and dried. 6.0 g (yield 73%) of an off-white powder with the melt. point of 146-147°C was obtained, HPLC 100,0%, optical purity 100.0%, $[\alpha]_D^{25}$ = +102,3° (CH_2Cl_2). The XRPD pattern, NMR and MS spectra are in accordance with Example 11.

EXAMPLE 13 (preparation of 4-{4-[(*S*)-5-[(((4-bromophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



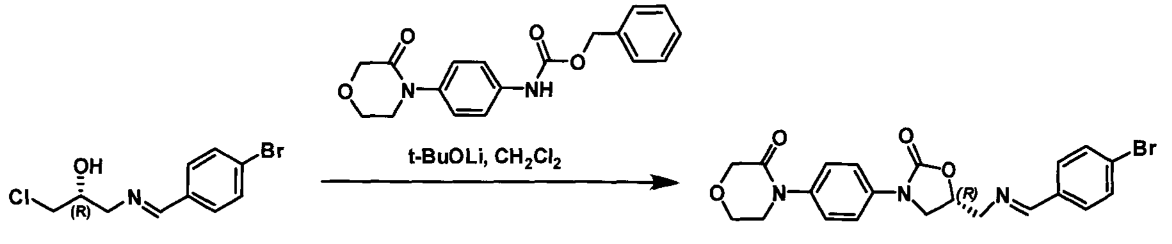
Lithium *tert*-butoxide (1.9 g) and 5 ml of dichloromethane were added to a mixture of 3.9 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 20 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 3.1 g of (*S*)-1-chloro-3-{[(4-bromophenyl)methylene]amino}propan-2-ol and 5 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 18 hours, then cooled below 35°C and 5 ml of water and 20 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 10 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 40 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 40 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 25 ml) and dried. 3.3 g (yield 60%) of an off-white powder with the melt. point of 150.5-151.5°C was obtained, HPLC 100,0%, optical purity 100.0%, $[\alpha]_D^{25}$ = -95.6° (CH_2Cl_2).

^{1}H NMR (500 MHz, $CDCl_3$), δ (ppm): 3.68 (m, 2H, CH_2); 3.81-3.91 (m, 2H, CH_2); 3.96 (m, 2H, CH_2); 4.02-4.12 (m, 2H, CH_2); 4.27 (s, 2H, CH_2); 4.90 (m, 1H, CH); 7.27 (m, 2H, 2xCH); 7.45-7.53 (m, 6H, 6xCH); 8.26 (m, 1H, CH).

^{13}C NMR (500 MHz, $CDCl_3$), δ (ppm): 48.1; 49.7; 63.2; 64.1; 68.6; 71.7; 119.0; 125.7; 126.1; 129.7; 131.9; 134.4; 137.0; 137.1; 154.5; 163.6; 166.8.

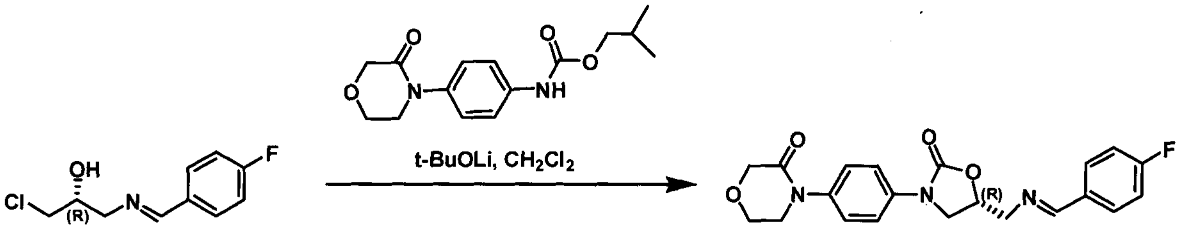
XRPD: 4.2; 6.3; 8.4; 12.5; 14.6; 20.8; 27.2 and 33.7 ± 0.2° (2θ).

EXAMPLE 14 (preparation of 4-{4-[(*R*)-5-[(((4-bromophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



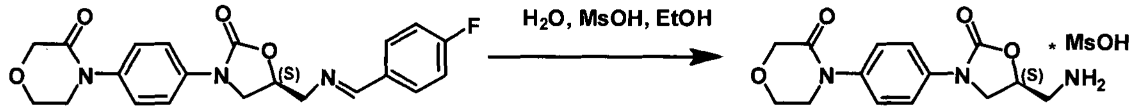
Lithium *tert*-butoxide (1.9 g) and 5 ml of dichloromethane were added to a mixture of 3.9 g of benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 20 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 3.1 g of (*R*)-1-chloro-3-{[(4-bromophenyl)methylene]amino}propan-2-ol and 5 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 18 hours, then cooled below 35°C and 5 ml of water and 20 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 10 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 40 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 40 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 25 ml) and dried. 3.0 g (yield 55%) of an off-white powder with the melt. point of 149-150°C was obtained, HPLC 99.9%, optical purity 100.0%, $[\alpha]_D^{25}$ = +95.7° (CH_2Cl_2). The NMR spectra and XRP pattern are identical with Example 13.

EXAMPLE 15 (preparation of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)



Lithium *tert*-butoxide (4.0 g) and 10 ml of dichloromethane were added to a mixture of 7.3 g of isobutyl 4-(3-oxomorpholin-4-yl)phenylcarbamate and 40 ml of dichloromethane. The mixture was stirred and heated at 40°C for ca. 10 minutes, subsequently cooled below 35°C and 6.5 g of (*R*)-1-chloro-3-{[(4-fluorophenyl)methylene]amino}propan-2-ol and 15 ml of dichloromethane were added. The suspension was stirred and heated at 40-45°C for 17 hours, then cooled below 30°C and 15 ml of water and 50 ml of dichloromethane were added. The layers were separated, the organic layer was washed with water (2 x 10 ml) and dried over sodium sulphate. The mixture was heated up to 40°C and the desiccant was filtered off. 50 ml of ethanol were added to the filtrate and dichloromethane was removed by vacuum distillation (at 300-400 mbar and bath temperature up to 45°C). 50 ml of ethanol were added to the concentrated residue and the mixture was heated at 40°C for 15 minutes, then filtered, the cake was washed with ethanol (2 x 25 ml) and dried. 4.5 g (yield 68%) of an off-white powder with the melt. point of 157-158°C was obtained. HPLC 99.8%, optical purity 99.7%, $[\alpha]_D^{25}$ = +95,4° (CH_2Cl_2). The NMR spectra are identical with Example 9.

EXAMPLE 16 (preparation of the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid)



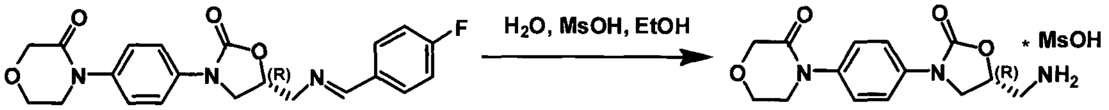
19.9 g of 4-{4-[(*S*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morfolin-3-one was suspended in 100 ml of ethanol with addition of 2 ml of water. Methanesulfonic acid (4 ml) was added all at once to the stirred and heated (60°C) suspension, which produced a turbid solution. Within ca. 1 minute a crystalline product was separated from the solution in the form of thick pulp. 50 ml of ethanol were added and the suspension was stirred in a bath at the temperature of 80°C, then slowly cooled to 40°C. The separated substance was filtered off, washed with ethanol (3 x 25 ml) and dried *in vacuo*. 18.9 g (yield 97%) of an off-white powder was obtained, HPLC 99.7%, content of the (*R*)-isomer 0.28%.

^{1}H NMR (250 MHz, DMSO-D_6), δ (ppm): 2.33 (s, 3H, CH_3); 3.28 (m, 2H, CH_2); 3.72 (m, 2H, CH_2); 3.87 and 4.22 (m, 2H, CH_2); 4.00 (m, 2H, CH_2); 4.20 (s, 2H, CH_2); 4.93 (m, 1H, CH); 7.44 (m, 2H); 7.54 (m, 2H); 8.13 (bs, 3H, -NH_2 + -SO_3H).

^{13}C NMR (250 MHz, DMSO-D_6), δ (ppm): 39.8; 41.7; 47.2; 49.0; 63.5; 67.7; 69.5; 118.5; 125.9; 136.3; 137.2; 153.6; 166.0.

XRPD: 2.6; 7.7; 10.3; 15.4; 17.7; 19.9; 22.0 and 25.4 ± 0.2° (2θ).

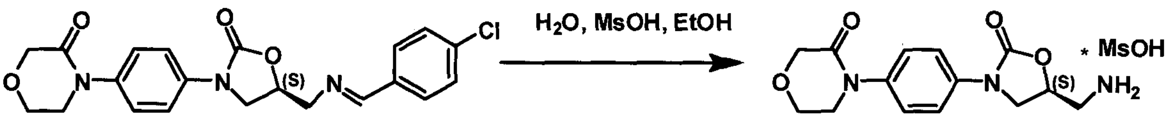
EXAMPLE 17 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid)



2 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one was suspended in 40 ml of ethanol with addition of 4 ml of water.

