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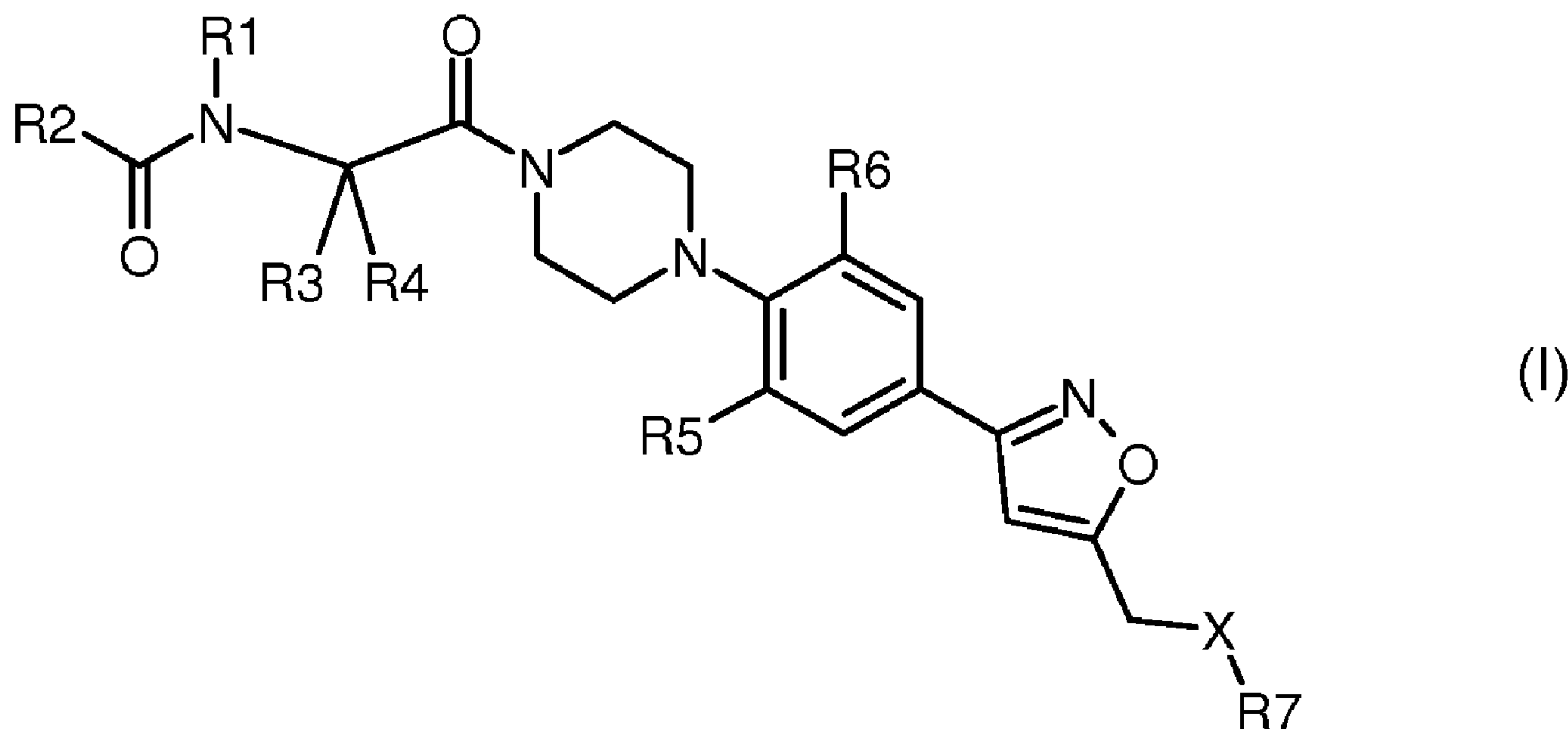
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(54) Titre : COMPOSES DICARBONYLIQUES A ACTIVITE ANTIBACTERIENNE

(54) Title: DICARBONYLIC COMPOUNDS WITH ANTIBACTERIAL ACTIVITY



(57) Abrégé/Abstract:

Compounds of formula (I), and their pharmaceutically acceptable salts and solvates, wherein X represents -O-, -NH-, -S-, -NHC(=O)- or -NHC(=S)-; R1 represents -H or a hydrocarbon chain; R2 represents -H, alkoxy, amino, a hydrocarbon chain or a radical of a cycle; R3 represents -H, a hydrocarbon chain or a radical of a cycle; R4 represents -H or a hydrocarbon chain; alternatively R3 and R4 form together a cycle; R5 and R6 represent -H or halogen, and R7 represents -H, a hydrocarbon chain or heteroaryl, are useful against bacterial infections in animals, including humans.

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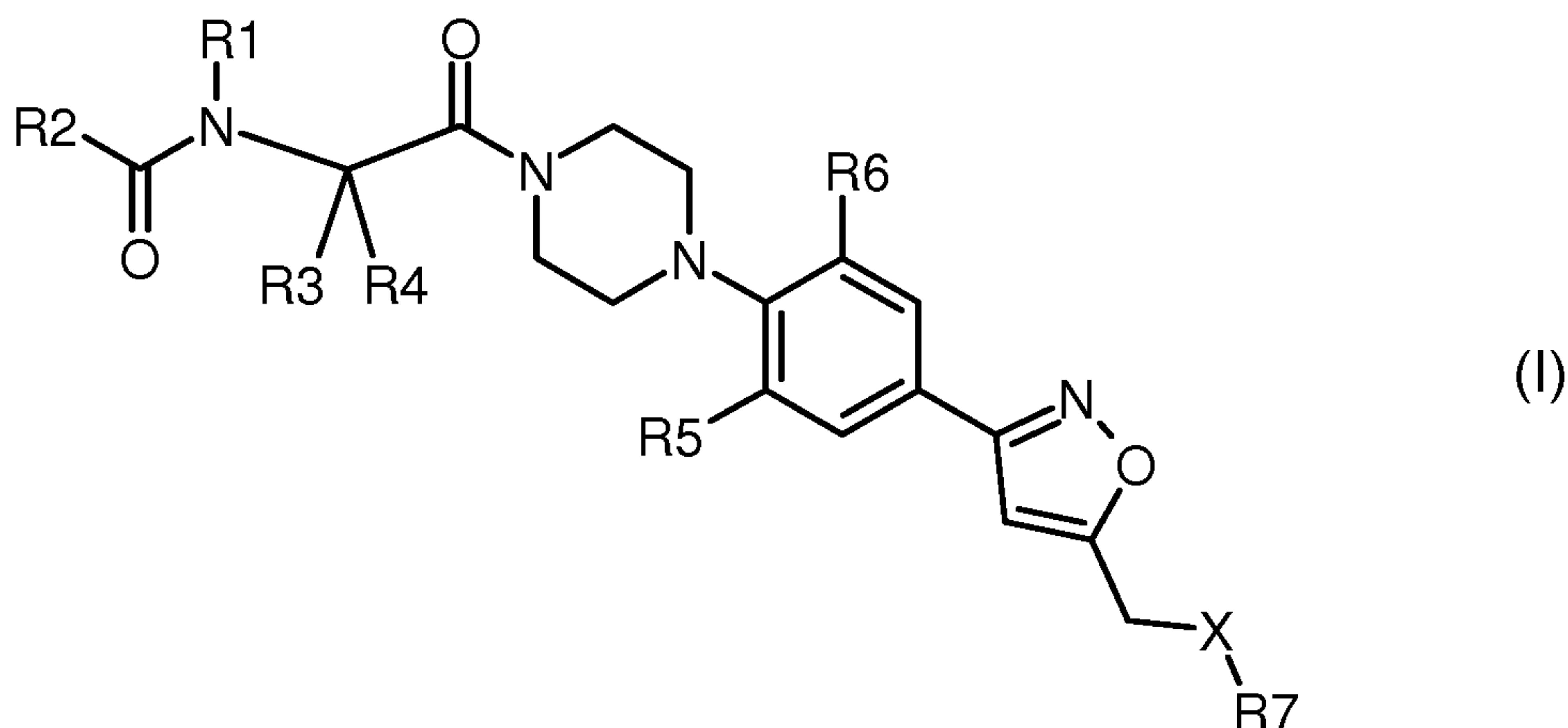
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(54) Title: DICARBONYLIC COMPOUNDS WITH ANTIBACTERIAL ACTIVITY



(57) Abstract: Compounds of formula (I), and their pharmaceutically acceptable salts and solvates, wherein X represents -O-, -NH-, -S-, -NHC(=O)- or -NHC(=S)-; R1 represents -H or a hydrocarbon chain; R2 represents -H, alkoxy, amino, a hydrocarbon chain or a radical of a cycle; R3 represents -H, a hydrocarbon chain or a radical of a cycle; R4 represents -H or a hydrocarbon chain; alternatively R3 and R4 form together a cycle; R5 and R6 represent -H or halogen, and R7 represents -H, a hydrocarbon chain or heteroaryl, are useful against bacterial infections in animals, including humans.

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*For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.*



Dicarbonylic compounds with antibacterial activity

The present invention relates to dicarbonylic compounds with antibacterial activity, as well as to pharmaceutical compositions containing them and to  
5 their use in medicine.

## BACKGROUND OF THE ART

The international microbiological community continues to express serious  
10 concern in view of the alarming increase of resistance to commercially available antibiotics, which reduces the range of possibilities of treatment of the different infectious processes. In general, bacterial pathogens may be classified as either Gram-positive or Gram-negative pathogens. Antibiotic compounds with effective activity against both Gram-positive and Gram-  
15 negative pathogens are generally regarded as having a broad spectrum of activity.

Gram-positive pathogens, for example staphylococci, enterococci, and streptococci, are particularly important due to the development of the resistant  
20 strains which are both difficult to treat and eradicate from the hospital environment. Examples of such strains are methicillin resistant staphylococci, methicillin resistant coagulase negative staphylococci, penicillin resistant *Streptococcus pneumoniae* and several vancomycin resistant enterococci.

25 Until oxazolidinones came out, the best clinically effective antibiotic for the treatment of such resistant Gram-positive pathogens was vancomycin. Vancomycin is a glycopeptide that shows certain nephrotoxicity and ototoxicity as well as low bioavailability and as a consequence it is parenterally administered. Nevertheless, antibacterial resistance to vancomycin and other  
30 glycopeptides is also appearing and this resistance is increasing, rendering these agents less and less effective in the treatment of infections produced by Gram-positive pathogens.

From 1989, diverse antibacterial compounds containing an oxazolidinone ring have been described, in particular eperezolid and linezolid both of Pharmacia Corporation (S.J. Brickner et al., *J. Med. Chem.* 1996, 39, 673-679). From them, only linezolid is commercially available at present.

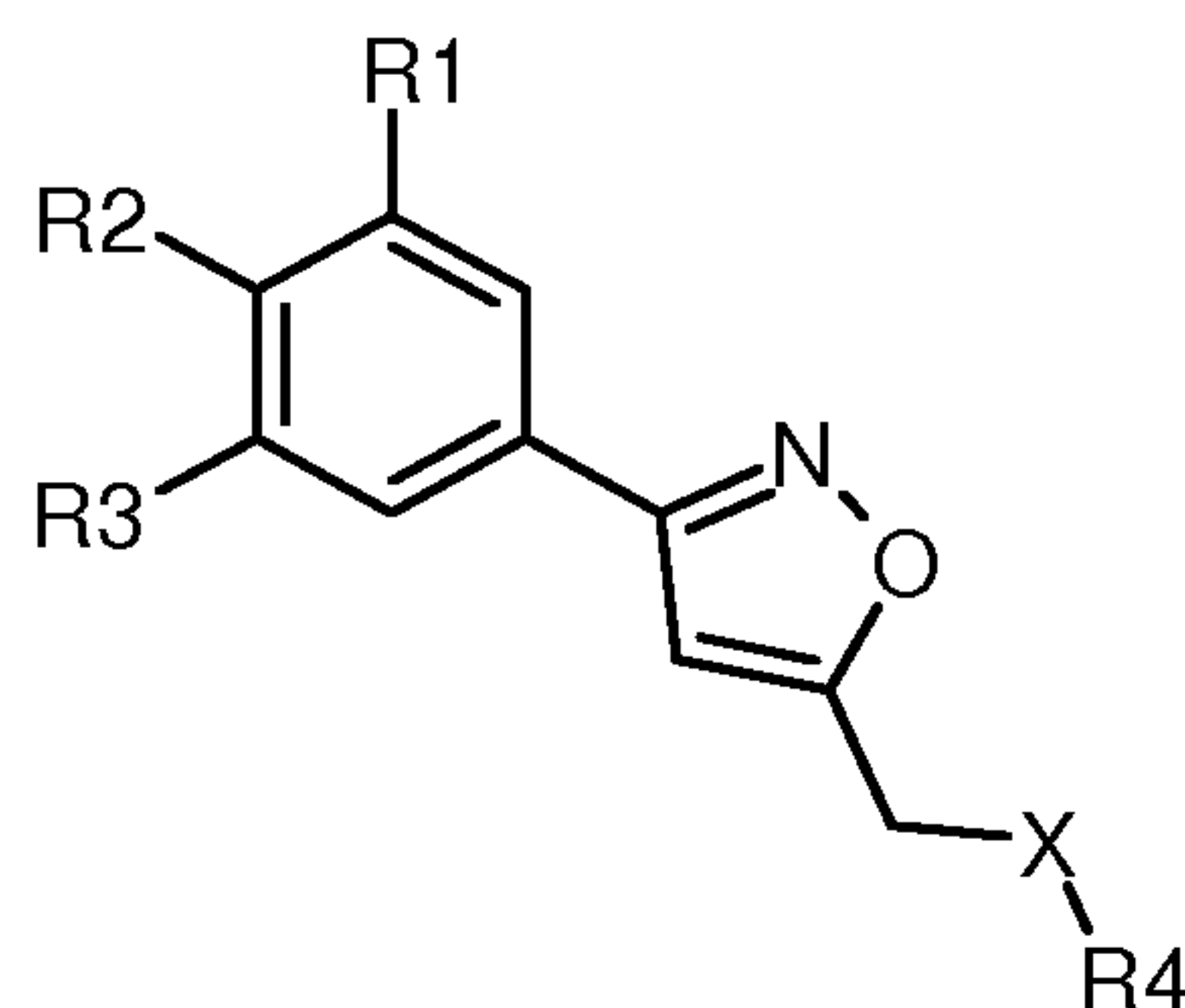
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Though the discovery of the mentioned oxazolidinones means a clear advance in the treatment of infections produced by Gram-positive pathogens, it is worth noting that bacterial resistance to known antibacterial agents may be developed, for example, by mutation of active binding sites in the bacteria rendering a decrease or total loss of activity of the previously active pharmacophore. Therefore, it is useful to obtain new antibacterial agents without crossed resistances .

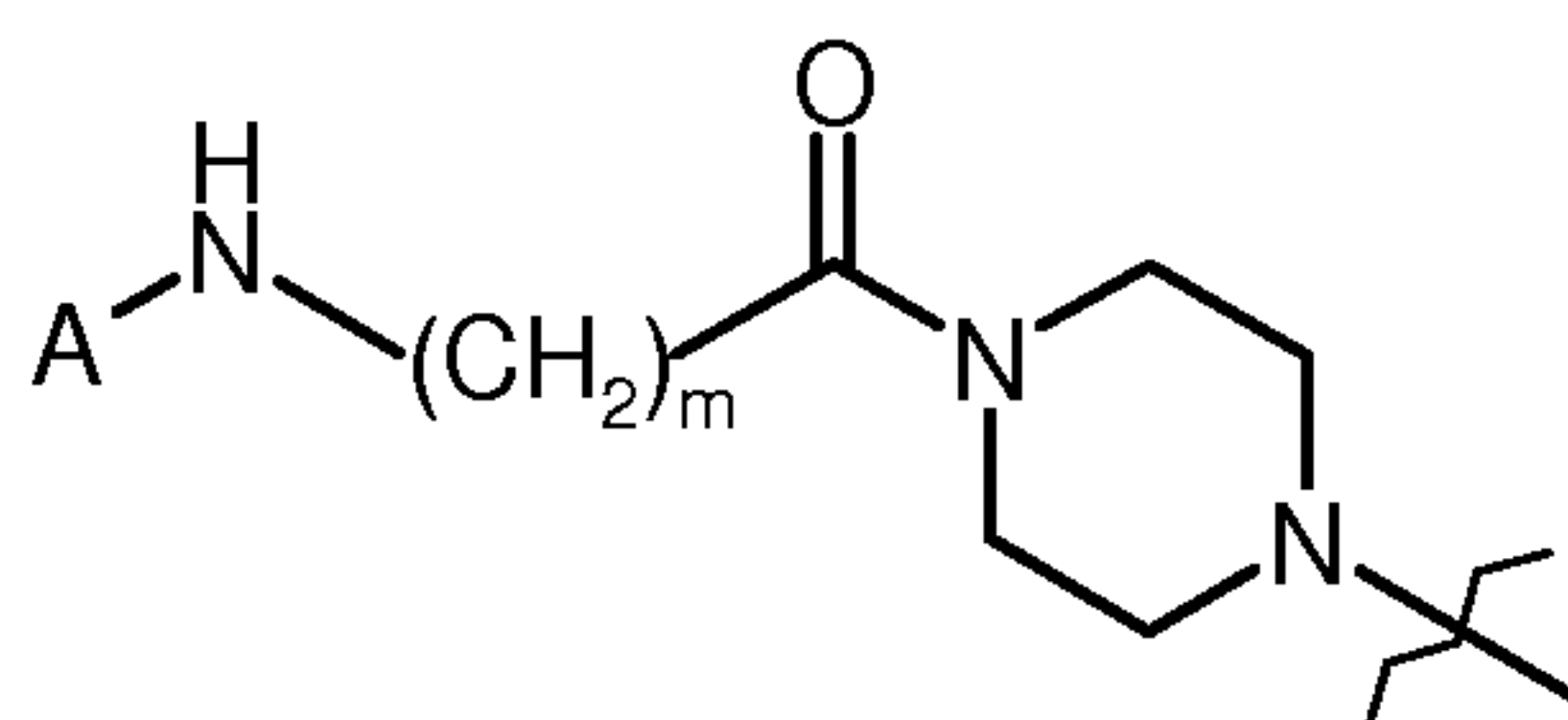
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WO 03/008395 A1 describes the preparation of antibacterial compounds structurally related to the compounds of the invention. Those compounds are encompassed by the following general formula

