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(57) **Abrégé/Abstract:**

The invention relates to novel amine derivatives and the use thereof as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.



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(57) Abstract: The invention relates to novel amine derivatives and the use thereof as active ingredients in the preparation of pharmaceutical compositions. The invention also concerns related aspects including processes for the preparation of the compounds, pharmaceutical compositions containing one or more of those compounds and especially their use as inhibitors of renin.



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New amines

The invention relates to novel compounds of the formula (I). The invention also concerns
5 related aspects including processes for the preparation of the compounds, pharmaceutical
compositions containing one or more compounds of formula (I) and especially their use as
renin inhibitors in cardiovascular events and renal insufficiency.

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is
generated by a two-step mechanism. The highly specific enzyme renin cleaves
10 angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the
less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least
two receptor subtypes called AT₁ and AT₂. Whereas AT₁ seems to transmit most of the
known functions of Ang II, the role of AT₂ is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular
15 diseases. ACE inhibitors and AT₁ blockers have been accepted to treat hypertension
(Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human
hypertension", in Birkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier
Science Publishing Co, **1986**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, 5, 247S). In
addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney*
20 *International*, **1994**, 45, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, 45, S156), in
the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**,
28, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, 84 (Suppl. 3A), 83) and myocardial
infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, 327, 669).

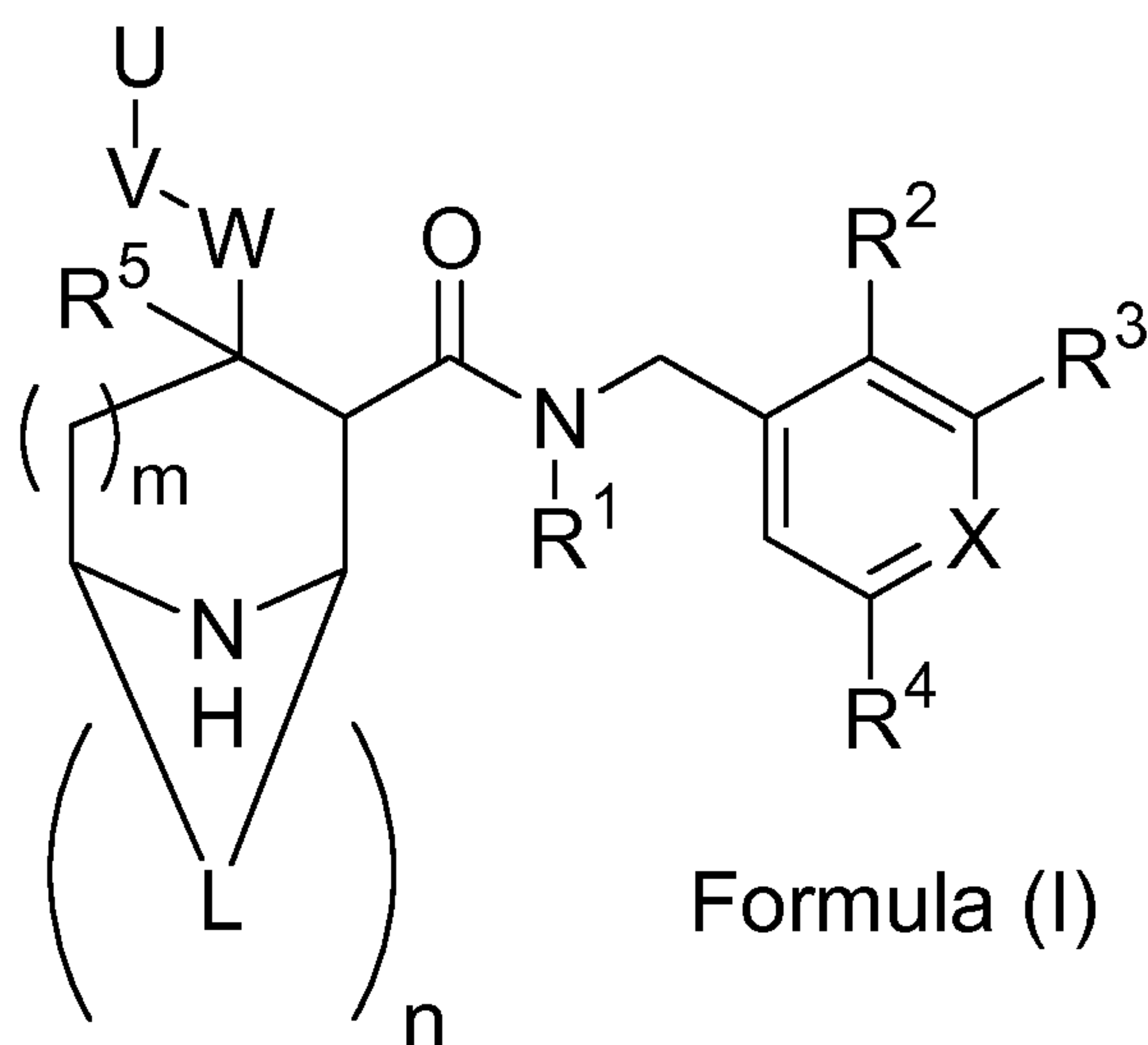
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D.,
25 *Cardiovasc. Drugs*, **1995**, 9, 645). The only substrate known for renin is angiotensinogen,
which can only be processed (under physiological conditions) by renin. In contrast, ACE
can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine
protease (Husain A., *J. Hypertens.*, **1993**, 11, 1155). In patients inhibition of ACE thus
leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening

angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, 117, 234). ACE inhibitors do not inhibit Chymase. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT₁ receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT₂) to Ang II, whose concentration is significantly increased by the blockade of AT₁ receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT₁ blockers with regard to efficacy in blocking the RAS and in safety aspects.

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, 12, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, 122, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, 9, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, 7, 493; Mealy N. E., *Drugs of the Future*, **2001**, 26, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, 6, 127; Patent Application WO 97/09311; Märki H. P. *et al.*, *Il Farmaco*, **2001**, 56, 21). However, the development status of these compounds is not known.

The present invention relates to renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of formula (I) which have a long duration of action and which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated leading to pathophysiologically altered local functions such as renal, cardiac and vascular remodelling, atherosclerosis, and possibly restenosis. So, the present invention describes these non-peptidic renin inhibitors of formula (I).

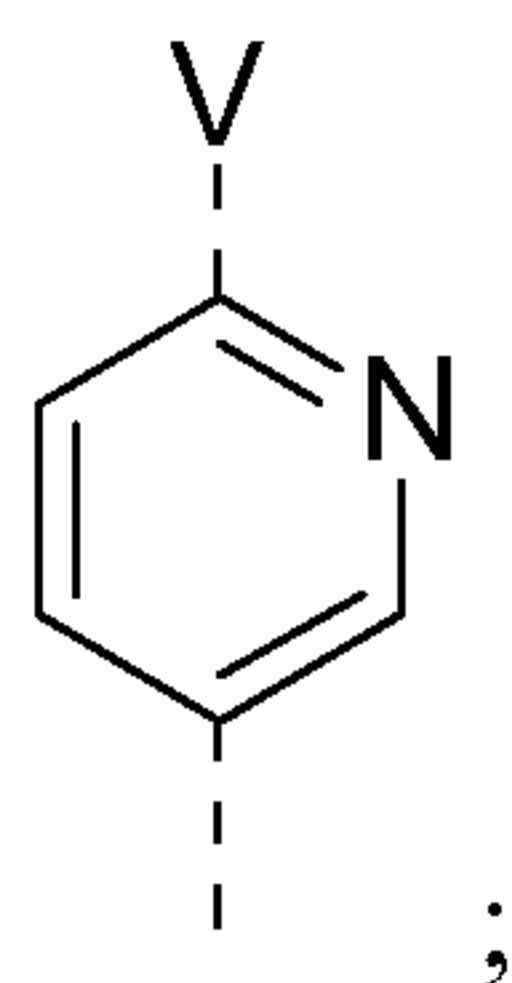
In particular, the present invention relates to novel compounds of the formula (I)



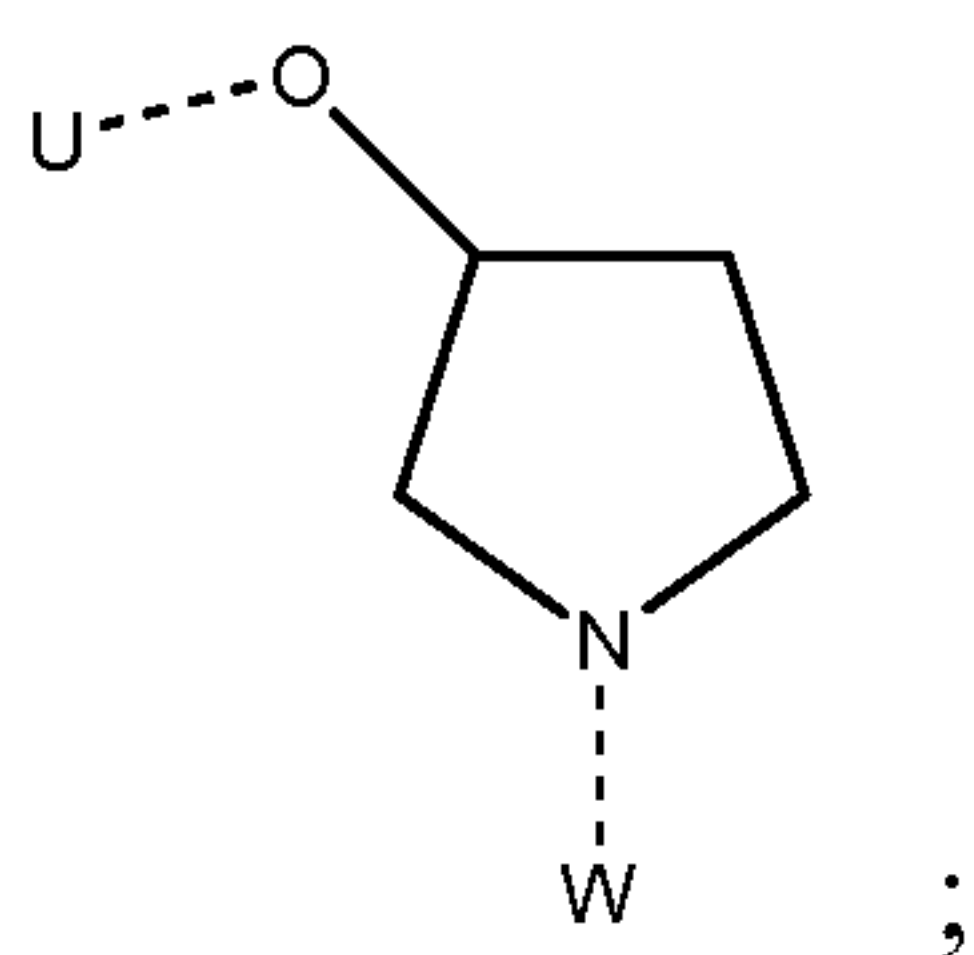
wherein

X represents CH, N, or N⁺-O⁻;

W represents a *para*-substituted phenyl, a *para*-substituted pyridinyl, or a thiazolyl, such as especially *para*-substituted phenyl or

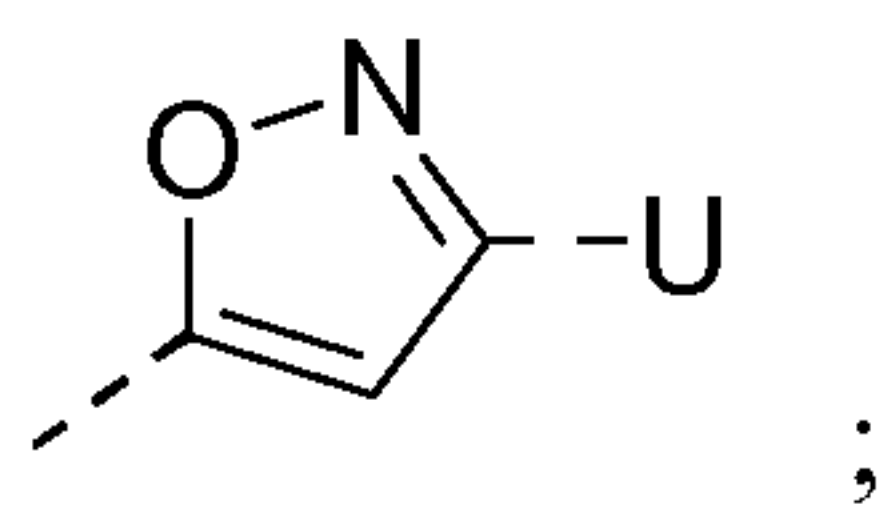


V represents -CH₂CH₂CH₂-, -CH₂CH₂-A-, -CH₂-A-CH₂-, -A-CH₂CH₂-, -CH₂CH₂CH₂CH₂-,
 , -A-CH₂CH₂CH₂-, -CH₂-A-CH₂CH₂-, -CH₂CH₂-A-CH₂-, -CH₂CH₂CH₂-A-, -A-CH₂CH₂-
 B- (preferred), -CH₂CH₂CH₂CH₂CH₂-, -A-CH₂CH₂CH₂CH₂-, -CH₂-A-CH₂CH₂CH₂-,
 -CH₂CH₂-A-CH₂CH₂-, -CH₂CH₂CH₂-A-CH₂-, -CH₂CH₂CH₂CH₂-A-, -A-CH₂CH₂CH₂-B-,
 -CH₂-A-CH₂CH₂-B-, -A-CH₂CH₂-B-CH₂-, -A-CH₂CH₂CH₂-B-CH₂-, -CH₂-A-
 CH₂CH₂CH₂-B-, or -O-CH₂-Q- (also preferred), wherein Q is bound to the group U of
 formula (I), or (also preferably) V represents a pyrrolidinyl of the formula:



U represents unsubstituted aryl, especially phenyl; mono-, di-, tri- or tetra-substituted aryl (especially mono- di-, tri-, or tetra-substituted phenyl), wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl (such as especially methyl),
 5 -CF₃, halogen, and hydroxy-C₁₋₇-alkyl; or five-membered heteroaryl with two heteroatoms independently selected from nitrogen, oxygen and sulphur (preferably pyrazolyl or isoxazolyl), wherein said heteroaryl radical is optionally mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, -CF₃, -OCF₃, and halogen;

10 Q represents a five-membered heteroaryl with two or three heteroatoms independently selected from O and N, preferably an isoxazolyl, especially an isoxazolyl that is connected to the rest of the molecule of formula (I) as follows:



L represents -CH₂-CH₂-, -CH₂-CH(R⁶)-CH₂-, -CH₂-N(R⁷)-CH₂-, -CH₂-O-CH₂-, or -CH₂-S-
 15 CH₂-;

A and B represent independently from each others -O- or -S-;

R¹ represents C₁₋₇-alkyl or cycloalkyl, preferably cycloalkyl such as especially cyclopropyl;

R² represents halogen or C₁₋₇-alkyl, preferably chloro or methyl;

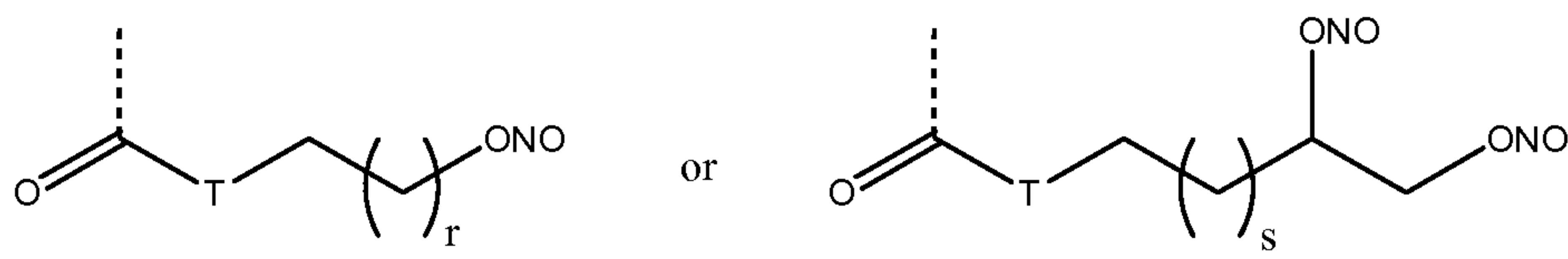
20 R³ represents hydrogen, halogen, C₁₋₇-alkyl (such as especially methyl), C₁₋₇-alkoxy, or -CF₃;

R^4 represents hydrogen; C_{1-7} -alkyl-O-(CH_2)₀₋₄-CH₂-; CF_3 -O-(CH_2)₀₋₄-CH₂-; R'_2N -(CH_2)₀₋₄-CH₂-, wherein R' is independently selected from the group consisting of hydrogen, C_{1-7} -alkyl (optionally but preferably substituted by one to three fluorine), cyclopropyl (optionally substituted by one to three fluorine), cyclopropyl- C_{1-7} -alkyl (optionally but preferably substituted by one to three fluorine), and -C(=O)- R'' wherein R'' is C_{1-4} -alkyl, C_{1-4} -alkoxy, -CF₃, -CH₂-CF₃, or cyclopropyl; or R^{13} -C(=O)-(O)₀₋₁-(CH₂)₀₋₄-, wherein R^{13} is C_{1-4} -alkyl, C_{1-4} -alkoxy, or cyclopropyl; wherein R' and R'' preferably do not both simultaneously represent hydrogen;

R^5 represents hydroxy, C_{1-7} -alkoxy, hydroxy- C_{1-7} -alkyl, dihydroxy- C_{1-7} -alkyl, C_{1-7} -alkoxy- C_{1-7} -alkyl, C_{1-7} -alkoxy- C_{1-7} -alkoxy- C_{1-7} -alkyl, hydroxy- C_{1-7} -alkoxy- C_{1-7} -alkyl, carbamoyl- C_{1-7} -alkoxy, or C_{1-7} -alkyl-carbonyloxy;

R^6 represents -H, -CH₂OR⁹, -CH₂NR⁸R⁹, -CH₂NR⁸COR⁹, -CH₂NR⁸SO₂R⁹, -CO₂R⁹, -CH₂OCONR⁸R⁹, -CONR⁸R⁹, -CH₂NR⁸CONR⁸R⁹, -CH₂SO₂NR⁸R⁹, -CH₂SR⁹, -CH₂SOR⁹, or -CH₂SO₂R⁹;

R^7 represents -R⁹, -COR⁹, -COOR¹¹, -CONR⁸R⁹, -C(NR⁸)NR⁸R⁹, -CSNR⁸R⁹, -SO₂R⁹, or -SO₂NR⁸R⁹; or R^7 represents a radical of the formula:



wherein T represents -CH₂-, -NH- or -O-, r is an integer from 1 to 6 and s is an integer from 1 to 4;

R^8 and $R^{8'}$ independently represent hydrogen, C_{1-7} -alkyl, C_{2-7} -alkenyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein C_{1-7} -alkyl, cycloalkyl, and cycloalkyl- C_{1-7} -alkyl can be substituted by one, two, or three halogens;

R^9 represents hydrogen, C_{1-7} -alkyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein C_{1-7} -alkyl, cycloalkyl, and cycloalkyl- C_{1-7} -alkyl may be mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, hydroxy, -OCOR¹², -COOR¹², C_{1-7} -alkoxy, cyano, SO₂R¹², -CONR¹²R^{12'}, morpholin-4-yl-CO-, ((4-

C₁₋₇-alkyl)piperazin-1-yl)-CO-, -NHC(NH)NH₂, -NR¹⁰R^{10'}, and C₁₋₇-alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp³-hybridized;

R¹⁰ and R^{10'} independently represent hydrogen, C₁₋₇-alkyl, cycloalkyl, cycloalkyl-C₁₋₇-alkyl, hydroxy-C₁₋₇-alkyl, -COOR⁸, or -CONH₂;

R¹¹ represents halogen, C₁₋₇-alkyl, C₁₋₇-alkoxy, -CF₃, or hydrogen;

R¹² and R^{12'} independently represent hydrogen, C₁₋₇-alkyl, C₂₋₇-alkenyl, cycloalkyl, or cycloalkyl-C₁₋₇-alkyl, wherein C₁₋₇-alkyl, cycloalkyl, and cycloalkyl-C₁₋₇-alkyl can be substituted by one, two, or three halogens;

n represents the integer 0 or 1, especially 0; and

m represents the integer 0 or 1, especially 1, with the proviso that m represents the integer 1 if n represents the integer 1;

and salts thereof.

The general terms used hereinbefore and hereinafter preferably have, within this disclosure, the following meanings, unless otherwise indicated:

Where the plural form is used for compounds, salts, pharmaceutical compositions, diseases and the like, this is intended to mean also a single compound, salt, or the like.

Any reference to a compound of formula (I) is to be understood as referring also to salts (especially pharmaceutically acceptable salts) of a compound of formula (I), as appropriate and expedient.

The term **C₁₋₇-alkyl**, alone or in combination with other groups, means saturated, straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms, i.e. C₁₋₄-alkyl. Examples of C₁₋₇-alkyl groups are methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term **C₁₋₇-alkoxy**, alone or in combination with other groups, refers to an R-O- group, wherein R is a C₁₋₇-alkyl group. Examples of C₁₋₇-alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

5 The term **hydroxy-C₁₋₇-alkyl**, alone or in combination with other groups, refers to an HO-R group, wherein R is a C₁₋₇-alkyl group. Examples of hydroxy-C₁₋₇-alkyl groups are HO-CH₂-, HO-CH₂CH₂-, HO-CH₂CH₂CH₂- and CH₃CH(OH)-.

10 The term **C₂₋₇-alkenyl**, alone or in combination with other groups, means straight or branched chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms. Examples of C₂₋₇-alkenyl are vinyl, propenyl and butenyl.

The term **halogen** means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine. In a more preferred embodiment of the invention the term halogen means fluorine or chlorine.

15 The term **cycloalkyl**, alone or in combination with other groups, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl, preferably cyclopropyl.

The term **aryl**, alone or in combination, refers to a phenyl, naphthyl or indanyl group, preferably a phenyl group.

20 The term **sp³-hybridized** refers to a carbon atom and means that this carbon atom forms four bonds to four substituents placed in a tetragonal fashion around this carbon atom.

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, phosphorous acid, nitrous acid, citric acid, formic acid, acetic acid, oxalic acid, maleic acid, lactic acid, tartaric acid, fumaric acid, 25 benzoic acid, mandelic acid, cinnamic acid, palmoic acid, stearic acid, glutamic acid, aspartic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, *p*-toluenesulfonic acid, salicylic acid, succinic acid, trifluoroacetic acid, and the like that are non toxic to living organisms or in case the compound of formula (I) is acidic in nature

with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like. For other examples of pharmaceutically acceptable salts, reference can be made to "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

- 5 The compounds of the formula (I) may contain asymmetric carbon atoms. Substituents at a double bond or a ring may be present in cis- (= Z-) or trans (= E-) form unless indicated otherwise. The compounds of formula (I) may thus be present as mixtures of stereoisomers or preferably as pure stereoisomers. Mixtures of stereoisomers may be separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, HPLC
10 or crystallization.