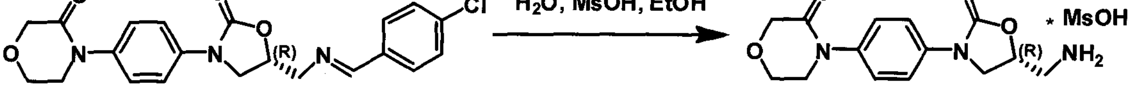
Methanesulfonic acid (0.4 ml) was added to the stirred and heated (60°C) suspension all at once, which produced a turbid solution. Within ca. 1 minute a crystalline product was separated from the solution in the form of thick pulp. 50 ml of ethanol were added and the suspension was stirred in a bath at the temperature of 80°C, then slowly cooled to 40°C. The separated substance was filtered off, washed with ethanol (3 x 25 ml) and dried *in vacuo*. 1.9 g (yield 98%) of an off-white powder was obtained, HPLC 99.5%, content of the (*S*)-isomer 0.21%. The NMR spectra and the XRPD record identical with Example 16.

EXAMPLE 18 (preparation of the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid)



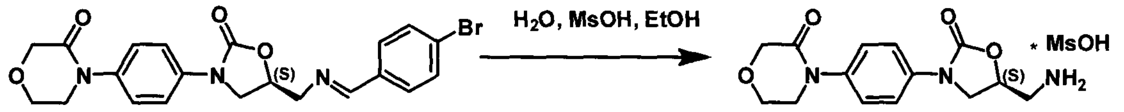
12.5 g of 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)-methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one was suspended in 75 ml of ethanol. A solution of methanesulfonic acid (2.4 ml) in a mixture of 75 ml of ethanol and 7 ml of water was added to the stirred and heated (45°C) suspension all at once, which produced a turbid solution. Within ca. 1 minute a crystalline product was separated from the solution. The suspension was stirred in a bath at the temperature of 45°C, then slowly cooled to 25°C. The separated substance was filtered off, washed with ethanol (2 x 50 ml) and dried *in vacuo*. 11.1 g (yield 95%) of an off-white powder with the melting point of 275-278°C (decomposition) was obtained, HPLC 99.8%, content of the (*R*)-isomer below 0.03%. The XRPD pattern was identical with that of the product prepared according to Example 16.

EXAMPLE 19 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid)



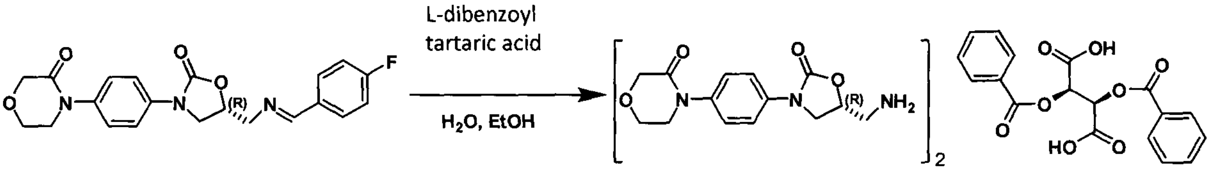
8.3 g of 4-{4-[(*R*)-5-[(((4-chlorophenyl)methylene)amino)-methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one was suspended in 50 ml of ethanol. A solution of methanesulfonic acid (1.6 ml) in a mixture of 50 ml of ethanol and 5 ml of water was added to the stirred and heated (45°C) suspension all at once, which produced a turbid solution. Within ca. 1 minute a crystalline product was separated from the solution. The suspension was stirred in a bath at the temperature of 45°C, then slowly cooled to 25°C. The separated substance was filtered off, washed with ethanol (2 x 50 ml) and dried *in vacuo*. 7.7 g (yield 99%) of an off-white powder was obtained, HPLC 98%, content of the (*S*)-isomer below 0.03%. The XRPD pattern was identical with the product prepared according to Example 16.

EXAMPLE 20 (preparation of the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid)



1.4 g of 4-{4-[(*S*)-5-[(((4-bromopfenyl)methylene)amino)-methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one was suspended in 8 ml of ethanol. A solution of methanesulfonic acid (0.25 ml) in a mixture of 8 ml of ethanol and 1 ml of water was added to the stirred and heated (50°C) suspension all at once, which produced a turbid solution. Within ca. 1 minute a crystalline product was separated from the solution. The suspension was stirred in a bath at the temperature of 50°C, then slowly cooled to 25°C. The separated substance was filtered off, washed with ethanol (2 x 10 ml) and dried *in vacuo*. 1.15 g (yield 97%) of an off-white powder was obtained, HPLC 99.7%, content of the (*R*)-isomer below 0.03%.

EXAMPLE 21 (preparation of the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with L-dibenzoyltartaric acid (2:1))



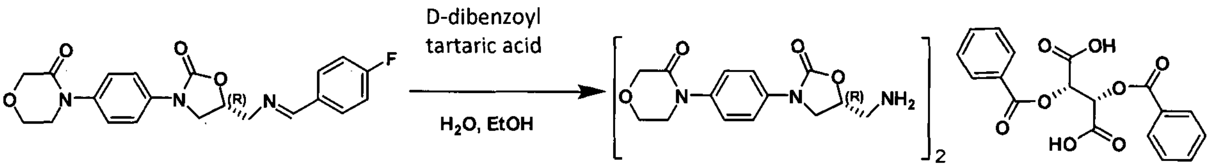
1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was suspended in 25 ml of ethanol. A solution of L-dibenzoyltartaric acid (0.9 ml) in a mixture of 5 ml of ethanol and 2.5 ml of water was added to the stirred and heated (50°C) suspension all

at once, which produced a turbid solution. The separated suspension was stirred in a bath at the temperature of 50°C, then slowly cooled to 25°C, filtered off, washed with ethanol (3 x 20 ml) and dried *in vacuo*. 0.94 g (yield 80 %) of an off-white powder with the melt. point of 197-199°C was obtained, HPLC 99.6%, content of the (*S*)-isomer 0.09%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.05 (m, 4H, 2xCH$_2$); 3.72 (m, 4H, 2xCH$_2$); 3.80 a 4.04 (2xm, 4H, 2xCH$_2$); 3.98 (m, 4H, 2xCH$_2$); 4.20 (s, 4H, 2xCH$_2$); 4.77 (pent, 2H, 2xCH); 5.64 (s, 2H, 2xCH); 7.38-7.62 (m, 14H); 7.96 (m, 4H).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 42.4; 47.1; 49.0; 63.4; 67.7; 70.9; 73.3; 118.3; 125.8; 128.5; 129.2; 130.1; 133.1; 136.4; 137.1; 153.8; 165.0; 165.9; 168.8.

EXAMPLE 22 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with D-dibenzoyltartaric acid (2:1))

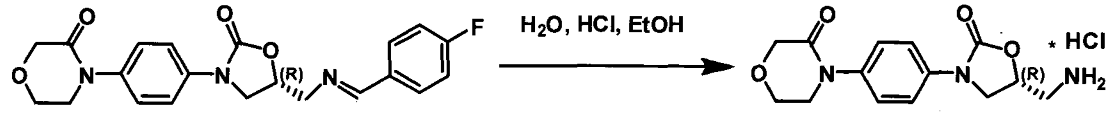


1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was suspended in 25 ml of ethanol. A solution of D-dibenzoyltartaric acid (0.9 ml) in a mixture of 5 ml of ethanol and 2.5 ml of water was added to the stirred and heated (50°C) suspension all at once, which produced a turbid solution. The separated suspension was stirred in a bath at the temperature of 50°C, then slowly cooled to 25°C, filtered off, washed with ethanol (3 x 20 ml) and dried *in vacuo*. 0.97 g (yield 82%) of an off-white powder with the melt. point of 199-201°C was obtained, HPLC 99.5%, content of the (*S*)-isomer 0.09%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.05 (m, 4H, 2xCH$_2$); 3.72 (m, 4H, 2xCH$_2$); 3.80 a 4.04 (2xm, 4H, 2xCH$_2$); 3.98 (m, 4H, 2xCH$_2$); 4.20 (s, 4H, 2xCH$_2$); 4.78 (pent, 2H, 2xCH); 5.64 (s, 2H, 2xCH); 7.25-7.70 (m, 14H); 7.95 (m, 4H).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 42.2; 47.1; 49.0; 63.4; 67.7; 71.0; 73.2; 118.3; 125.8; 128.5; 129.2; 130.0; 133.1; 136.4; 137.1; 153.8; 165.0; 165.9; 168.7.