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wherein, among other meanings, R2 may represent:



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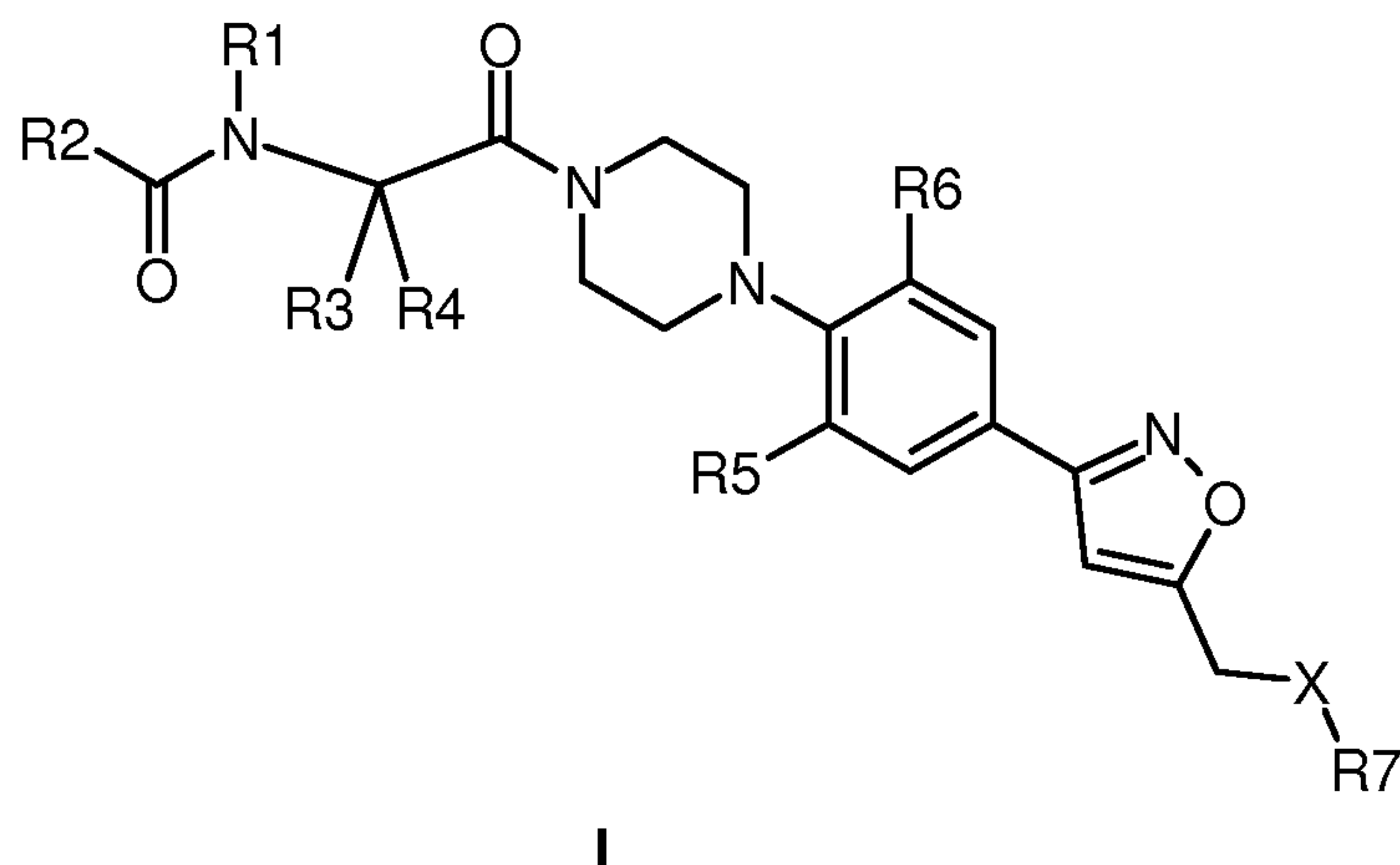
wherein A represents -H, (C<sub>1</sub>-C<sub>3</sub>)alkyl, vinyl, allyl, ethynyl, propargyl, phenyl or a radical of an optionally substituted aromatic ring system and m represents a value from 0 to 8.

The background art illustrates the present interest in providing new compounds with antibacterial activity preferably with broad spectrum of

activity, particularly against staphylococci or enterococci resistant to other antibiotics, the main cause of multiresistant hospital infections.

## SUMMARY OF THE INVENTION

The present invention relates to dicarbonylic compounds of general formula I,



their stereoisomers and mixtures thereof, its polymorphs and mixtures thereof, *N*-oxides, when there are oxidable nitrogen atoms, and the pharmaceutically acceptable solvates and addition salts thereof, wherein:

X represents -O-, -NH-, -S-, -NHC(=O)- or -NHC(=S)-;

R1 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Ra;

R2 represents -H, -OR<sub>b</sub>, -NR<sub>b</sub>R<sub>c</sub>, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl, -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, or -Cy<sub>1</sub> optionally substituted with one or more groups R<sub>d</sub> or R<sub>e</sub>, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups R<sub>d</sub> and/or one group R<sub>f</sub>;

R3 represents R1 or -Cy<sub>2</sub> optionally substituted with one or more groups Ra or R<sub>c</sub>;



R4 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted by one or more halogen atoms;

5 alternatively, R3 and R4 may form together a 3- to 7-membered monocyclic ring, partially unsaturated, saturated or aromatic, containing from one to three heteroatoms independently selected from O, S and N, optionally substituted at any available position by one or more substituents Rc or halogen atoms;

10 R5 and R6 independently represent -H or halogen;

R7 represents R4 or 5- or 6-membered heteroaryl, containing from one to three heteroatoms independently selected from O, S and N, optionally substituted with one or more groups Rc or halogen atoms;

15

each Ra independently represents halogen, =O, -ORc, -OC(=O)Rc, =CRcRc, -CN, -C(=O)Rc, -C(=O)ORc, -C(=O)NRcRc, -NO<sub>2</sub>, -NRcRc, -NRcC(=O)Rc, -NRcC(=O)ORc or -NRcC(=O)NRcRc;

20 Rb represents -H, Rg, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Ra and/or one group Rg;

each Rc independently represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or  
25 -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted by one or more halogen atoms;

each Rd independently represents halogen, =CRaRc, =CRcRc, -CN,  
-C(=O)Re', -C(=O)ORE', -C(=O)NRe'Rh', -C(=O)SRe', -C(=NRh')NRe'Rh',  
30 -C(=NRe')NRh'Rh', -C(=S)ORE', -C(=S)SRe', -ORE', =O, -OC(=O)Re',  
-OC(=O)NReRh', -OC(=S)Re', -O-N=O, -OSO<sub>2</sub>Re, -NRe'Rh', =NRe', =N-CN,  
=N-ORE', -N<sup>+</sup>Re'Rh'Rh', -N=NRe', -NRh'-NRe'Re', -NRe'-NRe'Rh', -N<sub>3</sub>, -N=O,



-NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re',  
 -NRh'C(=O)ORe, -NRe'C(=O)ORh, -NRh'C(=O)NReRh', -NRe'C(=O)NRhRh',  
 -NRe'C(=O)NRh'NRh'Rh', -NRh'C(=O)NRe'NRh'Rh',  
 -NRh'C(=O)NRh'NRe'Rh', -NRe'SO<sub>2</sub>Rh', -NRh'SO<sub>2</sub>Re', -SRe', -SORE',  
 5 -SO<sub>2</sub>Re, -SO<sub>2</sub>NRe'Rh' or -SO<sub>2</sub>ORe';

each Re independently represents Rf or -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or  
 -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may  
 be optionally substituted with one or more groups Ra and/or one group Rg;

10

each Re' independently represents -H or -Re;

each Rf independently represents -Cy1 optionally substituted with one or more  
 groups Ra or Rh;

15

each Rg independently represents -Cy1 optionally substituted with one or  
 more groups Ra or Rc;

each Rh independently represents -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or  
 20 -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, all of them optionally substituted with one or more groups Ra;

each Rh' independently represents -H or -Rh;

Cy1 represents a C- or N- radical of a 3- to 7-membered monocyclic or 6- to  
 25 10-membered bicyclic ring system, partially unsaturated, saturated or  
 aromatic, containing from one to three heteroatoms independently selected  
 from O, S and N; and

Cy2 represents a C- or N- radical of a 3- to 7-membered monocyclic ring,  
 30 partially unsaturated, saturated or aromatic, containing from one to three  
 heteroatoms independently selected from O, S and N.

In the previous definitions, the term (C<sub>1</sub>-C<sub>4</sub>)alkyl represents a straight or branched saturated hydrocarbon chain containing from one to four carbon atoms, for example methyl, ethyl, propyl, isopropyl, butyl, isobutyl, sec-butyl and *tert*-butyl. The term (C<sub>2</sub>-C<sub>4</sub>)alkenyl represents an unsaturated straight or branched saturated hydrocarbon chain containing from two to four carbon atoms and one or more double bonds, for example ethenyl, 1-propenyl, 2-propenyl, 1-butenyl, 2-butenyl, 3-butenyl and 1,3-butadienyl. The term (C<sub>2</sub>-C<sub>4</sub>)alkynyl represents an unsaturated straight or branched saturated hydrocarbon chain containing from two to four carbon atoms and one or more triple bonds, for example ethynyl, 1-propynyl, 2-propynyl, 1-butyne, 2-butyne, 3-butyne and 1,3-butadiynyl. The groups (C<sub>1</sub>-C<sub>4</sub>)alkyl, (C<sub>2</sub>-C<sub>4</sub>)alkenyl and (C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted according to the description whenever appropriate from a chemical view point.

The term halogen represents a radical of fluoro, chloro, bromo or iodo. A group =O may be attached to a carbon atom to form -C(=O)- or to a sulfur atom to form -S(=O)- or -S(=O)<sub>2</sub>-.

The term heteroaryl represents a C- or N- radical of an aromatic 5- or 6-membered monocyclic ring, containing from one to four heteroatoms independently selected from O, S and N, that may be substituted according to the description at any available ring position. Examples include, among others, radicals of pyrrol, furan, thiophene, imidazole, isoxazole, isothiazole, oxazole, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, 1,2,3-triazole, 1,2,4-triazole, pyridine, pyrimidine, pyridazine and pyrazine.

The term Cy1 represents a C- or N- radical of a 3- to 7-membered monocyclic or 6- to 10-membered bicyclic ring system, partially unsaturated, saturated or aromatic. The term Cy2 represents a C- or N- radical of a 3- to 7-membered monocyclic ring, partially unsaturated, saturated or aromatic. Both Cy1 and Cy2 may contain from one to four heteroatoms independently selected from

O, S and N, and may be substituted according to the description at any available ring position. Examples of Cy1 and Cy2 include, among others, radicals of cyclopropane, cyclobutane, cyclopentane, cyclohexane, cycloheptane, aziridine, dihydrofuran, pyrroline, pyrazoline, oxirane, oxethane, imidazolidine, isothiazolidine, isoxazolidine, oxazolidine, pyrazolidine, pyrrolidine, thiazolidine, dioxane, morpholine, piperazine, piperidine, pyran, tetrahydropyran, azepine, oxazine, oxazoline, pyrroline, thiazoline, pyrazoline, imidazoline, isoxazoline, isothiazoline, phenyl, naphthyl, 1,2,4-oxadiazole, 1,2,4-thiadiazole, 1,3,4-oxadiazole, 1,3,4-thiadiazole, furan, imidazole, isoxazole, isothiazole, oxazole, pyrazole, pyrrole, thiazole, thiophene, 1,2,3-triazole, 1,2,4-triazole, pyrazine, pyridazine, pyridine and pyrimidine. Examples of bicyclic ring systems Cy1 include, among others, radicals of bicyclo[3.3.0]octane, bicyclo[2.2.1]heptane, bicyclo[2.2.2]octane, bicyclo[4.3.0]nonene, bicyclo[4.4.0]decane, bicyclo[3.3.1]nonene, bicyclo[3.2.1]octane, naphthalene, benzimidazole, benzofuran, benzothiazole, benzothiophene, imidazopyrazine, imidazopyridazine, imidazopyridine, imidazopyrimidine, indazole, indole, isoindole, isoquinoline, tetrahydroisoquinoline, naphthiridine, pyrazolopyrazine, pyrazolopyridine, pyrazolopyrimidine, purine, quinazoline, quinoline and quinoxaline.

20

The expression "optionally substituted with one or more" means that a group may be unsubstituted or substituted with one or more, preferably with 1, 2, 3 or 4 substituents, provided that this group has 1, 2, 3 or 4 positions susceptible of being substituted.

25

As used therein the term "treatment" includes treatment, prevention and management of such condition. The term "pharmaceutically acceptable" as used herein refers to those compounds, compositions, and/or dosage forms which are, within the scope of medical judgement, suitable for use in contact with the tissues of humans and animals without excessive toxicity, irritation, allergic response, or other problem or complication, commensurate with a reasonable benefit/risk ratio.

30



The present invention relates to a process for the preparation of the new compounds previously described as well as derivatives, analogues, tautomeric forms, stereoisomers, polymorphs or pharmaceutically acceptable salts and solvates thereof.

5

The compounds of the present invention may be synthesized by different routes. They may be prepared by the methods described below, as well as by other standard methods in the field of organic synthesis, or variations thereof obvious to a person skilled in the art, who will understand that the functional groups present in the molecule should be consistent with the described reactions. This fact may require in some cases a modification in the order of the reaction or the choice of one particular method to obtain the desired compound. The use of some of the reactants may require conditions such as the use of anhydrous solvents and inert atmosphere. Moreover, in some of the methods showed below it may be desirable or necessary to protect the functional groups present in the compounds or intermediates of the invention by conventional protecting groups. Many protecting groups as well as procedures for their introduction and removal are described in Greene T.W. and Wuts P.G.M., "Protective Groups in Organic Synthesis", John Wiley & Sons, 3rd Edition, 1999.

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Unless otherwise stated, the meanings of the groups R1, R2, R3, R4, R5, R6, R7 and X are the ones described in the general formula I.

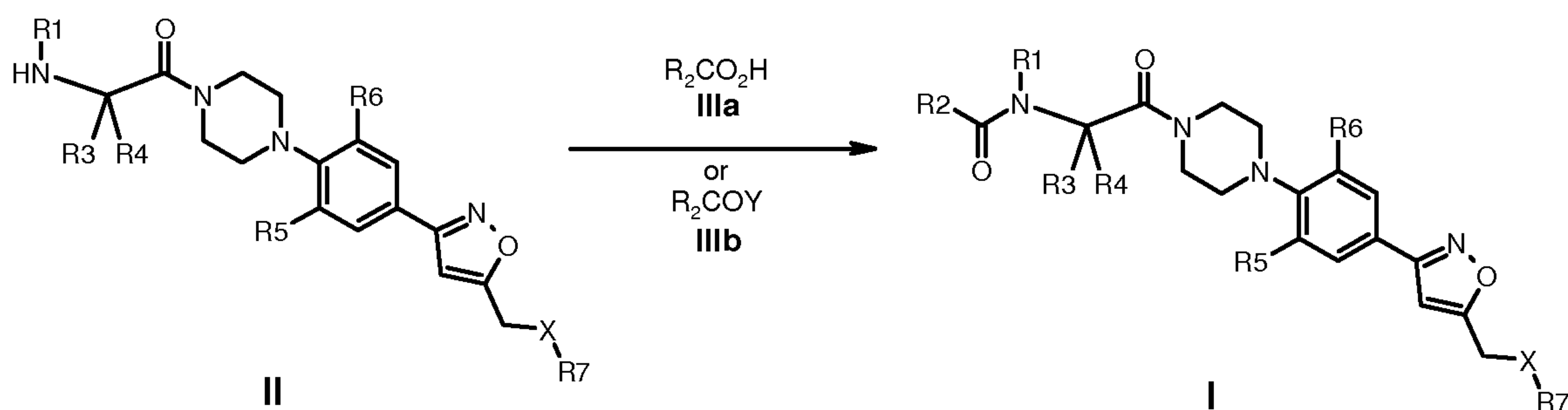
A compound of fomula I may be obtained starting form a compound of fomula

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II as shown below:



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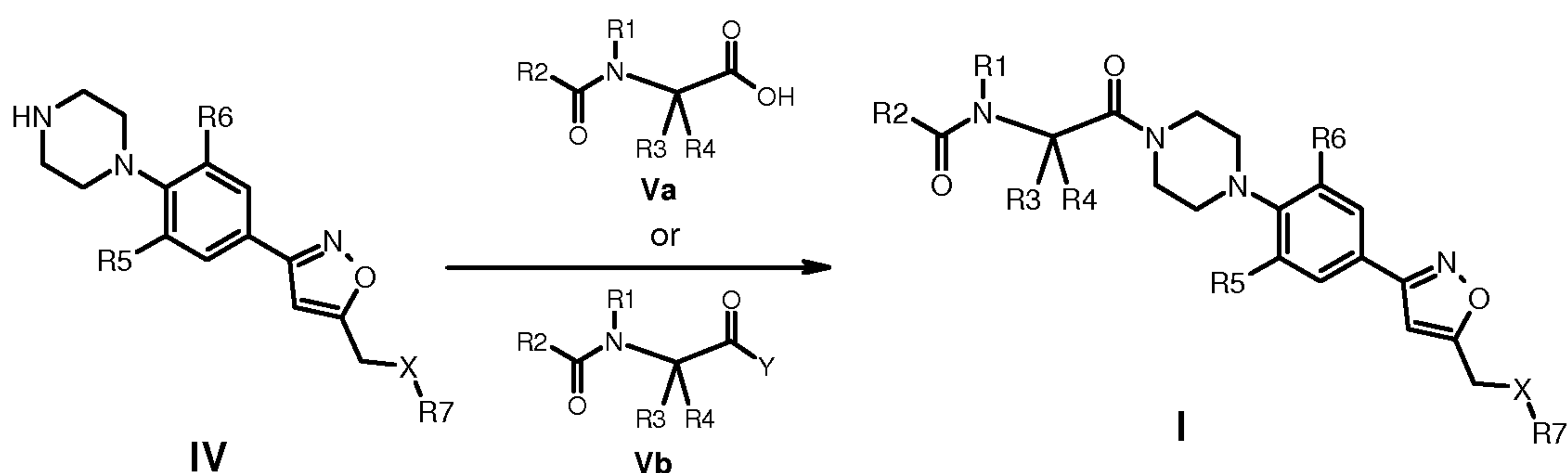
Thus, a compound of formula **II** may be reacted with a carboxylic acid of formula **IIIa** in the presence of an activating agent, such as the combination of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) and 1-hydroxybenzotriazole (HOBT) in the presence of a base, such as triethylamine, in a solvent, such as ethyl acetate, *N,N*-dimethylformamide or tetrahydrofuran, at a temperature between room temperature and the temperature of the boiling point of the solvent. Alternatively, a compound of formula **II** may be reacted with the corresponding carboxylic acid derivative of formula **IIIb**, wherein Y represents -CN, -OC(=O)(C<sub>1</sub>-C<sub>4</sub>)alkyl, -O(C<sub>1</sub>-C<sub>4</sub>)alkyl, -N[(C<sub>1</sub>-C<sub>4</sub>)alkyl]<sub>2</sub> or halogen, preferably chloro. This reaction is carried out in the presence of a base such as triethylamine, in a solvent, such as dichloromethane, ethyl acetate or *N,N*-dimethylformamide and at a temperature between room temperature and the temperature of the boiling point of the solvent.