Compounds of the invention also include nitrosated compounds of formula (I) that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfydryl condensation) and/or nitrogen. The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For
15 example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758, 5,703,073, 5,994,294, 6,242,432 and 6,218,417; WO 98/19672; and Oae et al., *Org. Prep. Proc. Int.*, 15(3): 165-198 (1983).

A preferred embodiment of the present invention relates to a compound of formula (I), wherein X represents N^+-O^- and R^4 represents C_{1-4} -alkoxy-C(=O)-NH-(CH₂)₀₋₄-CH₂- or
20 R^{13} -C(=O)-(O)₀₋₁-(CH₂)₀₋₄-, wherein R^{13} is C_{1-4} -alkyl, C_{1-4} -alkoxy, or cyclopropyl.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein X represents CH or N; and
 R^4 represents hydrogen; C_{1-7} -alkyl-O-(CH₂)₀₋₄-CH₂-; CF₃-O-(CH₂)₀₋₄-CH₂-; or R'₂N-(CH₂)₀₋₄-CH₂-, wherein R' is independently selected from the group consisting of
25 hydrogen, C_{1-7} -alkyl (optionally substituted by one to three fluorine), cyclopropyl (optionally substituted by one to three fluorine), cyclopropyl- C_{1-7} -alkyl (optionally substituted by one to three fluorine), and -C(=O)-R'' wherein R'' is C_{1-4} -alkyl, -CF₃, -CH₂-CF₃, or cyclopropyl.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein X represents CH or N^+-O^- .

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^7 represents $-R^9$, $-COR^9$, $-COOR^{11}$, $-CONR^8R^9$, $-C(NR^8)NR^8R^9$, $-CSNR^8R^9$,
5 $-SO_2R^9$, or $-SO_2NR^8R^9$.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein A and B both represent $-O-$.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^6 represents $-CO_2CH_3$ or $-CO_2H$.

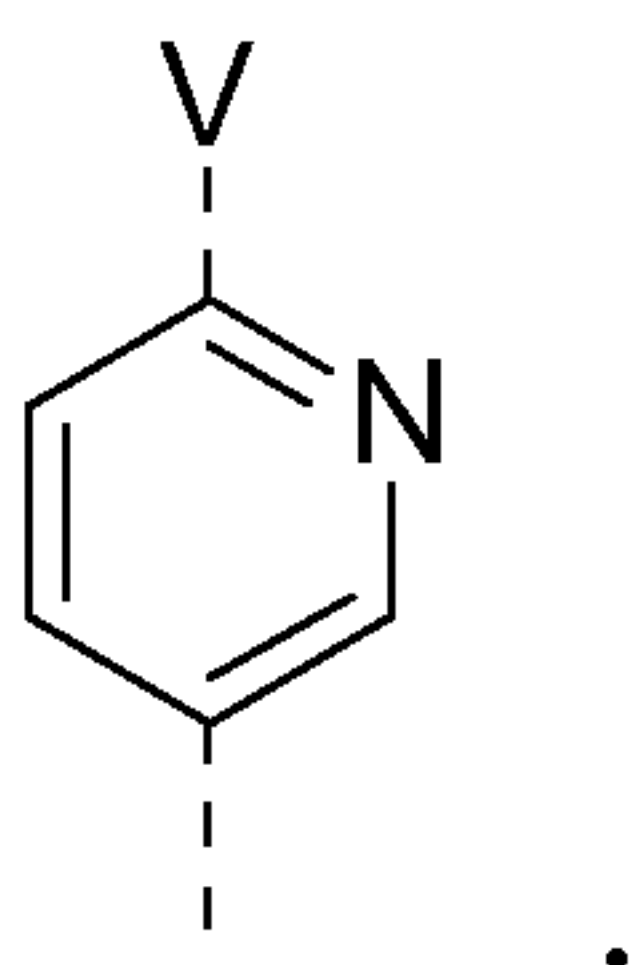
10 A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^7 represents $-H$, $-COCH_3$, $-C(NH)NH_2$, $-CONHCH_2C(CH_3)_2CONH_2$, $-CONHCH(CH_2)_2$, or $-CONHC(CH_2)_2CN$.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^7 represents $-H$.

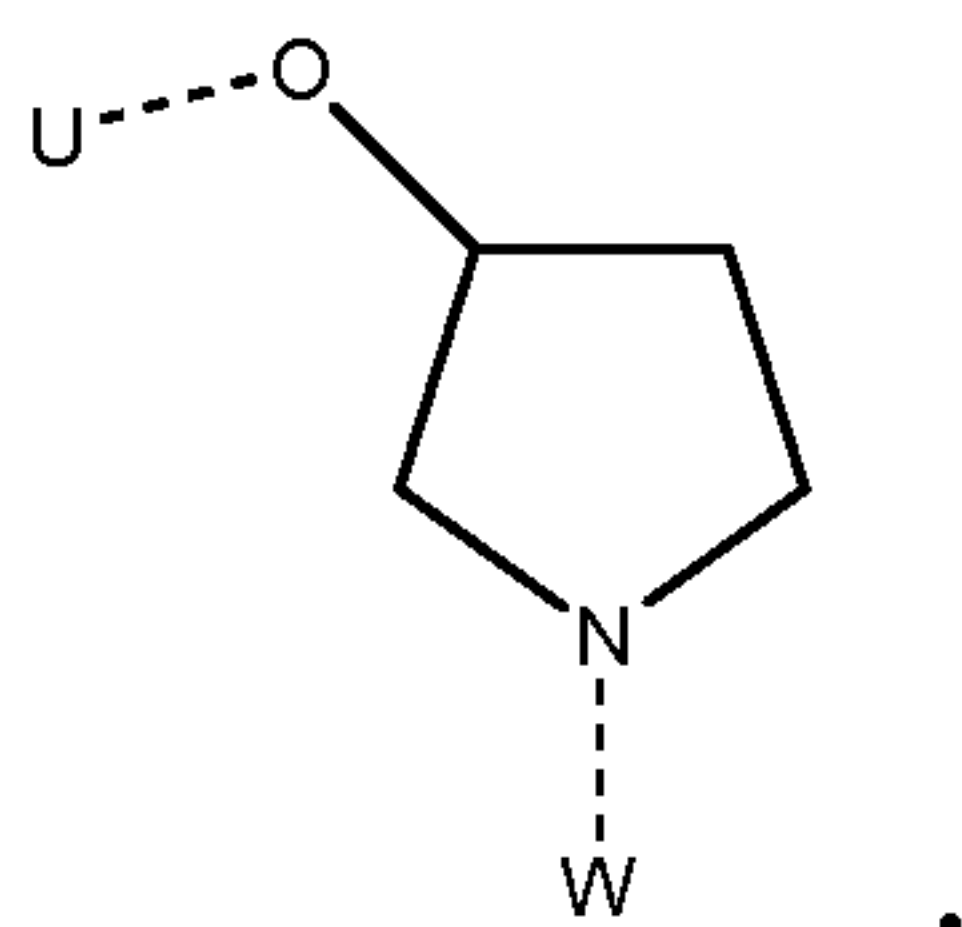
15 A preferred embodiment of the present invention relates to a compound of formula (I), wherein L represents $-CH_2-CH_2-$ or $-CH_2-NH-CH_2-$.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^1 represents cyclopropyl.

A preferred embodiment of the present invention relates to a compound of formula (I),
20 wherein W represents a *para*-substituted phenyl, or



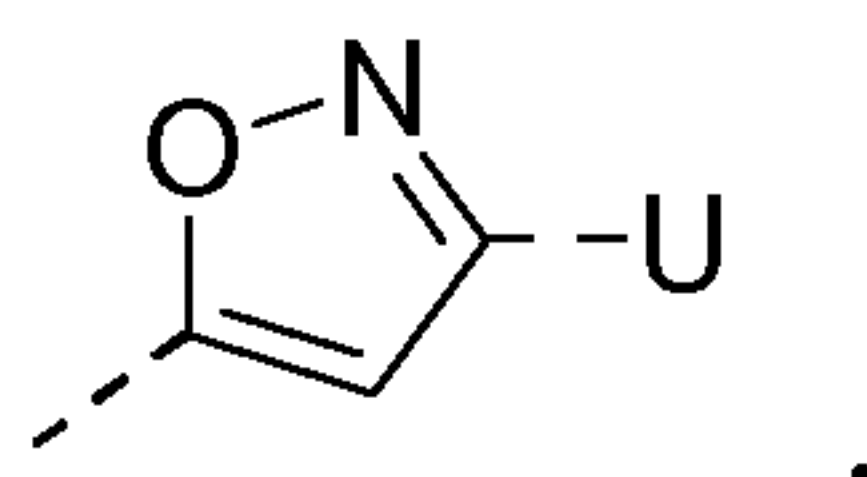
A preferred embodiment of the present invention relates to a compound of formula (I), wherein V represents -O-CH₂CH₂-O-, -O-CH₂-Q-, -CH₂-CH₂-O- wherein the -CH₂ part of -CH₂-CH₂-O- is bound to the group W of formula (I), or



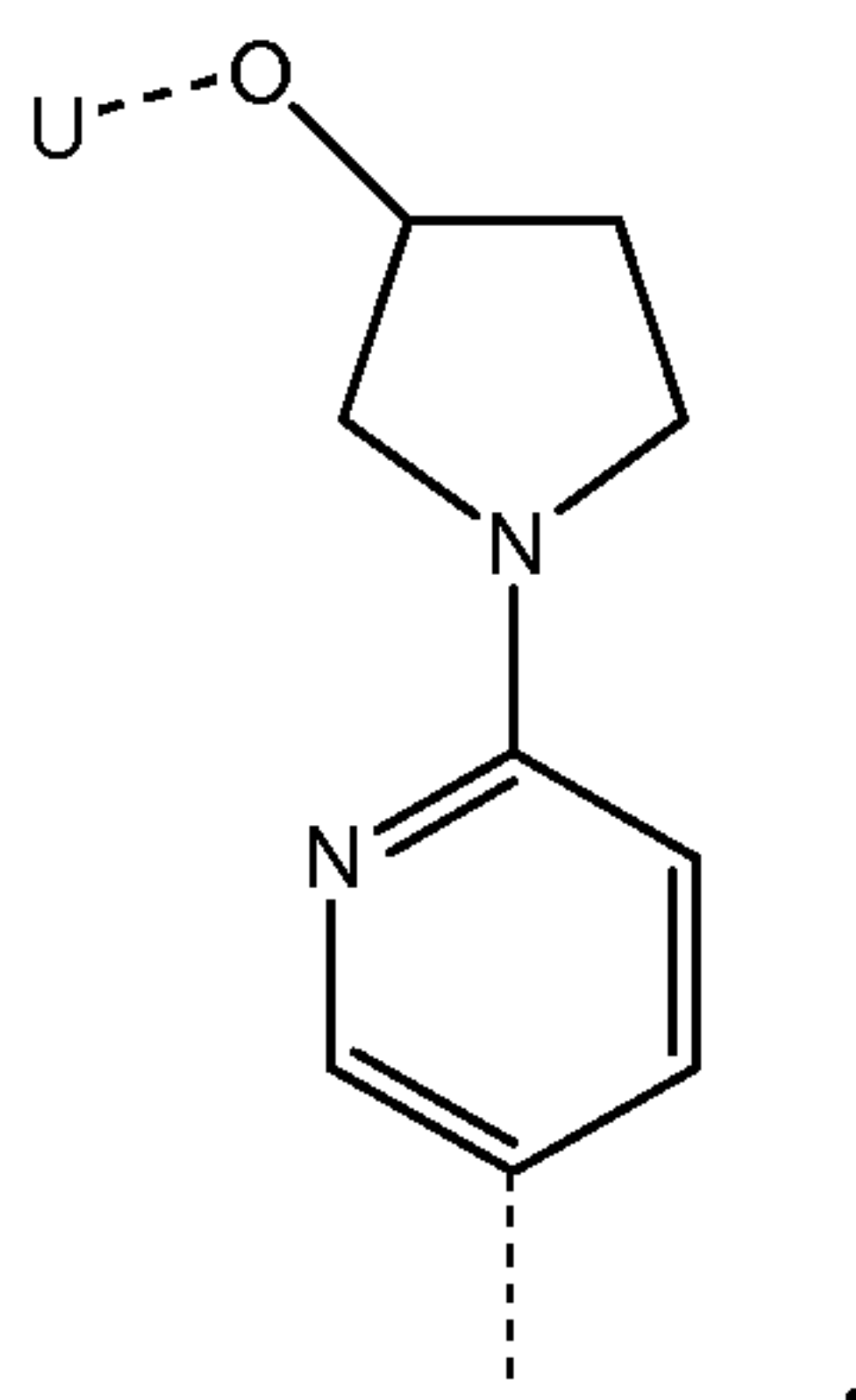
- 5 A preferred embodiment of the present invention relates to a compound of formula (I), wherein V represents -O-CH₂CH₂-O- or -O-CH₂-Q-.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein Q represents an isoxazolyl or an oxadiazolyl.

- 10 A preferred embodiment of the present invention relates to a compound of formula (I), wherein Q represents an isoxazolyl, especially an isoxazolyl that is connected to the rest of the molecule of formula (I) as follows:

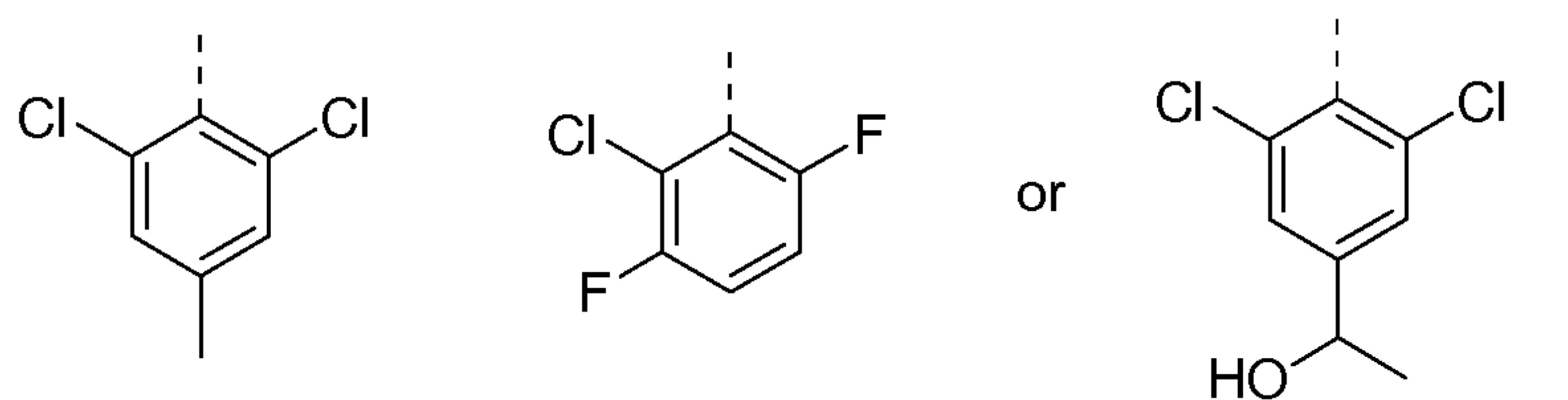


A preferred embodiment of the present invention relates to a compound of formula (I), wherein V-W represents:

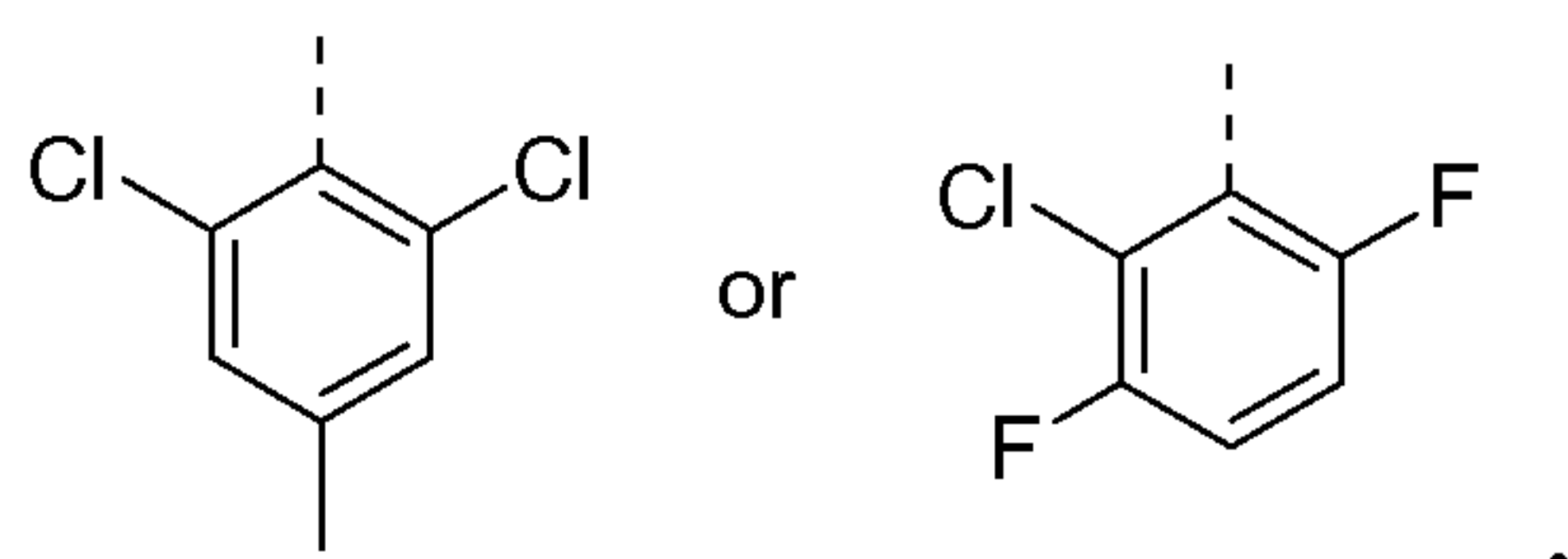


15

A preferred embodiment of the present invention relates to a compound of formula (I), wherein U represents:



A preferred embodiment of the present invention relates to a compound of formula (I), wherein U represents:



- 5 A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^2 represents Cl, and R^3 represents hydrogen.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^4 represents $\text{CH}_3\text{-O-(CH}_2\text{)}_{2-3}\text{-}$ or $\text{CH}_3\text{-C(=O)-NH-CH}_2\text{-CH}_2\text{-}$.

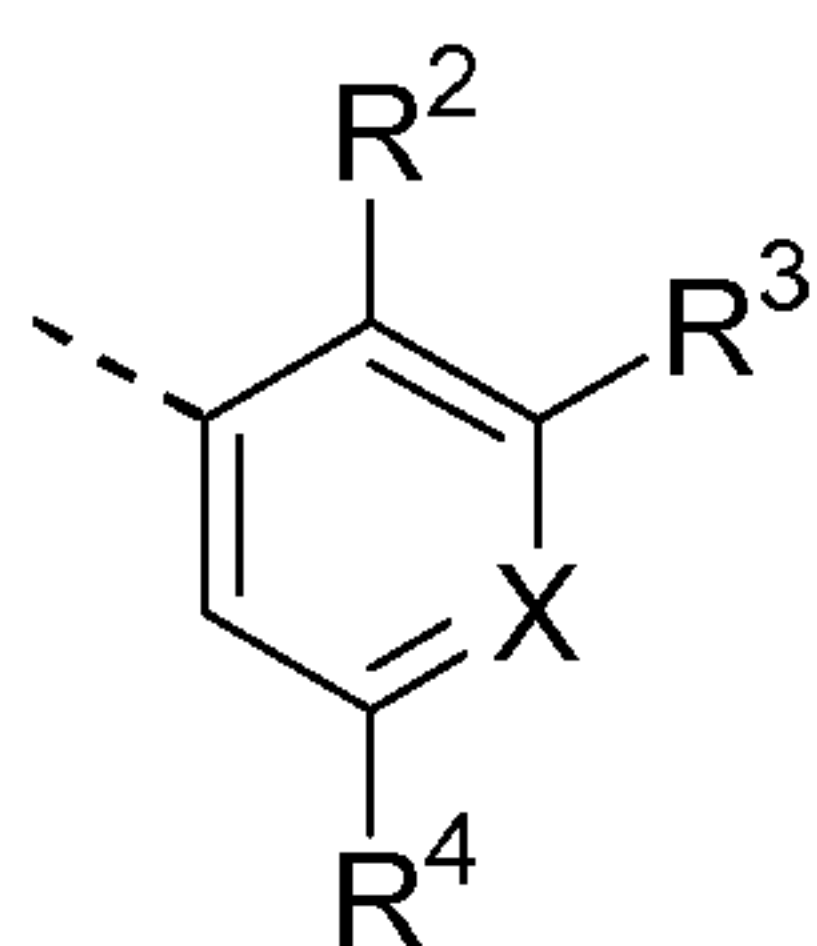
- 10 A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^4 represents $\text{-CH}_2\text{CH}_2\text{CH}_2\text{-O-CH}_3$ or $\text{-CH}_2\text{CH}_2\text{-O-CH}_3$.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^4 represents $\text{-CH}_2\text{CH}_2\text{-O-CH}_3$.

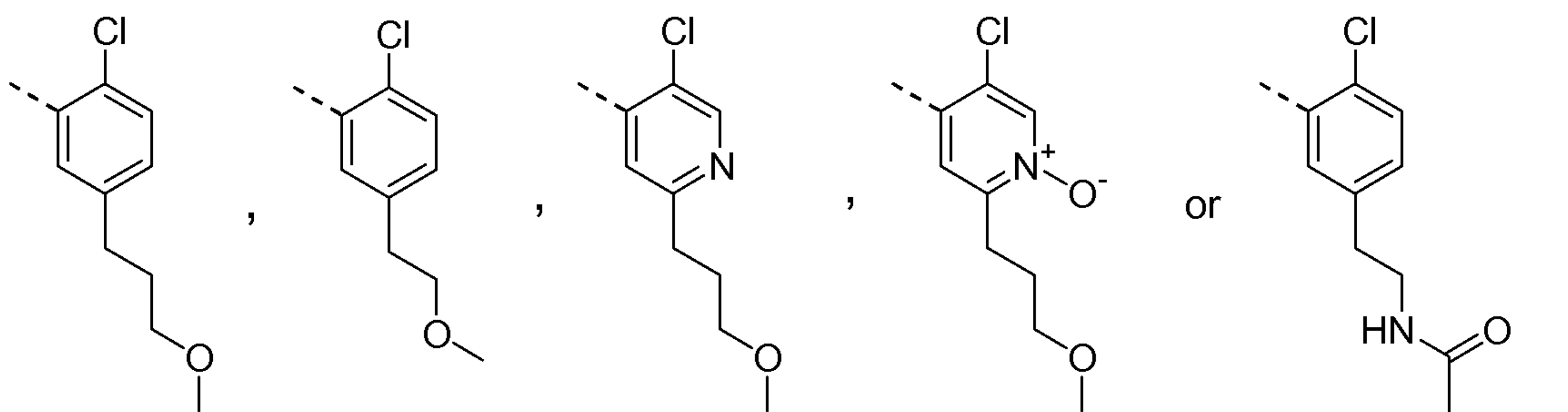
A preferred embodiment of the present invention relates to a compound of formula (I), wherein R^5 represents hydroxy.