EXAMPLE 23 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with hydrochloric acid)

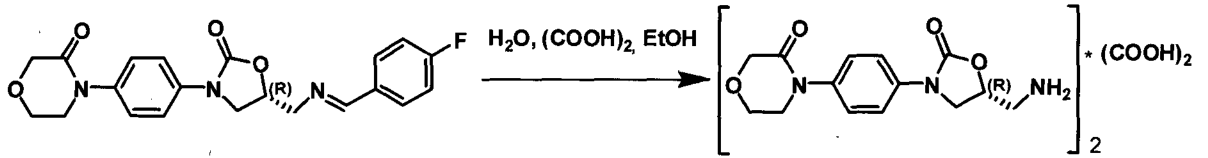


1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)-methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was suspended in a mixture of 25 ml of ethanol and 2.5 ml of water. Concentrated hydrochloric acid (1.5 ml) was added to the stirred and heated (65°C) suspension all at once, which produced a turbid solution from which a crystalline product was separated after a while. The separated suspension was stirred in a bath at the temperature of 60-65°C, then slowly cooled to 25°C during one hour, filtered off, washed with ethanol (2 x 20 ml) and dried *in vacuo*. 0.81 g (yield 98%) of an off-white powder with the melt. point of 258-262°C was obtained, HPLC 99.7, content of the (*S*)-isomer 0.08%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.24 (bs, 2H, CH$_2$); 3.72 (m, 2H, CH$_2$); 3.95 (m, 2H, CH$_2$); 3.95 and 4.21 (m, 2H, CH$_2$); 4.19 (s, 2H, CH$_2$); 5.00 (m, 1H, CH); 7.44 (m, 2H); 7.55 (m, 2H); 8.55 (bs, 3H, -NH$_2$ + HCl).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 41.4; 47.2; 49.0; 63.4; 67.7; 69.4; 118.5; 125.9; 136.2; 137.2; 153.6; 165.9.

EXAMPLE 24 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with oxalic acid)

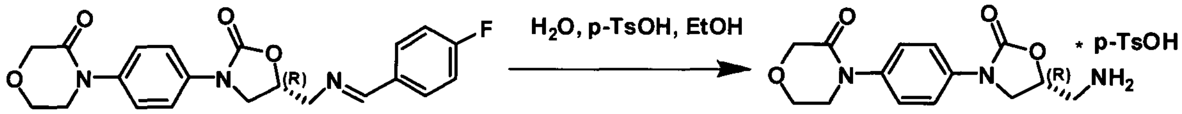


1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)-methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was suspended in a mixture of 25 ml of ethanol and 2.5 ml of water. A solution of oxalic acid dihydrate (0.35 g) in 2 ml of water was added to the stirred and heated (65°C) suspension all at once, which produced a turbid solution from which a crystalline product was separated after a while. The separated suspension was stirred in a bath at the temperature of 60-65°C, then slowly cooled to 22°C during one hour, filtered off, washed with ethanol (2 x 20 ml) and dried *in vacuo*. 0.83 g (yield 96%) of an off-white powder with the melt. point of 193-195°C was obtained, HPLC 99.7, content of the (*S*)-isomer 0.05%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.25 (m, 2H, CH$_2$); 3.68 (m, 2H, CH$_2$); 4.00 (m, 2H, CH$_2$); 3.95 and 4.21 (m, 2H, CH$_2$); 4.19 (s, 2H, CH$_2$); 4.94 (m, 1H, CH); 7.43 (m, 2H); 7.55 (m, 2H); 6.9-8.5 (bs, 6H, -NH$_2$ + (COOH)$_2$ + H$_2$O).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 41.6; 47.2; 49.0; 63.4; 67.7; 69.6; 118.5; 125.9; 136.3; 137.2; 153.6; 163.9. 165.9.

EXAMPLE 25 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with p-toluenesulfonic acid)

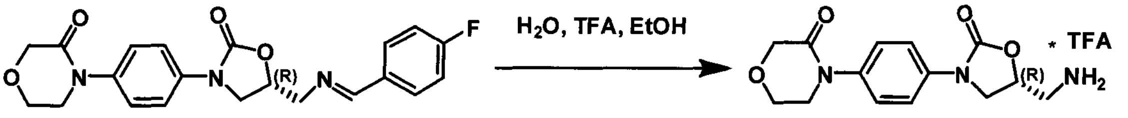


1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was suspended in 25 ml of ethanol. A solution of p-toluenesulfonic acid hydrate (0.5 g) in 2.5 ml of water was added to the stirred and heated (65°C) suspension all at once, which produced a turbid solution. The obtained solution was cooled to 22°C during one hour and then further to -15°C, where a solid product got separated and was filtered off, washed with ethanol (2 x 20 ml) and dried *in vacuo*. 0.70 g (yield 60%) of an off-white powder with melt. point of 237-240°C was obtained, HPLC 99.3%, content of the (*S*)-isomer 0.14%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 2,29 (s, 3H, CH$_3$); 3.27 (m, 2H, CH$_2$); 3.72 (m, 2H, CH$_2$); 3.72 and 3.98 (m, 2x2H, 2xCH$_2$); 3.85 and 4.21 (m, 2H, CH$_2$); 4.20 (s, 2H, CH$_2$); 4.92 (m, 1H, CH); 7.13 (m, 2H); 7.43 (m, 2H); 7.47 (m, 2H); 7.55 (m, 2H); 8.12 (bs, 3H, -NH$_2$ + -SO$_3$H).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 20.7; 41.6; 47.1; 49.0; 63.4; 67.7; 69.5; 118.4; 125.4; 125.9; 128.0; 136.2; 137.2; 137.6; 145.6; 153.5; 163.9.

EXAMPLE 26 (preparation of the salt of 4-{4-[(5*R*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with trifluoroacetic acid)



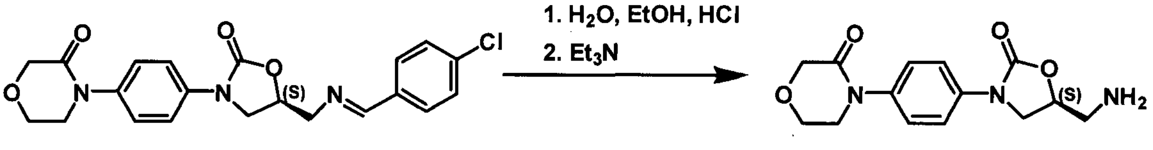
1 g of 4-{4-[(*R*)-5-[(((4-fluorophenyl)-methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one (containing 0.31% of the (*S*)-isomer according to HPLC) was

suspended in a mixture of 25 ml of ethanol and 2.5 ml of water. 0.3 ml of trifluoroacetic acid was added to the stirred and heated (65°C) suspension all at once, which produced a turbid solution. The obtained solution was cooled down to -15°C during 1 hour, yet no solid product did get separated. The solvent was then evaporated *in vacuo*, and 20 ml of ethanol were added to the concentrated residue. The separated solid product was filtered off, washed with ethanol (2 x 10 ml) and dried *in vacuo*. 0.74 g (yield 76%) of an off-white powder with the melt. point of 180-183°C was obtained, HPLC 99.6%, content of the (*S*)-isomer 0,06%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.26 (m, 2H, CH_2); 3.72 (m, 2H, CH_2); 3.98 (m, 2H, CH_2); 3.89 and 4.25 (m, 2H, CH_2); 4.20 (s, 2H, CH_2); 4.94 (m, 1H, CH); 7.42 (m, 2H); 7.57 (m, 2H); 8.27 (bs, 3H, $-NH_2$ + -COOH).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 41.6; 47.2; 49.0; 63.4; 67.7; 69.5; 116.6; 118.5; 125.9; 136.2; 137.2; 153.5; 158.1; 165.9.

EXAMPLE 26 (preparation of the free base of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one)

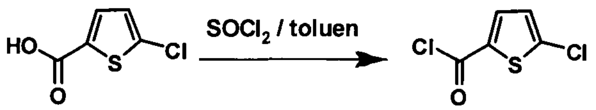


25 g of 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one was suspended in 200 ml of ethanol with addition of 10 ml of water. Concentrated hydrochloric acid (30 ml) was added to the stirred and heated (65°C) suspension all at once, which produced a turbid solution. 200 ml of ethanol were added and the suspension was stirred in a bath at the temperature of 65°C, then 100 ml of triethylamine were added and the obtained solution was stirred and heated to 65°C. The turbid solution was concentrated *in vacuo* and 400 ml of ethanol was added to the obtained oil. The produced suspension was stirred at 22°C for 1 hour, then the solid product was filtered off, washed with ethanol (2 x 50 ml) and dried *in vacuo*. 16.7 g (yield 95%) of an off-white powder with the melt. point of 143-144°C was obtained, HPLC 99.8%, content of the (*R*)-isomer below 0.03%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 2.76-2.90 (m, 2H, CH_2); 3.71 (m, 2H, CH_2); 3.88 (m, 2H, CH_2); 3.97 (m, 2H, CH_2); 4.07 (t, 2H, CH_2); 4.20 (s, 2H, CH_2); 4.62 (m, 1H, CH); 7.41 (m, 2H); 7.56 (m, 2H).