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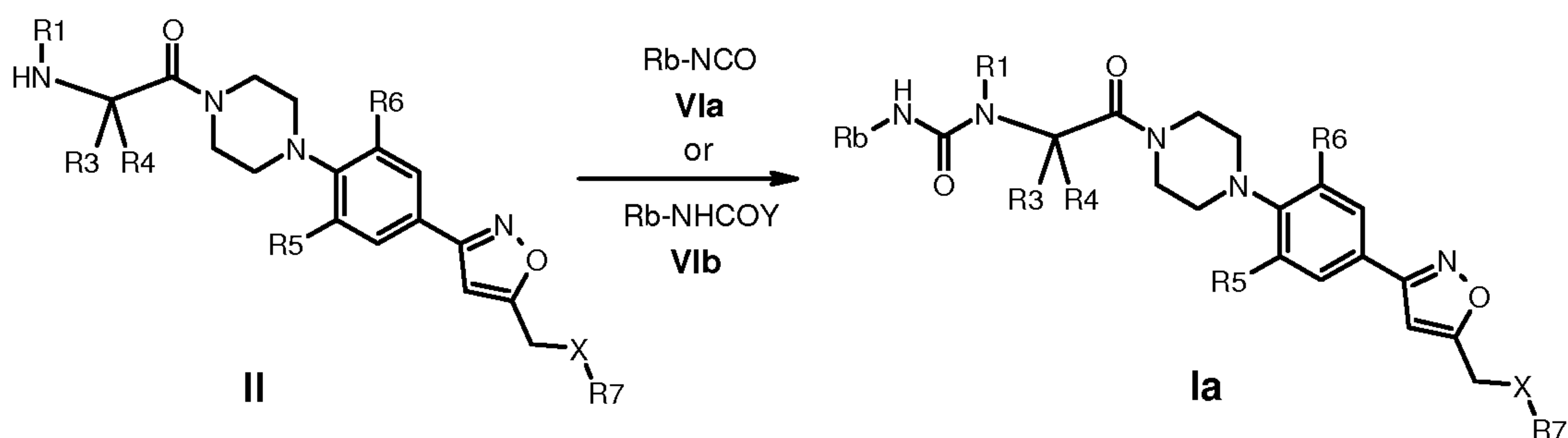
A compound of formula **I** may also be obtained by reaction of a compound of formula **IV** with a compound of formula **Va** or a compound of formula **Vb**, wherein Y represents -CN, -OC(=O)(C<sub>1</sub>-C<sub>4</sub>)alkyl, -O(C<sub>1</sub>-C<sub>4</sub>)alkyl, -N[(C<sub>1</sub>-C<sub>4</sub>)alkyl]<sub>2</sub> or halogen, preferably chloro, in analogous conditions to those described for the synthesis of **I** starting from **II** and **IIIa** or **IIIb**, as shown below:

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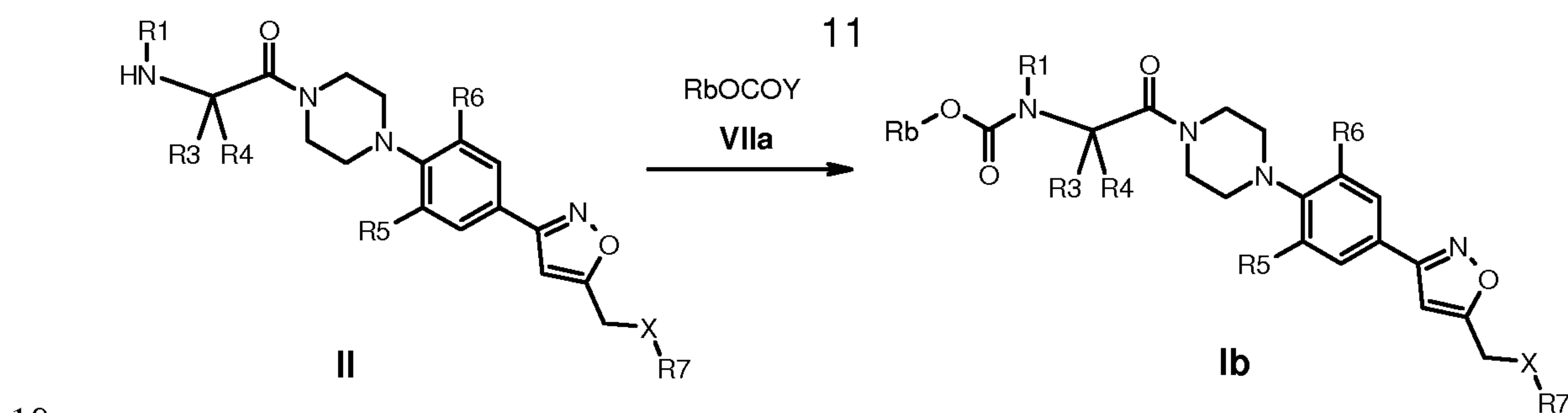


Compounds of formula **I** wherein R2 represents -NHRb and Rb has the meaning described in general formula **I** (that is compounds of formula **la**) may also be obtained as shown below:



- 5 Thus, a compound of formula **II** may be reacted with an isocyanate of formula **VIa** in the presence of a solvent, such as *N,N*-dimethylformamide, preferably at room temperature. Alternatively, a compound of formula **II** may be reacted with a compound of formula **VIb** wherein Y represents halogen, preferably chloro, in the presence of a base such as for example triethylamine, in a solvent, such as dichloromethane, ethyl acetate or *N,N*-dimethylformamide, preferably at room temperature.
- 10

- Compounds of formula **I** wherein R2 represents -ORb and Rb has the meaning previously described (that is compounds of formula **lb**) may also be obtained by reaction of a compound of formula **II** with a compound of formula **VIIa**, wherein Y represents -O-succinimidyl, -OC(=O)(C<sub>1</sub>-C<sub>4</sub>)alkyl or halogen, preferably chloro.
- 15



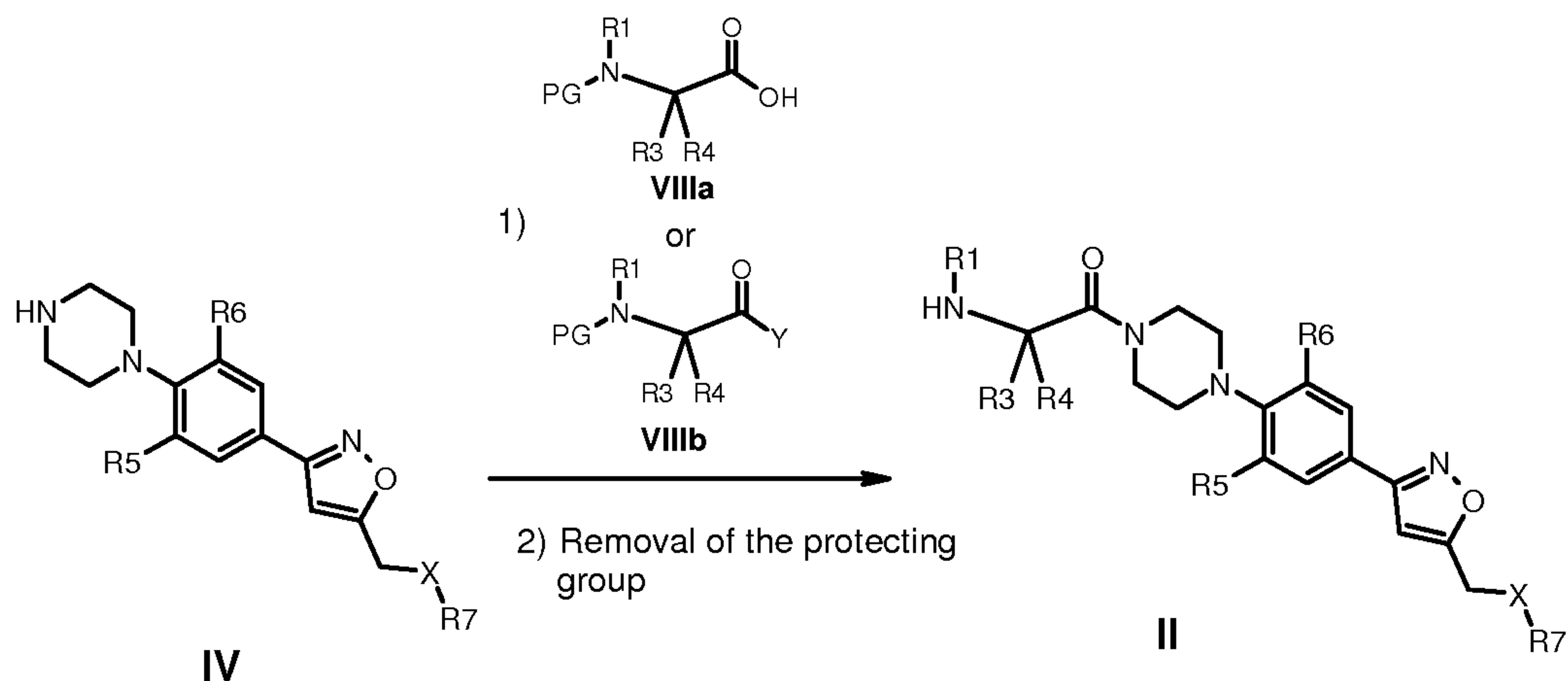
15 Usually, this reaction is carried out in the presence of a base such as triethylamine, sodium hydroxyde or sodium bicarbonate, in a solvent, such as dioxane, water, dichloromethane, tetrahydrofuran, ethyl acetate or *N,N*-dimethylformamide and at a temperature between room temperature and the temperature of the boiling point of the solvent.

20 Alternatively the preparation of ureas of formula **Ia** and carbamates of formula **Ib** may also be carried out by a sequence of two steps. In a first step an amine of formula **II** is reacted with a activating agent such as triphosgene or carbonyldiimidazole, in the presence of a base, such as diisopropylethylamine, triethylamine or *N*-methylemorpholine, in a solvent such as acetonitrile, chloroform, dichloromethane or *N,N*-dimethylformamide. Then, the resulting compound is reacted with an amine of formula Rb-NH<sub>2</sub> (**VIc**) (for the ureas) or with an alcohol of formula Rb-OH (**VIIb**) (for the carbamates) in a solvent, for example the same used in the first step, and at a temperature between room temperature and the temperature of the boiling point of the solvent.

30 Some compounds of formula **I** may be converted to other compounds of formula **I** by reactions well known in the field of organic synthesis, that include but are not limited to the hydrolysis of an ester or the protection/deprotection of a protecting group, among others.

35 Compounds of formula **II** may be obtained as shown below:

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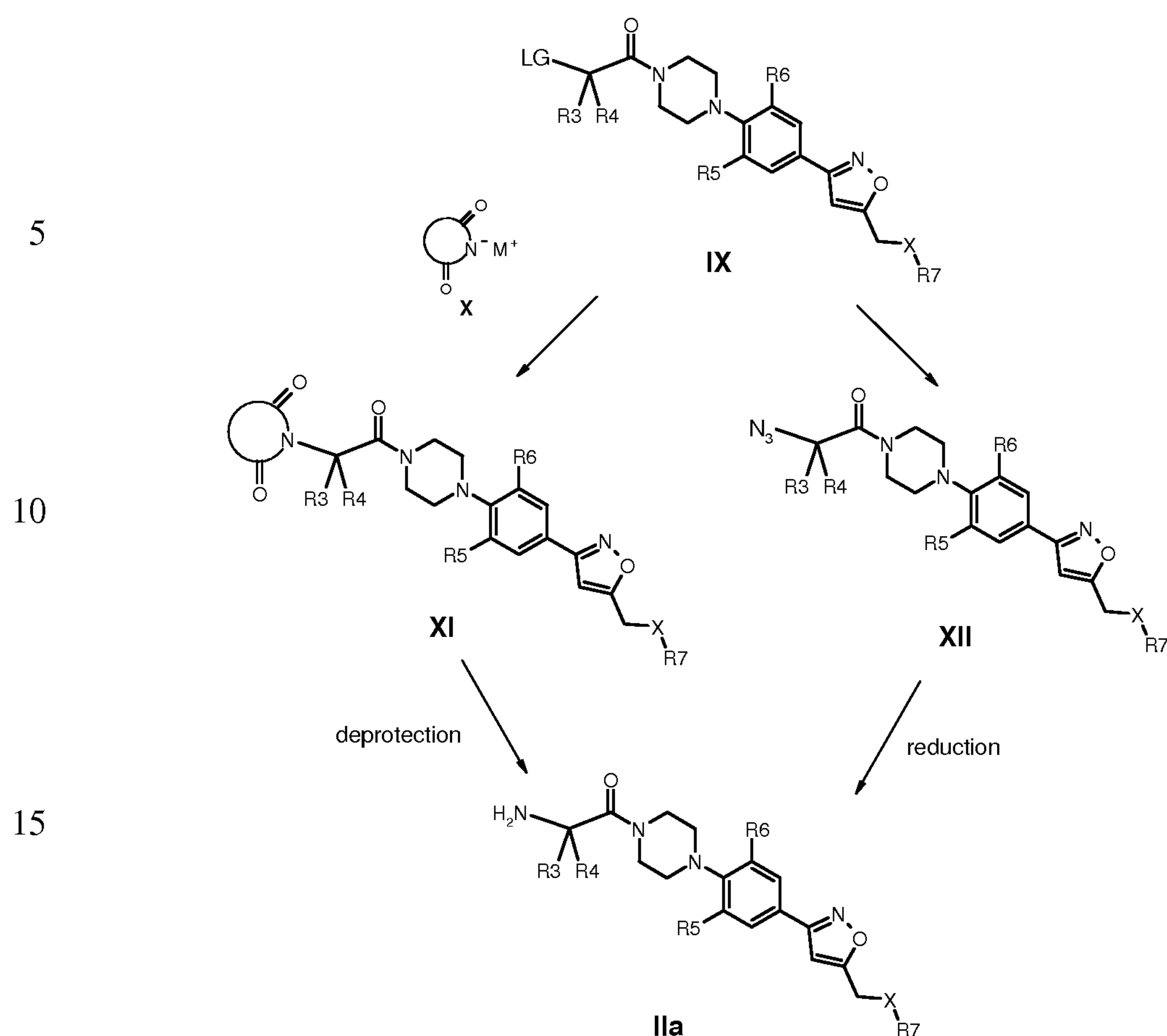


In a first step a compound of formula **IV** is reacted with a compound of formula **VIIIa** or a compound of formula **VIIIb**, wherein PG represents a protecting group, such as for example *tert*-butoxycarbonyl (Boc) or fluorenylmethoxycarbonyl (Fmoc) and Y represents -CN, -OC(=O)(C<sub>1</sub>-C<sub>4</sub>)alkyl, -OC<sub>1-4</sub>alkyl, -N[(C<sub>1</sub>-C<sub>4</sub>)alkyl]<sub>2</sub> or halogen, preferably chloro, in analogous conditions to those described for the preparation of amides. In a second step the protecting group of the resulting compound is removed following methods described in the literature.