- 15 A preferred embodiment of the present invention relates to a compound of formula (I), wherein n represents the integer 0.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein the moiety



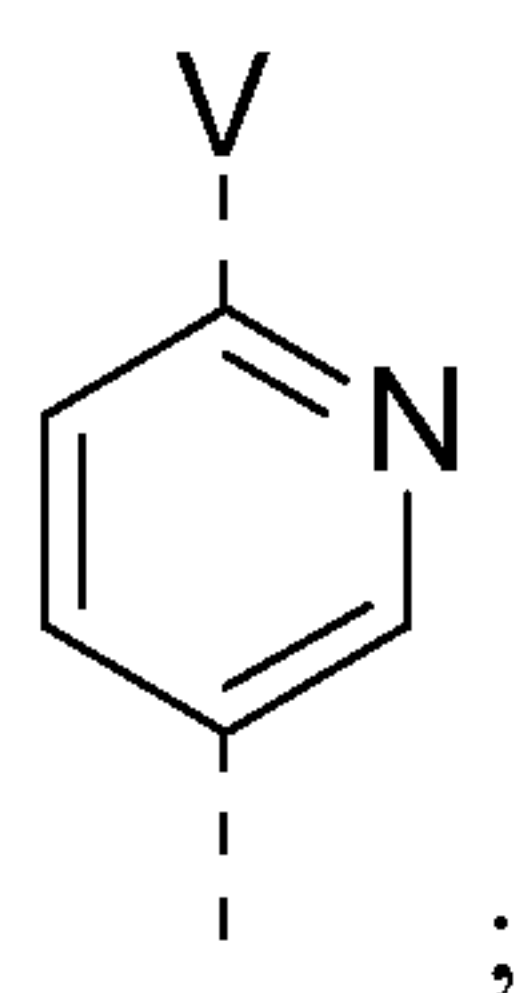
represents one of the following possibilities:



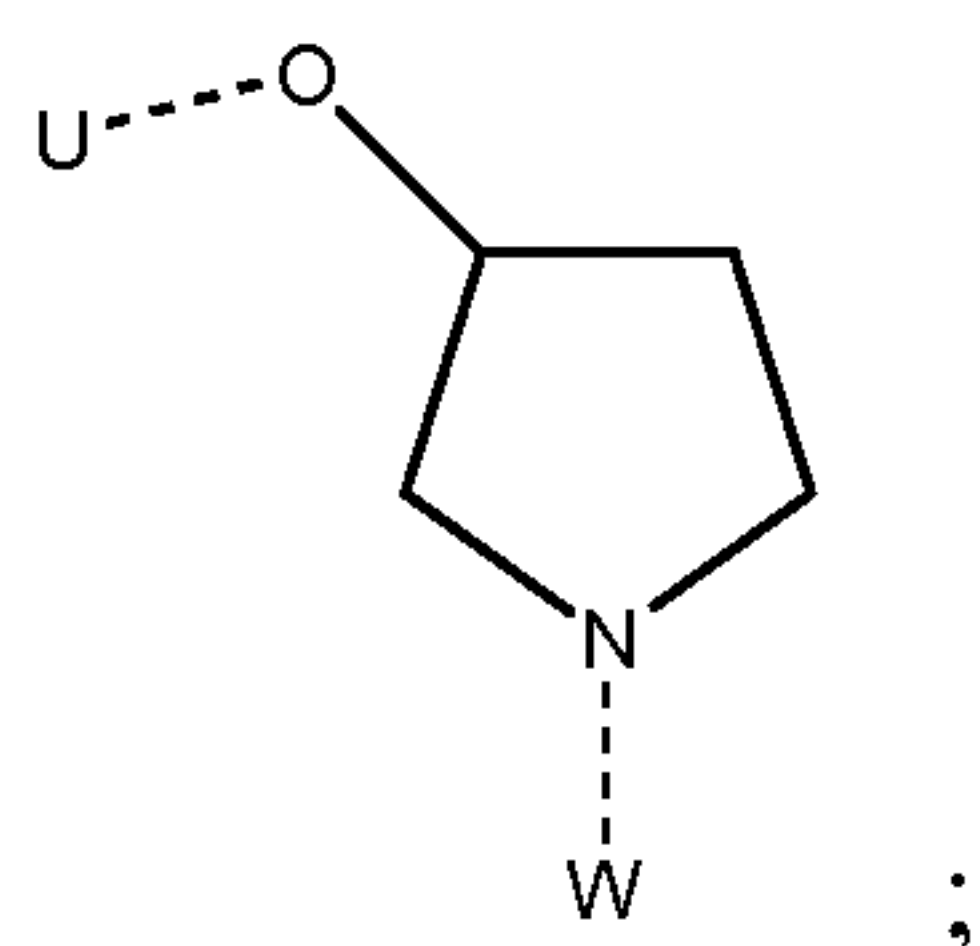
An especially preferred embodiment of the present invention relates to a compound of
5 formula (I), wherein

X represents CH, N, or N^+-O^- ;

W represents a *para*-substituted phenyl or a *para*-substituted pyridinyl, wherein the pyridinyl is especially connected to the rest of the molecule of formula (I) as follows:

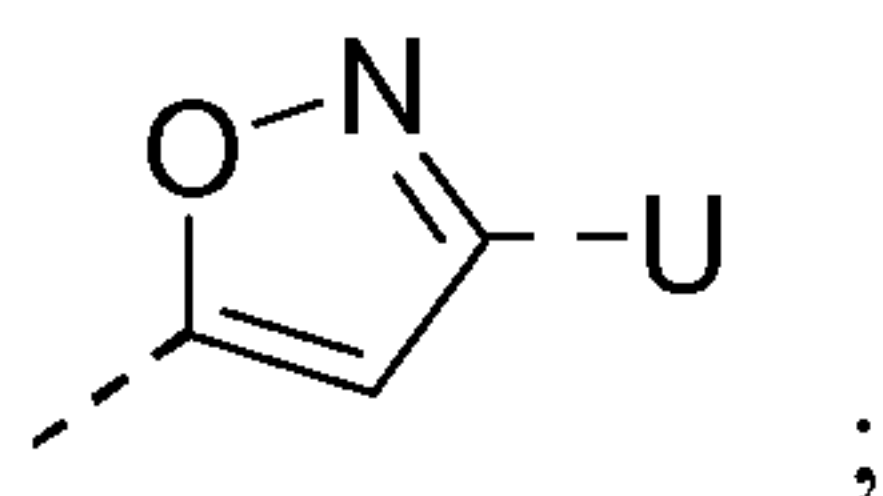


10 V represents $-A-CH_2CH_2-B-$ or $-O-CH_2-Q-$, wherein Q is bound to the group U of formula (I), or V represents a pyrrolidinyl of the formula:



U represents tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of C_{1-7} -alkyl (such as especially methyl) and halogen;

Q represents an isoxazolyl, especially an isoxazolyl that is connected to the rest of the molecule of formula (I) as follows:



A and B both represent -O-;

5 R^1 represents cyclopropyl;

R^2 represents halogen or C_{1-7} -alkyl, especially chloro or methyl;

R^3 represents hydrogen or C_{1-7} -alkyl, especially hydrogen or methyl;

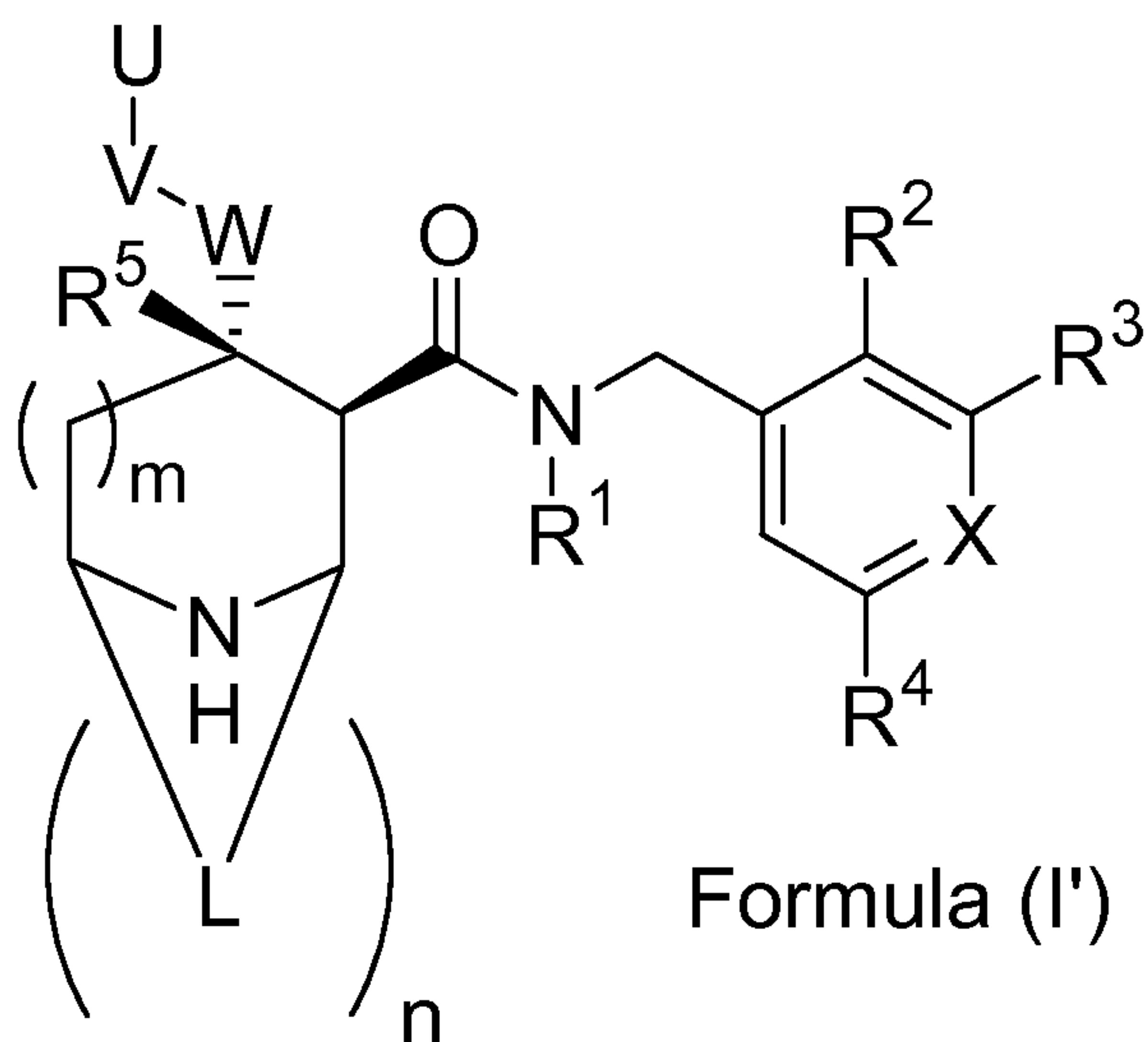
R^4 represents C_{1-7} -alkyl-O-(CH₂)₀₋₄-CH₂-, especially CH₃-O-(CH₂)₁₋₂-CH₂-;

R^5 represents hydroxy;

10 n represents the integer 0; and

m represents the integer 1.

A preferred embodiment of the present invention relates to a compound of formula (I), wherein the absolute configuration of a compound of formula (I) is as represented for formula (I'):



The present invention also relates to compounds of formula (I) wherein the meanings of one or more of the substituents and symbols as defined for formula (I), or a preferred embodiment of formula (I), are replaced by their preferred meanings as defined herein, such as those defined for the above-given preferred embodiments.

- 5 A preferred embodiment of the present invention relates to a compound of formula (I), which is (3*S**, 4*R**)-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide.

Another preferred embodiment of the present invention relates to a compound of formula (I) selected from:

- 10 (3*S*, 4*R*)-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,
(3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,
15 (3'*S*, 4'*R*)-6-[3-(2-chloro-3,6-difluoro-phenyl)-isoxazol-5-ylmethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,
(3'*S*, 4'*R*)-6-[(*R*)-3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,
20 (3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-amide, and
(3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-1-oxy-pyridin-4-ylmethyl]-cyclopropyl-amide.
25

The compounds of formula (I) are useful for the treatment and/or prophylaxis of diseases such as or related to hypertension, congestive heart failure, pulmonary hypertension, renal

insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases related to the renin-angiotensin system.

The compounds of formula (I) are especially useful for the treatment and/or prophylaxis of hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy.

In one embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system, in particular to a method for the treatment and/or prophylaxis of the above-mentioned diseases, said methods comprising administering to a patient a pharmaceutically active amount of a compound of formula (I).

A further aspect of the present invention relates to pharmaceutical compositions comprising a compound of formula (I) and a pharmaceutically acceptable carrier material. These pharmaceutical compositions may be used for the treatment and/or prophylaxis of the above-mentioned diseases. The pharmaceutical compositions can be used for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The invention also relates to the use of a compound of formula (I) for the preparation of pharmaceutical compositions for the treatment and/or prophylaxis of the above-mentioned diseases.

The production of the pharmaceutical compositions can be effected in a manner which will be familiar to any person skilled in the art (see for example Mark Gibson, Editor, Pharmaceutical Preformulation and Formulation, IHS Health Group, Englewood, CO, USA, 2001; Remington, *The Science and Practice of Pharmacy*, 20th Edition, Philadelphia College of Pharmacy and Science) by bringing the described compounds of formula (I) or their pharmaceutically acceptable salts, optionally in combination with other therapeutically valuable substances, into a galenical administration form together with suitable, non-toxic, inert, therapeutically compatible solid or liquid carrier materials and, if desired, usual pharmaceutical adjuvants.

Compounds of formula (I) or the above-mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds such as ACE-inhibitors, neutral endopeptidase inhibitors, aldosterone antagonists, angiotensin II receptor antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists, 11beta-hydroxysteroid dehydrogenase type 1 inhibitors, soluble guanylate cyclase activators and/or other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-drugs of the compound of formula (I), as appropriate and expedient.

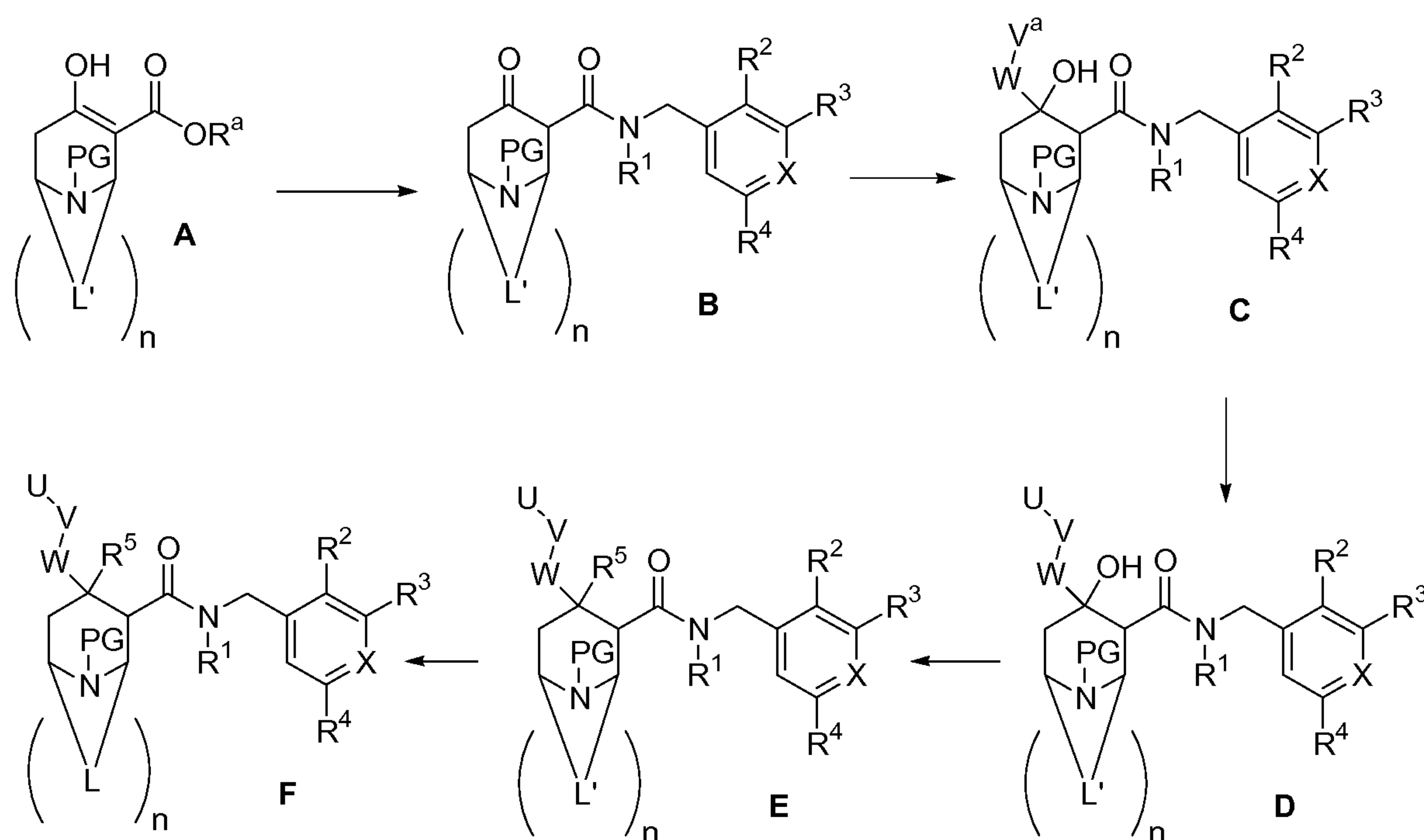
The compounds of formula (I) can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

A compound of type **A** (see patent applications WO 2003/093267, WO 2004/002957, WO 2004/096769, WO 2004/096803, WO 2004/096799, and WO 2004/096366) as described in Scheme 1 can be transformed into a compound of type **B**, wherein L' stands for a precursor of the group L as defined for formula (I), and R^a for a typical ester substituent, like methyl, ethyl, or benzyl. PG stands for a suitable protecting group, typically a carbamate, a benzyl, or a methyl. Scheme 1 represents a compound of formula (I) wherein m is the integer 1; the same scheme can be used if m and n represent the integers 0, but m was omitted in the

Scheme for the purpose of clarity. L' can be modified along the synthesis. The amine has to be prepared separately (*vide infra* for specific examples). An alkylation of the ketone of a compound of type **B** leads to a compound of type **C**, or, if the U-V-W-segment is already achieved, to a compound of type **D**. V^a stands for a precursor of V as defined for formula (I), and can be transformed along the synthesis. Achievement of the U-V-W-segment in a compound of type **C** leads to a compound of type **D**. Alkylation or acylation of the tertiary alcohol in a compound of type **D** leads to a compound of type **E**. Final achievement of the L-substituent leads to a compound of type **F**. Deprotection will finally yield a compound of formula (I).

10

Scheme 1



15

The alkylation of a compound of type **B** to a compound of type **C** yields a mixture of diastereoisomers. These diastereoisomers can be separated at this stage, or at any later stage (compounds of type **D**, **E**, **F**, or compound of formula (I)).

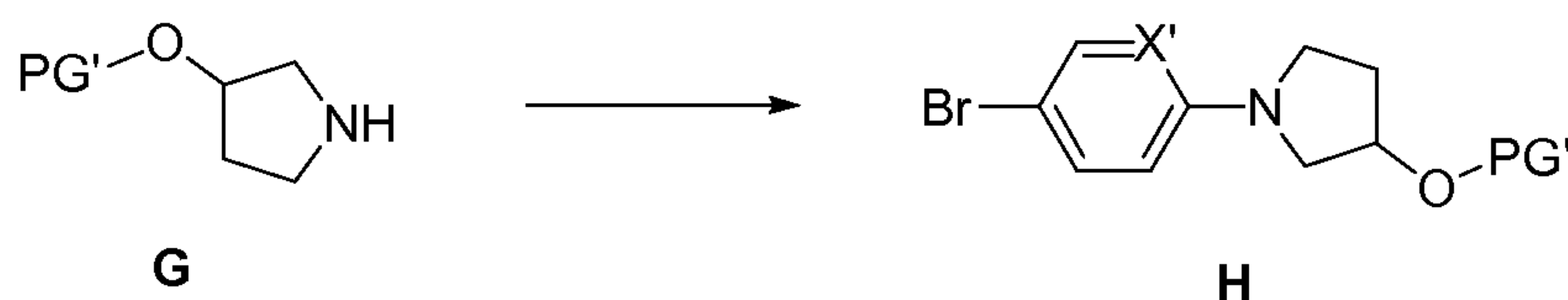
The preparation of several U-V-W- or V^a-W-substituents is described in the patent applications mentioned earlier. Otherwise a pyrrolidine substituent can be attached to an aromatic ring by a copper- or palladium-catalysed coupling as described in Scheme 2.

20

Under certain circumstances a transition metal is not necessary to catalyse this reaction. A compound of type **G**, wherein PG' stands for a suitable protecting group, will be transformed into a compound of type **H**, wherein X' stands for CH or N. If W in formula (I) represents a thiazolyl, the same chemistry can be applied as well.

5

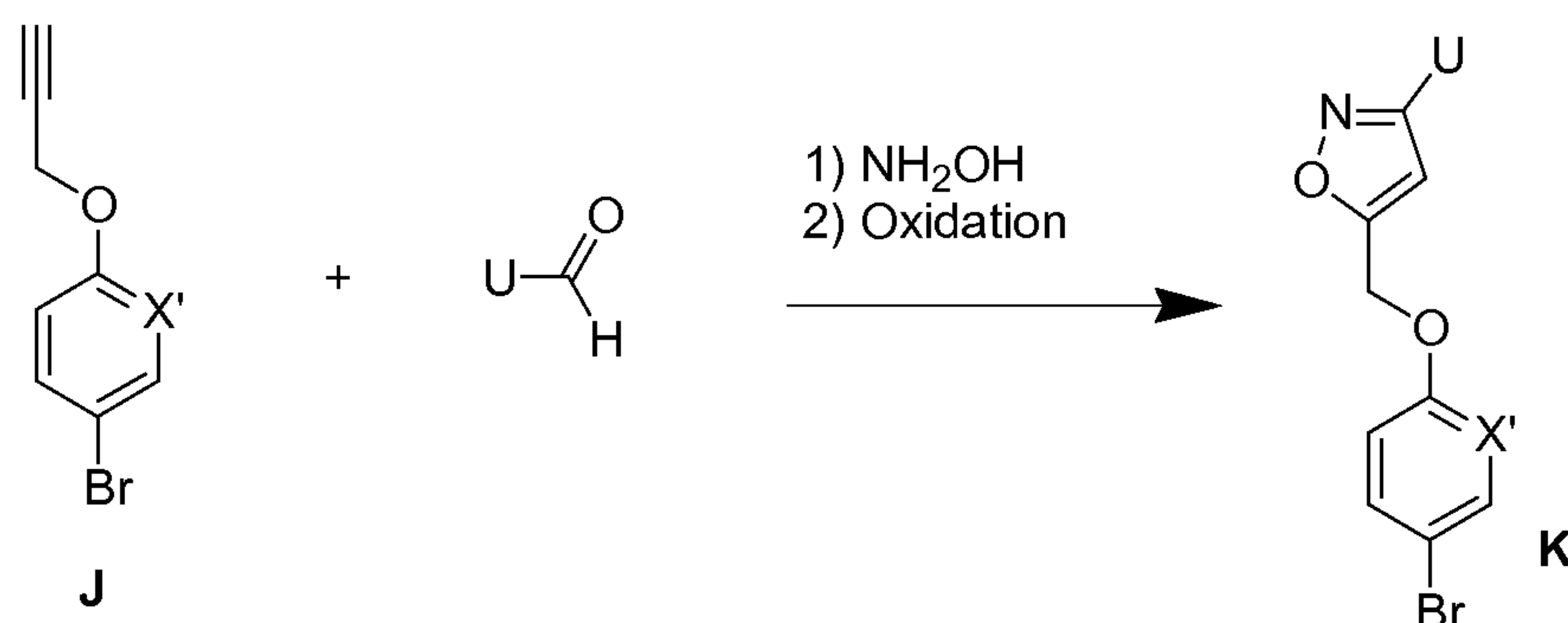
Scheme 2



If V represents -O-CH₂-Q-, the isoxazolyl moiety is prepared by cycloaddition. This cycloaddition can be realized on the W-V^a-fragment in a compound of type **C**, leading to a compound of type **D** as described in Scheme 1. Otherwise the cycloaddition can be performed separately as, for instance, described in Scheme 3. Cycloaddition on a compound of type **J** with an often commercially available aldehyde leads to a compound of type **K**. Of course the aldehyde moiety can be built on the W-V^a-fragment, and a compound of the form U-CCH can be constructed, to give after cycloaddition another isoxazolyl moiety. The same principles can be used to prepare oxadiazolyl moieties, using methodologies described in the literature.