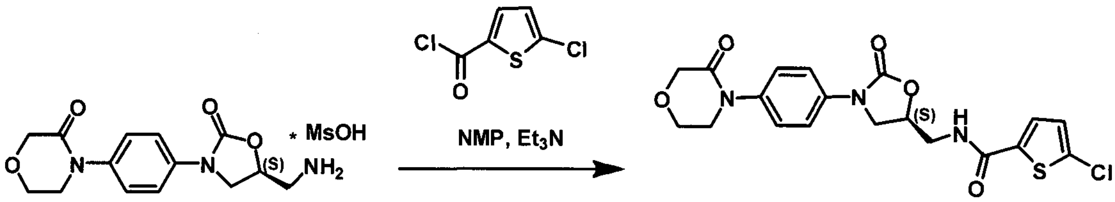
^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 44.2; 47.0; 49.0; 63.4; 67.7; 73.9; 118.1; 125.8; 136.7; 136.8; 154.4; 165.9.
MS (m/z): 292.1292 (M+H)$^+$.

EXAMPLE 27 (preparation of the chloride of 5-chlorothiophene-2-carboxylic acid)



40 g of 5-chlorothiophene-2-carboxylic acid were suspended in 135 ml of toluene and 21.5 ml of thionylchloride dissolved in 30 ml of toluene were added to the suspension. The mixture was stirred and heated at reflux for 3 hours and at the laboratory temperature for another 3 hours. 35 ml of a liquid were removed by distillation at the atmospheric pressure and still more liquid at the vacuum of 50 mbar and bath temperature of 70°C from the obtained solution. 101 ml of a solution with the concentration of 2.46 M of the active component were obtained. This solution was used for synthesis of rivaroxaban without any treatment.

EXAMPLE 28 (preparation of rivaroxaban)



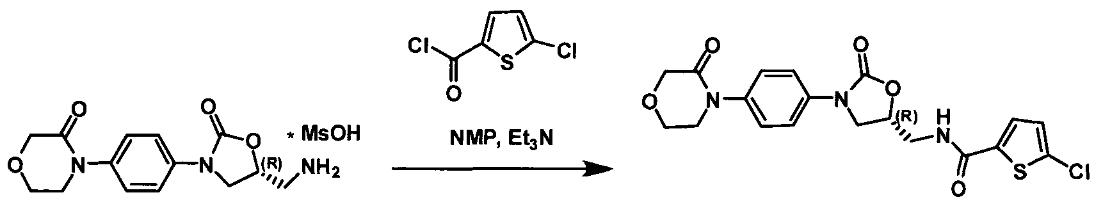
10 g of the salt prepared according to Example 18 were suspended in 75 ml of N-methylpyrolidone, the suspension was heated at 50°C, then 14 ml of triethylamine was added and the mixture was heated at 60°C. This was followed by addition of 15.7 ml of a solution of 5-chlorothiophene-2-carboxylic acid chloride in toluene (2.46 M) and the reaction mixture was stirred and heated at 55°C for 15 minutes, then slowly cooled below 30°C, 75 ml were added and the turbid solution was filtered. The clear filtrate was stirred at 50°C, which was followed by addition of 15 ml of water and 75 ml of ethanol and stirring for 1 hour under slow cooling. The separated product was filtered off, washed with water (15 ml, 60°C), ethanol (2 x 25 ml) and dried *in vacuo*. 9.1 g (yield 81%) of rivaroxaban in the form of an off-white powder with the melt. point of 229.5-231°C was obtained, HPLC 99.95%, content of the (*R*)-isomer below 0.03%.

^{1}H NMR (250 MHz, DMSO-D$_6$), δ (ppm): 3.61 (t, 2H, CH$_2$); 3.71 (m, 2H, CH$_2$); 3.85 and 4.19 (m, 2x1H, CH$_2$); 3.97 (m, 2H, CH$_2$); 4.19 (s, 2H, CH$_2$); 4.84 (pent, 1H, CH); 7.18 (d, 1H); 7.40 (m, 2H); 7.56 (m, 2H); 7.68 (d, 1H); 8.95 (bt, 1H, NH).

^{13}C NMR (250 MHz, DMSO-D$_6$), δ (ppm): 42.2; 47.4; 49.0; 63.4; 67.7; 71.3; 118.3; 125.9; 128.1; 128.4; 133.2; 136.4; 137.0; 138.4; 154.0; 160.8; 165.9.

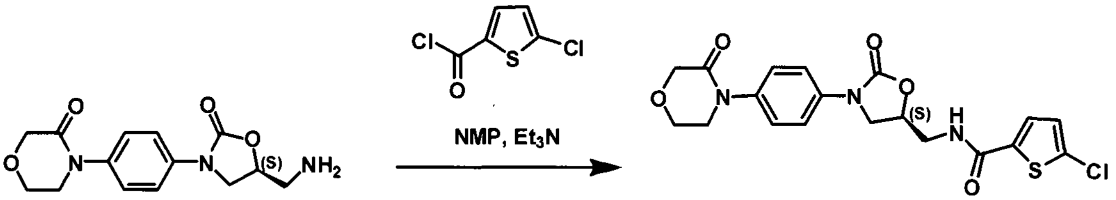
MS (m/z): 436.0729 (M+H)$^+$.

EXAMPLE 29 (preparation of the optical isomer of rivaroxaban with the (*R*)- configuration)



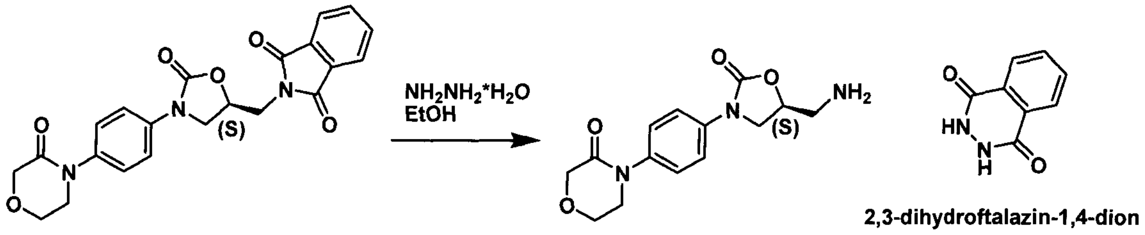
The optical isomer of rivaroxaban with the (*R*)- configuration was obtained by a process analogous to Example 28 starting from the salt prepared according to Example 19. The yield was 76%, HPLC 99.90%, content of the (*S*)-isomer below 0.03%. The NMR and MS spectra were in accordance with Example 28.

EXAMPLE 30 (preparation of rivaroxaban)



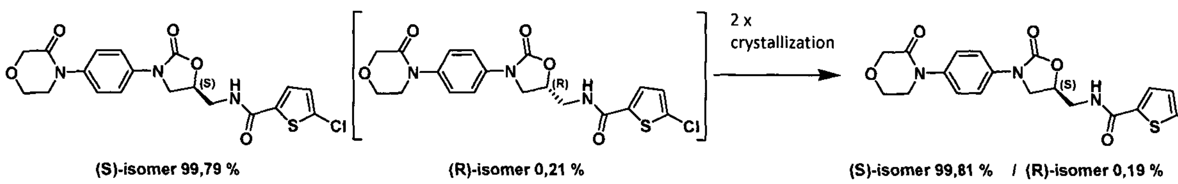
10.5 g of the amine prepared according to Example 26 were suspended in 200 ml of dichloromethane and then 5.4 ml of triethylamine dissolved in 50 ml of dichloromethane were added. This was followed by addition of 14.4 ml of a solution of 5-chlorothiophene-2-carboxylic acid chloride in toluene (2.46 M) and 25 ml of dichloromethane. The reaction mixture was stirred and heated at boiling for 1.5 hours and then slowly cooled below 30°C. The separated product was filtered off, washed with dichloromethane (15 ml) and ethanol (2 x 15 ml). The crude product was crystallized from a mixture of acetic acid (20 ml) and ethanol (200 ml). 10.5 g (yield 67%) of rivaroxaban was obtained in the form of an off-white powder with the melt. point of 228-230°C, HPLC 99.97%, content of the (*R*)-isomer below 0.03%. The NMR and MS spectra were in accordance with Example 28.