- 10 Compounds of formula **II** wherein R1 represents -H (that is compounds of formula **Ila**) may also be obtained by a sequence of two steps, as shown below:



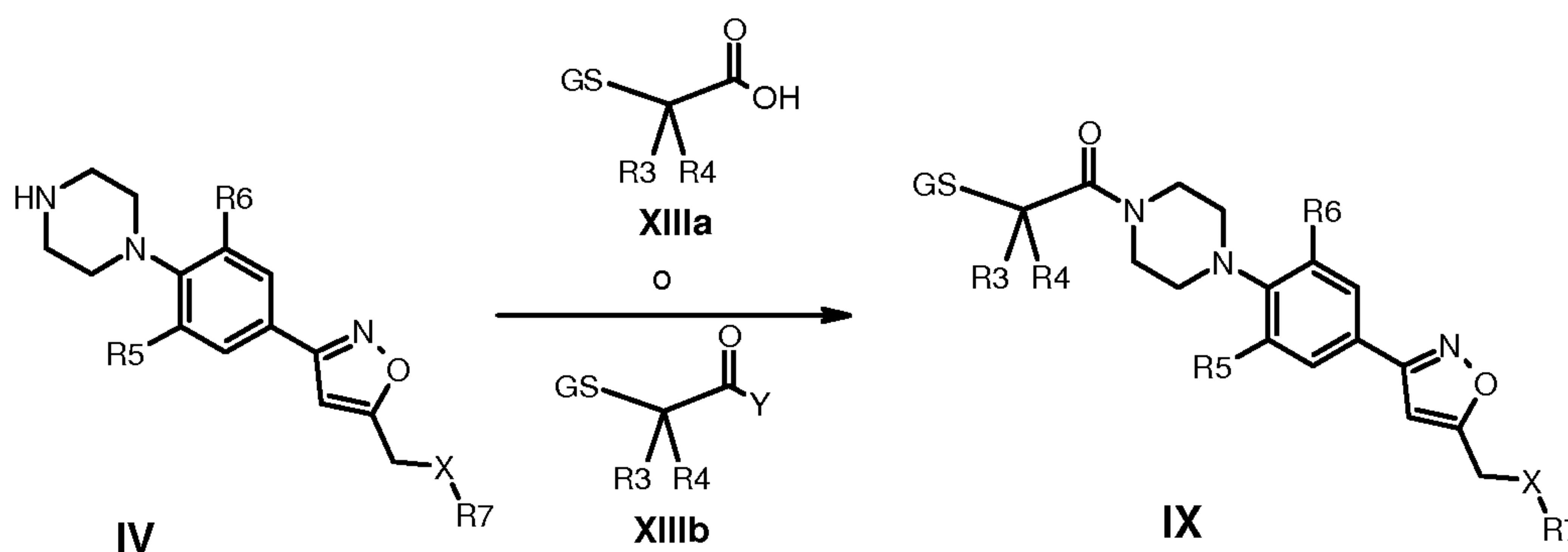
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- 20 In a first step a compound of formula **IX**, wherein LG represents halogen, methanesulfonyloxy or *p*-toluenesulfonyloxy among others is reacted with an azide, such as for example sodium or potassium azide, to give a compound of formula **XII**. Alternatively a compound of formula **IX** may be reacted with a compound of formula **X**, for example potassium phthalimide, to give a compound of formula **XI**. Both reactions are carried out in a solvent, such as for example *N,N*-dimethylformamide and preferably heating. Alternatively may be carried out using microwaves. Then compounds of formula **XI** and **XII** may be converted into a compound of formula **IIa** by deprotection and reduction reactions respectively. The deprotection reaction is carried out in the presence of hydrazine, in a solvent such as ethanol or methanol, preferably heating. The reduction reaction is carried out under hydrogen atmosphere, in the presence of a catalyst such as for example Pd-C, in a solvent, such as

ethanol, methanol, tetrahydrofuran or ethyl acetate, preferably at room temperature.

Compounds of formula **IX** may be obtained by reaction of a compound of formula **IV** and a compound of formula **XIIIa** or **XIIIb**, wherein Y represents -CN, -OC(=O)(C<sub>1</sub>-C<sub>4</sub>)alkyl, -O(C<sub>1</sub>-C<sub>4</sub>)alkyl -N[(C<sub>1</sub>-C<sub>4</sub>)alkyl]<sub>2</sub> or halogen, preferably chloro, in analogous conditions to those described for the preparation of compounds of formula **I** starting from compounds of formula **II** and compounds of formula **IIIa** and **IIIb** respectively.



10

The compounds **IIIa**, **IIIb**, **Va**, **Vb**, **Vla**, **Vlb**, **Vlc**, **Vlla**, **Vllb**, **VIIIa**, **VIIIb**, **X**, **XIIIa** and **XIIIb** are commercially available or may be easily obtained by conventional methods. For example compounds of formula **VIIIa** and **VIIIb** may be prepared according to B. S. Furniss "Textbook of practical Organic Chemistry" 5th Ed.(1989) Longman Scientific & Technical. Compounds of formula **IV** may be obtained as described in WO 03/008395. As it will be obvious for a skilled in the art, some of the reactions previously described may also be carried out on compounds of formula **I**.

20 An embodiment of the invention relates to compounds of formula **I** which are *N*-oxides. Another embodiment of the invention relates to compounds of formula **I** wherein Rd represents halogen, =CRaRc, =CRcRc, -CN, -C(=O)Re', -C(=O)ORe', -C(=O)NRe'Rh', =O, -ORe', -OC(=O)Re', -NRe'Rh', =NRe', -N<sup>+</sup>Re'Rh'Rh', -N<sub>3</sub>, -NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh',  
 25 -NRh'C(=O)Re', -NRe'C(=O)ORh', -NRh'C(=O)ORe', -NRe'C(=O)NRe'Rh' or -NRh'C(=O)NRe'Rh'.

Another embodiment of the invention relates to compounds of formula I wherein R1 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more groups Ra. Another embodiment of the invention relates to compounds of formula I wherein R1 represents -H.

5

Another embodiment of the invention relates to compounds of formula I wherein R2 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Rd and/or one group Rf. Another

10 embodiment of the invention relates to compounds of formula I wherein R2 represents -Cy1 optionally substituted with one or more groups independently selected from -Re, halogen, =CRaRc, =CRcRc, -CN, -C(=O)Re', -C(=O)ORe', -C(=O)NRe'Rh', =O, -ORe', -OC(=O)Re', -NRe'Rh', =NRe', -N<sup>+</sup>Re'Rh'Rh', -N<sub>3</sub>, -NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re',

15 -NRe'C(=O)ORh', -NRh'C(=O)ORe', -NRe'C(=O)NRe'Rh' or -NRh'C(=O)NRe'Rh'. Another embodiment of the invention relates to compounds of formula I wherein R2 is selected from the group consisting of phenyl, a C- or N- radical of an aromatic 5- or 6-membered monocyclic ring containing from one to three heteroatoms independently selected from O, S

20 and N, and a C- or N- radical of an aromatic bicyclic ring system containing from one to three heteroatoms independently selected from O, S and N, that comprises a 5- or 6-membered ring system fused to a 5- or 6-membered ring system, wherein all previous ring systems may be optionally substituted with -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl, -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, halogen, -CN, -C(=O)Re', =O,

25 -ORe', -NRe'Rh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re', wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Ra.

Another embodiment of the invention relates to compounds of formula I

30 wherein R3 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more Ra and R4 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more halogen atoms.



Another embodiment of the invention relates to compounds of formula I wherein R5 represents -F and R6 represents -H or -F.

Another embodiment of the invention relates to compounds of formula I wherein X represents -NH- and R7 represents 5- or 6-membered heteroaryl optionally substituted with halogen or Rc. Another embodiment of the invention relates to compounds of formula I wherein X represents -O- and R7 represents -H.

Another embodiment of the invention relates to compounds of formula I wherein R1 represents -H; R2 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Rd and/or one group Rf; or R2 represents -Cy1 optionally substituted with one or more groups independently selected from -Re, halogen, =CRaRc, =CRcRc, -CN, -C(=O)Re', -C(=O)ORe', -C(=O)NRe'Rh', =O, -ORe', -OC(=O)Re', -NRe'Rh', =NRe', -N<sup>+</sup>Re'Rh'Rh', -N<sub>3</sub>, -NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re', -NRe'C(=O)ORh', -NRh'C(=O)ORe', -NRe'C(=O)NRe'Rh' or -NRh'C(=O)NRe'Rh'; R3 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more Ra; R4 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more halogen atoms; R5 represents -F and R6 represents -H or -F; X represents -NH- and R7 represents 5- or 6-membered heteroaryl optionally substituted with halogen or Rc or wherein X represents -O- and R7 represents -H.

Moreover, all possible combinations of the particular embodiments previously mentioned are also part of the application.

The compounds of the present invention may contain one or more basic nitrogen atoms and, therefore, they may form salts with acids, that also form part of this invention. Examples of pharmaceutically acceptable salts include, among others, addition salts with inorganic acids such as hydrochloric, hydrobromic, hydroiodic, nitric, perchloric, sulphuric and phosphoric acid, as



well as addition salts of organic acids such as acetic, methanesulfonic, trifluoromethanesulfonic, ethanesulfonic, benzenesulfonic, *p*-toluenesulfonic, benzoic, camphorsulfonic, mandelic, oxalic, succinic, fumaric, tartaric, and maleic acid. Likewise, compounds of the present invention may contain one or  
5 more acid protons and, therefore, they may form salts with bases, that also form part of this invention. Examples of these salts include salts with metal cations, such as for example an alkaline metal ion, an alkaline-earth metal ion or an aluminium ion; or it may be coordinated with an organic or inorganic base. There is no limitation on the type of salt that may be used provided that  
10 these are pharmaceutically acceptable. Salts may be synthesized from the parent compound which contains a basic or acidic moiety by conventional chemical methods. Generally, such salts may be prepared by reacting the free acid or base forms of these compounds with a stoichiometric amount of the appropriate base or acid in water or in an organic solvent, such as ether, ethyl  
15 acetate, ethanol, isopropanol, or acetonitrile or in a mixture thereof. The compounds of formula I and their salts differ in some physical properties but they are equivalent for the purposes of the present invention.

Some of the compounds of formula I of the present invention may exist as  
20 unsolvated as well as solvated forms such as, for example, hydrates or alcohol solvates. The present invention encompasses all such above-mentioned forms which are pharmaceutically active.

Some compounds of formula I may exist as *N*-oxides of any oxidable nitrogen  
25 atom of the cited compounds, this invention comprising all *N*-oxides of the described compounds.

Some of the compounds of general formula I may exhibit polymorphism, encompassing the present invention all the possible polymorphic forms, and  
30 mixtures thereof. Various polymorphs may be prepared by crystallization under different conditions or by heating or melting the compound followed by gradual or fast cooling.

Compounds of formula I of the present invention may comprise one or more chiral centers. Additionally, compounds of formula I of the present invention may have further chiral centres. The present invention includes each one of the possible stereoisomers and mixtures thereof, particularly racemic mixtures thereof. A single enantiomer may be prepared by any of the commonly used processes, for example, by chromatographic separation of the racemic mixture on a stationary chiral phase, by resolution of the racemic mixture by fractional crystallisation techniques of the diastereomeric salts thereof, by chiral synthesis, by enzymatic resolution or by biotransformation. This resolution may be carried out on any chiral synthetic intermediate or on products of general Formula I. Alternatively, any enantiomer of a compound of the general Formula I may be obtained by enantiospecific synthesis using optically pure starting materials or reagents of known configuration. Some of the compounds of the present invention may exist as several diastereoisomers, which may be separated by conventional techniques such as chromatography or fractional crystallization. Some compounds of the present invention may exhibit cis/trans isomers. The present invention includes each of the geometric isomers and its mixtures. The present invention covers all isomers and mixtures thereof (for example racemic mixtures) whether obtained by synthesis and also by physically mixing them. Compounds of formula I have antibiotic activity and therefore useful as active ingredients. Therefore, an aspect of the present invention relates to pharmaceutical compositions that comprise an effective amount of a compound as defined in general formula I and one or more pharmaceutically acceptable excipients.

The present invention further provides for pharmaceutical compositions comprising a compound of formula I or a pharmaceutical salt or solvate thereof together with one or more pharmaceutically acceptable excipients, in either single or multiple doses. The examples of the excipients mentioned below are given by way of illustration only and are not to be construed as limiting the scope of the invention.



The compounds of the present invention may be administered in the form of any pharmaceutical formulation. The pharmaceutical formulation will depend upon the nature of the active compound and its route of administration. Any route of administration may be used, for example such as oral, buccal,  
5 pulmonary, topical, parenteral (including subcutaneous, intramuscular, and intravenous), transdermal, ocular (ophthalmic), by inhalation, intranasal, otic, transmucosal, implant or rectal administration.

Solid compositions for oral administration include among others tablets, granulates and hard gelatin capsules, formulated both as immediate release  
10 or modified release formulations.

The manufacturing method may be based on a simple mixture, dry granulation, wet granulation or lyophilization of the active compound optionally with excipients such as binding agents, fillers, lubricants, disintegrants, wetting agents, sweetening agents, bioadhesive agents, glidants, release modifiers or  
15 osmotic agents.

The tablets may be coated according to methods well-known in the art such as aqueous dispersion coating, solvent-based coating or drying coating. The active compound may also be incorporated by coating onto inert pellets using film-coating agents, plasticizers, opacifiers or antiadherent agents. The active  
20 compound may also be incorporated by extrusion and spheronization process, by hot melting pelletization. When a dosage unit form is a capsule, it may contain, in addition to materials of the above type, a liquid carrier such as a fatty oil or wax.

Powders and granulates for the preparation of oral suspensions by the  
25 addition of water may be obtained by mixing the active compound with dispersing or wetting agents; suspending agents, anticaking agents, buffering agents and preservatives. Other excipients may also be added, for example sweetening, flavouring and colouring agents.

Alternatively, the compounds of the present invention may be incorporated  
30 into oral liquid or semisolid preparations such as emulsions, solutions, dispersions, suspensions, syrups, elixirs or in the form of soft gelatin capsules.

Solutions or suspensions may be prepared in water suitably mixed with a surfactant, if necessary. Dispersions may also be prepared in glycerol, liquid polyethylene glycols and mixtures thereof in oils. These preparations may contain a preservative to prevent the growth of microorganisms.

- 5   Injectable preparations for parenteral administration comprise sterile solutions, suspensions or emulsions in oily or aqueous vehicles, and may contain coadjuvants, such as suspending, stabilizing, tonicity agents or dispersing agents.

The compound may also be formulated for its topical application. Formulations  
10   include creams, lotions, gels, powders, solutions, shampoo preparations, oral paste, mouth wash preparations and patches wherein the compound is dispersed or dissolved in suitable excipients such as antimicrobial preservatives, emulsifying agents, emulsion stabilizers, humectants, skin penetrants, buffering agents, surfactants and thickening agents.

- 15   Preferably, compounds are administered orally, parenterally or topically.

The compounds of the present invention are especially active against pathogen microorganisms including Gram-positives agents, Gram-negatives agents and mycoplasmas, among others. Thus, the present invention relates  
20   to the use of a compound of formula I for the manufacture of a medicament for the treatment and/or prevention of bacterial infections in an animal including a human. Therefore, the present invention also relates to a method for the treatment and/or prevention of bacterial infections in an animal including a human, that comprises administering a compound of formula I.

25

The effective dosage of active ingredient may vary depending on the particular compound administered, the route of administration, the nature and severity of the disease to be treated, as well as the age, the general condition and body weight of the patient, among other factors. A representative example of a  
30   suitable dosage range is from about 0.001 to about 100 mg/kg body weight per day, which may be administered as a single or divided doses. However,



the dosage administered will be generally left to the discretion of the physician.

Throughout the description and claims the word "comprise" and variations of the word, such as "comprising", are not intended to exclude other additives, components, elements or steps. The present invention will be further illustrated by the following examples. The examples are given by way of illustration only and are not to be construed as limiting the scope of the invention.

10

## EXAMPLES

<sup>1</sup>H-NMR spectra of the compounds have been recorded using a VARIAN UNITY-300 or MERCURY 400 MHz equipment and chemical shifts are expressed as ppm ( $\delta$ ) from the internal reference trimethylsilane. Mass spectra have been obtained with an Agilent 1100 VL mass spectrometer.

HPLC-ESI-MS spectra have been performed using the following chromatographic equipment: Agilent model 1000, equipped with a selective mass detector model 1100 VL (atmospheric pressure ionisation with positive ion detection), autosampler, ChemStation software and a laser and using the following chromatographic methods:

Method A: Column Kromasil 100 C18, 40 x 4.0 mm, 3.5  $\mu$ m, flow: 0.7 mL/min, eluent: A= 0.1% formic acid in water, B = 0.1% formic acid in acetonitrile, gradient: 0 min 5% B - 8 min 90% B.

Method B: Column Gemini 5u C18 110, 40 x 4.0 mm, flow: 0.7 mL/min, eluent: A= 0.1% formic acid in water, B = 0.1% formic acid in acetonitrile, gradient: 0 min 5% B - 8 min 90% B.

Unless otherwise stated the HPLC-ESI-MS data indicated in the tables below was obtained using method A.

The following abbreviations have been used in the examples:

DMAP: 4-dimethylaminopyridine

DMF: *N,N*-dimethylformamide

EDC: 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

5 eq: molar equivalent

EtOAc: ethyl acetate

HOBt: 1-hydroxybenzotriazole

HPLC-ESI-MS: high resolution liquid chromatography - electrospray  
ionization - mass spectrometry

10 m/z: relationship mass/charge

rt: retention time

THF: tetrahydrofuran

Examples of intermediates of formula IV:

15 Compound **IV\_1** [3-(3-fluoro-4-piperazin-1-ylphenyl)isoxazol-5-ylmethyl]isoxazol-3-ylamine corresponds to the intermediate 10 of patent WO 03/008395 and its synthesis was carried out as described in page 38.