15

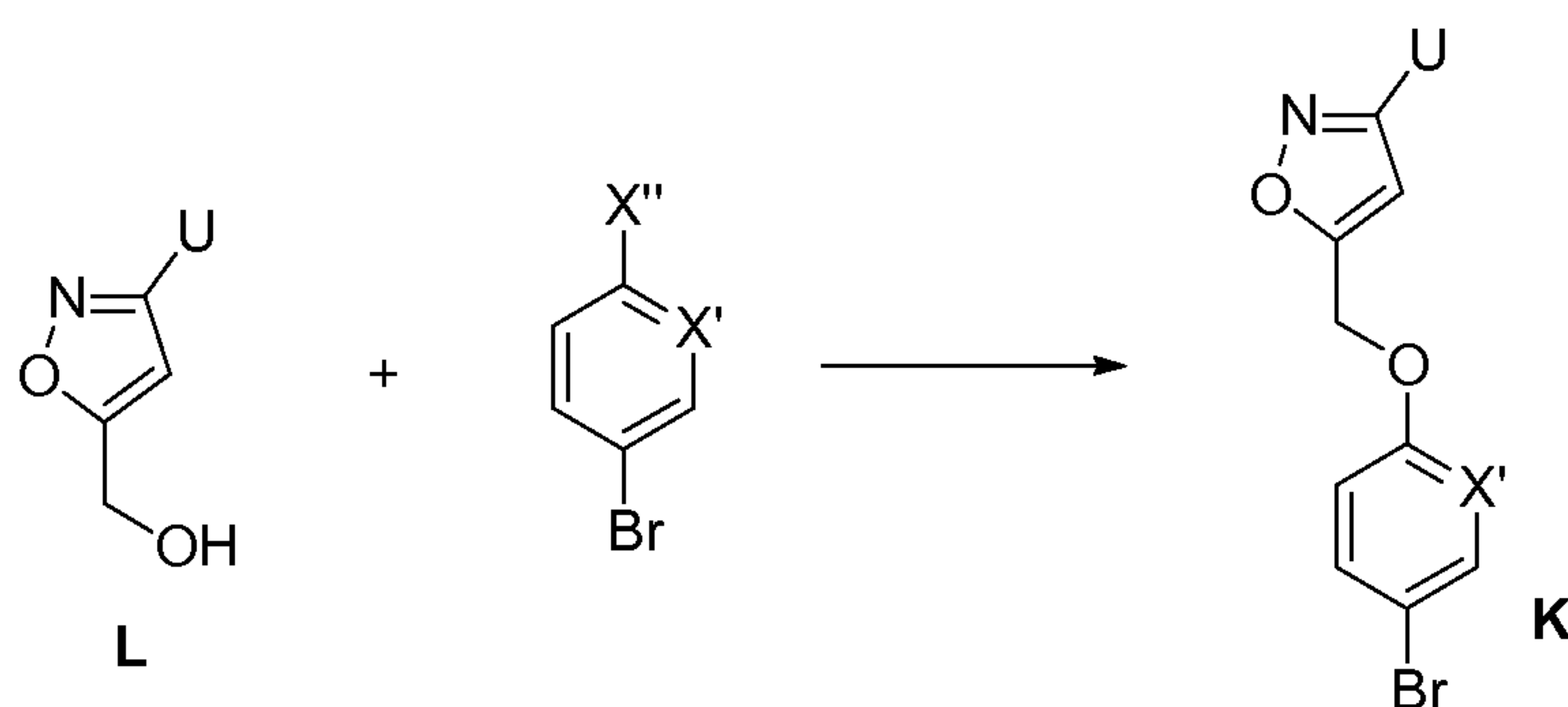
Scheme 3



Also a hydroxymethyl isoxazole (Scheme 4) can be prepared from the aldehyde mentioned in Scheme 3 and propargyl alcohol. Coupling to a phenyl or heteroaryl derivative, wherein X'' typically stands for -OH, -Br, or -I, leads to a compound of type **K**.

20

Scheme 4



The following examples serve to illustrate the present invention in more details. They are,
 5 however, not intended to limit its scope in any manner.

Experimental Part

Abbreviations (as used herein):

10	AcOH	acetic acid
	Ang	angiotensin
	aq.	aqueous
	Boc	<i>tert</i> -butoxycarbonyl
	BSA	bovine serum albumine
15	Bu	butyl
	BuLi	<i>n</i> -butyllithium
	Cy	cyclohexyl
	dba	dibenzylidene acetone
	DIPEA	diisopropylethylamine
20	DMAP	4- <i>N,N</i> -dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
	DMPU	1,3-dimethyl-3,4,5,6-tetrahydro-2(1 <i>H</i>)-pyrimidinone
	DMSO	dimethylsulfoxide
	dppp	1,3-bis(diphenylphosphino)propane
25	EDC·HCl	ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	enzyme immunoassay

	ELSD	evaporative light scattering detection
	eq.	equivalent(s)
	ES	electrospray
	ES+	electrospray, positive ionization
5	Et	ethyl
	EtOAc	ethyl acetate
	EtOH	ethanol
	FC	flash chromatography
	h	hour(s)
10	HOBt	hydroxybenzotriazol
	HPLC	high performance liquid chromatography
	LC-MS	liquid chromatography – mass spectroscopy
	Me	methyl
	MeOH	methanol
15	min	minute(s)
	MS	mass spectroscopy
	NCS	<i>N</i> -chlorosuccinimide
	org.	organic
	<i>p</i>	para
20	PG	protecting group
	rt	room temperature
	sat.	saturated
	sol.	solution
	TBAC	tetra- <i>n</i> -butylammonium chloride
25	TBME	<i>tert</i> -butyl-methyl-ether
	<i>t</i> Bu	<i>tert</i> -butyl
	TFA	trifluoroacetic acid
	THF	tetrahydrofuran
	TLC	thin layer chromatography
30	t_R	retention time (in LC-MS or HPLC) given in minutes
	UV	ultra violet
	Vis	visible
	xantphos	4,5-bis(diphenylphosphino)-9,9-dimethylxanthene

HPLC- or LC-MS-conditions (if not indicated otherwise):

Analytic: Zorbax 59 SB Aqua column, 4.6 x 50 mm from Agilent Technologies. Eluents:
A: acetonitrile; B: H₂O + 0.5% TFA. Gradient: 90% B → 5% B over 2 min. Flow: 1
5 mL/min. Detection: UV/Vis + MS.

Preparative: Zorbax SB Aqua column, 20 x 500 mm from Agilent Technologies. Eluent:
A: Acetonitrile; B: H₂O + 0.05% ammonium hydroxide (25% aq.). Gradient: 80% B →
10% B over 6 min. Flow: 40 mL/min. Detection: UV + MS, or UV + ELSD.

Chiral, analytic:

- 10 a) Regis Whelk column, 4.6 x 250 mm, 10 μm. Eluent A: EtOH + 0.05% Et₃N.
Eluent B: hexane. Flow: 1 mL/min.
- b) ChiralPak AD, 4.6x250 mm, 5 μm. Eluent A: EtOH + 0.05% Et₃N. Eluent B:
hexane. Flow: 1 mL/min.
- c) ChiralCel OD, 4.6x250 mm, 10 μm. Eluent A: EtOH + 0.1% Et₃N. Eluent B:
15 hexane. Flow: 0.8 mL/min.

Chiral, preparative:

- a) Regis Whelk 01 column, 50x250 mm and a flow of 100 mL/min. Eluent A: EtOH +
0.05% Et₃N. Eluent B: hexane.
- b) ChiralCel OD, 20 μm, 50 mm x 250 mm, flow 100 mL/min. Eluent A: EtOH +
20 0.1% Et₃N. Eluent B: hexane.

5-Bromo-2-chloro-N-cyclopropylbenzamide

Into a flame-dried 250 mL round-bottom flask equipped with a magnetic stir bar and under
N₂ were added 5-bromo-2-chlorobenzoic acid (10.0 g, 42.5 mmol) and DMF (3.9 mL, 51.0
25 mmol) in toluene (80 mL). The sol. was cooled to 0 °C, and oxalyl chloride (4.4 mL, 51.0
mmol) was added dropwise over 1 h. The resulting mixture was stirred at 0 °C for 2 h and
then the volatiles were removed. The resulting crude reaction mixture was dissolved in
CH₂Cl₂ (100 mL) and cooled to 0 °C in an ice bath. Cyclopropylamine (4.5 mL, 63.7
mmol) was added dropwise over 1 h followed by addition of DIPEA (11.8 mL, 85.0
30 mmol). The resulting sol. was stirred at rt for 16 h. The reaction mixture was poured into
a 1 L separatory funnel containing 1M aq. HCl (600 mL). The mixture was extracted with
CH₂Cl₂ (6 x 250 mL). The combined org. layers were washed with brine, dried over

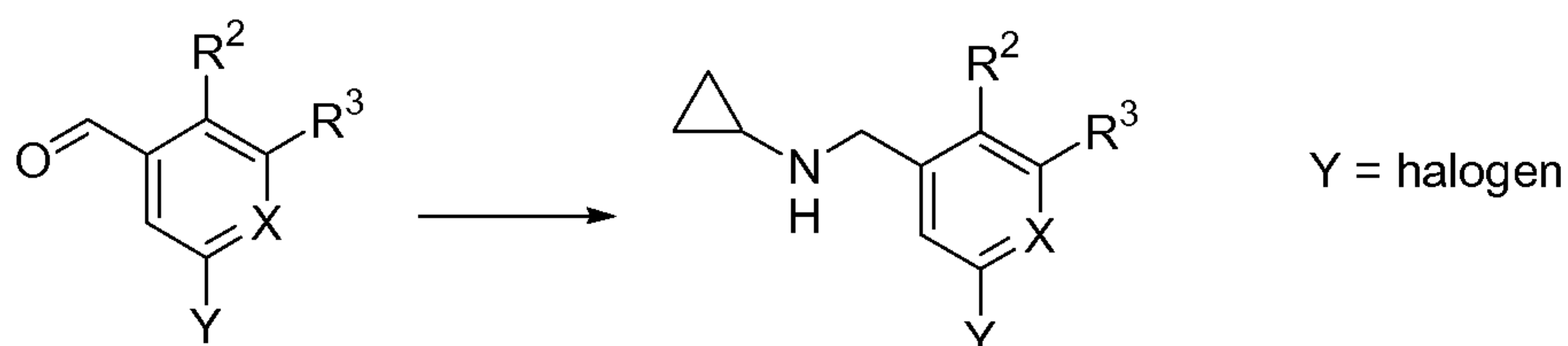
MgSO₄, filtered and concentrated under reduced pressure. The product was crystallized from hexanes/CH₂Cl₂ and isolated by filtration to give the title compound (8.24 g, 71%).

***N*-(5-bromo-2-chlorobenzyl)cyclopropylamine**

5 A sol. of 5-bromo-2-chloro-*N*-cyclopropylbenzamide (12.0 g, 43.7 mmol) in THF (100 mL) was placed into a 250 mL round-bottom flask, equipped with a magnetic stir bar and under N₂. The sol. was treated with dropwise addition of BH₃·Me₂S (13.1 mL, 131 mmol), and the resulting suspension was stirred at rt for 1 h. The mixture was heated to reflux for 1 h, cooled to rt, and slowly quenched with dropwise addition of 1M aq. HCl (25 mL). The
10 suspension was again refluxed for 1 h, cooled to rt, and basified to pH = 10-11 with 1M aq. NaOH. The mixture was poured into a 500 mL separatory funnel containing 1M aq. NaOH (350 mL). The mixture was extracted with EtOAc (3 x 100 mL). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. The crude amine was used directly in the next step.

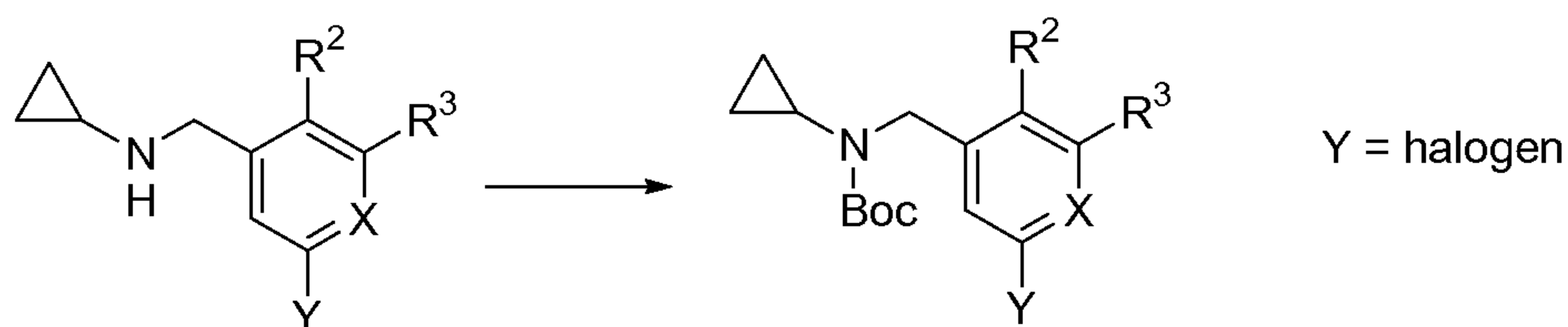
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General procedure for the reductive amination of substituted benzaldehydes with cyclopropylamine:



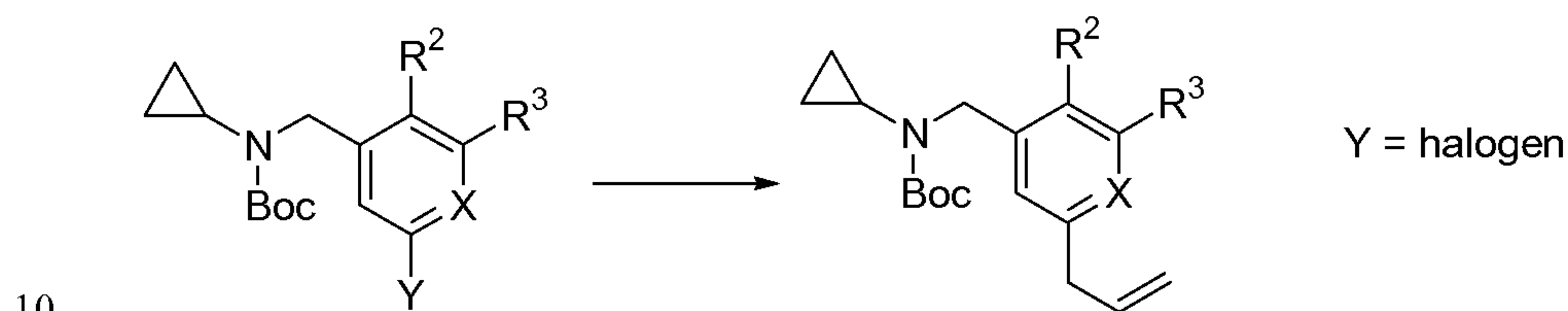
A sol. of substituted benzaldehyde (17.8 mmol, 1.0 eq.), cyclopropylamine (3.13 mL, 44.5
20 mmol, 2.5 eq.) and sodium cyanoborohydride (1.34 g, 21.4 mmol, 1.2 eq.) in MeOH (100 mL) was treated with dropwise addition of glacial AcOH (3.06 mL, 53.4 mmol, 3.0 eq.). The resulting sol. was stirred at rt for 16 h overnight. The reaction mixture was quenched with dropwise addition of sat. aq. NaHCO₃, and concentrated under reduced pressure to remove the MeOH. The crude residue was poured into a 250 mL separatory funnel
25 containing sat. aq. NaHCO₃ (150 mL), and extracted with EtOAc (3 x 50 mL). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by FC yielded the benzamine product.

General procedure for the Boc-protection of cyclopropylbenzamines:



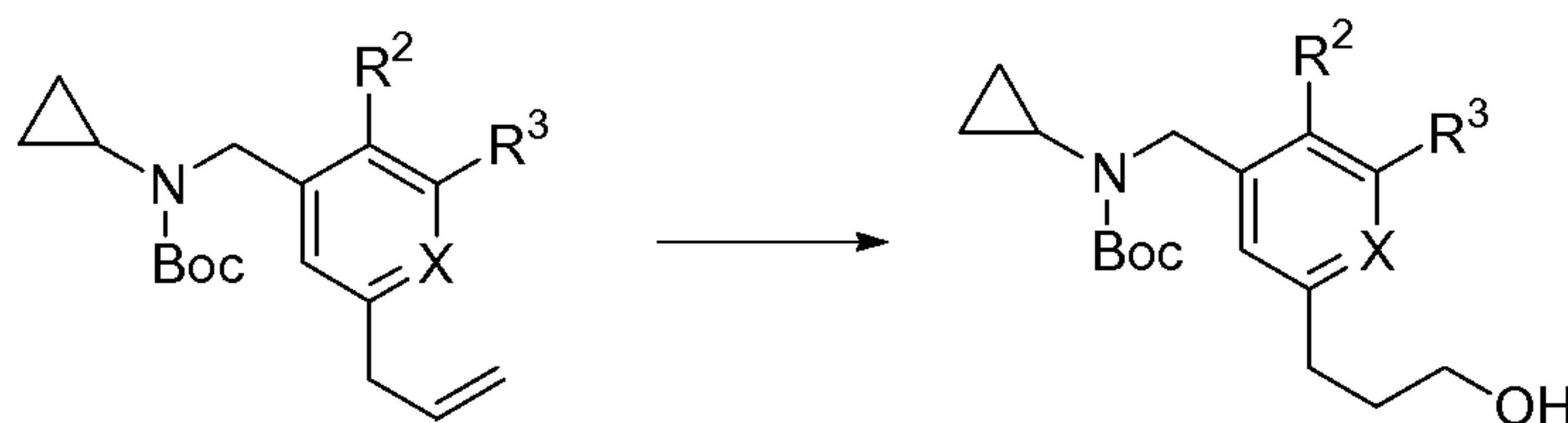
A sol. of the cyclopropylbenzamine (43.7 mmol, 1.0 eq.) in a biphasic mixture of CH_2Cl_2 (50 mL) and 1M aq. NaOH (50 mL) was treated with Boc_2O (15.1 mL, 65.6 mmol, 1.5 eq.). The mixture was stirred at rt vigorously for 16 h. The mixture was poured into a 500 mL separatory funnel containing H_2O (300 mL), and extracted with CH_2Cl_2 (3 x 100 mL). The combined org. layers were washed with brine, dried over MgSO_4 , filtered and concentrated under reduced pressure. Purification by FC yielded the Boc-protected amine.

General procedure for the allylation of Boc-protected cyclopropylbenzamines:



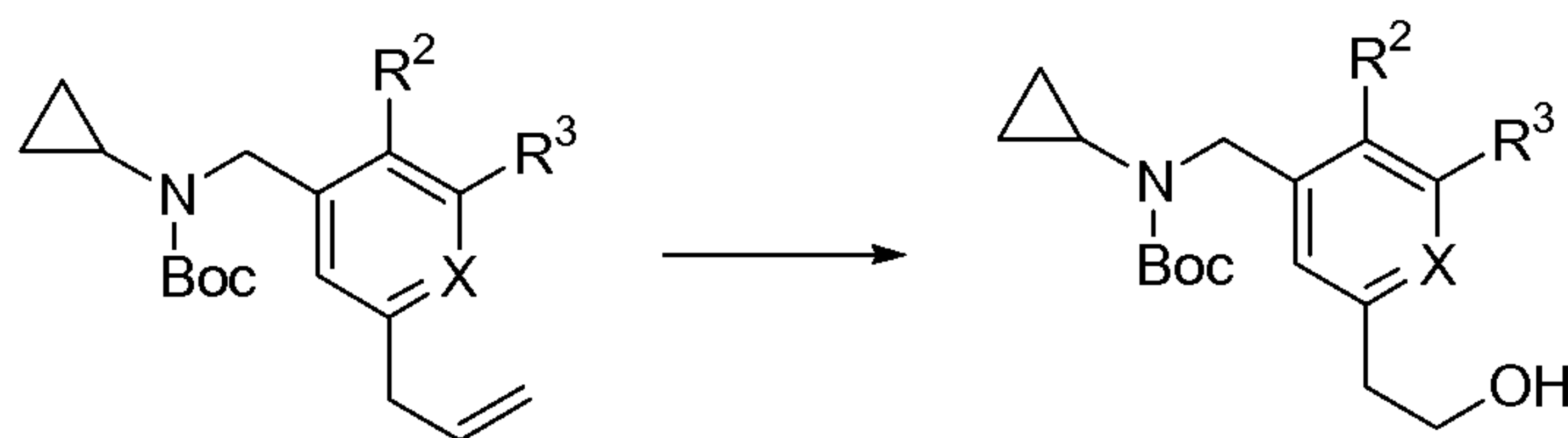
Into a flame-dried round-bottom flask or Schlenk tube, under N_2 was added $\text{Pd}[\text{PCy}_3]_2$ (0.05 eq.), CsF (2.0 eq.) and the corresponding aryl bromide (1.0 eq.). If the aryl chloride was being used as a starting material, the $(\text{Pd}[\text{PtBu}_3]\text{Br})_2$ dimer (0.025 eq.) was used in place of the $\text{Pd}[\text{PCy}_3]_2$ catalyst. The flask was evacuated under reduced pressure (0.1 mm Hg) and backfilled with N_2 (repeated 3 times). The resulting solids were dissolved in anhydrous THF or dioxane (0.15 M sol.) and tri-*n*-butyl allyltin (1.5 eq.) was added and the resulting mixture was refluxed for 8–16 h, until TLC shows complete consumption of starting material. The reaction mixture was cooled to rt, and filtered through a pad of silica gel on a sintered glass funnel, washing with Et_2O . The filtrate was concentrated and purified by FC to give the corresponding allylbenzamide derivative.