EXAMPLE 31 (comparative example – deprotection of the protecting group)



20 g of 2-({(5*S*)-2-oxo-3-[4-(3-oxomorpholin-4-yl)phenyl]-1,3-oxazolidin-5-yl}methyl)-1*H*-isoindole-1,3(2*H*)-dione was suspended in 450 ml of ethanol, which was followed by addition of 6 ml of hydrazinehydrate in 50 ml of ethanol and the mixture was stirred and refluxed for 3 hours. Then, the suspension was cooled down to 65°C and filtered and the cake was washed with 2x50 ml of nearly boiling ethanol. After drying 7.2 g of an off-white powder were obtained, which slowly melted at a temperature over 260°C (this fraction contained 99.9% of 2,3-dihydrophtalazine-1,4-dione according to HPLC). After cooling of the hot filtrate another solid fraction separated. After its isolation by filtration and drying, 12.5 g of white lumpy powder with the melt. point of 141-144°C was obtained (this fraction contained 86.7% of the desired product, 12.7% of 2,3-dihydrophtalazine-1,4-dione, and the rest to 100 % were other unidentifiable impurities according to HPLC). The yield of the isolated amine calculated to the pure substance was 73%.

EXAMPLE 32 (crystallization of rivaroxaban with an excessive content of the (*R*)-isomer)



Crude rivaroxaban with the chemical purity of 99.5%, containing 0.21% of the (*R*)-enantiomer and 0.50% of unidentified impurities, was crystallized from a mixture of acetic acid and ethanol.

Crystallization 1: 22 g of crude rivaroxaban were dissolved in 180 ml of acetic acid at boiling and the obtained solution was still hot filtered. The filtrate was brought to boil again and 400 ml of ethanol was gradually added to the boiling solution. The mixture was stirred under slow cooling for ca. 1 hour (resulting temperature of the suspension ca. 28°C). Subsequently, filtration was performed, the cake was washed with 2x30 ml of ethanol and vacuum-dried.

20.3 g of the product was obtained, melt. point 227.5-228.5°C. The yield of the crystallization was 92%, HPLC 99.8%, content of the (*R*)-enantiomer 0.21%, contents of unidentified impurities 0.15%.

Crystallization 2: 20 g of once crystallized rivaroxaban were dissolved in 150 ml of acetic acid at boiling and the obtained solution was still hot filtered (the filter was washed with 20 ml of boiling acetic acid to the filtrate). The filtrate was brought to boil again and 340 ml of ethanol was gradually added to the boiling solution. The mixture was stirred under slow cooling for ca. 1.5 hours (resulting temperature of the suspension ca. 26°C). Subsequently, filtration was performed, the cake was washed with 2x50 ml of ethanol and vacuum-dried. 19.1 g of the product was obtained, melt. point 230-231°C. Crystallization yield 96%, HPLC 99.96%, content of the (*R*)-enantiomer 0.19%, the contents of unidentified impurities was 0.04%.

After two crystallizations the final chemical purity of rivaroxaban achieved was 99.96%, the contents of unidentified impurities was reduced from 0.50% to 0.04%. After two crystallizations the achieved content of the (*R*)-isomer was 0.19%, which is an excessive value (limit 0.15%) and is comparable to the initial level of 0.21%. The yield of rivaroxaban after the two crystallizations was 88% (calculated to the starting crude rivaroxaban).

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

A X-Ray Powder Diffraction (XRPD)

The diffraction patterns were measured using an X'PERT PRO MPD PANalytical diffractometer with a graphite monochromator, radiation used CuKα (λ=1.542 Å), excitation voltage: 45 kV, anode current: 40 mA, measured range: 2 - 40° 2θ, increment: 0.01° 2θ. The measurement was carried out using a flat powder sample that was placed on a Si plate. For the primary optic setting programmable divergence diaphragms with the irradiated sample area of 10 mm, Soller diaphragms 0.02 rad and an anti-dispersion diaphragm ¼ were used. For the secondary optic setting an X'Celerator detector with the maximum opening of the detection slot, Soller diaphragms 0.02 rad and an anti-dispersion diaphragm 5.0 mm were used.

Table 2 Data of the X-Ray Powder Diffraction for (*S*)-(**9**), Ar stands for 4-fluorophenyl

Pos. [°2Th.]	Interplanar distance [A] =0.1nm	Rel. Int. [%]
2.16	40.776	100.0
6.54	13.496	8.8
8.74	10.114	11.9
10.94	8.084	8.1
13.13	6.736	49.1
17.48	5.071	45.5
20.58	4.312	75.2
22.77	3.902	5.1
24.03	3.700	4.7
25.71	3.463	9.2
26.63	3.345	15.0
28.16	3.167	8.1

Table 3 Data of the X-Ray Powder Diffraction for (*S*)-(**9**), Ar stands for 4- chlorophenyl

Pos. [°2Th.]	Interplanar distance [A] =0.1nm	Rel. Int. [%]
6.58	13.427	18.1
8.71	10.142	17.2
12.98	6.814	100.0
17.57	5.044	44.0
19.06	4.652	13.6
19.43	4.564	15.0
20.03	4.430	12.3
20.93	4.242	60.1
24.29	3.662	6.7
25.92	3.435	14.6
26.95	3.305	23.7
28.50	3.130	10.6
32.46	2.756	4.7
39.23	2.294	5.3

Table 4 Data of the X-Ray Powder Diffraction for (*S*)-**(9)**, Ar stands for 4- bromophenyl

Pos. [°2Th.]	Interplanar distance [A] = 0.1nm	Rel. Int. [%]
4.24	20.817	59.2
6.30	14.008	100.0
8.38	10.544	55.6
10.46	8.451	9.4
12.53	7.057	48.4
14.62	6.055	12.6
18.80	4.715	9.0
20.85	4.257	13.7
27.23	3.273	9.5
29.36	3.040	7.4
33.65	2.662	10.7
37.99	2.367	8.1

Table 5 Data of the X-Ray Powder Diffraction for the compound (*S*)-**(12)**

Pos. [°2Th.]	Interplanar distance [A] =0.1nm	Rel. Int. [%]
2.61	33.871	100.0
5.16	17.119	9.8
7.70	11.479	11.8
10.26	8.618	42.4
15.38	5.758	58.6
17.70	5.007	64.6
18.71	4.738	14.3
19.87	4.465	51.9
20.54	4.321	56.9
22.01	4.035	24.6
22.66	3.920	13.4
25.40	3.504	40.4
26.17	3.403	16.9
27.97	3.187	7.6
30.14	2.962	7.1
32.03	2.792	6.2
33.61	2.665	5.5
38.97	2.309	5.0

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 specified for the respective compounds in the corresponding examples.

C Proton and Carbon NMR Spectrometry (^{1}H and ^{13}C NMR)

NMR spectra of the prepared compounds were measured in Avance 250 (Bruker) and Avance 500 (Bruker) spectrometers, for solutions of compounds in $CDCl_3$ or DMSO-*d6*. ^{1}H chemical shifts are related to the signal of TMS (δ) 0.00 ppm and ^{13}C chemical shifts are related to the signal of the solvent used, DMSO-*d6* (δ) 39.5 ppm or $CDCl_3$ (δ) 77.0 ppm.

D Mass Spectrometry (MS)

The mass spectra were measured in an LTQ Orbitrap Hybrid Mass Spectrometer device (Thermo Finnigan, U.S.A.) with direct injection into the APCI source in the positive mode.

E Gas Chromatography (GC)

The related substances and optical purity of substances were measured in Agilent technologies GC system 6890N and GC system 7890A gas chromatographs with split/splitless injection. Unless otherwise specified, a flame-ionization detector was used for the detection.

Conditions for determination of related substances of epichlorohydrin (Examples 1 to 6): column: DB-624 (30 m; 0.53 mm; 3.0 μm); temperature program: 40°C(2 min), 5°C/min to 180°C (0 min); carrier gas: helium at the rate of 30 cm/s, constant flow; injector temperature 180°C; detector temperature 280°C.

Conditions for determination of optical purity of epichlorohydrin (Examples 1 to 6): column: Astec chiraldex GP-N(30 m; 0.35 mm; 0.25 μm); temperature program: 60°C (35 min); carrier gas: helium, constant flow 0.4 ml/min; injector temperature 160°C; Pulse discharge detector, 200°C.

Conditions for determination of related substances of 4-fluorobenzaldehyde, 4-chlorobenzaldehyde and 4-bromobenzaldehyde (Examples 1 to 6):

column: DB-624 (30 m; 0.53 mm; 3.0 μm); temperature program: 60°C(0 min), 10°C/min to 250°C (10 min); carrier gas: helium at the rate of 35 cm/s, constant flow; injector temperature 250°C; detector temperature 260°C.

Conditions for determination of related substances of products in Examples 1 to 6:
column: Rtx-5 Amine (30 m; 0.53 mm; 3.0 μm); temperature program: 60°C(0 min), 10°C/min to 280°C (8 min); carrier gas: helium at the rate of 35 cm/s, constant flow; injector temperature 250°C; detector temperature 290°C.