Compound **IV\_2** *N*-[3-(3-fluoro-4-piperazin-1-ylphenyl)isoxazol-5-ylmethyl]acetamide was prepared in analogous form to the intermediate **IV\_1**  
20 replacing isoxazol-3-yl-[3-(3,4-difluorophenyl)isoxazol-5-ylmethyl]amine by *N*-[3-(3,4-difluorophenyl)isoxazol-5-ylmethyl]acetamide (intermediate 9 patent WO 03/008395).

25 Compound **IV\_3** [3-(3,5-difluoro-4-piperazin-1-ylphenyl)isoxazol-5-ylmethyl]isoxazol-3-ylamine corresponds to the intermediate 18 of patent WO 03/008395 and its synthesis was carried out as described in page 40.

Compound **IV\_4** [3-(3-fluoro-4-piperazin-1-ylphenyl)isoxazol-5-yl]methanol  
30 corresponds to the intermediate 3 of patent WO 03/008395 and its synthesis was carried out as described in page 34.

Examples of intermediates of formula IX:

Compounds of formula **IX** shown in table 1 were obtained by one of the following methods.

- 5     METHOD 1: To a solution 0.15 M of a carboxylic acid of formula **XIIla** (1 eq) in DMF, EDC (1.5 eq), HOBt (1.5 eq) and triethylamine (2 eq) were added. The mixture was stirred for 15 minutes at room temperature. Then, an amine of formula **IV** (1 eq) was added and the mixture was stirred for 14 hours. Water in an amount of about 10 parts by volume of DMF was added and the
- 10    precipitate obtained was filtered and washed thoroughly with water. In case that no precipitate was formed, the mixture was extracted three times with EtOAc and then, the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on
- 15    silica gel.

- METHOD 2: To a 0.1 M solution of a compound of fomula **IV** (1 eq) in DMF, triethylamine (1.1 eq), DMAP (0.1 eq) and an acyl chloride of formula **XIIlb** (1.1 eq) were added. The reaction was followed by thin-layer chromatography
- 20    until the starting material disappeared. Water in an amount of about 10 parts by volume of DMF was added and the precipitate obtained was filtered and washed thoroughly con water. In case that no precipitate was formed, the mixture was extracted three times with EtOAc and then the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered
- 25    and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

TABLE 1

Ex.	Name	Starting materials	HPLC-ESI-MS
IX_1	2-Bromo-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)propan-1-one	IV_1 and 2-bromo-propanoic acid (XIIla_1)	rt: 6.370 m/z: 478/480
IX_2	2-Chloro-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)ethanone	IV_3 and chloroacetyl chloride (XIIlb_1)	rt: 6.016 m/z: 438/440



Examples of intermediates of formula IIIa:

The following intermediates of formula IIIa shown in table 2 were prepared following the four-step synthesis described in P. L. Beaulieu, *J. Med. Chem.* 2004, 47 (27), 6884 with a slight modification in the last step as described in M. A. Phillips, *J. Chem. Soc.* 1929, 2820.

TABLE 2

Ex.	Name	Starting materials	HPLC-ESI-MS
IIIa_68	2-Methylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and benzylamine	rt: --- m/z:177
IIIa_69	1,2-Dimethylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and methylamine	rt: 0.846 m/z:191
IIIa_70	1-Cyclopropylmethyl-2-methylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and cyclopropylmethylamine	rt: 2.962 m/z:231
IIIa_71	2-Methyl-1-propylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate of methyl and propylamine	rt: 2.816 m/z:219
IIIa_72	2-Methyl-1-(2-propynyl)benzimidazole-5-carboxylic acid	Acetic acid, 4-chloro-3-nitrobenzoate and 2-propynylamine	rt: 3.307 m/z:215
IIIa_73	1-Allyl-2-methylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and allylamine	rt: 2.646 m/z:217
IIIa_74	1-Cyclopentyl-2-methylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and cyclopentylamine	rt: 3.467 m/z:245
IIIa_75	1-Cyclohexyl-2-methylbenzimidazole-5-carboxylic acid	Acetic acid, methyl 4-chloro-3-nitrobenzoate and cyclohexylamine	rt: 3.939 m/z:259
IIIa_137	6-(N-Ethyl-N-methyl)amino-pyridine-3-carboxylic acid	Ethyl 6-chloropyridine-3-carboxyate and ethylmethylamine	rt: 1.330 m/z:181
IIIa_138	6-(N,N-dimethyl)aminopyridine-3-carboxylic acid	Ethyl 6-chloropyridine-3-carboxyate and dimethylamine	rt: - m/z:167
IIIa_139	6-[N-(2-methoxy)ethylamino]-pyridine-3-carboxylic acid	Ethyl 6-chloropyridine-3-carboxyate and 2-methoxyethylamine	rt: - m/z:197
IIIa_140	6-(N-methylamino)pyridine-3-carboxylic acid	Ethyl 6-chloropyridine-3-carboxyate and methylamine	rt: - m/z:153
IIIa_141	Hydroxypyridin-3-ylacetic acid	pyridine-3-carbaldehyde and potassium cyanide	rt: 0.443 m/z:154

10 Examples of intermediates of formula II:

Compounds of formula II shown in table 3 were obtained by one of the methods 1-2 described below.

METHOD 1: Corresponds to a sequence of 2 steps. The first step corresponds to the method 1 described for the preparation of compounds of formula **IX**, using as starting materials an amine of formula **IV** and an acid of formula **VIIIa**.

- 5 Then, when PG represents *tert*-butoxycarbonyl the resulting product was dissolved in ethanol to give a 0.1 M solution and *para*-toluenesulfonic acid monohydrate (1.5 eq) was added. The reaction was stirred at reflux until the starting material disappeared on thin-layer chromatography. The resulting mixture was concentrated under reduced pressure. An aqueous solution
- 10 sodium bicarbonate was added to the crude and the mixture extracted three times with EtOAc. Then the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.
- 15 When PG represents *N*-(9-fluorenylmethoxycarbonyl) the resulting product was dissolved in THF:DMF 9:1 to give a 0.1 M solution and piperidine (5 eq) was added. The reaction was stirred at room temperature reflux until the starting material disappeared on thin-layer chromatography. THF was removed by evaporation under reduced pressure. An aqueous solution
- 20 sodium bicarbonate was added to the crude and the mixture extracted three times with EtOAc. Then the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

25

- METHOD 2: Corresponds to a sequence of 2 steps. In the first step, to a solution 0.5 M of a compound of formula **IX** (1 eq) in dried DMF in a closed-vessel, sodium azide (1.1 eq) was added. The mixture was heated in a microwave oven with simultaneous cooling (150 W; 150 °C) until the
- 30 starting material disappeared on thin-layer chromatography. Water in an amount of about 10 parts by volume of DMF was added at room temperature and the mixture was stirred. The obtained precipitate was filtered and



washed thoroughly with water. In case that no precipitate was formed, the mixture was extracted three times with EtOAc and then the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

The resulting compound of formula **XII** was dissolved in methanol to give a 0.1 M solution and Pd-C at 10% (10% by weight of the product obtained in the first step) was added. The suspension was stirred under hydrogen atmosphere until the starting material disappeared on thin-layer chromatography. The mixture was filtered through celite and the filtrate was concentrated by evaporation under reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

TABLE 3

Ex.	Name	Starting materials	HPLC-ESI-MS
II_1	2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)ethanone	IV_1 and <i>N</i> -tert-butoxycarbonylglycine (VIIIa_1)	rt: 3.677 m/z: 401
II_2	2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)propanone	IX_1 and sodium azide	rt: 3.895 m/z: 415
II_3	2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-phenylethanone	IV_1 and <i>N</i> -tert-butoxycarbonyl-DL- $\alpha$ -phenylglycine (VIIIa_2)	rt: 4.467 m/z: 477
II_4	<i>N</i> -(3-{4-[4-(2-Aminoacetyl)piperazin-1-yl]-3-fluorophenyl}isoxazol-5-ylmethyl)acetamide	IV_2 and <i>N</i> -tert-butoxycarbonylglycine (VIIIa_1)	rt: 3.147 m/z: 376
II_5	1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-methylaminoethanone	IV_1 and <i>N</i> -(9-fluorenylmethoxycarbonyl)- <i>N</i> -methylglycine (VIIIa_3)	rt: 7.428 m/z: 415
II_6	2-Amino-1-(4-{2,6-difluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)ethanone	IX_2 and sodium azide	rt: 3.942 m/z: 419
II_7	( <i>S</i> )-2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)propanone	IV_1 and <i>N</i> -tert-butoxycarbonyl-L-alanine (VIIIa_4)	rt: 3.941 m/z: 415
II_8	( <i>R</i> )-2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)propanone	IV_1 and <i>N</i> -tert-butoxycarbonyl-D-alanine (VIIIa_5)	rt: 3.950 m/z: 415
II_9	( <i>R</i> )-2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-3-methylbutanone	IV_1 and <i>N</i> -tert-butoxycarbonyl-D-valine (VIIIa_6)	rt: 4.317 m/z: 443



Ex.	Name	Starting materials	HPLC-ESI-MS
II_10	(S)-2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-3-methylbutanone	IV_1 and <i>N-tert</i> -butoxycarbonyl-L-valine (VIIIa_7)	rt: 4.338 m/z: 443
II_011	2-Amino-1-{4-[4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}ethanone	IV_4 and VIIIa_1 ( <i>N-tert</i> -butoxycarbonyl-glycine)	rt:3.146 m/z: 335
II_012	2-Amino-1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)2-methylpropanone	IV_001 and VIIIa_8 (Boc-alfa-methyl-alanine)	rt:4.026 m/z: 429
II_013	(1-Aminocyclopentyl)-(4-{4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)methanone	IV_001 and VIIIa_9 (1-( <i>N-Boc</i> -amino)cyclopentane carboxylic acid)	rt:4.275 m/z: 455
II_014	(S)-2-Amino-1-{4-[4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}propan-1-one	IV_004 and VIIIa_4 ( <i>N-tert</i> -butoxycarbonyl-L-alanine)	rt:3.384 m/z: 349

#### Examples of compounds of formula I:

Compounds of formula I shown in table 4 were obtained by one of the methods 1-4 described below.

5

METHOD 1: Corresponds to the method 1 described for the preparation of compounds of formula IX, using as starting materials an amine of formula II and an acid of formula IIIa.

10 METHOD 2: Corresponds to the method 2 described for the preparation of compounds of formula IX, using as starting materials an amine of formula II and an acyl chloride of formula IIIb.

METHOD 3: To a solution of a compound of fomula I (1 eq) wherein R2  
 15 represents alkyl substituted with -OC(=O)Rc, wherein Rc represents alkyl or aryl, in a mixture THF:methanol:water 4:1:1 to give a 0.1 M solution, a solution 1 N of sodium hydroxyde (1.1 eq) was added. The reaction was stirred at room temperature until the starting material disappeared on thin-layer chromatography. The resulting mixture was concentrated by evaporation  
 20 under reduced pressure. Water was added to the crude and the mixture was extracted three times with dichloromethane and then the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and

concentrated under reduced pressure, to yield the corresponding alcohol of formula I.

METHOD 4: A compound I comprising a *tert*-butoxycarbonylamino group (1 eq) was dissolved in dichloromethane to give a 0.1 M solution. Trifluoroacetic acid (20 eq) was added and the reaction was stirred at room temperature until the starting material disappeared on thin-layer chromatography. The resulting mixture was concentrated by evaporation under reduced pressure. An aqueous solution of sodium bicarbonate was added to the crude and the mixture was extracted three times with dichloromethane. Then, the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure. The obtained product was purified by column chromatography on silica gel, to yield the corresponding amine of formula I.

TABLE 4

Ex.	Name	Starting materials	HPLC-ESI-MS
I_1	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]formamide	II_1 and <i>N,N</i> -dimethylformamide (IIIb_1)	rt: 4.546 m/z: 429
I_2	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]acetamide	II_1 and acetyl chloride (IIIb_2)	rt: 4.588 m/z: 443
I_3	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]cyclopentanecarboxamide	II_1 and cyclopentanecarbonylchloride (IIIb_3)	rt: 5.757 m/z: 497
I_4	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]thiazolidine-5-carboxamide	II_1 and thiazolidine-5-carboxylic acid (IIIa_1)	rt: 4.391 m/z: 516
I_5	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]carbamoyl]methyl acetate	II_1 and acetoxyacetyl chloride (IIIb_4)	rt: 4.942 m/z: 501
I_6	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methoxyacetamide	II_1 and methoxyacetyl chloride (IIIb_5)	rt: 4.905 m/z: 473
I_7	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxyacetamide	I_5	rt: 4.446 m/z: 459
I_8	<i>tert</i> -Butyl <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]carbamoyl]methyl]carbamate	II_1 and <i>N-tert</i> -butoxycarbonylglycine (IIIa_2)	rt: 5.611 m/z: Not detected
I_9	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-ureidopropionamide	II_1 and 3-ureidopropionic acid (IIIa_3)	rt: 4.289 m/z: 515



Ex.	Name	Starting materials	HPLC-ESI-MS
I_10	2-(2,5-Dioxoimidazolidin-4-yl)- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]acetamide	II_1 and 5-hydantoinacetic acid (IIIa_4)	rt: 4.363 m/z: 541
I_11	2-(2,6-Dioxo-1,2,3,6-tetrahydropyrimidin-4-yl)- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]acetamide	II_1 and 4-uracylacetic acid (IIIa_5)	rt: 4.330 m/z: 553
I_12	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}ipiperazin-1-yl)-2-oxoethyl]cyclopropane-1,1-dicarboxamide	II_1 and 1-(aminocarbonyl)-1-cyclopropanecarboxylic acid (IIIa_6)	rt: 4.653 m/z: 512
I_13	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-nitrobenzamide	II_1 and 2-nitrobenzoyl chloride (IIIb_6)	rt: 5.650 m/z: 550
I_14	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-methoxybenzamide	II_1 and 4-methoxybenzoyl chloride (IIIb_7)	rt: 5.789 m/z: 535
I_15	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxybenzamide	II_1 and 3-hydroxybenzoic acid (IIIa_7)	rt: 5.210 m/z: 521
I_16	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-hydroxybenzamide	II_1 and 4-hydroxybenzoic acid (IIIa_8)	rt: 5.096 m/z: 521
I_17	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxybenzamide	II_1 and 2-hydroxybenzoic acid (IIIa_9)	rt: 6.038 m/z: 521
I_18	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxy-4-methylbenzamide	II_1 and 2-hydroxy-4-methylbenzoic acid (IIIa_10)	rt: 6.395 m/z: 535
I_19	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxy-3-methylbenzamide	II_1 and 2-hydroxy-3-methylbenzoic acid (IIIa_11)	rt: 6.752 m/z: 535
I_20	4-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxybenzamide	II_1 and 4-fluoro-2-hydroxybenzoic acid (IIIa_12)	rt: 6.313 m/z: 539
I_21	5-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxybenzamide	II_1 and 5-fluoro-2-hydroxybenzoic acid (IIIa_13)	rt: 6.116 m/z: 539
I_22	3-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-hydroxybenzamide	II_1 and 3-fluoro-4-hydroxybenzoic acid (IIIa_14)	rt: 5.267 m/z: 539
I_23	2-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-hydroxybenzamide	II_1 and 2-fluoro-6-hydroxybenzoic acid (IIIa_15)	rt: 6.715 m/z: 539
I_24	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxy-2,4,5-trifluorobenzamide	II_1 and 3-hydroxy-2,4,5-trifluorobenzoic acid (IIIa_16)	rt: 5.835 m/z: 575
I_25	2,3-Dihydroxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2,3-dihydroxybenzoic acid (IIIa_17)	rt: 5.487 m/z: 537
I_26	3,4-Dihydroxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3,4-dihydroxybenzoic acid (IIIa_18)	rt: 4.870 m/z: 537



Ex.	Name	Starting materials	HPLC-ESI-MS
I_27	2,6-Dihydroxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2,6-dihydroxybenzoic acid (IIIa_19)	rt: 5.968 m/z: 537
I_28	2,4-Dihydroxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2,4-dihydroxybenzoic acid (IIIa_20)	rt: 5.411 m/z: 537
I_29	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxy-5-methoxybenzamide	II_1 and 2-hydroxy-5-methoxybenzoic acid (IIIa_21)	rt: 5.983 m/z: 551
I_30	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxy-4-methoxybenzamide	II_1 and 2-hydroxy-4-methoxybenzoic acid (IIIa_22)	rt: 6.168 m/z: 551
I_31	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxy-4-nitrobenzamide	II_1 and 3-hydroxy-4-nitrobenzoic acid (IIIa_23)	rt: 5.760 m/z: 566
I_32	4-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxybenzamide	II_1 and 4-amino-2-hydroxybenzoic acid (IIIa_24)	rt: 5.354 m/z: 536
I_33	5-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxybenzamide	II_1 and 5-amino-2-hydroxybenzoic acid (IIIa_25)	rt: 4.363 m/z: 536
I_34	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-hydroxybenzamide	II_1 and 2-amino-5-hydroxybenzoic acid (IIIa_26)	rt: 4.362 m/z: 536
I_35	4-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxybenzamide	II_1 and 4-amino-3-hydroxybenzoic acid (IIIa_27)	rt: 4.749 m/z: 536
I_36	3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-hydroxybenzamide	II_1 and 3-amino-4-hydroxybenzoic acid (IIIa_28)	rt: 4.398 m/z: 536
I_37	4-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 4-aminobenzoic acid (IIIa_29)	rt: 4.973 m/z: 520
I_38	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2-aminobenzoic acid (IIIa_30)	rt: 5.564 m/z: 520
I_39	3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3-aminobenzoic acid (IIIa_31)	rt: 4.778 m/z: 520
I_40	3,4-Diamino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3,4-diaminobenzoic acid (IIIa_32)	rt: 4.384 m/z: 535
I_41	3,5-Diamino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3,5-diaminobenzoic acid (IIIa_33)	rt: 4.168 m/z: 535
I_42	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-nitrobenzamide	II_1 and 2-amino-5-nitrobenzoic acid (IIIa_34)	rt: 5.824 m/z: 565
I_43	3-Dimethylamino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3-dimethylaminobenzoic acid (IIIa_35)	rt: 5.574 m/z: 548
I_44	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzo[1,3]dioxole-5-carboxamide	II_1 and 3,4-(methylendioxy)benzoyl chloride (IIIb_8)	rt: 5.708 m/z: 549