General procedure for the hydroboration/oxidation of allylbenzamines:



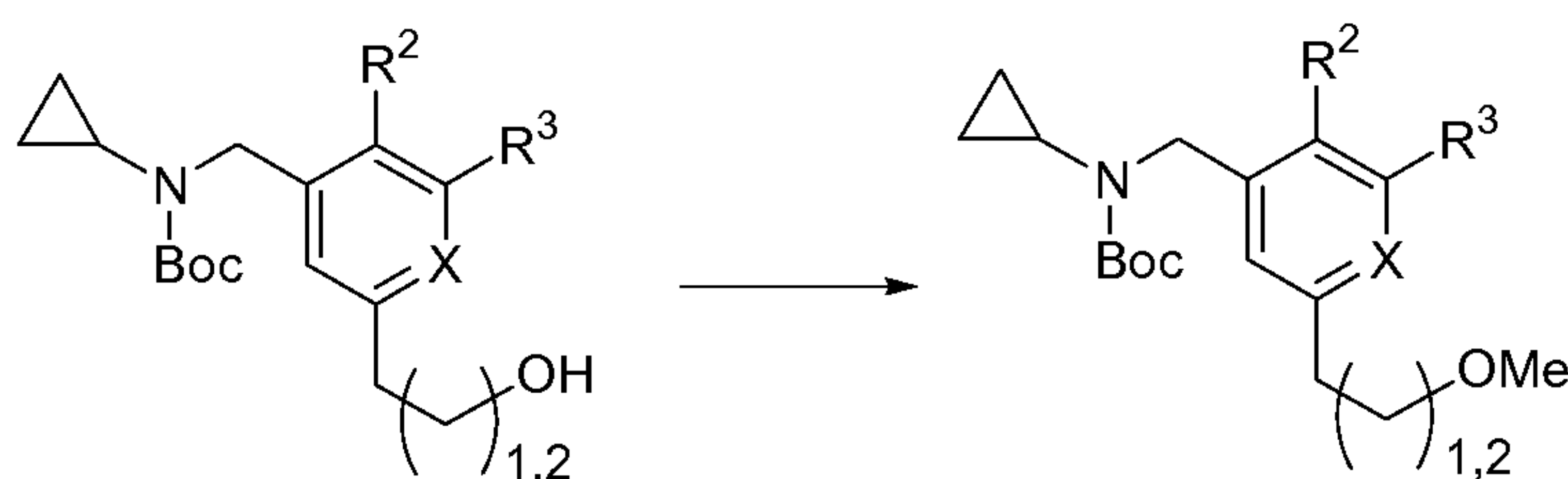
Into a flame-dried round-bottom flask equipped with a magnetic stir bar was added the allylbenzamine (1.0 eq.) and anhydrous THF (0.3 M sol.). The sol. was cooled to 0 °C and BH₃·Me₂S (1.1 eq.) was added dropwise over 20 min. The sol. was stirred at 0 °C for 1 h, then allowed to warm to rt, and stirred for an additional 2 h. The sol. was cooled to 0 °C and 1M aq. NaOH was added dropwise (CAUTION – EXOTHERMIC REACTION), followed by dropwise addition of 30% aq. H₂O₂. The mixture was allowed to warm to rt, and stirred for 2 h. The mixture was poured into a separatory funnel containing H₂O and extracted with Et₂O (3 times). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by FC yielded the desired alcohol product.

General procedure for the oxidative cleavage/reduction of allylbenzamines:



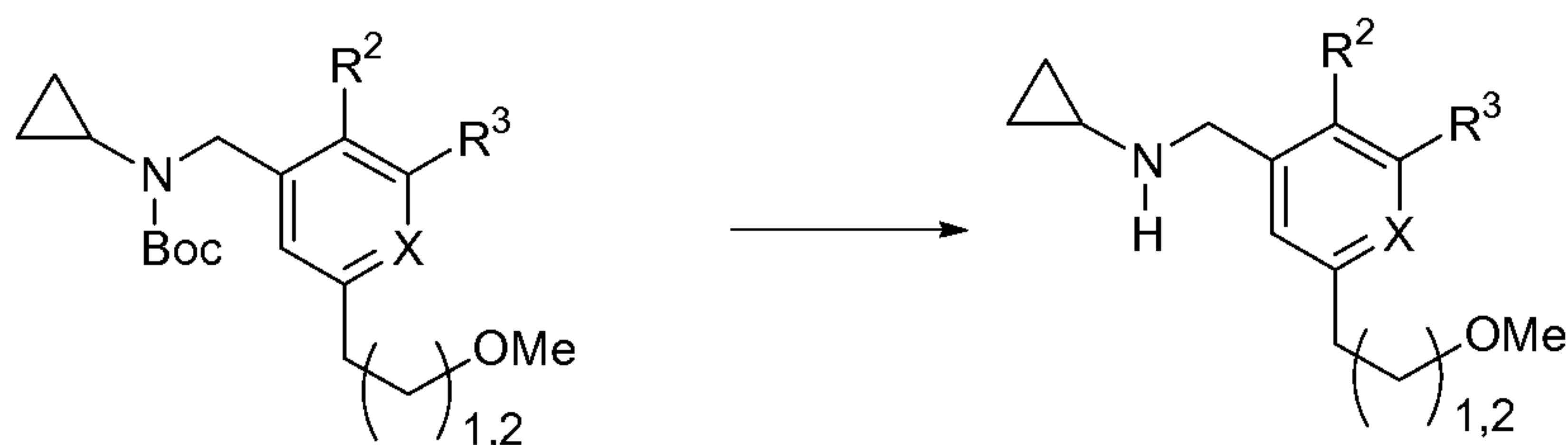
A sol. of allylbenzamine (1.0 eq.) in CH₂Cl₂ (0.4 M sol.) was cooled to -78 °C and O₃ gas was introduced into the sol. using a gas dispersion tube. The ozone gas was introduced until all of the starting material had been consumed, as determined by TLC, and the reaction mixture maintained a slight blue colour. The reaction was stirred at -78 °C for 20 min, then EtOH (0.5 M sol.) and NaBH₄ (2.5 eq.) were added. The mixture was allowed to warm to rt overnight (16 h). The reaction mixture was quenched with dropwise addition of sat. aq. NH₄Cl (5 mL), and poured into a separatory funnel containing sat. aq. NH₄Cl. The mixture was extracted with Et₂O (3 times). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by FC yielded the desired alcohol.

General procedure for the etherification of aromatic primary alcohols with methyl iodide:



A suspension of the primary alcohol (1.0 eq.) in THF (0.25 M sol.) was cooled to 0 °C and treated with NaH (60% in oil, 2.0 eq.). The resulting mixture was stirred at 0 °C for 30 min and then at rt for another 30 min. The suspension was re-cooled to 0 °C and then MeI (8.0 eq.) was added in a single portion. The reaction mixture was stirred at 0 °C for 30 min, at rt for 30 min, and then heated to reflux for 4 h until all of the starting material was consumed as determined by TLC. The cooled reaction mixture was quenched with dropwise addition of sat. aq. NH₄Cl and poured into a separatory funnel containing sat. aq. NH₄Cl, and extracted with EtOAc (3 times). The combined org. layers were washed with brine, dried over MgSO₄, filtered and concentrated under reduced pressure. Purification by FC yielded the methyl ether.

General procedure for the deprotection of Boc-protected cyclopropylbenzamines:



To a sol. of Boc-protected cyclopropylbenzamine (1.0 eq.) in CH₂Cl₂ (0.1-0.5 M sol.) was added 4 M HCl in dioxane (5.0 eq.). The resulting mixture was stirred at rt for 8-16 h until TLC shows complete conversion of starting material. The reaction was poured into a separatory funnel containing 1M aq. NaOH, and extracted with CH₂Cl₂ (3 times). Purification by FC yielded the corresponding free amine.

2-Bromo-5-chloro-pyridine-4-carbaldehyde

To a stirred sol. of diisopropylamine (20.9 mL, 148 mmol) in dry THF (350 mL) at -5 °C was added dropwise BuLi (1.6M in hexane, 89.5 mL, 143 mmol), and the resulting sol.

was stirred for 30 min at -5°C . The sol. was allowed to cool to -70°C , and a sol. of 2-bromo-5-chloropyridine (25.0 g, 130 mmol) in THF (100 mL) was added dropwise at -70°C over 15 min such that the internal temperature did not exceed -65°C . The mixture was stirred at -70°C for 30 min. DMF (10.52 mL, 136 mmol) was added dropwise over 20 min such that the internal temperature did not exceed -70°C . The orange mixture was stirred at -70°C for 40 min. The mixture was allowed to warm up to rt, and was poured onto a mixture of water (200 mL) and aq. 1M NaOH (50 mL). The mixture was extracted with EtOAc (2x), and the combined org. extracts were washed back with aq. 1M NaOH (2x). The org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:9 $\rightarrow$ 1:8 $\rightarrow$ 1:6 $\rightarrow$ 1:4 $\rightarrow$ 1:2 $\rightarrow$ 1:1) yielded the title compound (21.55 g, 72 %). LC-MS: t_{R} = 0.74 min; ES+: 295.01.

2-Bromo-5-chloro-4-dimethoxymethyl-pyridine

To a sol. of 2-bromo-5-chloro-pyridine-4-carbaldehyde (43.9 g, 199 mmol) in MeOH (800 mL) were successively added at rt trimethyl orthoformate (65.3 mL, 597 mmol) and *p*-toluenesulfonic acid monohydrate (1.90 g, 10.0 mmol). This reaction mixture was then heated to reflux for 3 h. The mixture was allowed to cool to rt and was concentrated under reduced pressure. The residue was dissolved in CH_2Cl_2 , and this mixture was washed with aq. 10% K_2CO_3 . The org. layer was dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Drying under high vacuum yielded the title compound (51.7 g, 97 %). LC-MS: t_{R} = 0.92 min; ES+: 309.06.

5-Chloro-4-dimethoxymethyl-2-(3-methoxy-propyl)-pyridine

To a suspension of Mg (911 mg, 37.5 mmol) and of iodine (one crystal) in dry THF (30 mL) was added dropwise 5% of the total amount of 1-bromo-3-methoxypropane (4.59 g, 30.0 mmol). The mixture was heated to reflux with the help of a heat gun until the Grignard formation had started. The rest of the 1-bromo-3-methoxypropane was added slowly, while an exothermic reaction proceeded. After the end of the addition, the reaction mixture was stirred under reflux for 20 min, and was allowed to cool to rt. This Grignard sol. (1M in THF, 23.5 mL, 23.5 mmol) was added dropwise to a mixture of 2-bromo-5-chloro-4-dimethoxymethyl-pyridine (2.50 g, 9.38 mmol) and $\text{Ni}(\text{dppp})\text{Cl}_2$ (495 mg, 0.938

mmol) in THF (50 mL) at 0 °C. The reaction mixture was stirred at rt for 30 min, and was then heated to reflux for 2 h. The mixture was allowed to cool to rt, and was dissolved with EtOAc. This mixture was washed with aq. sat. NaHCO₃. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → EtOAc/heptane 1:1) yielded the title compound (1.51 g, 62%). LC-MS: t_R = 0.80 min; ES+: 260.15.

5-Chloro-2-(3-methoxy-propyl)-pyridine-4-carbaldehyde

5-Chloro-4-dimethoxymethyl-2-(3-methoxy-propyl)-pyridine (25.5 g, 98.2 mmol) was dissolved in aq. 1M HCl (500 mL), and the mixture was heated to 80 °C for 2 h. The mixture was allowed to cool to rt, and EtOAc was added. The mixture was cooled to 0 °C, and was basified with aq. 2.5M NaOH until a pH = 10 was reached. The layers were separated, and the org. layer was dried over MgSO₄, filtered, and concentrated under reduced pressure. Drying the residue under high vacuum yielded the crude title compound (98.1 mmol, 99%) that was used further without purification. LC-MS: t_R = 0.62 min; ES+: 246.12.

[5-Chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-amine

A mixture of 5-chloro-2-(3-methoxy-propyl)-pyridine-4-carbaldehyde (21.0 g, 98.2 mmol) and cyclopropylamine (13.8 mL, 196 mmol) in MeOH (450 mL) was stirred at rt overnight. NaBH₄ (4.83 g, 128 mmol) was added at 0 °C, and the mixture was stirred at rt overnight. Ice was added, and the mixture was concentrated under reduced pressure. The crude product was dissolved in EtOAc, and this mixture was washed with aq. 1M NaOH. The aq. layer was extracted back with EtOAc. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:5 → 1:4 → 1:3 → 1:1 → 3:1 → EtOAc) yielded the title compound (11.8 g) and [5-chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethylene]-cyclopropyl-amine (10.7 g). This unreacted imine was dissolved in MeOH (20 mL), and this sol. was cooled to 0 °C. NaBH₄ (3.20 g, 84.6 mmol) was added, and the mixture was stirred at rt overnight. NaBH₄ (3.20 g, 84.6 mmol) was added again, and the mixture was stirred for 3 days. Ice was added to the reaction mixture, and the mixture was concentrated under reduced pressure. The crude product was dissolved in EtOAc and the resulting

mixture was washed with aq. 1M NaOH. The aq. phase was extracted back with EtOAc. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:3 → 1:2 → 1:1 → EtOAc) yielded the title compound (9.4 g). The fractions of the title
5 compounds were mixed together (21.2 g, 85%). LC-MS: t_R = 0.55 min; ES+: 296.16.

2-(4-Bromo-phenoxy)-ethanol

4-Bromophenol (1003 g, 0.58 mol) was dissolved in in xylenes (220 mL). [1,3]Dioxolan-2-one (53.7 g, 0.61 mol) and imidazole (592 mg, 8.70 mmol) were added. The mixture was heated to 140 °C for 3 days. The mixture was allowed to cool to rt, and the solvents were
10 removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (130 g, quantitative). LC-MS: t_R = 0.81 min.

Methanesulfonic acid 2-(4-bromo-phenoxy)-ethyl ester

2-(4-Bromo-phenoxy)-ethanol (125 g, 0.576 mol) was dissolved in CH₂Cl₂ (650 mL), and
15 the sol. was cooled to 0 °C. Et₃N (110 mL, 0.864 mol), then mesyl chloride (67.1 mL, 0.864 mol) were dropped at such a speed that the temperature did not raise above 10 °C (about 60 min). The mixture was stirred at 0 °C for 1 h, then at rt overnight. The mixture was diluted with CH₂Cl₂, and washed with brine (2x). The aq. phase was extracted back with CH₂Cl₂. The combined org. extracts were dried over MgSO₄, filtered, and the
20 solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the raw title compound (174 g, quantitative yield) that was used further without purification. LC-MS: t_R = 0.92 min.

1-[2-(4-Bromo-phenoxy)-ethoxy]-2,6-dichloro-4-methyl-benzene

25 K₂CO₃ (29.3 g, 212 mmol) was dissolved in water (162 mL). 1-Propanol (150 mL) was added. A sol. of 2,6-dichloro-*p*-cresol (25 g, 141 mmol) in 1-propanol (150 mL) was added. Methanesulfonic acid 2-(4-bromo-phenoxy)-ethyl ester (41.6 g, 141 mmol) was added. The mixture was stirred at 85 °C for 6 h. The heating oil bath was removed, and water (330 mL) was added dropwise when the internal temperature had reached 78 °C.
30 The beige suspension was allowed to cool to rt. The mixture was filtered, and the

precipitate was washed with water. Drying the precipitate under high vacuum at 30 °C for 48 h yielded the title compound (43 g, 81 %). LC-MS: t_R = 1.15 min.

2-(2,6-Dichloro-4-methyl-phenoxy)-ethanol

5 In a three-necked flask equipped with a gas droplet counter and an efficient cooling system, a mixture of 2,6-dichloro-*p*-cresol (20.0 g, 113 mmol), [1,3]dioxolan-2-one (9.95 g, 113 mmol) and imidazole (115 mg, 1.70 mmol) was heated to 160 °C for 25 h. The mixture was allowed to cool to rt. Purification by FC (Et₂O/heptane 1:1) yielded the title compound (18.7 g, 75%). LC-MS: t_R = 0.88 min.

10

5-Bromo-2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-pyridine

A sol. of 2-(2,6-dichloro-4-methyl-phenoxy)-ethanol (18.6 g, 84 mmol) in THF (360 mL) was cooled to 0 °C. NaH (about 55% in oil, 6.60 g, about 153 mmol) was added in portions, and the mixture was stirred at rt for 30 min. A sol. of 2,5-dibromopyridine (18.0 g, 76.3 mmol) in THF (60 mL) was added dropwise, and the mixture was heated to reflux for 90 min. The mixture was allowed to cool to rt, and ice was added carefully. The solvents were partially removed under reduced pressure, and the residue was diluted with EtOAc. This mixture was washed with aq. sat. NH₄Cl. The aq. layer was extracted back with EtOAc (2x). The combined org. extracts were washed with brine, dried over MgSO₄,
15 filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 3:97) yielded the title compound (22.7 g, 79%). LC-MS: t_R = 1.13 min; ES+: 378.08.

20

2-Chloro-3,6-difluoro-benzaldehyde oxime

25 2-Chloro-3,6-difluoro-benzaldehyde (25.0 g, 142 mmol) was dissolved in CH₃CN (175 mL). To this sol. was added NaHCO₃ (35.7 g, 424 mmol), and the mixture was stirred vigorously for 5 min. Water (350 mL) was added, and the mixture was stirred for 10 min. NH₂OH·HCl (19.7 g, 283 mmol) and TBAC (1.97 g, 7.08 mmol) were added, and the reaction mixture was stirred at rt for 1 h. AcOH (20 mL) was added dropwise to pH 6-7.
30 The mixture was extracted with Et₂O (3x). The combined org. extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure.

Drying under high vacuum yielded the title compound (25.0 g, 92%). LC-MS: t_R = 0.93 min.

(S)-1-(5-Bromo-pyridin-2-yl)-pyrrolidin-3-ol

5 A mixture of 2,5-dibromopyridine (12.2 g, 51.5 mmol) and (S)-hydroxypyrrolidine (2.80 g, 32.1 mmol) in toluene (50 mL) was heated to reflux overnight. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved with EtOAc (150 mL), and the mixture was washed with aq. 10 % K_2CO_3 . The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced
10 pressure. Purification of the residue by FC (heptane $\rightarrow$ heptane/EtOAc 1:2) yielded the title compound (3.62 g, 46%). LC-MS: t_R = 0.48 min; ES+: 243.15.

(R)-5-Bromo-2-[3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-pyridine

Azodicarboxylate dipiperidide (11.7 g, 45.4 mmol) was added to a sol. of (S)-1-(5-bromo-pyridin-2-yl)-pyrrolidin-3-ol (8.82 g, 36.3 mmol) and 2,6-dichloro-*p*-cresol (7.37 g, 40.0
15 mmol) in toluene (200 mL). The mixture was degassed with nitrogen for 5 min, and PBu_3 (85%, 15.8 mL, 46.2 mmol) was added. The mixture was heated rapidly to 100 °C, and stirred at this temperature for 2 h. The mixture was allowed to cool to rt, and was diluted with heptane (200 mL). The mixture was filtered, and the filtrate was evaporated under
20 reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:7) yielded a crude title compound that was diluted with CH_2Cl_2 . This mixture was washed with aq. 1M NaOH. The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the pure title compound (13.5 g, 93%). LC-MS: t_R = 0.92 min; ES+: 402.98.

25

(rac.)-3-[Cyclopropyl-(2,3-dimethyl-benzyl)-carbamoyl]-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (B1)

A sol. of 4-hydroxy-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (WO 2004/105738, 1.00 g, 3.89 mmol), cyclopropyl-(2,3-dimethyl-benzyl)-
30 amine (681 mg, 3.89 mmol) and *p*-toluenesulfonic acid monohydrate (92.4 mg, 0.486 mmol) in anhydrous toluene (40 mL) was stirred at reflux overnight in a Dean-Stark trap equipped flask. The reaction mixture was allowed to cool to rt. EtOAc (120 mL) was

added, and the resulting mixture was washed successively with aq. sat. NaHCO₃ (2x), aq. 1M HCl (1x), and finally with aq. sat. NaHCO₃ (1x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → heptane/EtOAc 50:50) yielded the title compound (566 mg, 36%). LC-MS: t_R = 1.02 min; ES⁺: 401.02.

(rac.)-3-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (B2)

A sol. of 4-hydroxy-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (WO 2004/105738, 4.83 g, 18.8 mmol), [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amine (3.00 g, 12.5 mmol) and *p*-toluenesulfonic acid monohydrate (298 mg, 1.56 mmol) in anhydrous toluene (188 mL) was stirred at reflux (oil bath at 130°C) for 24 h in a Dean-Stark trap equipped flask. The mixture was allowed to cool to rt and left over the week-end. EtOAc (100 mL) was added, and the resulting mixture was washed successively with aq. sat. NaHCO₃, aq. 1M HCl (2x), and with brine. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → heptane/EtOAc 40:60) yielded the title compound (2.39 g, 41%). LC-MS: t_R = 1.03 min; ES⁺: 465.43.

(rac.)-3-{[5-Chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-carbamoyl}-4-oxo-piperidine-1-carboxylic acid *tert*-butyl ester (B3)

A sol. of 4-hydroxy-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (WO 2004/105738, 2.00 g, 7.77 mmol), [5-chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-amine (1.98 g, 7.77 mmol) and *p*-toluenesulfonic acid monohydrate (185 mg, 0.972 mmol) in anhydrous toluene (78 mL) was stirred at reflux overnight in a Dean-Stark trap equipped flask. 4-Hydroxy-5,6-dihydro-2*H*-pyridine-1,3-dicarboxylic acid 1-*tert*-butyl ester 3-methyl ester (500 mg, 1.94 mmol) was added, and the mixture was heated to reflux for 4 h. The mixture was allowed to cool to rt. EtOAc was added, and the mixture was washed with aq. sat. NaHCO₃, aq. 1M HCl and aq. sat. NaHCO₃. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 7:3) yielded the title compound (1.70 g, 46%). LC-MS: t_R = 0.90 min; ES⁺: 480.39.

(rac.)-(3*S, 4*R**)-3-[Cyclopropyl-(2,3-dimethyl-benzyl)-carbamoyl]-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (D1)**

5 A sol. of 1-[2-(4-bromo-phenoxy)-ethoxy]-2,6-dichloro-4-methyl-benzene (537 mg, 1.43 mmol) in dry THF (15 mL) at -78°C was treated with BuLi (1.6M in hexane, 0.428 mL, 1.56 mmol). After 30 min this sol. was cannulated on a sol. of compound **B1** (520 mg, 1.30 mmol) in dry THF (15 mL) at -78°C . After 1 h, the mixture was poured in aq. sat. NH_4Cl , extracted with EtOAc (2x), dried over Na_2SO_4 , filtered, and the solvents were
10 removed under reduced pressure. Purification of the residue by FC (heptane $\rightarrow$ heptane/EtOAc 70:30) yielded the title compound (89 mg, 10%). LC-MS: $t_{\text{R}} = 1.23$ min; ES+: 697.16.