Conditions for determination of optical purity of products in Examples 1 to 4:
For determination of optical purity the product was derivatized through a reaction with (-)-R-menthyl chloroformate. The reaction proceeded at 80°C in dichloromethane for 1 hour.
Chromatographic conditions:
column: DB-1701 (30 m; 0,32 mm; 1.0 μm); temperature program: 200°C(2 min), 5°C/min to 280°C (20 min); carrier gas: helium at the rate of 35 cm/s, constant flow; injector temperature 250°C; detector temperature 300°C.

F High-Performance Liquid Chromatography (HPLC)

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

For determination of related substances of products in Examples 7, 28, 29 and 30 an Ascentis Express RP-Amide column, 100 x 3.0 mm, 2.7μm was used at 15°C. Gradient elution with a two-component mobile phase was used (component A: 10 mM aqueous solution of ammonium acetate, pH = 5.0; component B: acetonitrile) according to the following table.

Time (min)	Flow (ml/min)	Component A (%)	Component B (%)
0	0.6	90	10
2	0.6	90	10
7	0.6	35	65
11	0.6	25	75
13	0.6	25	75
14	0.6	90	10
16	0.6	90	10

The detection was performed at the wavelength of 245 nm

For determination of optical purity of rivaroxaban a Chiralpak IA column, 250 x 4.6 mm; 5μm was used at 40°C. Isocratic elution with a two-component mobile phase was used (component A: hexane; component B: 2-butanol) in the proportion of A:B = 40:60 (*V/V*) at the flow of 1 ml/min; the detection was performed at 251 nm.

For determination of related substances of products in Examples 9, 10, 11, 12, 13, 14, and 15 a Gemini-NX C18 110A column, 100 x 4.6 mm, 3 μm was used at 35°C. Isocratic elution with a two-component mobile phase was used (component A: 10 mM aqueous solution of triethylamine, pH = 11.5; component B: methanol) in the proportion of A:B = 60:40 (*V/V*) at the flow of 1.5 ml/min; the detection was performed at 250 nm.

For determination of optical purity of products in Examples 9, 10, 11, 12, 13, 14, and 15 a Lux 3u Amylose-2 column, 150 x 4.6 mm, 3μm was used at 35°C. Isocratic elution with a single-component mobile phase was used with the composition of hexane : ethanol in the proportion of 25:75 (*V/V*) with the addition of 0.2 % diethylamine at the flow of 1.5 ml/min; the detection was performed at 252 nm.

For determination of related substances of products in Examples 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, and 26 an Ascentis Express RP-Amide column, 100 x 3.0 mm, 2.7μm was used at the temperature of 10°C. Gradient elution with a two-component mobile phase was used (component A: 10 mM aqueous solution of sodium octanesulfonate, pH = 2.5; component B: acetonitrile) according tot he following table.

Time (min)	Flow (ml/min)	Component A (%)	Component B (%)
0	0,5	85	15
13	0,5	85	15
18	0,5	50	50
23	0,5	50	50
25	0,5	85	15
30	0,5	85	15

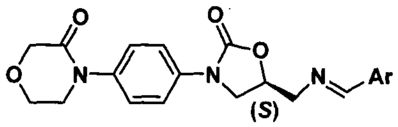
The detection was performed at the wavelength of 245 nm

For determination of optical purity of products in Examples 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, and 26 a Lux 3u Cellulose-4 column, 150 x 4.6 mm, 3μm was used at 40°C. Isocratic elution with a single-component mobile phase was used with the composition of hexane : ethanol in the proportion of 10:90 (*V/V*) with the addition of 0.1 % diethylamine at the flow of 1 ml/min; the detection was performed at 245 nm.

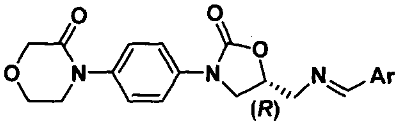
For determination of optical purity of products in Examples 5 and 6 a Chiralpak AD-3 column, 150 x 4.6 mm; 3μm was used at 40°C. Isocratic elution with a single-component mobile phase was used with the composition of hexane : ethanol in the proportion of 85:15 (*V/V*) at the flow of 1.5 ml/min; the detection was performed at 256 nm.

CLAIMS

1. Stereoisomers of 4-{4-[(S/R)-5-[(((aryl)methylene)amino)methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-ones, described by chemical formulae (*S*)-**(9)** and (*R*)-**(9)**, wherein (*S*)- and (*R*)- mean the absolute stereometric configuration, wherein Ar-aryl is selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl.



(S)-(9)



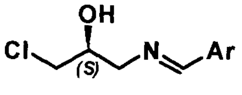
(*R*)-(9)

2. The stereoisomers according to claim 1, described by formulae (*S*)-**(9)** and (*R*)-**(9)**, in crystalline form, preferably crystalline derivatives wherein Ar stands for 4-fluorophenyl, 4-chlorophenyl or 4-bromophenyl, which are characterized by the following reflections in the X-Ray Powder Diffraction:
   (a) 2.2; 6.5; 8.7; 13.1; 17.5; 20.6 and 26.6 ± 0.2° (2θ) for the derivative where Ar stands for 4-fluorophenyl,
   (b) 6.6; 8.7; 13.0; 17.6; 20.9; 27.0 and 28.5 ± 0.2° (2θ) for the derivative where Ar stands for 4-chlorophfenyl,
   (c) 4.2; 6.3; 8.4; 12.5; 14.6; 20.8; 27.2 and 33.7 ± 0.2° (2θ) for the derivative where Ar stands for 4-bromophenyl,

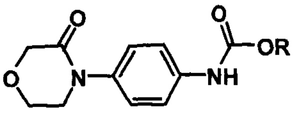
   said values of reflections corresponding to XRPD patterns obtained by means of copper-emitted radiation with the wavelength of 0.15418 nm.

3. A process for the preparation of the compound of formula (*S*)-**(9)** as defined in claim 1, wherein the process consists of the following steps:
   (a) reaction of (*S*)-epichlorohydrin with ammonia and an aromatic aldehyde of formula **(13)**, wherein Ar-aryl is selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl, producing (*S*)-1-chloro-3-(((aryl)methylene)amino)propan-2-ol of formula (*S*)-**(14)**, wherein Ar corresponds to the Ar of the aldehyde **(13)** used,

ArCHO
(13)



(S)-(14)

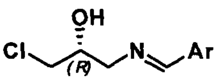


(15)

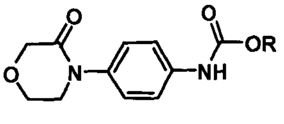
(b) reaction of (*S*)-**(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate of formula **(15)**, wherein R stands for an alkyl, preferably benzyl, under catalysis by bases.

4. A process for the preparation of the compound of formula (*R*)-**(9)** as defined in claim 1, wherein the process consists of the following steps:
   (a) reaction of (*R*)-epichlorohydrin with ammonia and an aromatic aldehyde of formula **(13)**, wherein Ar-aryl is selected from the group of 4-fluorophenyl, 4-chlorophenyl and 4-bromophenyl, producing (*R*)-1-chloro-3-(((aryl)methylene)-amino)propan-2-ol of formula (*R*)-**(14)**, wherein Ar corresponds to the Ar of the aldehyde **(13)** used,

ArCHO
(13)



(R)-(14)

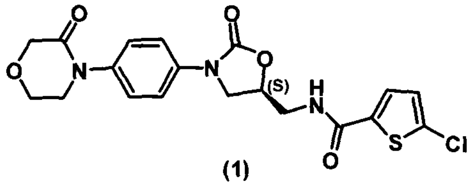


(15)

   (b) reaction of (*R*)-**(14)** with an alkyl 4-(3-oxomorpholin-4-yl)phenylcarbamate of formula **(15)**, wherein R stands for an alkyl, preferably benzyl, under catalysis by bases.

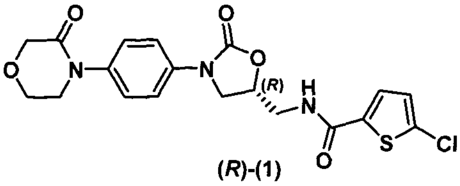
5. The process according to claims 3 and 4, characterized in that the base in step (b) is selected from the group of n-butyllithium, lithium *tert*-butoxide, lithium hydroxide, lithium diisopropylamide or lithium hexamethyldisilazide.

6. Use of the stereoisomer (*S*)-**(9)** for the preparation of (*S*)-rivaroxaban of formula **(1)**.



(1)

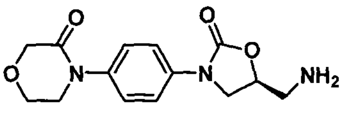
7. Use of the stereoisomer (*R*)-**(9)** for the preparation of (*R*)-rivaroxaban of formula (*R*)-**(1)**.