Ex.	Name	Starting materials	HPLC-ESI-MS
I_45	3-Cyano- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 3-cyano-benzoyl chloride (IIIb_9)	rt: 5.667 m/z: 530
I_46	2-Cyano- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2-cyanobenzoic acid (IIIa_36)	rt: 5.254 m/z: 530
I_47	2-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzamide	II_1 and 2-fluorobenzoic acid (IIIa_37)	rt: 6.004 m/z: 523
I_48	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-(imidazol-1-yl)benzamide	II_1 and 4-(imidazol-1-yl)benzoic acid (IIIa_38)	rt: 4.283 m/z: 571
I_49	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-imidazol-1-ylbenzamide	II_1 and 3-(imidazol-1-yl)benzoic acid (IIIa_39)	rt: 4.360 m/z: 571
I_50	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-pyrazol-1-ylbenzamide	II_1 and 3-(pyrazol-1-yl)benzoic acid (IIIa_40)	rt: 5.846 m/z: 571
I_51	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(2-methylthiazol-5-yl)benzamide	II_1 and 3-(2-methylthiazol-5-yl)benzoic acid (IIIa_41)	rt: 6.264 m/z: 602
I_52	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-pyridin-4-ylbenzamide	II_1 and 4-(pyridin-4-yl)benzoic acid (IIIa_42)	rt: 4.548 m/z: 582
I_53	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-pyridin-4-ylbenzamide	II_1 and 3-(pyridin-4-yl)benzoic acid (IIIa_43)	rt: 4.564 m/z: 582
I_54	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-methylthiophene-2-carboxamide	II_1 and 5-methylthiophene-2-carboxylic acid (IIIa_44)	rt: 5.954 m/z: 525
I_55	5-Bromo- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]thiophene-2-carboxamide	II_1 and 5-bromothiophene-2-carboxylic acid (IIIa_45)	rt: 6.352 m/z: 589, 591
I_56	4,5-Dibromo- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]thiophene-2-carboxamide	II_1 and 4,5-dibromothiophene-2-carboxylic acid (IIIa_46)	rt: 6.933 m/z: 667, 669, 671
I_57	5-Chloro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]thiophene-2-carboxamide	II_1 and 5-chlorothiophene-2-carboxylic acid (IIIa_47)	rt: 6.293 m/z: 545, 547
I_58	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-nitrofur-2-carboxamide	II_1 and 5-nitrofur-2-carbonyl chloride (IIIb_10)	rt: 5.663 m/z: 540
I_59	5-Bromo- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]furan-2-carboxamide	II_1 and 5-bromofuran-2-carboxylic acid (IIIa_48)	rt: 5.993 m/z: 573, 575
I_60	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]furan-2-carboxamide	II_1 and furan-2-carbonyl chloride (IIIb_11)	rt: 5.352 m/z: 495



Ex.	Name	Starting materials	HPLC-ESI-MS
I_61	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]furan-3-carboxamide	II_1 and furan-3-carboxylic acid (IIIa_49)	rt: 5.279 m/z: 495
I_62	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]benzofuran-2-carboxamide	II_1 and benzofuran-2-carboxylic acid (IIIa_50)	rt: 6.339 m/z: 545
I_63	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -pyrrole-2-carboxamide	II_1 and pyrrole-2-carboxylic acid (IIIa_51)	rt: 5.286 m/z: 494
I_64	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1-methyl-1 <i>H</i> -pyrrole-2-carboxamide	II_1 and 1-methylpyrrole-2-carboxylic acid (IIIa_52)	rt: 5.702 m/z: 508
I_65	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -pyrrole-3-carboxamide	II_1 and pyrrole-3-carboxylic acid (IIIa_53)	rt: 4.891 m/z: 494
I_66	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -imidazole-4-carboxamide	II_1 and imidazole-4-carboxylic acid (IIIa_54)	rt: 4.238 m/z: 495
I_67	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -pyrazole-4-carboxamide	II_1 and pyrazole-4-carboxylic acid (IIIa_55)	rt: 4.566 m/z: 495
I_68	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-nitro-1 <i>H</i> -pyrazole-3-carboxamide	II_1 and 5-nitropyrazole-3-carboxylic acid (IIIa_56)	rt: 5.308 m/z: 540
I_69	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-nitro-1 <i>H</i> -pyrazole-3-carboxamide	II_1 and 4-nitropyrazole-3-carboxylic acid (IIIa_57)	rt: 5.141 m/z: 540
I_70	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-methyl-1 <i>H</i> -pyrazole-3-carboxamide	II_1 and 5-methylpyrazole-3-carboxylic acid (IIIa_58)	rt: 5.005 m/z: 509
I_71	3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -pyrazole-4-carboxamide	II_1 and 3-aminopyrazole-4-carboxylic acid (IIIa_59)	rt: 4.496 m/z: 510
I_72	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-2-carboxamide	II_1 and indole-2-carboxylic acid (IIIa_60)	rt: 6.158 m/z: 544
I_73	5-Fluoro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-2-carboxamide	II_1 and 5-fluoroindole-2-carboxylic acid (IIIa_61)	rt: 6.269 m/z: 562
I_74	5-Benciloxi- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-2-carboxamide	II_1 and 5-benciloxindole-2-carboxylic acid (IIIa_62)	rt: 7.091 m/z: 650
I_75	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1-methyl-1 <i>H</i> -indole-2-carboxamide	II_1 and 1-methylindole-2-carboxylic acid (IIIa_63)	rt: 6.615 m/z: 558



Ex.	Name	Starting materials	HPLC-ESI-MS
I_76	2,3-Dihydro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-2-carboxamide	II_1 and indoline-2-carboxylic acid (IIIa_64)	rt: 6.157 m/z: 546
I_77	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-6-carboxamide	II_1 and indole-6-carboxylic acid (IIIa_65)	rt: 5.743 m/z: 544
I_78	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indole-5-carboxamide	II_1 and indole-5-carboxylic acid (IIIa_66)	rt: 5.566 m/z: 544
I_79	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and benzimidazole-5-carboxylic acid (IIIa_67)	rt: 4.276 m/z: 545
I_80	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 2-methylbenzimidazole-5-carboxylic acid (IIIa_68)	rt: 5.139 m/z: 559
I_81	1,2-Dimethyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 1,2-dimethylbenzimidazole-5-carboxylic acid (IIIa_69)	rt: 4.328 m/z: 573
I_82	1-Cyclopropylmethyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 1-cyclopropylmethyl-2-methylbenzimidazole-5-carboxylic acid (IIIa_70)	rt: 4.728 m/z: 613
I_83	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1-propyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 2-methyl-1-propylbenzimidazole-5-carboxylic acid (IIIa_71)	rt: 4.717 (method B) m/z: 601
I_84	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1-prop-2-ynyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 2-methyl-1-(2-propynyl)benzimidazole-5-carboxylic acid (IIIa_72)	rt: 5.522 (method B) m/z: 597
I_85	1-Allyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 1-allyl-2-methylbenzimidazole-5-carboxylic acid (IIIa_73)	rt: 4.773 (method B) m/z: 599
I_86	1-Cyclopentyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 1-cyclopentyl-2-methylbenzimidazole-5-carboxylic acid (IIIa_74)	rt: 5.010 (method B) m/z: 627
I_87	1-Cyclohexyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_1 and 1-cyclohexyl-2-methylbenzimidazole-5-carboxylic acid (IIIa_75)	rt: 5.221 m/z: 641
I_88	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]imidazo[1,2- <i>a</i> ]pyridine-3-carboxamide	II_1 and imidazo[1,2- <i>a</i> ]pyridine-3-carboxylic acid (IIIa_76)	rt: 4.525 m/z: 545

Ex.	Name	Starting materials	HPLC-ESI-MS
I_89	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]imidazo[1,2- <i>a</i> ]pyridine-2-carboxamide	II_1 and imidazo[1,2- <i>a</i> ]pyridine-2-carboxylic acid (IIIa_77)	rt: 4.953 m/z: 545
I_90	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -indazole-3-carboxamide	II_1 and indazole-3-carboxylic acid (IIIa_78)	rt: 5.804 m/z: 545
I_91	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isoxazole-5-carboxamide	II_1 and isoxazole-5-carbonyl chloride (IIIb_12)	rt: 5.136 m/z: 496
I_92	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-methylisoxazole-3-carboxamide	II_1 and 5-methylisoxazole-3-carboxylic acid (IIIa_79)	rt: 5.634 m/z: 510
I_93	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and pyridine-3-carbonyl chloride (IIIb_13)	rt: 4.632 m/z: 506
I_94	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isonicotinamide	II_1 and pyridine-4-carboxylic acid (IIIa_80)	rt: 4.561 m/z: 506
I_95	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]pyridine-2-carboxamide	II_1 and pyridine-2-carboxylic acid (IIIa_81)	rt: 5.638 m/z: 506
I_96	2-Chloro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 2-chloropyridine-3-carboxylic acid (IIIa_82)	rt: 5.256 m/z: 540, 542
I_97	6-Chloro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 6-chloropyridine-3-carboxylic acid (IIIa_83)	rt: 5.544 m/z: 540, 542
I_98	2,6-Dichloro- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 2,6-dichloropyridine-3-carboxylic acid (IIIa_84)	rt: 5.968 m/z: 573, 575, 576, 577
I_99	5-Bromo- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 5-bromopyridine-3-carboxylic acid (IIIa_85)	rt: 5.623 m/z: 583, 585
I_100	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-methylnicotinamide	II_1 and 6-methylpyridine-3-carboxylic acid (IIIa_86)	rt: 5.687 m/z: 520
I_101	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide 1-oxide	II_1 and pyridine-3-carboxylic acid <i>N</i> -oxide (IIIa_87)	rt: 4.424 m/z: 522
I_102	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]pyridine-2-carboxamide 1-oxide	II_1 and pyridine-2-carboxylic acid <i>N</i> -oxide (IIIa_88)	rt: 4.913 m/z: 522
I_103	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isonicotinamide 1-oxide	II_1 and pyridine-4-carboxylic acid <i>N</i> -oxide (IIIa_89)	rt: 4.426 m/z: 522



Ex.	Name	Starting materials	HPLC-ESI-MS
I_104	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-nitronicotinamide 1-oxide	II_1 and 4-nitropyridine-3-carboxylic acid <i>N</i> -oxide (IIIa_90)	rt: 4.911 m/z: 567
I_105	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-hydroxynicotinamide	II_1 and 6-hydroxypyridine-3-carboxylic acid (IIIa_91)	rt: 4.510 m/z: 522
I_106	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-hydroxypyridine-2-carboxamide	II_1 and 6-hydroxypyridine-2-carboxylic acid (IIIa_92)	rt: 4.732 m/z: 522
I_107	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxypyridine-2-carboxamide	II_1 and 3-hydroxypyridine-2-carboxylic acid (IIIa_93)	rt: 6.218 m/z: 522
I_108	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methoxynicotinamide	II_1 and 2-methoxypyridine-3-carboxylic acid (IIIa_94)	rt: 5.787 m/z: 536
I_109	2-Ethoxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 2-ethoxypyridine-3-carboxylic acid (IIIa_95)	rt: 6.340 m/z: 550
I_110	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-4-methoxypyridine-2-carboxamide	II_1 and 4-methoxy-pyridine-2-carboxylic acid (IIIa_96)	rt: 5.733 m/z: 536
I_111	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 2-amino-pyridine-3-carboxylic acid (IIIa_97)	rt: 4.212 m/z: 521
I_112	6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 6-amino-pyridine-3-carboxylic acid (IIIa_83)	rt: 4.081 m/z: 521
I_113	6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]pyridine-2-carboxamide	II_1 and 6-amino-pyridine-2-carboxylic acid (IIIa_98)	rt: 6.697 m/z: 521
I_114	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isonicotinamide	II_1 and 2-amino-pyridine-4-carboxylic acid (IIIa_99)	rt: 4.116 m/z: 521
I_115	2-Amino-4,6-dimethyl- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 2-amino-4,6-dimethylpyridine-3-carboxylic acid (IIIa_100)	rt: 4.313 m/z: 549
I_116	4-(2,2-Dimethylpropionylamino)- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 4-(2,2-dimethylpropionylamino)pyridine-3-carboxylic acid (IIIa_101)	rt: 5.600 m/z: 605



Ex.	Name	Starting materials	HPLC-ESI-MS
I_117	6-Acetylamino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 6-acetylamino-3-pyridine-carboxylic acid (IIIa_102)	rt: 4.917 m/z: 563
I_118	6-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]carbamoyl]nicotinic acid	II_1 and pyridine-2,5-dicarboxylic acid (IIIa_103)	rt: 5.209 m/z: 550
I_119	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-trifluoromethylnicotinamide	II_1 and 6-trifluoromethylpyridine-3-carboxylic acid (IIIa_104)	rt: 5.998 m/z: 574
I_120	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isoquinoline-1-carboxamide	II_1 and isoquinoline-1-carboxylic acid (IIIa_105)	rt: 6.375 m/z: 556
I_121	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-2-carboxamide	II_1 and quinoline-2-carboxylic acid (IIIa_106)	rt: 6.567 m/z: 556
I_122	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-8-carboxamide	II_1 and quinoline-8-carboxylic acid (IIIa_107)	rt: 5.962 m/z: 556
I_123	<i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-3-carboxamide	II_1 and quinoline-3-carboxylic acid (IIIa_108)	rt: 5.455 m/z: 556
I_124	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-4-carboxamide	II_1 and quinoline-4-carboxylic acid (IIIa_109)	rt: 5.202 m/z: 556
I_125	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-5-carboxamide	II_1 and quinoline-5-carboxylic acid (IIIa_110)	rt: 4.808 m/z: 556
I_126	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxyquinoline-4-carboxamide	II_1 and 2-hydroxyquinoline-4-carboxylic acid (IIIa_111)	rt: 5.116 m/z: 572
I_127	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoline-6-carboxamide	II_1 and quinoline-6-carboxylic acid (IIIa_112)	rt: 4.909 m/z: 556
I_128	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-8-hydroxyquinoline-2-carboxamide	II_1 and 8-hydroxyquinoline-2-carboxylic acid (IIIa_113)	rt: 6.212 m/z: 572
I_129	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoxaline-2-carboxamide	II_1 and quinoxaline-2-carboxylic acid (IIIa_114)	rt: 6.103 m/z: 557
I_130	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxyquinoxaline-2-carboxamide	II_1 and 3-hydroxyquinoxaline-2-carboxylic acid (IIIa_115)	rt: 5.098 m/z: 573
I_131	2,4-Dihydroxy- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]pyrimidine-5-carboxamide	II_1 and 2,4-dihydroxypyrimidine-5-carboxylic acid (IIIa_116)	rt: 4.669 m/z: 539

Ex.	Name	Starting materials	HPLC-ESI-MS
I_132	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-hydroxysoxazole-5-carboxamide	II_1 and 3-hydroxysoxazole-5-carboxylic acid (IIIa_117)	rt: 4.915 m/z: 512
I_133	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxynicotinamide	II_1 and 2-hydroxypyridine-3-carboxylic acid (IIIa_118)	rt: 4.751 m/z: 522
I_134	3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]pyridine-2-carboxamide	II_1 and 3-amino-pyridine-2-carboxylic acid (IIIa_119)	rt: 5.374 m/z: 521
I_135	3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isonicotinamide	II_1 and 3-amino-pyridine-4-carboxylic acid (IIIa_120)	rt: 4.189 m/z: 521
I_136	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]isoquinoline-5-carboxamide	II_1 and isoquinoline-5-carboxylic acid (IIIa_121)	rt: 4.434 m/z: 556
I_137	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]quinoxaline-6-carboxamide	II_1 and quinoxaline-6-carboxylic acid (IIIa_122)	rt: 5.207 m/z: 557
I_138	4-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 4-amino-pyridine-3-carboxylic acid (IIIa_123)	rt: 4.119 m/z: 521
I_139	5-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and 5-amino-pyridine-3-carboxylic acid (IIIa_124)	rt: 4.140 m/z: 521
I_140	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-pyridin-3-ylacetamide	II_1 and 3-pyridylacetic acid (IIIa_125)	rt: 4.065 m/z: 520
I_141	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-pyridin-2-ylacetamide	II_1 and 2-pyridylacetic acid (IIIa_126)	rt: 4.228 m/z: 520
I_142	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-(1 <i>H</i> -imidazol-4-yl)acetamide	II_1 and 4-imidazolylacetic acid (IIIa_127)	rt: 3.962 m/z: 509
I_143	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-(1-methyl-1 <i>H</i> -indol-3-yl)acetamide	II_1 and (1-methyl-indol-4-yl)acetic acid (IIIa_128)	rt: 6.194 m/z: 572
I_144	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(1 <i>H</i> -imidazol-4-yl)acrylamide	II_1 and 4-imidazolylacrylic acid (IIIa_129)	rt: 4.090 m/z: 521
I_145	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]carbamoyl]methyl]furan-2-carboxamide	II_1 and <i>N</i> -(2-furoyl)glycine (IIIa_130)	rt: 4.906 m/z: 552