(rac.)-(3*R, 4*S**)-3-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-1-carboxylic acid *tert*-butyl ester (D2)**

A sol. of 1-[2-(4-bromo-phenoxy)-ethoxy]-2,6-dichloro-4-methyl-benzene (4.04 g, 10.8 mmol) in THF (107 mL) at -78°C was treated with BuLi (1.6M in hexane, 7.38 mL, 11.8 mmol). After 30 min, DMPU (2.85 mL, 23.7 mmol) was added, and the mixture was
20 stirred for 5 min. A sol. of compound **B2** (2.00 g, 4.30 mmol) in THF (14 mL) was added slowly. The mixture was stirred for 15 min at -78°C , and aq. sat. NH_4Cl (100mL) was added. The mixture was allowed to warm up to rt, and the solvents were partially removed under reduced pressure. The aq. residue was diluted with aq. sat. NH_4Cl (50 mL), and the mixture was extracted with EtOAc (3x). The combined org. extracts were dried over
25 MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane $\rightarrow$ EtOAc/heptane 40:60) yielded the title compound (380 mg, 12%). LC-MS: $t_{\text{R}} = 1.27$ min; ES+: 763.22.

(rac.)-(3*R, 4*S**)-3'-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy 3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester (D3)**

30

Mg turnings (535 mg, 22.0 mmol) and anhydrous LiCl (848 mg, 20.0 mmol) were placed in a dried flask in an oil bath at 120°C overnight under high vacuum. Once this was cooled under N₂, without opening the flask, THF (10 mL) was added. A sol. of *iso*-propyl chloride in THF (10 mL) was slowly added at rt, and the mixture was stirred for 12 h at rt.

5 The resulting grey 1M-sol. is ready to be used but should not be kept more than 24 h. 5-Bromo-2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-pyridine (3040 mg, 8.07 mmol) in dry THF (80.6 mL) was treated with the previously prepared Grignard sol. (1M, 8.48 mL, 8.48 mmol). The mixture was stirred for 4 h at rt. The *iso*-propyl Grignard sol. (1M, 8.00 mL, 8.00 mmol) was added again, and the mixture was stirred for 2 h. A sol. of compound

10 **B2** (1500 mg, 3.226 mmol) in dry THF (15 mL) was added, and the mixture was stirred at rt for 15 min. The mixture was poured onto aq. sat. NH₄Cl, and extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → heptane/EtOAc 70:30) yielded the title compound (1.74 g, 71%). LC-MS: t_R = 1.23 min;

15 ES+: 764.49.

(rac.)-(3*R, 4*S**)-6-[3-(2-Chloro-3,6-difluoro-phenyl)-isoxazol-5-ylmethoxy]-3'-{[2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid**

20 ***tert*-butyl ester (D4)**

Mg turnings (535 mg, 22.0 mmol) and anhydrous LiCl (848 mg, 20.0 mmol) were placed in a dried flask in an oil bath at 120°C overnight under high vacuum. Once this was cooled under N₂, without opening the flask, THF (10 mL) was added. A sol. of *iso*-propyl chloride in THF (10 mL) was slowly added at rt, and the mixture was stirred for 12 h at rt.

25 The resulting grey 1M-sol. is ready to be used but should not be kept more than 24 h. A sol. of compound **K1** (1.08 g, 2.69 mmol) in dry THF (27 mL) was treated at rt with the previously prepared Grignard sol. (1M, 3.76 mL, 3.76 mmol). The mixture was stirred at rt and the formation of the Grignard was checked every hour. After 5 h, a sol. of compound **B2** (500 mg, 1.08 mmol) in dry THF (10 mL) was added, and the reaction was stirred at rt

30 for 1 h. The mixture was poured onto aq. sat. NH₄Cl, and the mixture was extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane →

EtOAc/heptane 30:70) afforded the title compound (275 mg, 33%). LC-MS: t_R = 1.20 min; ES+: 787.64.

Mixture of (3'R, 4'S)-3'-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-6-[(R)-3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester and (3'S, 4'R)-3'-{[2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-carbamoyl}-6-[(R)-3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester (D5)

Mg turnings (535 mg, 22.0 mmol) and anhydrous LiCl (848 mg, 20.0 mmol) were placed in a dried flask in an oil bath at 120°C overnight under high vacuum. Once this was cooled under N₂, without opening the flask, THF (10 mL) was added. A sol. of *iso*-propyl chloride in THF (10 mL) was slowly added at rt, and the mixture was stirred for 12 h at rt. The resulting grey 1M-sol. is ready to be used but should not be kept more than 24 h. (R)-5-Bromo-2-[3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-pyridine (2.16 g, 5.38 mmol) in dry THF (61 mL) was treated at rt with the previously prepared Grignard sol. (1M, 8.47 mL, 8.47 mmol). The mixture was stirred at rt and the formation of the Grignard was checked every hour. After 8 h, a sol. of compound B2 (1.13 g, 2.42 mmol) in dry THF (11 mL) was added and the reaction was stirred at rt for 1 h. The mixture was poured onto aq. sat. NH₄Cl, and the mixture was extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → EtOAc/heptane 30:70) afforded the title compounds mixture (1.29 g, 68%). LC-MS: t_R = 1.03 min; ES+: 787.77.

(*rac.*)-(3'R*, 4'S*)-3'-{[5-Chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-carbamoyl}-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester (D6)

Mg turnings (535 mg, 22.0 mmol) and anhydrous LiCl (848 mg, 20.0 mmol) were placed in a dried flask in an oil bath at 120°C overnight under high vacuum. Once this was cooled under N₂, without opening the flask, THF (10 mL) was added. A sol. of *iso*-propyl chloride in THF (10 mL) was slowly added at rt, and the mixture was stirred for 12 h at rt. The resulting grey 1M-sol. is ready to be used but should not be kept more than 24 h. 5-

Bromo-2-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-pyridine (2.02 g, 5.37 mmol) in dry THF (54 mL) was treated at rt with the previously prepared Grignard sol. (1M, 7.51 mL, 7.51 mmol). The mixture was stirred at rt and the formation of the Grignard was checked every hour. After 5 h, a sol. of compound **B3** (1.03 g, 2.15 mmol) in dry THF (10 mL) was added and the reaction was stirred at rt for 1 h. The mixture was poured onto aq. sat. NH₄Cl, and the mixture was extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → EtOAc/heptane 2:7) afforded the title compound (921 mg, 55%). LC-MS: t_R = 1.19 min; ES+: 779.64.

(rac.)-(3'R*, 4'S*)-3'-{[5-Chloro-2-(3-methoxy-propyl)-1-oxy-pyridin-4-ylmethyl]-cyclopropyl-carbamoyl}-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-3',4',5',6'-tetrahydro-2'H-[3,4']bipyridinyl-1'-carboxylic acid *tert*-butyl ester (D7)

A sol. of compound **D6** (46 mg, 0.603 mmol) in dry CH₂Cl₂ (6.00 mL) was treated at rt with 3-chloroperbenzoic acid (70%, 166 mg, 0.675 mmol), and the mixture was stirred at rt for 2 h. The mixture was poured onto aq. sat. NaHCO₃, and extracted with EtOAc. The org. extract was washed with aq. sat. NaHCO₃ (2x), was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane → heptane/EtOAc 50:50) yielded the title compound (347 mg, 73%).

5-Bromo-2-[3-(2-chloro-3,6-difluoro-phenyl)-isoxazol-5-ylmethoxy]-pyridine (K1)

2,5-Dibromopyridine (31.4 g, 132 mmol) and compound **L1** (25.0 g, 102 mmol) were dissolved in dry toluene (1.00 L) under nitrogen. *tert*-BuONa (14.7 g, 153 mmol), xantphos (3.54 g, 6.12 mmol) and Pd₂(dba)₃·CHCl₃ (1.83 g, 2.00 mmol) were added to the mixture. The mixture was heated to reflux overnight, and was allowed to cool to rt. The mixture was washed with aq. sat. NaHCO₃ and brine. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 10:90) yielded the title compound (17.4 g, 43%). LC-MS: t_R = 1.08 min.

[3-(2-Chloro-3,6-difluoro-phenyl)-isoxazol-5-yl]-methanol (L1)

A sol. of 2-chloro-3,6-difluoro-benzaldehyde oxime (21.3 g, 111 mmol) in DMF (66.7 mL) was added dropwise to a sol. of NCS (14.9 g, 111 mmol) and pyridine (1.78 mL) in DMF (222 mL). The mixture was stirred for 1 h at rt, and a sol. of propargyl alcohol (4.99 g, 89.1 mmol) in DMF (71 mL) was added dropwise. The reaction mixture was heated to 85 °C, and a sol. of Et₃N (15.5 mL, 111 mmol) in DMF (89.3 mL) was slowly added. The reaction mixture was stirred at 85 °C for 60 min, and was allowed to cool to rt. The mixture was diluted with water (533 mL), and was extracted with EtOAc (2x). The combined org. extracts were washed with water and brine, were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 40:60) yielded the title compound (17.0 g, 78%). LC-MS: t_R = 0.84 min; ES+: 287.12.

3-(Benzyl-*tert*-butoxycarbonyl-amino)-propionic acid ethyl ester (M1)

Boc₂O (5.53 g, 25.3 mmol) was added to a sol. of *N*-benzyl-β-alanine ethyl ester (3.40 mL, 16.9 mmol) and DIPEA (11.6 mL, 67.6 mmol) in CH₂Cl₂ (200 mL) at 0 °C. The mixture was stirred overnight while warming up to rt. The mixture was cooled to 0°C, and was partitioned with aq. 1M HCl. The org. layer was washed again with aq. 1M HCl and with aq. sat. NaHCO₃. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 3:20) yielded the title compound (5.16 g, 99%). LC-MS: t_R = 1.02 min.

3-(Benzyl-*tert*-butoxycarbonyl-amino)-propionic acid (N1)

A mixture of compound **M1** (838 mg, 2.73 mmol) in EtOH (34 mL) and aq. 1M NaOH (13.7 mL) was stirred at 70 °C for 2 h. The mixture was allowed to cool to rt, and aq. 1M HCl was added until a pH = 4 was reached. The solvents were partially removed under reduced pressure, and the aq. residue was extracted with EtOAc. The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying under high vacuum yielded the crude title compound (769 mg, quantitative yield) that was used further without purification. LC-MS: t_R = 0.89 min; ES+: 280.33.

Benzyl-(2-{{2-chloro-5-(2-methoxy-ethyl)-benzyl}-cyclopropyl-carbamoyl}-ethyl)-carbamic acid *tert*-butyl ester (O1)

A mixture of compound **N1** (769 mg, 2.75 mmol), DMAP (84.1 mg, 0.688 mmol), HOBt (446 mg, 3.30 mmol), DIPEA (1.78 g, 2.36 mmol) and EDC·HCl (1.32 g, 6.88 mmol) in CH₂Cl₂ (65 mL) was stirred at rt for 45 min. [2-Chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amine (1.14 g, 4.13 mmol) was added, and the mixture was stirred overnight. CH₂Cl₂ was added, and the mixture was washed with aq. 1M HCl (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (MeOH/CH₂Cl₂ 1:99) yielded the title compound (1.12 g, 76%). LC-MS: *t*_R = 1.11 min; ES+: 501.30.

4-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-benzaldehyde (Q1)

BuLi (1.6M in hexane, 17.0 mL, 26.9 mmol) was added to a sol. 1-[2-(4-bromo-phenoxy)-ethoxy]-2,6-dichloro-4-methyl-benzene (8.81 g, 23.4 mmol) in THF (91 mL) at -78 °C. The mixture was stirred for 10 min at -78 °C, and DMF (2.72 mL, 35.1 mmol) was added. The mixture was stirred at -78 °C for 2.5 h, and aq. sat. NH₄Cl was added. The mixture was allowed to warm up to rt, and was extracted with TBME (2x). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:4) yielded the title compound (3.64 g, 48%). LC-MS: *t*_R = 1.07 min; ES+: 325.03.

Examples

Example 1

(*rac.*)-(3*S, 4*R**)-4-{4-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide**

A sol. of compound **D1** (51 mg, 0.073 mmol) in dioxane (1 mL) at 0 °C was treated with HCl (4M in dioxane, 0.5 mL), and the mixture was stirred at 0 °C for 2 h. The reaction mixture was concentrated to dryness. Purification by FC (CH₂Cl₂ → CH₂Cl₂/MeOH 90:10) yielded the title compound (18 mg, 39%). LC-MS: *t*_R = 0.96 min; ES+: 597.16.

Example 2

(3*S*, 4*R*)-4-{4-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide HCl (4M in dioxane, 2.40 mL) was added to a sol. of compound **D2** (380 mg, 0.499 mmol) in CH₂Cl₂ (2.40 mL) at 0 °C. The mixture was stirred for 2 h while warming up to rt, and the solvents were then removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂/MeOH 90:10) yielded the racemic title compound (249 mg, 75%). This mixture was separated by chiral, preparative HPLC (Regis Whelk, isocratic eluent B 85%). The title compound was obtained (42 mg, 19%). LC-MS: *t*_R = 0.96 min; ES+: 663.56. Chiral, analytic HPLC (Regis Whelk, isocratic eluent B 85%): *t*_R = 33.0 min.

Example 3

(3'*S*, 4'*R*)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide

Compound **D3** (1.132 g, 1.485 mmol) was dissolved in CH₂Cl₂ (7.40 mL). The sol. was cooled to 0 °C. HCl (4M in dioxane, 7.40 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at rt, and was carefully poured onto a mixture of aq. sat. NaHCO₃ and EtOAc. The mixture was extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) yielded the racemic title compound still mixed with little silica gel. This mixture was diluted with CH₂Cl₂, and filtered over cotton. The solvents were removed under reduced pressure to yield the pure, racemic title compound (904 mg, 92%). This racemate was separated by chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 45%). The title compound was obtained (350 mg, 42%). LC-MS: *t*_R = 0.94 min; ES+: 662.43. Chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 65%): *t*_R = 11.4 min.

Example 4

(3'*S*, 4'*R*)-6-[3-(2-Chloro-3,6-difluoro-phenyl)-isoxazol-5-ylmethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide

Compound **D4** (275 mg, 0.349 mmol) was dissolved in CH₂Cl₂ (1.75 mL). The sol. was cooled to 0 °C. HCl (4M in dioxane, 1.75 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at rt, and was carefully poured onto a mixture of aq. sat. NaHCO₃ and EtOAc. The mixture was extracted with EtOAc. The combined org. extracts
5 were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂ → CH₂Cl₂/MeOH 90:10) yielded the racemic title compound (162 mg, 67%). This racemate was separated by chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%). The title compound was obtained (45 mg, 30%). LC-MS: t_R = 0.92 min; ES+: 687.63. Chiral, analytic HPLC (Chiralpack AD, isocratic
10 eluent B 50%): t_R = 11.5 min.

Example 5

(3'S, 4'R)-6-[(R)-3-(2,6-Dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide
15

Compounds **D5** (1.29 g, 1.64 mmol) were dissolved in CH₂Cl₂ (8.2 mL). The sol. was cooled to 0 °C. HCl (4M in dioxane, 8.2 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at rt, and was carefully poured onto a mixture of aq. sat. NaHCO₃ and EtOAc. The mixture was extracted with EtOAc. The combined org. extracts
20 were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) yielded the title compound still mixed with its corresponding stereoisomer and with little silica gel. This mixture was diluted with CH₂Cl₂, and filtered over cotton. The solvents were removed under reduced pressure to yield the pure title compound mixed with its corresponding
25 diastereoisomer (904 mg, 80%). Part of this mixture (150 mg) was separated by chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%). The title compound was obtained (50 mg, 33%). LC-MS: t_R = 0.81 min; ES+: 689.66. Chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%): t_R = 10.7 min.

30 Example 6

(3'S, 4'R)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-amide

Compound **D6** (920 mg, 1.18 mmol) was dissolved in CH₂Cl₂ (5.9 mL). The sol. was cooled to 0 °C. HCl (4M in dioxane, 5.9 mL) was added dropwise to the mixture. The mixture was stirred for 1 h at rt, and was carefully poured onto a mixture of aq. sat. NaHCO₃ and EtOAc. The mixture was extracted with EtOAc. The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂ to CH₂Cl₂/MeOH 90:10) yielded the title compound still mixed its corresponding stereoisomer and with little silica gel. This mixture was diluted with CH₂Cl₂, and filtered over cotton. The solvents were removed under reduced pressure to yield the pure title compound mixed with its corresponding diastereoisomer (682 mg, 85%). Part of this mixture (80 mg) was separated by chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%). The title compound was obtained (31 mg, 39%). LC-MS: t_R = 0.88 min; ES+: 679.23. Chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%): t_R = 16.4 min.

Example 7

(3'S, 4'R)-6-[2-(2,6-Dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-1-oxy-pyridin-4-ylmethyl]-cyclopropyl-amide

Compound **D7** (347 mg, 0.500 mmol) was dissolved in CH₂Cl₂ (2.5 mL). HCl (4M in dioxane, 2.50 mL) was added dropwise to the sol. The mixture was stirred at rt for 1 h, and was carefully poured onto a mixture of aq. sat. NaHCO₃ and EtOAc. The mixture was extracted with EtOAc, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂ → CH₂Cl₂/MeOH 9:1) yielded the title compound still mixed with silica gel. This mixture was taken in CH₂Cl₂, and filtered over cotton, which yielded the racemic title compound (266 mg, 77%). Part of this racemate (83 mg) was separated by chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%). The title compound was obtained (29 mg, 35%). Chiral, analytic HPLC (Chiralpack AD, isocratic eluent B 50%): t_R = 31.1 min.

Biological Assays

1. Enzyme immuno assay (EIA) to estimate AngI accumulation and renin inhibition

5 1.1 Preparation of AngI-BSA conjugate

1.3 mg (1 μ mol) of AngI [1-10 (Bachem, H-1680)] and 17 mg (0.26 μ mol) of BSA (Fluka, 05475) were dissolved in 4 mL of 0.1M phosphate buffer, pH 7.4, after which 2 mL of a 1:100 dilution of glutaraldehyde in H₂O (Sigma G-5882) was added dropwise. The mixture was incubated overnight at 4 °C, then dialyzed against 2 liters of 0.9% NaCl, twice
10 for 4 h at rt, followed by dialysis against 2 liters of PBS 1X overnight at rt. The solution was then filtered with a Syringe filter, 0.45 μ m (Nalgene, Cat. No. 194-2545). The conjugate can be stored in polypropylene tubes in 0.05% sodium azide at 4 °C for at least 12 months.

15 1.2 Preparation of BSA-AngI coated MTP

Microtiter plates (MPT384, MaxiSorpTM, Nunc) were incubated overnight at 4 °C with 80 μ l of AngI (1-10)/BSA conjugate, diluted 1:100'000 in PBS 1X in a teflon beaker (exact dilution dependent on batch of conjugate), emptied, filled with 90 μ l of blocking solution [0.5% BSA (Sigma A-2153) in PBS 1X, 0.02% NaN₃], and incubated for at least 2 h at rt,
20 or overnight at 4 °C. 96 well MTP (MaxiSorpTM, Nunc) were coated with 200 μ l conjugate and blocked with 250 μ l blocking solution as above, except that the blocking solution contained 3% BSA. The plates can be stored in blocking solution at 4 °C for 1 month.

1.3 AngI-EIA in 384 well MTP

25 The AngI (1-10)/BSA coated MTP were washed 3 times with wash buffer (PBS 1X, 0.01% Tween 20) and filled with 75 μ l of primary antibody solution (anti-AngI antiserum, pre-diluted 1:10 in horse serum), diluted to a final concentration of 1:100'000 in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4). 5 μ l of the renin reaction (or standards in assay buffer) (see below) were added to the primary antibody solution and the plates were
30 incubated overnight at 4 °C. After the incubation the plates were washed 3 times with wash buffer and incubated with secondary antibody [anti-rabbit IgG, linked to horseradish peroxidase (Amersham Bioscience, NA 934V), diluted 1:2'000 in wash buffer] for 2 h at

rt. The plates were washed 3 times with wash buffer and then incubated for 1 h at rt with substrate solution [1.89mM ABTS (2,2'-azino-di-(3-ethyl-benzthiazolinsulfonate)] (Roche Diagnostics, 102 946) and 2.36mM H₂O₂ [30%, (Fluka, 95300)] in substrate buffer (0.1M sodium acetate, 0.05M sodium dihydrogen phosphate, pH 4.2). The OD of the plate was
5 read at 405 nm in a microplate reader (FLUOStar Optima from BMG). The production of AngI during the renin reaction was quantified by comparing the OD of the sample with the OD of a standard curve of AngI(1-10), measured in parallel.

2. Primary renin inhibition assay: IC₅₀ in buffer, 384 well MTP

10 The renin assay was adapted from an assay described before (Fischli W. *et al.*, *Hypertension*, **1991**, 18:22-31) and consists of two steps: in the first step, recombinant human renin is incubated with its substrate (commercial human tetradecapeptide renin substrate) to create the product Angiotensin I (AngI). In the second step, the accumulated AngI is measured by an immunological assay (enzyme immuno assay, EIA). The detailed
15 description of this assay is found below. The EIA is very sensitive and well suited for renin activity measurements in buffer or in plasma. Due to the low concentration of renin used in this assay (2 fmol per assay tube or 10 pM) it is possible to measure inhibitor affinities in this primary assay down to low pM concentration.