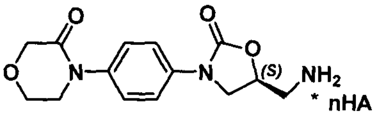


(*R*)-(1)

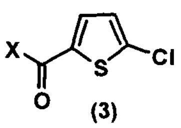
8. A process for the manufacture of (*S*)-rivaroxaban of formula (**1**), wherein the process consists of the following steps:

   (a) hydrolysis of (*S*)-(**9**), producing 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one described by formula (*S*)-(**10**) or its salt with acids described by formula (*S*)-(**11**), wherein HA stands for an acid selected from the group of methanesulfonic, benzenesulfonic, p-toluenesulfonic, (*R*)- and (*S*)-camphorsulfonic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, D- and L- tartaric, D- and L- dibenzoyltartaric, oxalic and trifluoroacetic acids,


(S)-(10)



(S)-(11) n = 1/2, 1


(3)

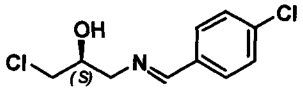
   (b) reaction of the product of the previous stage with an acylation agent of formula **3**, wherein X stands for a halogen, producing rivaroxaban.

9. The process according to claim 8, characterized in that the hydrolysis in step (a) is performed with water in the presence of an acid selected from the group of methanesulfonic, benzenesulfonic, p-toluenesulfonic, (*R*)- and (*S*)- camphorsulfonic, hydrochloric, hydrobromic, phosphoric, nitric, sulphuric, D- and L- tartaric, D- and L-dibenzoyltartaric, oxalic and trifluoroacetic acids, in a solvent selected from the group of C_1 to C_5 aliphatic alcohols, methyl acetate, ethyl acetate, isopropyl acetate, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran and dioxin or any mixtures of these solvents, producing the salts described by the chemical formula (*S*)-(**11**).

10. The process according to claim 8, characterized in that the salt of formula (*S*)-(**11**) in step (a) is reacted with a base selected from the group of triethylamine, diisopropylethylamine, N-alkylpiperidine, N-alkylmorpholine, pyridine and sodium hydrogen carbonate, producing the free base of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one described by formula (*S*)-(**10**).

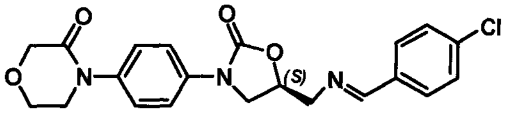
11. A process for the preparation of rivaroxaban **(1)**, wherein the process consists of the following steps:

(a) reaction of (*S*)-epichlorohydrin with ammonia and 4-chlorobenzaldehyde, producing (*S*)-1-chloro-3-[((4-chlorophenyl)methylene)amino]propan-2-ol **(16)**,



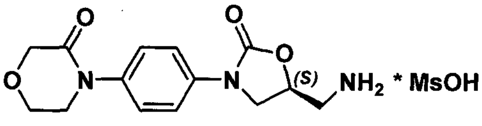
(16)

(b) reaction of the product of step (a) with benzyl 4-(3-oxomorpholin-4-yl)phenylcarbamate (**15**, R means benzyl) and lithium *tert*-butoxide performed in dichloromethane, producing 4-{4-[(*S*)-5-[(((4-chlorophenyl)methylene)amino)-methyl]-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one **(17)**,



(17)

(c) reaction of the product of step (b) with water and methanesulfonic acid performed in ethanol, producing the salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one with methanesulfonic acid (*S*)-**(12)**,



(S)-(12)

(d) reaction of the product of step (c) with 5-chlorothiophene-2-carbonyl chloride (**3**, X means chlorine) performed in a solvent selected from the group of dimethylformamide, dimethylacetamide, dimethylsulfoxide, N-methylpyrolidone, acetonitrile, tetrahydrofuran, 2-methyltetrahydrofuran, dioxane, dichloromethane, chloroform or a mixture of these solvents and in the presence of a base selected from the group of triethylamine, diisopropylethylamine, N-alkylpiperidine, N-alkylmorpholine, pyridine and sodium hydrogen carbonate.

12. Crystalline salt of 4-{4-[(5*S*)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}-morpholin-3-one with methanesulfonic acid described by formula (*S*)-**(12)**, which manifests the following values of reflections in the X-Ray Powder Diffraction: 2.6; 7.7; 10.3; 15.4; 17.7; 19.9; 22.0 and 25.4 ± 0.2° (2θ), said values of reflections

corresponding to XRPD patterns obtained by means of copper-emitted radiation with the wavelength of 0.15418 nm.

13. Use of rivaroxaban prepared by the process according to any one of claims 8 or 11 for the manufacture of a drug from the therapeutic group of anticoagulants.

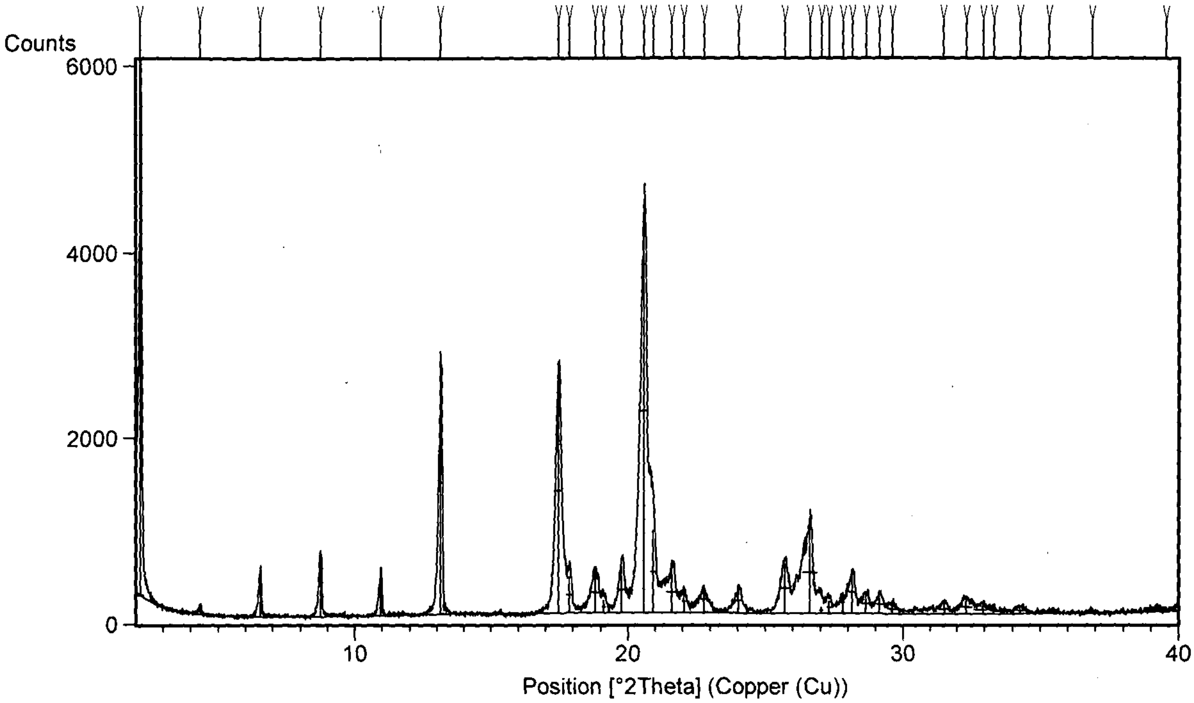
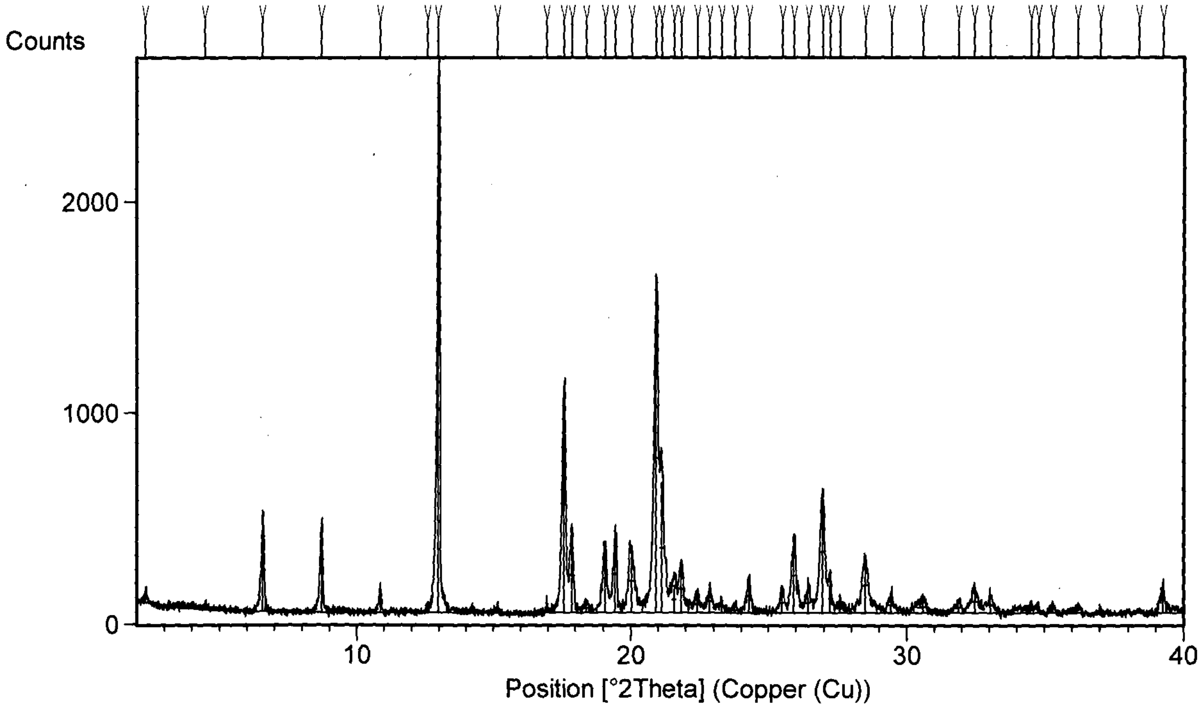