Ex.	Name	Starting materials	HPLC-ESI-MS
I_146	6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]nicotinamide	II_2 and 6-amino-pyridine-3-carboxylic acid (IIIa_83)	rt: 4.302 m/z: 535
I_147	6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxo-1-phenylethyl]nicotinamide	II_3 and 6-amino-pyridine-3-carboxylic acid (IIIa_83)	rt: 5.075 m/z: 597
I_148	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxo-1-phenylethyl]-6-methylnicotinamide	II_3 and 6-methyl-pyridine-3-carboxylic acid (IIIa_86)	rt: 5.722 m/z: 596
I_149	2-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]acetamide	I_8	rt: 3.825 m/z: 458
I_150	<i>N</i> -[2-(4-{4-[5-(Acetylaminomethyl)isoxazol-3-yl]-2-fluorophenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_4 and benzimidazole-5-carboxylic acid (IIIa_67)	rt: 3.746 m/z: 520
I_151	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(1 <i>H</i> -imidazol-4-yl)propionamide	II_1 and 3-(1 <i>H</i> -imidazol-4-yl)propanoic acid (IIIa_131)	rt: 4.017 m/z: 523
I_152	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-methylaminoacetamide	II_1 and <i>N</i> -(9-fluorenylmethoxycarbonyl)- <i>N</i> -methylglycine (IIIa_132)	rt: 3.932 m/z: 472
I_153	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxo-1-phenylethyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_3 and benzimidazole-5-carboxylic acid (IIIa_67)	rt: 5.206 m/z: 621
I_154	6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]- <i>N</i> -methylnicotinamide	II_5 and 6-amino-pyridine-3-carboxylic acid (IIIa_83)	rt: 4.137 m/z: 535
I_155	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]- <i>N</i> -methyl-1 <i>H</i> -benzimidazole-5-carboxamide	II_5 and benzimidazole-5-carboxylic acid (IIIa_67)	rt: 4.265 m/z: 559
I_156	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6, <i>N</i> -dimethylnicotinamide	II_5 and 6-methylpyridine-3-carboxylic acid (IIIa_86)	rt: 4.501 m/z: 534
I_157	6-Amino- <i>N</i> -[2-(4-{2,6-difluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_6 and 6-amino-pyridine-3-carboxylic acid (IIIa_83)	rt: 4.361 m/z: 539
I_158	<i>N</i> -[2-(4-{2,6-Difluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-methylnicotinamide	II_6 and 6-methylpyridine-3-carboxylic acid (IIIa_86)	rt: 4.818 m/z: 538
I_159	<i>N</i> -[2-(4-{2,6-Difluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_6 and benzimidazole-5-carboxylic acid (IIIa_67)	rt: 4.466 m/z: 563



Ex.	Name	Starting materials	HPLC-ESI-MS
I_160	<i>N</i> -[2-(4-{2,6-Difluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-8-hydroxyquinoline-2-carboxamide	II_6 and 8-hydroxyquinoline-2-carboxylic acid (IIIa_113)	rt: 6.533 m/z: 590
I_161	( <i>S</i> )-6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]nicotinamide	II_7 and 6-amino-pyridine-3-carboxylic acid (IIIa_083)	rt: 4.307 m/z: 535
I_162	( <i>R</i> )-6-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]nicotinamide	II_8 and 6-amino-pyridine-3-carboxylic acid (IIIa_083)	rt: 4.310 m/z: 535
I_163	( <i>R</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-6-methylnicotinamide	II_8 and 6-methylpyridine-3-carboxylic acid (IIIa_086)	rt: 4.307 m/z: 534
I_164	( <i>R</i> )-3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]isonicotinamide	II_8 and 3-amino-pyridine-4-carboxylic acid (IIIa_120)	rt: 4.310 m/z: 535
I_165	( <i>R</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]pyrazole-4-carboxamide	II_8 and pyrazole-4-carboxylic acid (IIIa_055)	rt: 4.677 m/z: 509
I_166	( <i>R</i> )- <i>N</i> -[1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-carbonyl)-2-methylpropyl]-1 <i>H</i> -benzimidazole-5-carboxamide	II_9 and benzimidazole-5-carboxylic acid (IIIa_067)	rt: 4.428 m/z: 587
I_167	( <i>S</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-6-methylnicotinamide	II_7 and 6-methylpyridine-3-carboxylic acid (IIIa_086)	rt: 4.815 m/z: 562
I_168	( <i>S</i> )-3-Amino- <i>N</i> -[1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-carbonyl)-2-methylpropyl]pyridine-2-carboxamide	II_10 and 3-aminopyridine-2-carboxylic acid (IIIa_119)	rt: 4.981 m/z: 563
I_169	( <i>R</i> )- <i>N</i> -[1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-carbonyl)-2-methylpropyl]-6-methylnicotinamide	II_9 and 6-methylpyridine-3-carboxylic acid (IIIa_086)	rt: 5.355 m/z: 534
I_170	( <i>S</i> )- <i>N</i> -[1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-carbonyl)-2-methylpropyl]-6-methylnicotinamide	II_10 and 6-methylpyridine-3-carboxylic acid (IIIa_086)	rt: 6.721 m/z: 562
I_171	( <i>R</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]3-aminopyridine-2-carboxamide	II_8 and IIIa_119 (3-aminopyridine-2-carboxylic acid)	rt:6.025 m/z:535
I_172	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1,1-dimethyl-2-oxoethyl]-6-methylnicotinamide	II_12 and IIIa_086 (6-methylpyridine-3-carboxylic acid)	rt:4.643 m/z: 548
I_173	<i>N</i> -[1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazine-1-carbonyl)cyclopentyl]-6-methylnicotinamide	II_13 and IIIa_086 (6-methylpyridine-3-carboxylic acid)	rt:5.017 m/z: 574

Ex.	Name	Starting materials	HPLC-ESI-MS
I_174	3-Amino- <i>N</i> -[1-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazine-1-carbonyl)cyclopentyl]isonicotinamide	II_13 and IIIa_120 (3-aminopyridine-4-carboxylic acid)	rt:4.686 m/z: 575
I_175	( <i>R</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-1 <i>H</i> -benzoimidazole-5-carboxamide	II_8 and IIIa_067 (benzimidazole-5-carboxylic acid)	rt:4.465 m/z: 559
I_176	( <i>S</i> )- <i>N</i> -[1-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazine-1-carbonyl)-2-methylpropyl]-1 <i>H</i> -benzoimidazole-5-carboxamide	II_10 and IIIa_067 (benzimidazole-5-carboxylic acid)	rt:4.979 m/z: 587
I_177	( <i>S</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-1 <i>H</i> -pyrazole-4-carboxamide	II_7 and IIIa_055 (pyrazole-4-carboxylic acid)	rt:4.816 m/z: 509
I_178	( <i>S</i> )-3-Amino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]isonicotinamide	II_7 and IIIa_120 (3-aminopyridine-4-carboxylic acid)	rt:4.431 m/z: 535
I_179	( <i>S</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-3-aminopyridine-2-carboxamide	II_7 and IIIa_119 (3-aminopyridine-2-carboxylic acid)	rt:6.024 m/z: 535
I_180	( <i>S</i> )- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-1 <i>H</i> -benzoimidazole-5-carboxamide	II_7 and IIIa_067 (benzimidazole-5-carboxylic acid)	rt:4.470 m/z: 559
I_181	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-imidazo[1,2- <i>a</i> ]pyridine-6-carboxamide	II_1 and IIIa_133 (imidazo[1,2- <i>a</i> ]pyridine-6-carboxylic acid)	rt:4.179 m/z: 545
I_182	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]thieno[2,3- <i>b</i> ]pyridine-2-carboxamide	II_1 and IIIa_134 (Thieno[2,3- <i>b</i> ]pyridine-2-carboxylic acid)	rt:5.637 m/z: 562
I_183	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylamino-methyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-7-nitro-1 <i>H</i> -indole-2-carboxamide	II_1 and IIIa_135 (7-nitroindole-2-carboxylic acid)	rt:6.327 m/z: 589
I_184	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-5-nitrobenzofuran-2-carboxamide	II_1 and IIIa_136 (5-nitrobenzofuran-2-carboxylic acid)	rt:6.318 m/z: 590
I_185	6-Amino- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)nicotinamide	II_11 and IIIa_083 (6-aminopyridine-3-carboxylic acid)	rt:3.575 m/z: 455
I_186	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-5-methylthiophene-2-carboxamide	II_11 and IIIa_044 (5-methylthiophen-2-carboxylic acid)	rt:5.444 m/z: 459
I_187	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)benzofuran-2-carboxamide	II_11 and IIIa_050 (benzofuran-2-carboxylic acid)	rt:5.849 m/z: 479
I_188	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-1 <i>H</i> -pyrazole-4-carboxamide	II_11 and IIIa_055 (pyrazole-4-carboxylic acid)	rt:3.991 m/z: 429
I_189	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-1 <i>H</i> -indole-5-carboxamide	II_11 and IIIa_066 (indole-5-carboxylic acid)	rt:5.029 m/z: 478



Ex.	Name	Starting materials	HPLC-ESI-MS
I_190	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)imidazo[1,2- <i>a</i> ]pyridine-6-carboxamide	II_11 and IIIa_133 (imidazo[1,2- <i>a</i> ]pyridine-6-carboxylic acid)	rt:3.643 m/z: 479
I_191	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-6-methylnicotinamide	II_11 and IIIa_086 (6-methylpyridine-3-carboxylic acid)	rt:3.864 m/z: 454
I_192	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-8-hydroxyquinoline-2-carboxamide	II_11 and IIIa_113 (8-hydroxyquinoline-2-carboxylic acid)	rt:5.752 m/z: 506
I_193	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-3-hydroxybenzamide	II_11 and IIIa_007 (3-hydroxybenzoic acid)	rt:4.676 m/z: 455
I_194	6-(Ethylmethylamino)- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and IIIa_137	rt:4.478 m/z: 563
I_195	6-Dimethylamino- <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]nicotinamide	II_1 and IIIa_138	rt:4.305 m/z: 549
I_196	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-(2-methoxyethylamino)nicotinamide	II_1 and IIIa_139	rt:4.334 m/z: 579
I_197	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-6-methylaminonicotinamide	II_1 and IIIa_140	rt:4.150 m/z: 535
I_198	<i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-2-hydroxy-2-pyridin-3-ylacetamide	II_1 and IIIa_141	rt:4.479 m/z: 536
I_199	6-(Ethylmethylamino)- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)nicotinamide	II_11 and IIIa_137	rt:4.002 m/z: 497
I_200	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-6-(2-methoxyethylamino)nicotinamide	II_11 and IIIa_139	rt:3.852 m/z: 513
I_201	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-2-nitrobenzamide	II_11 and IIIa_142 (2-nitrobenzoic acid)	rt:5.092 m/z: 484
I_202	4-Amino- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)-3-hydroxybenzamide	II_11 and IIIa_027 (4-amino-3-hydroxybenzoic acid)	rt:4.128 m/z: 470
I_203	3-Cyano- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)benzamide	II_11 and IIIa_143 (3-cyanobenzoic acid)	rt:5.124 m/z: 464
I_204	3-Amino- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)isonicotinamide	II_11 and IIIa_120 (3-aminopyridine-4-carboxylic acid)	rt:3.684 m/z: 455
I_205	<i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-2-oxoethyl)quinoline-5-carboxamide	II_11 and IIIa_110 (quinoline-5-carboxylic acid)	rt:4.131 m/z: 490



Ex.	Name	Starting materials	HPLC-ESI-MS
I_206	(S)-6-Amino- <i>N</i> -(2-{4-[2-fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)nicotinamide	II_14 and IIIa_083 (6-aminopyridine-3-carboxylic acid)	rt:3.800 m/z: 469
I_207	(S)- <i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)imidazo[1,2- <i>a</i> ]pyridine-6-carboxamide	II_14 and IIIa_133 (imidazo[1,2- <i>a</i> ]pyridine-6-carboxylic acid)	rt:3.856 m/z: 493
I_208	(S)- <i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)-7-nitro-1 <i>H</i> -indole-2-carboxamide	II_14 and IIIa_135 (7-nitroindole-2-carboxylic acid)	rt:6.131 m/z: 537
I_209	(S)- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]imidazo[1,2- <i>a</i> ]pyridine-6-carboxamide	II_7 and IIIa_133 (imidazo[1,2- <i>a</i> ]pyridine-6-carboxylic acid)	rt:4.335 m/z: 559
I_210	(S)- <i>N</i> -[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-1-methyl-2-oxoethyl]-7-nitro-1 <i>H</i> -indole-2-carboxamide	II_7 and IIIa_135 (7-nitroindole-2-carboxylic acid)	rt:6.553 m/z: 603
I_211	(S)- <i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)-5-bromothiophene-2-carboxamide	II_14 and IIIa_045 (5-bromothiophene-2-carboxylic acid)	rt:6.199 m/z: 538
I_212	(S)- <i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)imidazo[1,2- <i>a</i> ]pyridine-3-carboxamide	II_14 and IIIa_076 (imidazo[1,2- <i>a</i> ]pyridine-3-carboxylic acid)	rt:4.220 m/z: 493
I_213	(S)- <i>N</i> -(2-{4-[2-Fluoro-4-(5-hydroxymethylisoxazol-3-yl)phenyl]piperazin-1-yl}-1-methyl-2-oxoethyl)-6-methylnicotinamide	II_14 and IIIa_086 (6-methylpyridine-3-carboxylic acid)	rt:4.112 m/z:468

#### Examples of compounds of formula **la**:

Compounds of formula **la** shown in table 5 were obtained by one of the methods 1-3 described below.

5

METHOD 1: To a 0.1 M solution of an amine of formula **II** (1 eq) in dried DMF an isocyanate of formula **Vla** (1.1 eq) was added. The reaction was stirred until the starting material disappeared on thin-layer chromatography. Water in an amount of about 10 parts by volume of DMF was added and the precipitate obtained was filtered and washed thoroughly with water. In case that no precipitate was formed, the mixture was extracted three times with EtOAc and then, the organic phases were washed twice with brine, dried over anhydrous sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

15

METHOD 2: Corresponds to the method 2 described for the preparation of compounds of formula **XI**, using as starting materials an amine of formula **II** and an acyl chloride of formula **Vlb**.

- 5 METHOD 3: To a 0.1 M solution of an amine of formula **II** (1 eq) in dried DMF, carbonyldiimidazole (1.1 eq) was added at room temperature. The reaction was stirred until the starting material disappeared on thin-layer chromatography. Then, an amine of formula **Vlc** (1.5 eq) and triethylamine (1.5 eq) were added at room temperature. The reaction was stirred until the
- 10 starting material disappeared on thin-layer chromatography. Water in an amount of about 10 parts by volume of DMF was added and the precipitate obtained was filtered and washed thoroughly with water. In case that no precipitate was formed, the mixture was extracted three times with EtOAc and then, the organic phases were washed twice with brine, dried over anhydrous
- 15 sodium sulfate, filtered and concentrated at reduced pressure. If necessary, the obtained product was purified by column chromatography on silica gel.

TABLE 5

Ex.	Name	Starting materials	HPLC-ESI-MS
la_1	1-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(4-nitrophenyl)urea	II_1 and 4-nitrophenyl isocyanate (VIa_1)	rt: 4.691 m/z: 565
la_2	1-(3-Cyanophenyl)-3-[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]urea	II_1 and 3-cyanophenyl isocyanate (VIa_2)	rt: 5.353 m/z: 545
la_3	1-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(3-methoxyphenyl)urea	II_1 and 3-methoxyphenyl isocyanate (VIa_3)	rt: 5.838 m/z: 550
la_4	1-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(3-nitrophenyl)urea	II_1 and 3-nitrophenyl isocyanate (VIa_4)	rt: 6.054 m/z: 565
la_5	1-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-(5-methyl-2-trifluoromethylfuran-3-yl)urea	II_1 and 5-methyl-2-(trifluoromethyl)-3-furyl isocyanate (VIa_5)	rt: 6.580 m/z: 592
la_6	1-(6-Fluoro-4 <i>H</i> -benzo[1,3]dioxin-8-yl)-3-[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]urea	II_1 and 6-fluoro-4 <i>H</i> -1,3-benzodioxin-8-yl isocyanate (VIa_6)	rt: 6.093 m/z: 596



Ex.	Name	Starting materials	HPLC-ESI-MS
la_7	1-Ethyl-3-[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]urea	II_1 and ethyl isocyanate (VIa_7)	rt: 4.836 m/z: 472
la_8	3-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-1,1-dimethylurea	II_1 and dimethylcarbamoyl chloride (VIb_1)	rt: 4.787 m/z: 472
la_9	1-[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]-3-isopropylurea	II_1 and isopropyl isocyanate (VIa_8)	rt: 5.157 m/z: 486
la_10	<i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]morpholine-4-carboxamide	II_1 and 4-morpholinocarbonyl chloride (VIb_2)	rt: 4.753 m/z: 514
la_11	[2-(4-{2-Fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]urea	II_1 and ammonium chloride (VIc_1)	rt: 4.369 m/z: 444

#### Examples of compounds of formula Ib:

Compounds of formula **Ib** shown in table 6 were obtained following the method 2 described for the preparation of compounds of formula **XI**, using an amine of formula **IV** and chloroformate of formula **VIIa** as starting materials.