20 2.1 Methodology

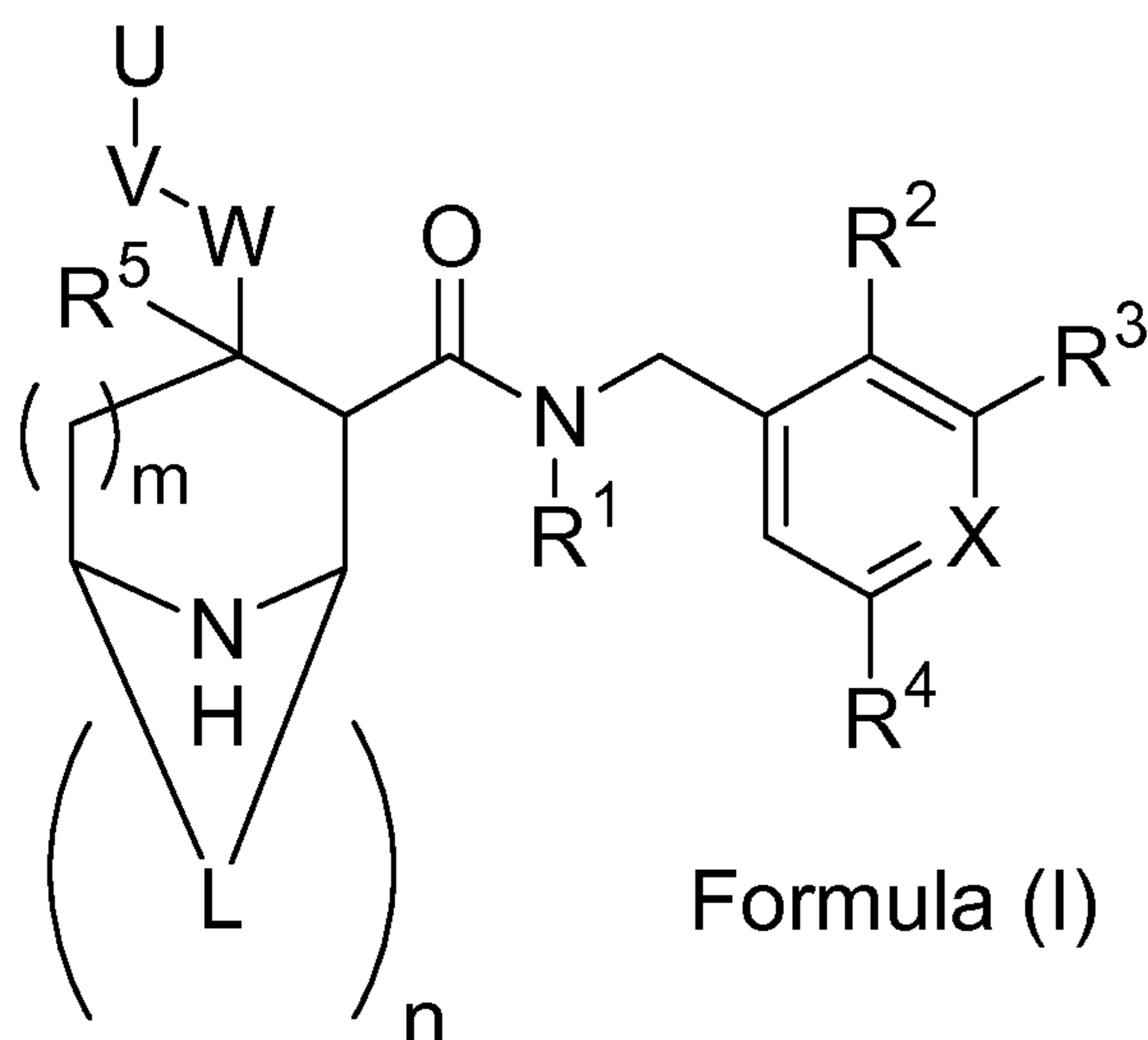
Recombinant human renin (3 pg/μl) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μM in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H₂O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 μl per well of this premix was transferred into
25 polypropylene plates (MTP384, Nunc). Test compounds were dissolved and diluted in 100% DMSO and 2.5 μl added to the premix, then incubated at 37 °C for 3 h. At the end of the incubation period, 5 μl of the renin reaction (or standards in assay buffer) were transferred into EIA assays (as described above) and AngI produced by renin was quantified. The percentage of renin inhibition (AngI decrease) was calculated for each
30 concentration of compound and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC₅₀). The compounds exhibit a very good bioavailability and are metabolically more stable than prior art compounds.

Examples of inhibition:

Compound of Example No.	IC₅₀ values [nM]
1	0.18
3	0.12
5	0.15
7	0.23

Claims

1. A compound of the formula (I)

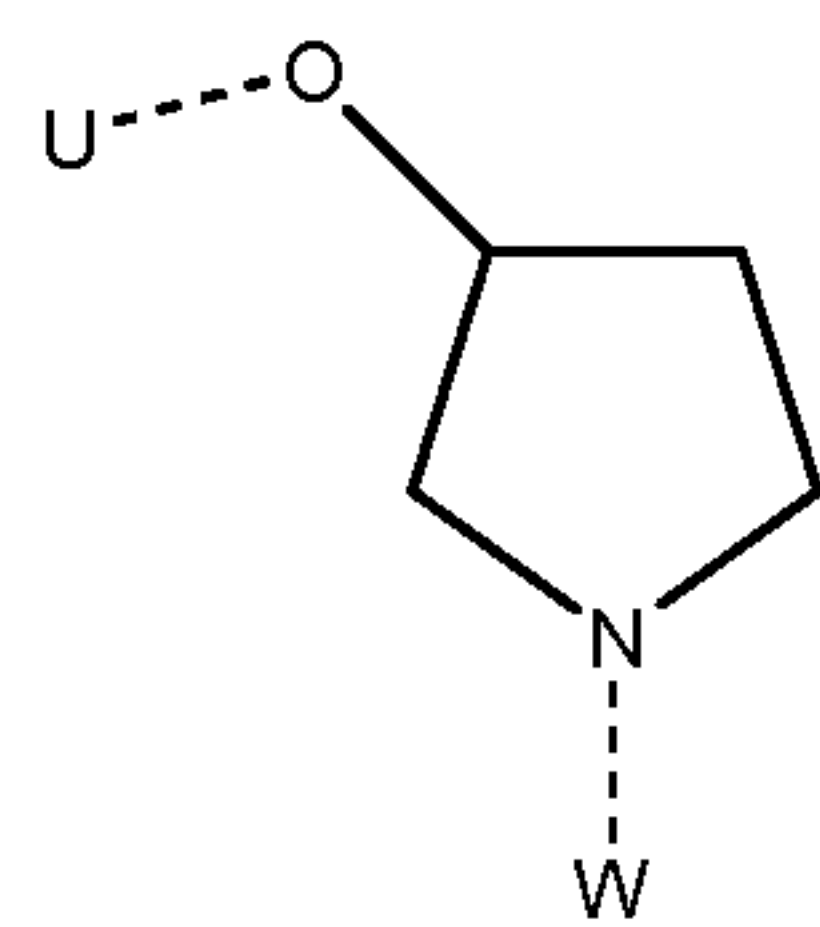


5 wherein

X represents CH, N, or N⁺-O⁻;

W represents a *para*-substituted phenyl, a *para*-substituted pyridinyl, or a thiazolyl;

V represents -CH₂CH₂CH₂-, -CH₂CH₂-A-, -CH₂-A-CH₂-, -A-CH₂CH₂-, -CH₂CH₂CH₂CH₂-,
 , -A-CH₂CH₂CH₂-, -CH₂-A-CH₂CH₂-, -CH₂CH₂-A-CH₂-, -CH₂CH₂CH₂-A-, -A-CH₂CH₂-
 10 B-, -CH₂CH₂CH₂CH₂CH₂-, -A-CH₂CH₂CH₂CH₂-, -CH₂-A-CH₂CH₂CH₂-, -CH₂CH₂-A-
 CH₂CH₂-, -CH₂CH₂CH₂-A-CH₂-, -CH₂CH₂CH₂CH₂-A-, -A-CH₂CH₂CH₂-B-, -CH₂-A-
 CH₂CH₂-B-, -A-CH₂CH₂-B-CH₂-, -A-CH₂CH₂CH₂-B-CH₂-, -CH₂-A-CH₂CH₂CH₂-B-, or
 -O-CH₂-Q-, wherein Q is bound to the group U of formula (I), or V represents a
 pyrrolidinyl of the formula:



15

U represents unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl, -CF₃,

halogen, and hydroxy-C₁₋₇-alkyl; or five-membered heteroaryl with two heteroatoms independently selected from nitrogen, oxygen and sulphur, wherein said heteroaryl radical is optionally mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, -CF₃, -OCF₃, and halogen;

- 5 Q represents a five-membered heteroaryl with two or three heteroatoms independently selected from O and N;

L represents -CH₂-CH₂-, -CH₂-CH(R⁶)-CH₂-, -CH₂-N(R⁷)-CH₂-, -CH₂-O-CH₂-, or -CH₂-S-CH₂-;

A and B represent independently from each others -O- or -S-;

- 10 R¹ represents C₁₋₇-alkyl or cycloalkyl;

R² represents halogen or C₁₋₇-alkyl;

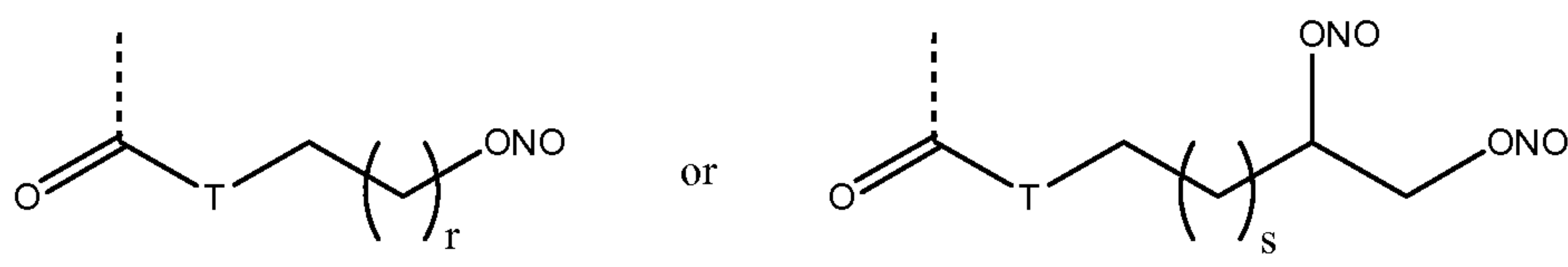
R³ represents hydrogen, halogen, C₁₋₇-alkyl, C₁₋₇-alkoxy, or -CF₃;

- R⁴ represents hydrogen; C₁₋₇-alkyl-O-(CH₂)₀₋₄-CH₂-; CF₃-O-(CH₂)₀₋₄-CH₂-; R'₂N-(CH₂)₀₋₄-CH₂-, wherein R' is independently selected from the group consisting of hydrogen, C₁₋₇-alkyl (optionally substituted by one to three fluorine), cyclopropyl (optionally substituted by one to three fluorine), cyclopropyl-C₁₋₇-alkyl (optionally substituted by one to three fluorine), and -C(=O)-R'' wherein R'' is C₁₋₄-alkyl, C₁₋₄-alkoxy, -CF₃, -CH₂-CF₃, or cyclopropyl; or R¹³-C(=O)-(O)₀₋₁-(CH₂)₀₋₄-, wherein R¹³ is C₁₋₄-alkyl, C₁₋₄-alkoxy, or cyclopropyl; wherein R' and R'' preferably do not both simultaneously represent
20 hydrogen;

R⁵ represents hydroxy, C₁₋₇-alkoxy, hydroxy-C₁₋₇-alkyl, dihydroxy-C₁₋₇-alkyl, C₁₋₇-alkoxy-C₁₋₇-alkyl, C₁₋₇-alkoxy-C₁₋₇-alkoxy-C₁₋₇-alkyl, hydroxy-C₁₋₇-alkoxy-C₁₋₇-alkyl, carbamoyl-C₁₋₇-alkoxy, or C₁₋₇-alkyl-carbonyloxy;

- R⁶ represents -H, -CH₂OR⁹, -CH₂NR⁸R⁹, -CH₂NR⁸COR⁹, -CH₂NR⁸SO₂R⁹, -CO₂R⁹,
25 -CH₂OCONR⁸R⁹, -CONR⁸R⁹, -CH₂NR⁸CONR⁸R⁹, -CH₂SO₂NR⁸R⁹, -CH₂SR⁹, -CH₂SOR⁹,
or -CH₂SO₂R⁹;

R^7 represents $-R^9$, $-\text{COR}^9$, $-\text{COOR}^{11}$, $-\text{CONR}^8R^9$, $-\text{C}(\text{NR}^8)\text{NR}^8R^9$, $-\text{CSNR}^8R^9$, $-\text{SO}_2R^9$, or $-\text{SO}_2\text{NR}^8R^9$; or R^7 represents a radical of the formula:



wherein T represents $-\text{CH}_2-$, $-\text{NH}-$ or $-\text{O}-$, r is an integer from 1 to 6 and s is an integer from 1 to 4;

R^8 and $R^{8'}$ independently represent hydrogen, C_{1-7} -alkyl, C_{2-7} -alkenyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein C_{1-7} -alkyl, cycloalkyl, and cycloalkyl- C_{1-7} -alkyl can be substituted by one, two, or three halogens;

R^9 represents hydrogen, C_{1-7} -alkyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein C_{1-7} -alkyl, cycloalkyl, and cycloalkyl- C_{1-7} -alkyl may be mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, hydroxy, $-\text{OCOR}^{12}$, $-\text{COOR}^{12}$, C_{1-7} -alkoxy, cyano, SO_2R^{12} , $-\text{CONR}^{12}R^{12'}$, morpholin-4-yl-CO-, ((4- C_{1-7} -alkyl)piperazin-1-yl)-CO-, $-\text{NHC}(\text{NH})\text{NH}_2$, $-\text{NR}^{10}R^{10'}$ and C_{1-7} -alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp^3 -hybridized;

R^{10} and $R^{10'}$ independently represent hydrogen, C_{1-7} -alkyl, cycloalkyl, cycloalkyl- C_{1-7} -alkyl, hydroxy- C_{1-7} -alkyl, $-\text{COOR}^8$, or $-\text{CONH}_2$;

R^{11} represents halogen, C_{1-7} -alkyl, C_{1-7} -alkoxy, $-\text{CF}_3$, or hydrogen;

R^{12} and $R^{12'}$ independently represent hydrogen, C_{1-7} -alkyl, C_{2-7} -alkenyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein C_{1-7} -alkyl, cycloalkyl, and cycloalkyl- C_{1-7} -alkyl can be substituted by one, two, or three halogens;

n represents the integer 0 or 1; and

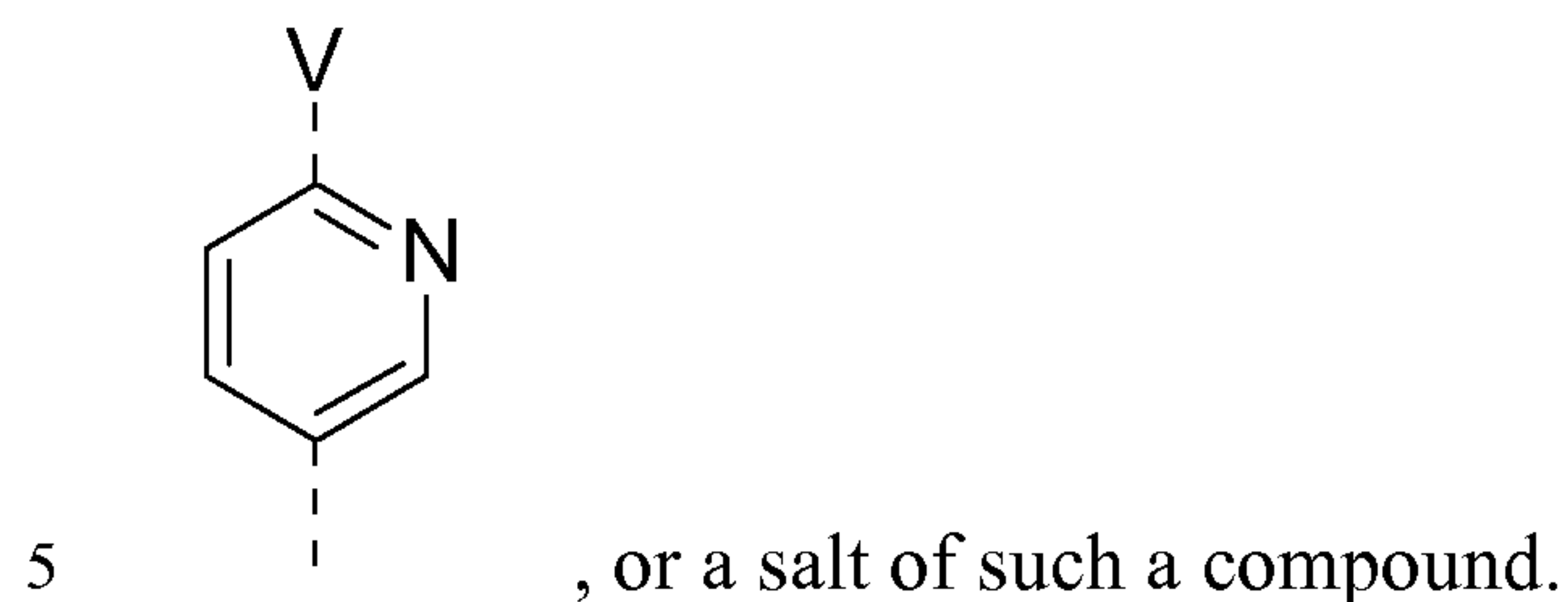
m represents the integer 0 or 1, with the proviso that m represents the integer 1 if n represents the integer 1;

and salts thereof.

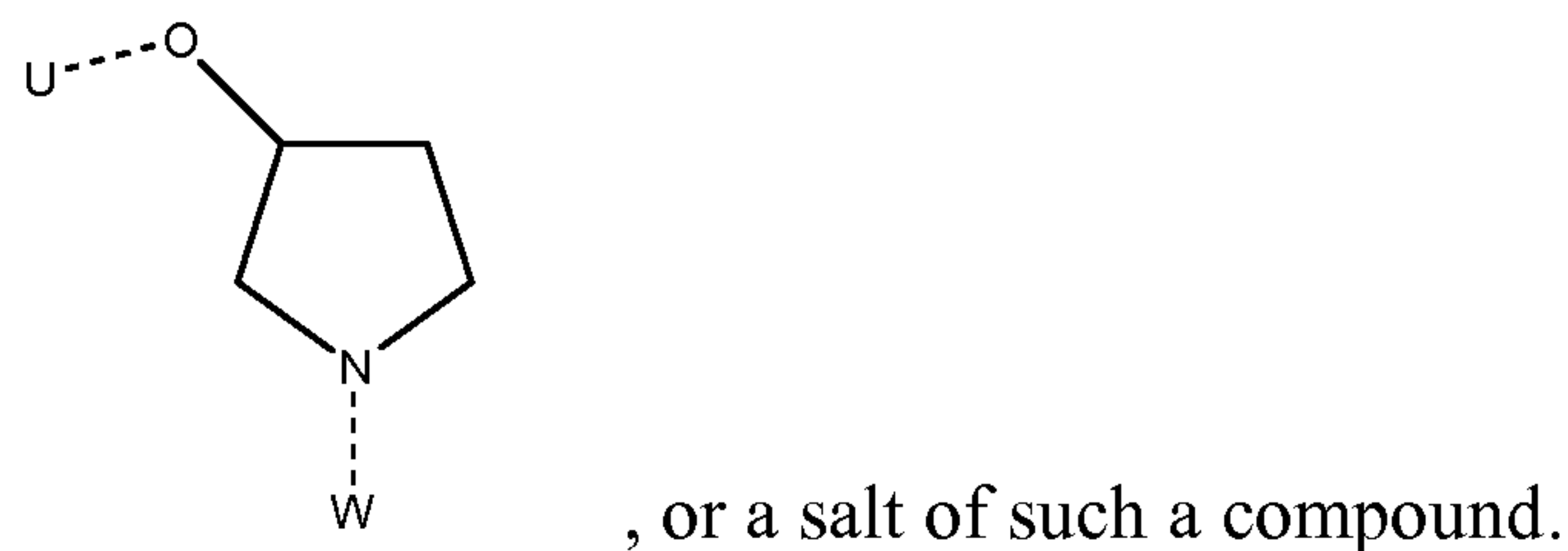
2. A compound according to claim 1, wherein X represents N^+-O^- and R^4 represents C_{1-4} -alkoxy- $C(=O)-NH-(CH_2)_{0-4}-CH_2-$ or $R^{13}-C(=O)-(O)_{0-1}-(CH_2)_{0-4}-$, wherein R^{13} is C_{1-4} -alkyl, C_{1-4} -alkoxy, or cyclopropyl, or a salt of such a compound.
3. A compound according to claim 1, wherein X represents CH or N; and
 5 R^4 represents hydrogen; C_{1-7} -alkyl- $O-(CH_2)_{0-4}-CH_2-$; $CF_3-O-(CH_2)_{0-4}-CH_2-$; or $R'_2N-(CH_2)_{0-4}-CH_2-$, wherein R' is independently selected from the group consisting of hydrogen, C_{1-7} -alkyl (optionally substituted by one to three fluorine), cyclopropyl (optionally substituted by one to three fluorine), cyclopropyl- C_{1-7} -alkyl (optionally substituted by one to three fluorine), and $-C(=O)-R''$ wherein R'' is C_{1-4} -alkyl, $-CF_3$, $-CH_2-$
 10 CF_3 , or cyclopropyl;
 or a salt of such a compound.
4. A compound according to claim 1, wherein X represents CH or N^+-O^- , or a salt of such a compound.
5. A compound according to any one of claims 1 to 4, wherein R^7 represents $-R^9$, $-COR^9$,
 15 $-COOR^{11}$, $-CONR^8R^9$, $-C(NR^8)NR^8R^9$, $-CSNR^8R^9$, $-SO_2R^9$, or $-SO_2NR^8R^9$, or a salt of such a compound.
6. A compound according to any one of claims 1 to 5, wherein A and B both represent $-O-$, or a salt of such a compound.
7. A compound according to any one of claims 1 to 6, wherein R^6 represents $-CO_2CH_3$ or
 20 $-CO_2H$, or a salt of such a compound.
8. A compound according to any one of claims 1 to 7, wherein R^7 represents $-H$, $-COCH_3$, $-C(NH)NH_2$, $-CONHCH_2C(CH_3)_2CONH_2$, $-CONHCH(CH_2)_2$, or $-CONHC(CH_2)_2CN$, or a salt of such a compound.
9. A compound according to claim 8, wherein R^7 represents $-H$, or a salt of such a
 25 compound.
10. A compound according to any one of claims 1 to 6, wherein L represents $-CH_2-CH_2-$ or $-CH_2-NH-CH_2-$, or a salt of such a compound.