Counts
6000
4000
2000
0
10
20
30
40
Position [°2Theta] (Copper (Cu))

Fig. 1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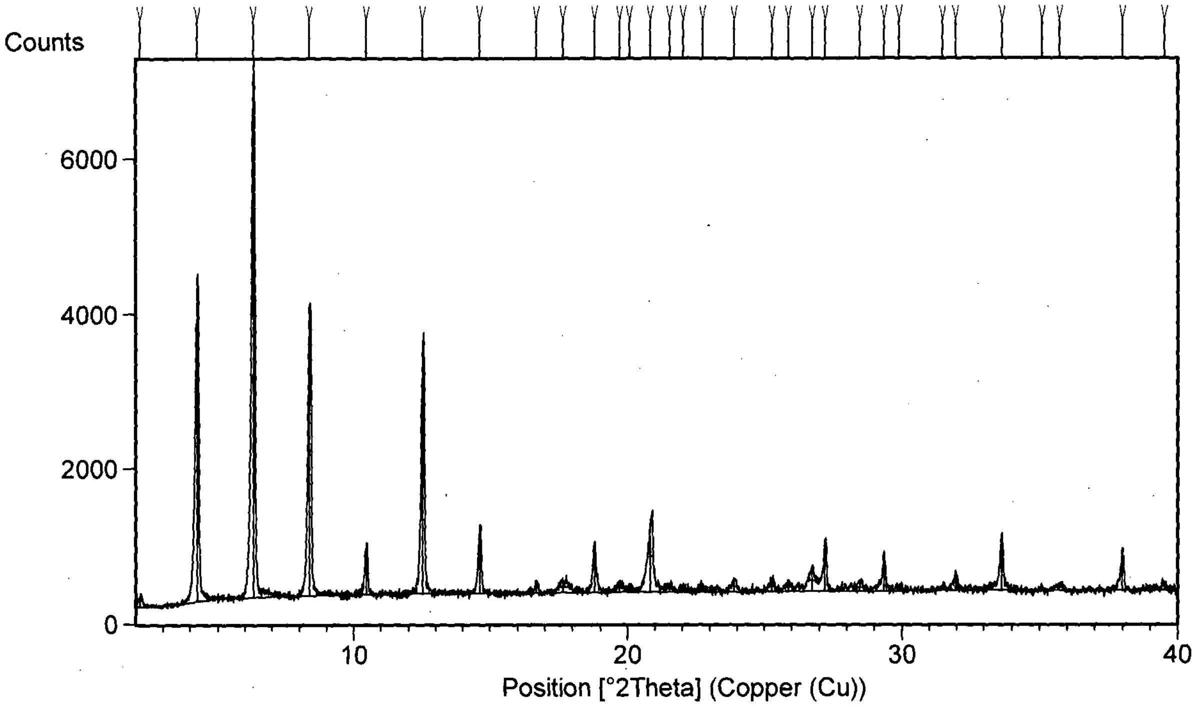
Position [°2Theta] (Copper (Cu))

Fig. 2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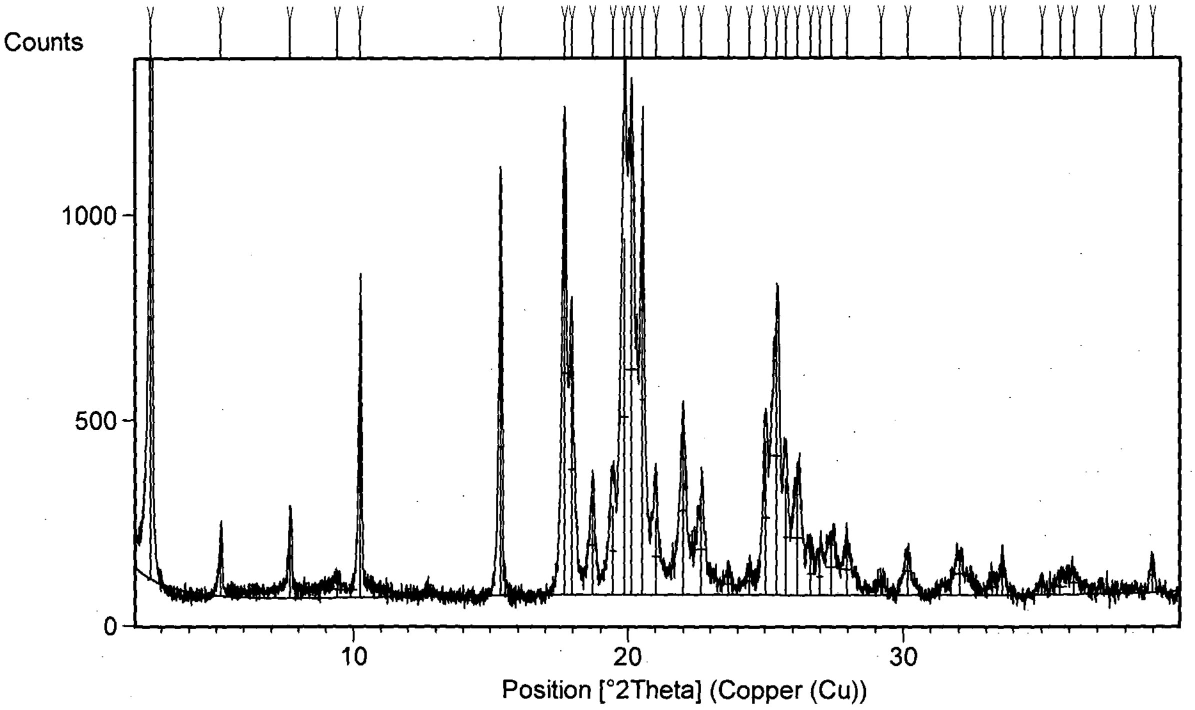
Position [°2Theta] (Copper (Cu))

Fig. 3


Counts
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20
30
Position [°2Theta] (Copper (Cu))

Fig. 4

INTERNATIONAL SEARCH REPORT

International application No
PCT/CZ2013/000015

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D413/10 C07D413/14
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, 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.
X	"Crystalline forms of 4-{4-[(5S)-5-(aminomethyl)-2-oxo-1,3-oxazolidin-3-yl]phenyl}morpholin-3-one", IP.COM JOURNAL, IP.COM INC., WEST HENRIETTA, NY, US, 7 December 2009 (2009-12-07), XP013135806, ISSN: 1533-0001 figure 5 ----- -/--	12

☒ 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 8 April 2013	Date of mailing of the international search report 15/04/2013
Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Authorized officer Lauro, Paola

1

International application No
PCT/CZ2013/000015

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	ROEHRIG S 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)thiophene-2-carboxamide (BAY 59-7939): An Oral, Direct Factor Xa Inhibitor", JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY, US, vol. 48, 22 September 2005 (2005-09-22), pages 5900-5908, XP002418821, ISSN: 0022-2623, DOI: 10.1021/JM050101D cited in the application	13
Y	Scheme 1; compound 5 -----	1-12
Y	US 7 816 355 B1 (BODHURI PRABHUDAS [CA] ET AL) 19 October 2010 (2010-10-19) columns 1-4 -----	1-12
Y	WO 2007/116284 A1 (PFIZER PROD INC [US]; IMBORDINO RICK JOSEPH [US]; PERRAULT WILLIAM ROL) 18 October 2007 (2007-10-18) cited in the application examples 1-3 -----	1-12
X,P	WO 2012/159992 A1 (INTERQUIM SA [ES]; BERZOSA RODRIGUEZ XAVIER [ES]; MARQUILLAS OLONDRIZ) 29 November 2012 (2012-11-29) page 4; example 5 -----	1-13
X,P	CN 102 786 516 A (UNIV HUNAN NORMAL) 21 November 2012 (2012-11-21) paragraph [0009] -----	1-13

1

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/CZ2013/000015

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