TABLE 6

Ex.	Name	Starting materials	HPLC-ESI-MS
Ib_1	Ethyl <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]carbamate	II_1 and ethyl chloroformate (VIIa_1)	rt: 5.432 m/z: 473
Ib_2	Vinyl <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}-piperazin-1-yl)-2-oxoethyl]carbamate	II_1 and vinyl chloroformate (VIIa_2)	rt: 5.632 m/z: 471
Ib_3	4-Fluorophenyl <i>N</i> -[2-(4-{2-fluoro-4-[5-(isoxazol-3-ylaminomethyl)isoxazol-3-yl]phenyl}piperazin-1-yl)-2-oxoethyl]carbamate	II_1 and 4-fluorophenyl chloroformate (VIIa_3)	rt: 6.221 m/z: 539

#### 10 Tests of antimicrobial activity

In order to assess the antimicrobial activity of the compounds of the present invention a method of microdilution in microtiter plate was used. The compounds were diluted in a nutritious medium and, subsequently, distributed by two-fold serial dilutions in 96 well plates. Then, plates were inoculated with a bacterial suspension. After incubation for 24 h at 35 °C the minimum



inhibitory concentration (MIC) of the drug in  $\mu\text{g/mL}$  was determined as the lowest concentration of compound which inhibits the growth of the bacterium. Results included in table 7 illustrate the antimicrobial activity of some of the compounds of the present invention in comparison with thus obtained with two compounds (linezolid and eperezolid) of a known antimicrobial activity. The antimicrobial activity of the compound *versus Streptococcus faecalis* (BCM-010, strain designation as for SALVAT collection) and *Staphylococcus aureus* (BCM-012, strain designation as for SALVAT collection), respectively, is shown in the different columns.

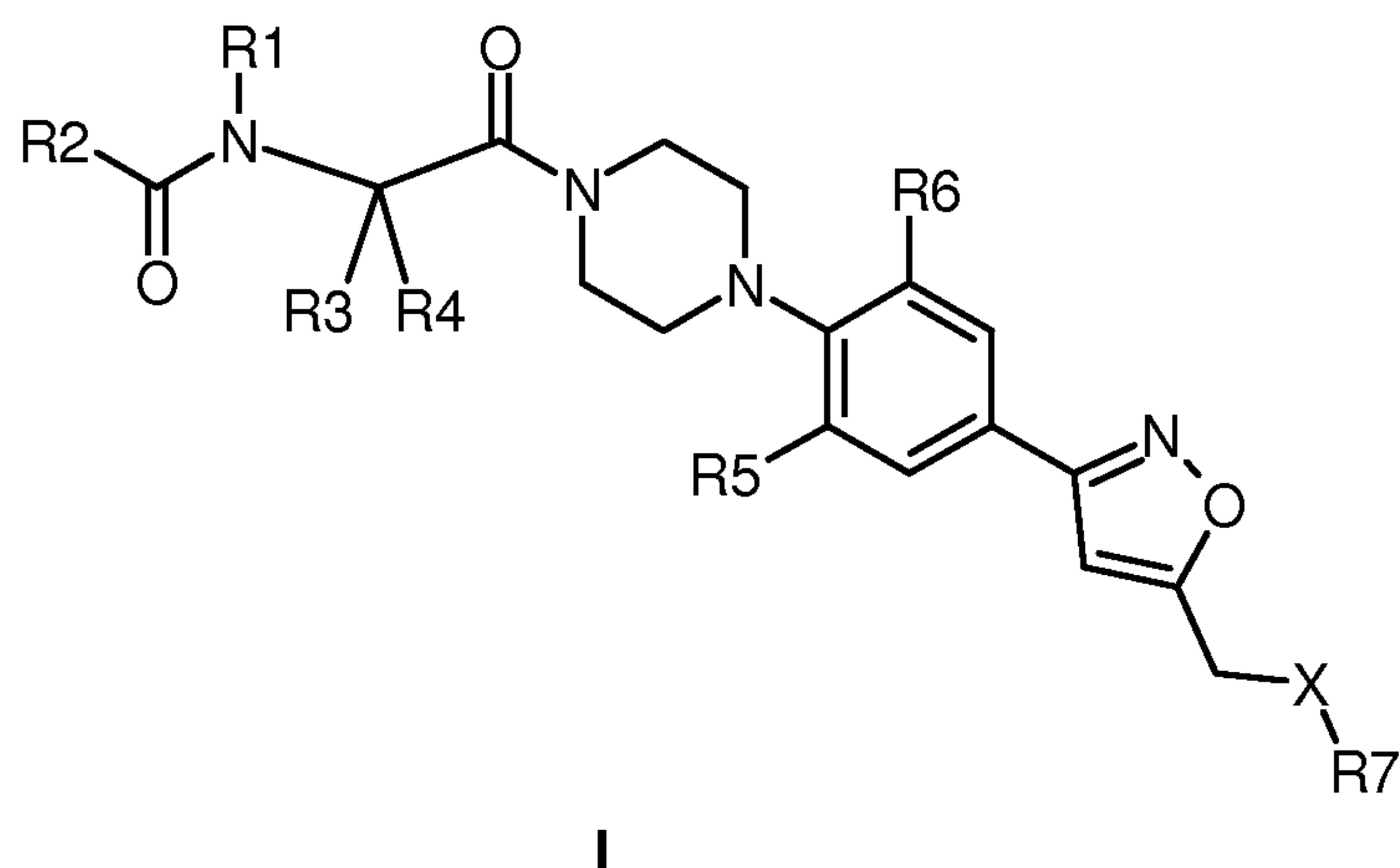
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TABLE 7

COMPOUND	BCM-010 MIC ( $\mu\text{g/mL}$ )	BCM-012 MIC ( $\mu\text{g/mL}$ )
Linezolid	4	2
Eperezolid	4	2
I_1	2	1
I_15	0.25-0.5	0.25-0.5
I_32	0.25-0.5	0.25-0.5
I_51	1	1
I_58	0.5-1	0.25
I_82	2	2
I_84	2	1
I_104	0.125-0.5	0.25-0.5
I_117	1	1
I_152	2	2
I_153	2	2
I_155	2	2
I_160	0.25	0.25
I_170	4	4
I_171	1	2
I_192	0.5	0.5
I_213	1	1
Ia_1	2	1

## CLAIMS

1. A compound of general formula I,



its stereoisomers and mixtures thereof, its polymorphs and mixtures thereof,  
 5 *N*-oxides when there are oxidable nitrogen atoms, and the pharmaceutically acceptable solvates and addition salts of all of them, wherein:

X represents -O-, -NH-, -S-, -NHC(=O)- or -NHC(=S)-;

10 R1 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups Ra;

R2 represents -H, -OR<sub>b</sub>, -NR<sub>b</sub>R<sub>c</sub>, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl,  
 15 -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, or -Cy<sub>1</sub> optionally substituted with one or more groups R<sub>d</sub> or R<sub>e</sub>, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups R<sub>d</sub> and/or one group R<sub>f</sub>;

R3 represents R1 or -Cy<sub>2</sub> optionally substituted with one or more groups Ra  
 20 or R<sub>c</sub>;

R4 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted by one or more halogen atoms;

- 5 alternatively, R3 and R4 may form together a 3- to 7-membered monocyclic ring, partially unsaturated, saturated or aromatic, containing from one to three heteroatoms independently selected from O, S and N, optionally substituted at any available position by one or more substituents R<sub>c</sub> or halogen atoms;

- 10 R5 and R6 independently represent -H or halogen;

R7 represents R4 or heteroaryl optionally substituted with one or more groups R<sub>c</sub> or halogen atoms, wherein heteroaryl represents a C- or N- radical of an aromatic 5- or 6-membered monocyclic ring containing from one to three

- 15 heteroatoms independently selected from O, S and N;

each R<sub>a</sub> independently represents halogen, =O, -OR<sub>c</sub>, -OC(=O)R<sub>c</sub>, =CR<sub>c</sub>R<sub>c</sub>, -CN, -C(=O)R<sub>c</sub>, -C(=O)OR<sub>c</sub>, -C(=O)NR<sub>c</sub>R<sub>c</sub>, -NO<sub>2</sub>, -NR<sub>c</sub>R<sub>c</sub>, -NR<sub>c</sub>C(=O)R<sub>c</sub>, -NR<sub>c</sub>C(=O)OR<sub>c</sub> or -NR<sub>c</sub>C(=O)NR<sub>c</sub>R<sub>c</sub>;

20

R<sub>b</sub> represents -H, R<sub>g</sub>, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or more groups R<sub>a</sub> and/or one group R<sub>g</sub>;

- 25 each R<sub>c</sub> independently represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted by one or more halogen atoms;

each R<sub>d</sub> independently represents halogen, =CR<sub>a</sub>R<sub>c</sub>, =CR<sub>c</sub>R<sub>c</sub>, -CN, -C(=O)Re', -C(=O)ORe', -C(=O)NRe'Rh', -C(=O)SRe', -C(=NRh')NRe'Rh', -C(=NRe')NRh'Rh', -C(=S)ORe', -C(=S)SRe', -ORe', =O, -OC(=O)Re', -OC(=O)NRe'Rh', -OC(=S)Re', -O-N=O, -OSO<sub>2</sub>Re, -NRe'Rh', =NRe', =N-CN,

30



=N-ORe', -N<sup>+</sup>Re'Rh'Rh', -N=NRe', -NRh'-NRe'Re', -NRe'-NRe'Rh', -N<sub>3</sub>, -N=O, -NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re', -NRh'C(=O)ORe, -NRe'C(=O)ORh, -NRh'C(=O)NReRh', -NRe'C(=O)NRhRh', -NRe'C(=O)NRh'NRh'Rh', -NRh'C(=O)NRe'NRh'Rh',  
 5 -NRh'C(=O)NRh'NRe'Rh', -NRe'SO<sub>2</sub>Rh', -NRh'SO<sub>2</sub>Re', -SRe', -SORE', -SO<sub>2</sub>Re, -SO<sub>2</sub>NRe'Rh' or -SO<sub>2</sub>ORe';

each Re independently represents Rf or -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may  
 10 be optionally substituted with one or more groups Ra and/or one group Rg;

each Re' independently represents -H or -Re;

each Rf independently represents -Cy1 optionally substituted with one or more  
 15 groups Ra or Rh;

each Rg independently represents -Cy1 optionally substituted with one or more groups Ra or Rc;

20 each Rh independently represents -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, all of them optionally substituted with one or more groups Ra;

each Rh' independently represents -H or -Rh;

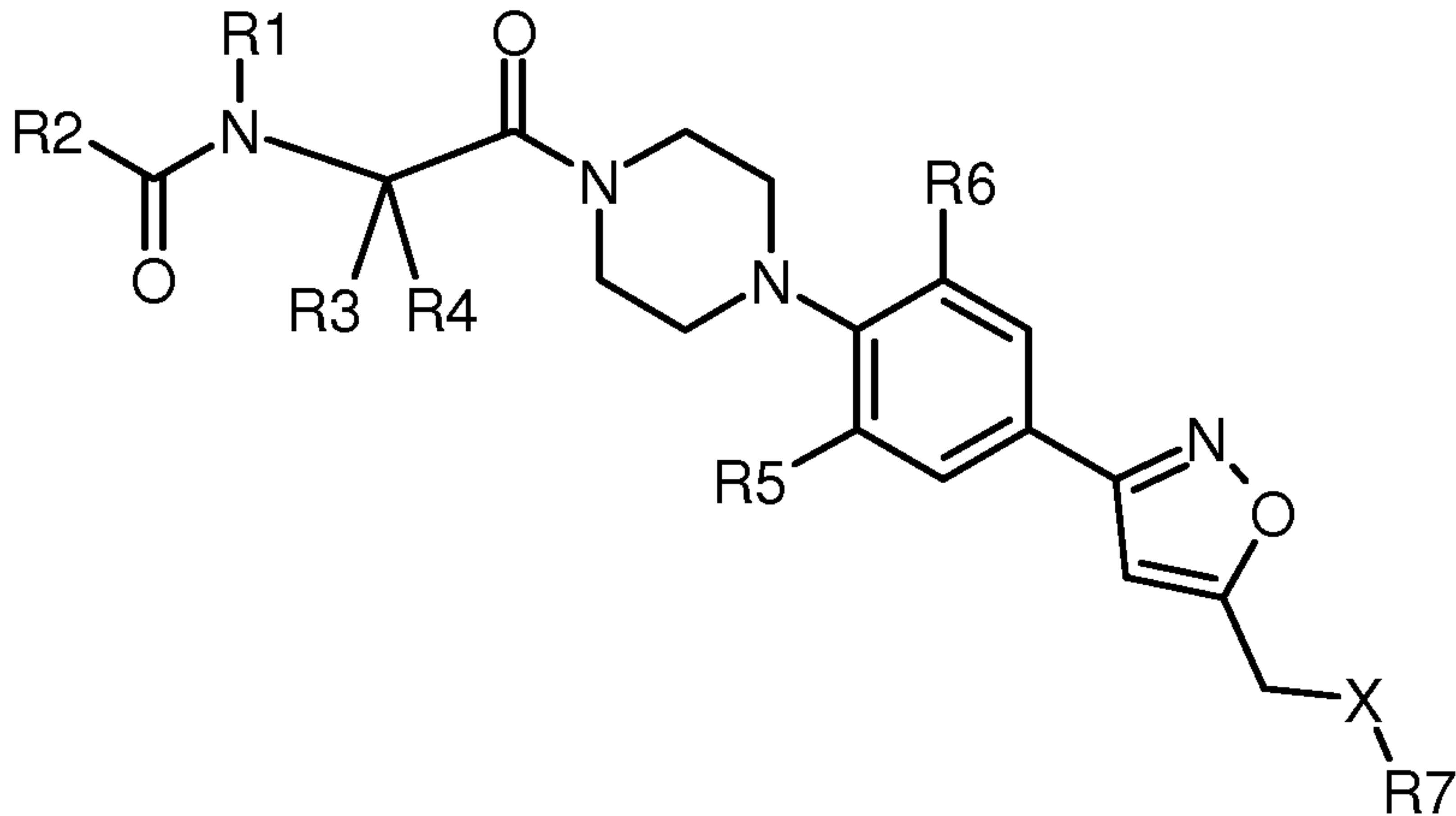
25 Cy1 represents a C- or N- radical of a 3- to 7-membered monocyclic or 6- to 10-membered bicyclic ring system, partially unsaturated, saturated or aromatic, containing from one to three heteroatoms independently selected from O, S and N; and

30 Cy2 represents a C- or N- radical of a 3- to 7-membered monocyclic ring, partially unsaturated, saturated or aromatic, containing from one to three heteroatoms independently selected from O, S and N.

2. The compound according to claim 1, wherein R1 represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more groups Ra.
- 5 3. The compound according to claim 2, wherein R1 represents -H.
4. The compound according to any of claims 1 to 3, wherein R2 represents -H, -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally substituted with one or  
10 more groups Rd and/or one group Rf.
5. The compound according to any of claims 1 to 3, wherein R2 represents -Cy1 optionally substituted with one or more groups independently selected from -Re, halogen, =CRaRc, =CRcRc, -CN, -C(=O)Re', -C(=O)ORe',  
15 -C(=O)NRe'Rh', =O, -ORe', -OC(=O)Re', -NRe'Rh', =NRe', -N<sup>+</sup>Re'Rh'Rh', -N<sub>3</sub>, -NRh'ORe', -NRe'ORh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re', -NRe'C(=O)ORh', -NRh'C(=O)ORe', -NRe'C(=O)NRe'Rh' or -NRh'C(=O)NRe'Rh'.
- 20 6. The compound according to claim 5, wherein Cy1 is selected from the group consisting of phenyl, a C- or N- radical of an aromatic 5- or 6-membered monocyclic ring containing from one to three heteroatoms independently selected from O, S and N, and a C- or N- radical of an aromatic bicyclic ring system containing from one to three heteroatoms independently selected from  
25 O, S and N, that comprises a 5- or 6-membered ring fused with a 5- or 6-membered ring, wherein all previously ring systems may be optionally substituted with -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl, -(C<sub>2</sub>-C<sub>4</sub>)alkynyl, halogen, -CN, -C(=O)Re', =O, -ORe', -NRe'Rh', -NO<sub>2</sub>, -NRe'C(=O)Rh', -NRh'C(=O)Re', wherein -(C<sub>1</sub>-C<sub>4</sub>)alkyl, -(C<sub>2</sub>-C<sub>4</sub>)alkenyl or -(C<sub>2</sub>-C<sub>4</sub>)alkynyl may be optionally  
30 substituted with one or more groups Ra.



7. The compound according to any of claims 1 to 6, wherein R<sub>3</sub> represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more R<sub>a</sub> and R<sub>4</sub> represents -H or -(C<sub>1</sub>-C<sub>4</sub>)alkyl optionally substituted with one or more halogen atoms.
- 5 8. The compound according to any of claims 1 to 7, wherein R<sub>5</sub> represents -F and R<sub>6</sub> represents -H or -F.
9. The compound according to any of claims 1 to 8, wherein X represents -NH- and R<sub>7</sub> represents heteroaryl optionally substituted with one or more
- 10 groups R<sub>c</sub> or halogen atoms, wherein heteroaryl represents a C- or N- radical of an aromatic 5- or 6-membered monocyclic ring containing from one to three heteroatoms independently selected from O, S and N.
10. A pharmaceutical composition comprising a therapeutically effective
- 15 amount of a compound as defined in any of the claims 1 to 9 and appropriate amounts of one or more pharmaceutically acceptable excipients.
11. Use of a compound as defined in any of the claims 1 to 9 for the manufacture of a medicament for the treatment and/or prevention of bacterial
- 20 infections in an animal including a human.
12. Use according to claim 11, wherein the medicament is administered topically or parenterally.



(I)