11. A compound according to any one of claims 1 to 10, wherein R^1 represents cyclopropyl, or a salt of such a compound.

12. A compound according to any one of claims 1 to 11, wherein W represents a *para*-substituted phenyl, or



13. A compound according to any one of claims 1 to 12, wherein V represents -O-CH₂CH₂-O-, -O-CH₂-Q-, -CH₂-CH₂-O- wherein the -CH₂ part of -CH₂-CH₂-O- is bound to the group W of formula (I), or

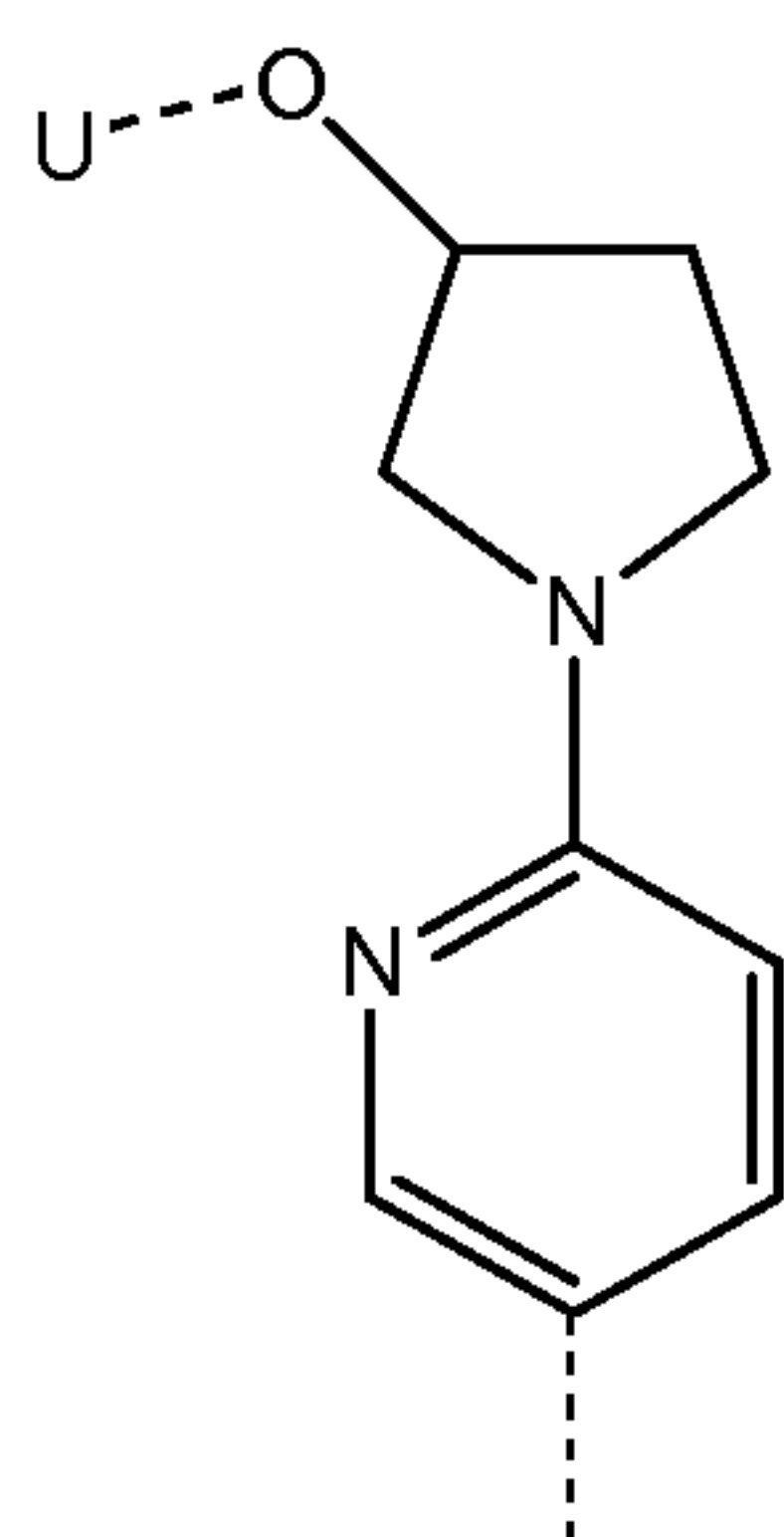


10 14. A compound according to claim 13, wherein V represents -O-CH₂CH₂-O- or -O-CH₂-Q-, or a salt of such a compound.

15. A compound according to any one of claims 1 to 14, wherein Q represents an isoxazolyl or an oxadiazolyl, or a salt of such a compound.

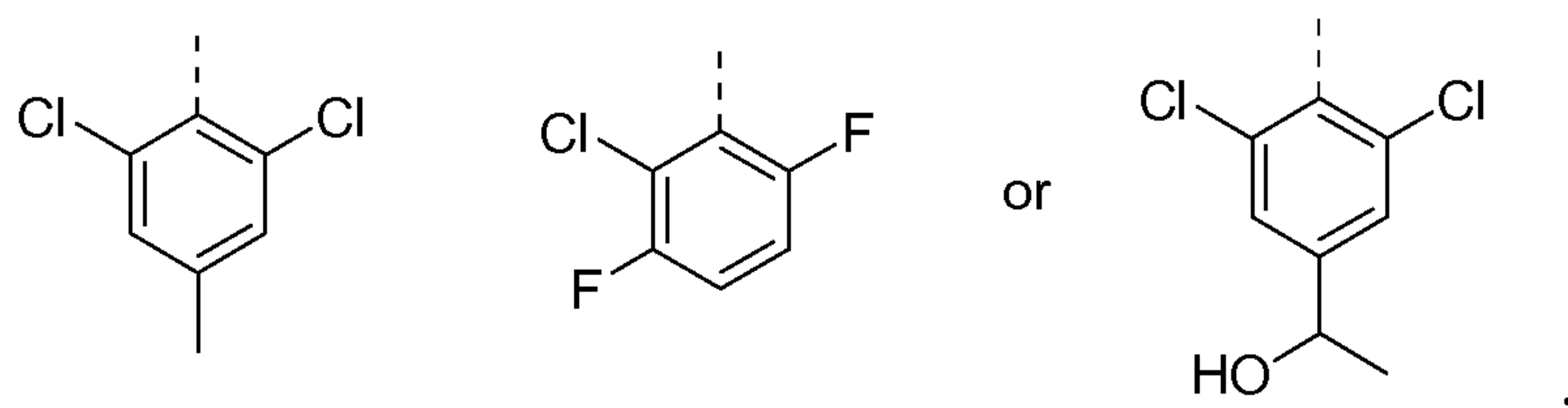
15 16. A compound according to claim 15, wherein Q represents an isoxazolyl, or a salt of such a compound.

17. A compound according to any one of claims 1 to 11, wherein V-W represents:



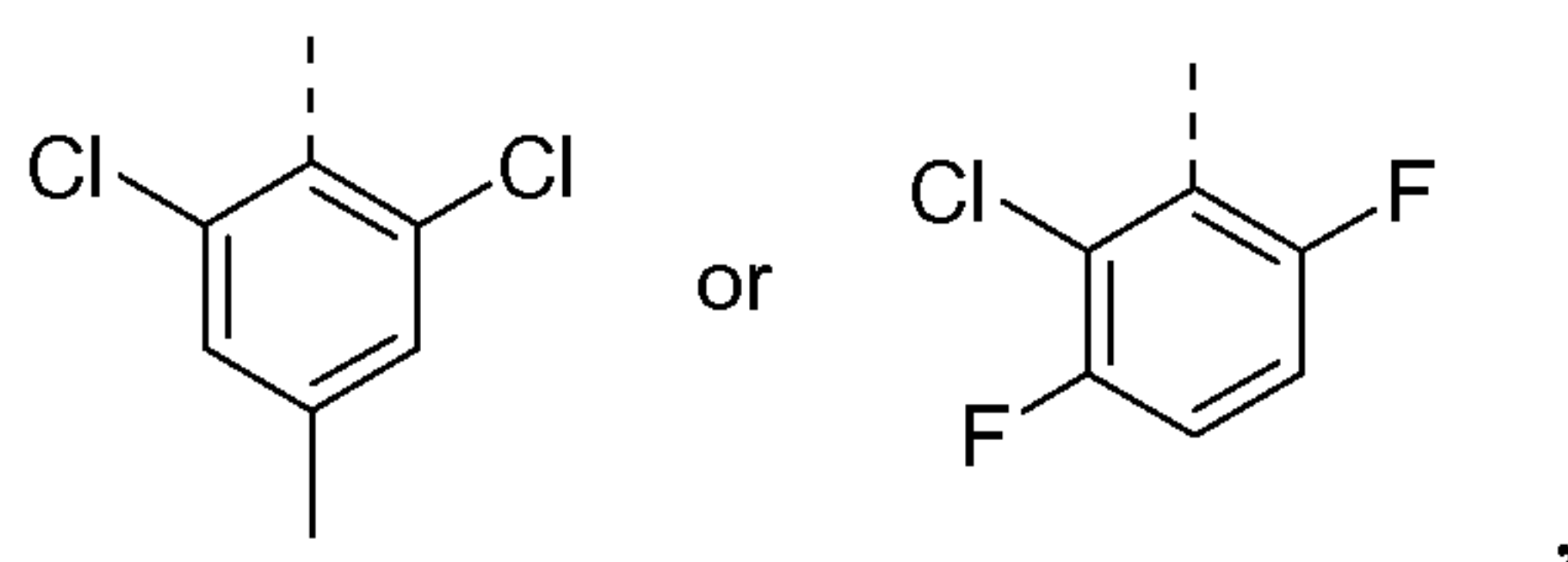
, or a salt of such a compound.

18. A compound according to any one of claims 1 to 17, wherein U represents:



or a salt of such a compound.

5 19. A compound according to claim 18, wherein U represents:



or a salt of such a compound.

20. A compound according to any one of claims 1 to 19, wherein R^2 represents Cl, and R^3 represents hydrogen, or a salt of such a compound.

10 21. A compound according to any one of claims 1 and 3 to 20, wherein R^4 represents $\text{CH}_3\text{-O-(CH}_2\text{)}_{2-3}\text{-}$ or $\text{CH}_3\text{-C(=O)-NH-CH}_2\text{-CH}_2\text{-}$, or a salt of such a compound.

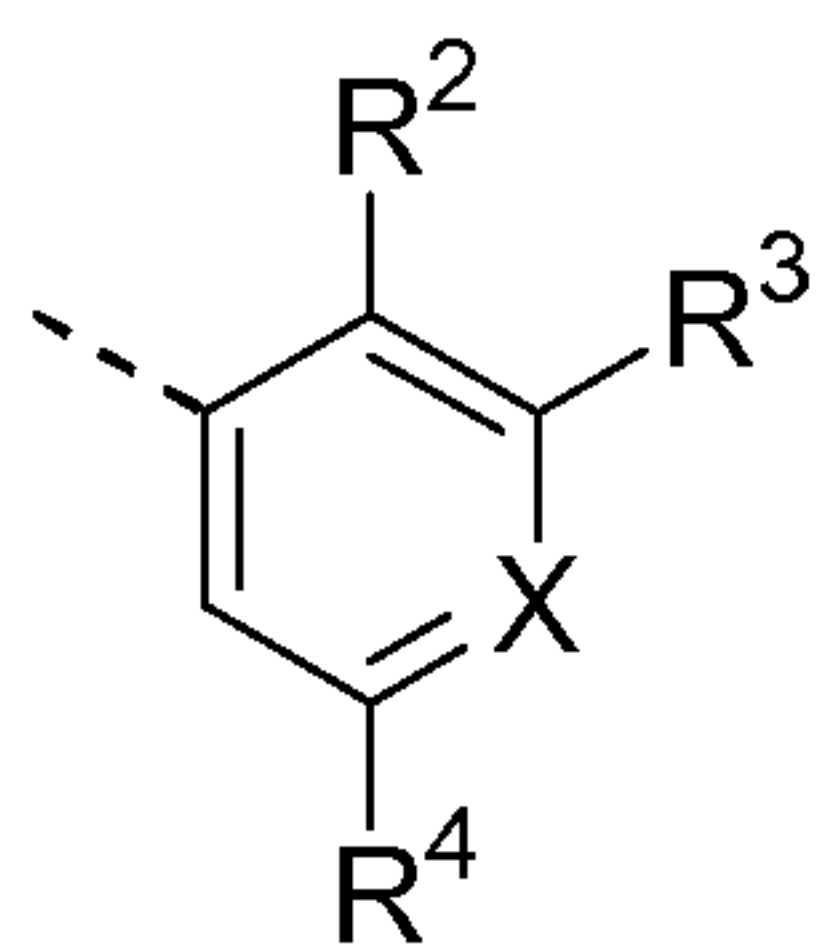
22. A compound according to claim 21, wherein R^4 represents $\text{-CH}_2\text{CH}_2\text{CH}_2\text{-O-CH}_3$ or $\text{-CH}_2\text{CH}_2\text{-O-CH}_3$, or a salt of such a compound.

15 23. A compound according to claim 22, wherein R^4 represents $\text{-CH}_2\text{CH}_2\text{-O-CH}_3$, or a salt of such a compound.

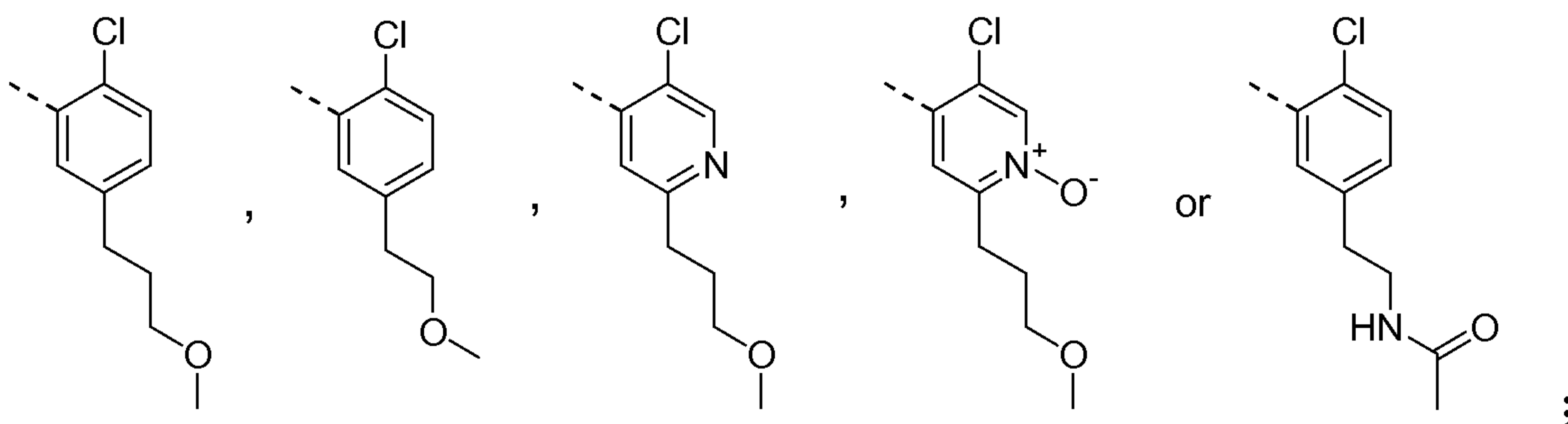
24. A compound according to any one of claims 1 to 23, wherein R^5 represents hydroxy, or a salt of such a compound.

25. A compound according to any one of claims 1 to 24, wherein n represents the integer 0, or a salt of such a compound.

26. A compound according to any one of claims 1, 5 to 19 and 24 to 25, wherein the moiety



represents one of the following possibilities:



or a salt of such a compound.

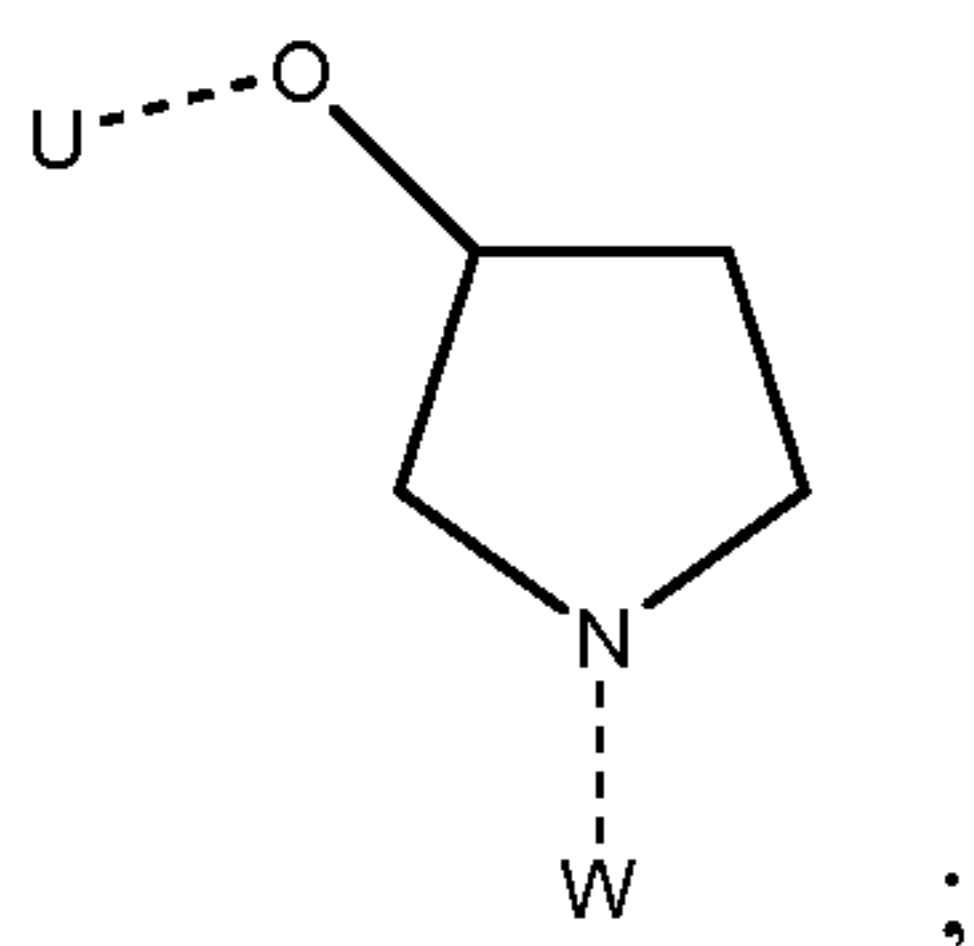
27. A compound according to claim 1, wherein

X represents CH , N , or N^+-O^- ;

W represents a *para*-substituted phenyl or a *para*-substituted pyridinyl;

V represents $-A-CH_2CH_2-B-$ or $-O-CH_2-Q-$, wherein Q is bound to the group U of formula

(I), or V represents a pyrrolidinyl of the formula:



U represents tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl and halogen;

Q represents an isoxazolyl;

A and B both represent -O-;

5 R¹ represents cyclopropyl;

R² represents halogen or C₁₋₇-alkyl;

R³ represents hydrogen or C₁₋₇-alkyl;

R⁴ represents C₁₋₇-alkyl-O-(CH₂)₀₋₄-CH₂-;

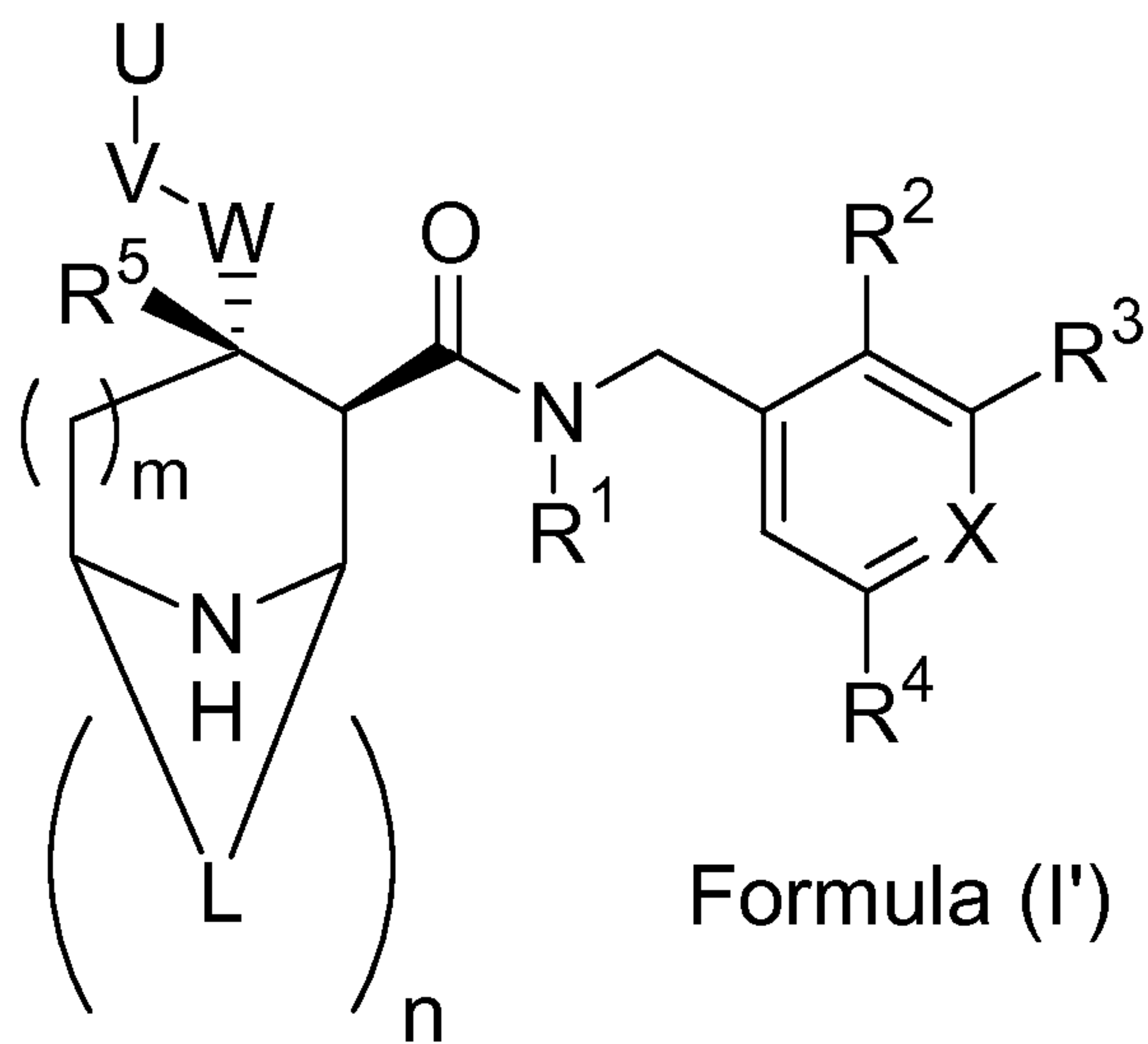
R⁵ represents hydroxy;

10 n represents the integer 0; and

m represents the integer 1,

or a salt of such a compound.

28. A compound according to any one of claims 1 to 27, or a salt thereof, wherein the absolute configuration of a compound of formula (I) is as represented for formula (I'):



29. A compound according to claim 1, which is (3*S**, 4*R**)-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid cyclopropyl-(2,3-dimethyl-benzyl)-amide, or a salt thereof.

5 30. A compound according to claim 1, selected from:

(3*S*, 4*R*)-4-{4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-phenyl}-4-hydroxy-piperidine-3-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,

(3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,

(3'*S*, 4'*R*)-6-[3-(2-chloro-3,6-difluoro-phenyl)-isoxazol-5-ylmethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,

(3'*S*, 4'*R*)-6-[(*R*)-3-(2,6-dichloro-4-methyl-phenoxy)-pyrrolidin-1-yl]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [2-chloro-5-(2-methoxy-ethyl)-benzyl]-cyclopropyl-amide,

(3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-pyridin-4-ylmethyl]-cyclopropyl-amide, and

(3'*S*, 4'*R*)-6-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-4'-hydroxy-1',2',3',4',5',6'-hexahydro-[3,4']bipyridinyl-3'-carboxylic acid [5-chloro-2-(3-methoxy-propyl)-1-oxy-pyridin-4-ylmethyl]-cyclopropyl-amide,

or salts of such compounds.

25 31. A pharmaceutical composition comprising a compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier material.

32. A compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, or a pharmaceutical composition according to claim 31, for use as a medicament.

- 5 33. Use of a compound according to any one of claims 1 to 30, or a pharmaceutically acceptable salt thereof, for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of diseases selected from hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, 10 cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, 15 and other diseases related to the renin-angiotensin system.