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(54) Title: AZABICYCLONONENE DERIVATIVES AS RENIN INHIBITORS

(57) Abstract: The invention relates to novel bicyclononene derivatives, related compounds and 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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AZABICYCLONONENE DERIVATIVES AS RENIN INHIBITORS

The invention relates to novel compounds of the formula (I). The invention also concerns 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 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 AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 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 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).

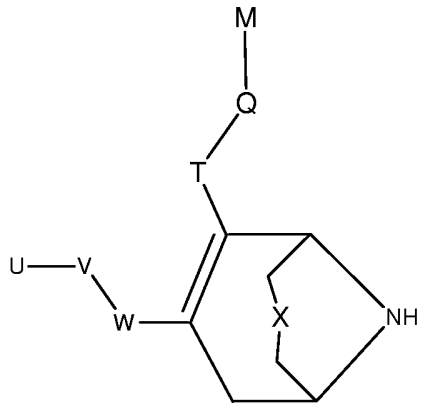
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, 1995, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides 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). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT_2) to Ang II, whose concentration is significantly increased by the blockade of AT_1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT_1 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 the identification of 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 remodeling, atherosclerosis, and possibly restenosis. So, the present invention describes these non-peptidic renin inhibitors of formula (I).

The present invention relates to novel bicyclononene compounds of the formula (I):



(I)

wherein

X represents -NH-, -N(L)-, -O-, or -S-;

W represents phenyl, substituted by V in *para* position;

V represents a radical of the formula $-E^1-Z-E^2-$;

E^1 represents $-O-CH_2-$ or $-CH_2-CH_2-$;

E^2 represents a bond, -O-, or $-CH_2-$, especially a bond;

Z represents a five-membered heteroaryl with 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur, preferably from oxygen and nitrogen;

U represents phenyl or mono-, di-, tri- or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, $-CF_3$, C_{1-7}-alkyl and hydroxy-C_{1-7}-alkyl; or five-membered heteroaryl with two heteroatoms independently selected from nitrogen, oxygen and sulfur, wherein said five-membered heteroaryl can optionally be mono, di, or tri-substituted, wherein the substituents are independently selected from the group consisting of halogen, $-CF_3$, C_{1-7}-alkyl and hydroxy-C_{1-7}-alkyl;

T represents $-CONR^1-$;

Q represents methylene;

M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, $-OCF_3$, $-CF_3$, hydroxy-C_{1-7}-alkyl and halogen, and especially represents 3-methoxy-2-methyl-phenyl or 2,3-dichloro-phenyl;

L represents $-R^3$, $-COR^3$, $-COOR^3$, $-CONR^2R^3$, $-SO_2R^3$, or $-SO_2NR^2R^3$;

R^1 and $R^{1'}$ independently represent C_{1-7}-alkyl or C_3-C_6-cycloalkyl;

R^2 and $R^{2'}$ independently represent hydrogen, C_{1-7}-alkyl, C_{2-7}-alkenyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-C_{1-7}-alkyl; and

R^3 represents C_{1-7}-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-C_{1-7}-alkyl, wherein these groups may be unsubstituted or mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of hydroxy, $-NH_2$, $-OCOR^2$, $-COOR^2$, $-SO_3H$, $-SO_2CH_3$, C_{1-7}-alkoxy, cyano, $-CONR^2R^{2'}$, $-NH(NH)NH_2$, $-NR^1R^{1'}$, tetrazolyl, 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;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, mixtures of enantiomers and diasteromers such as diastereomeric racemates, and meso-forms, as well as salts and solvent complexes of such compounds, and morphological forms.

In one embodiment, the present invention relates to a compound of formula (I), wherein

X represents -NH-;

W represents phenyl, substituted by V in *para* position;

V represents a radical of the formula $-E^1-Z-E^2-$;

E^1 represents $-O-CH_2-$ or $-CH_2-CH_2-$;

E^2 represents a bond, -O-, or $-CH_2-$;

Z represents a five-membered heteroaryl with 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur;

U represents phenyl or mono-, di-, tri- or tetra-substituted phenyl, wherein the substituents are selected from the group consisting of halogen, $-CF_3$, C_{1-7}-alkyl, and hydroxy-C_{1-7}-alkyl;

T represents $-CONR^1-$;

Q represents methylene;

M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, $-OCF_3$, $-CF_3$, hydroxy-C_{1-7}-alkyl, and halogen; and

R^1 represents C_{1-7}-alkyl or C_3-C_6-cycloalkyl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, mixtures of enantiomers and diasteromers such as diastereomeric racemates, and meso-forms, as well as salts and solvent complexes of such compounds, and morphological forms.

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 optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, mixtures of enantiomers and diasteromers such as diastereomeric racemates, and meso-forms, as well as salts (especially pharmaceutically acceptable salts) and solvent complexes (including hydrates) of such compounds, and morphological forms, as appropriate and expedient.

The term C_{1-7}-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. C_{1-4}-alkyl. Examples of C_{1-7}-alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

The term hydroxy-C_{1-7}-alkyl, alone or in combination with other groups, refers to an HO-R group, wherein R is a C_{1-7}-alkyl. Examples of hydroxy-C_{1-7}-alkyl groups are HO-CH_2-, HO-CH_2CH_2-, -CH(OH)CH_3, and HO-$CH_2CH_2CH_2$-.

The term C_{2-7}-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 C_{2-7}-alkenyl are vinyl, propenyl and butenyl.

The term C_{1-7}-alkoxy refers to an R-O- group, wherein R is a C_{1-7}-alkyl. Examples of C_{1-7}-alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term C_{1-7}-alkylene, alone or in combination with other groups, means straight or branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms.

The term C_{2-7}-alkenylene, alone or in combination with other groups, means straight or branched divalent chain groups comprising an olefinic bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms. Examples of C_{2-7}-alkenylene are vinylene, propenylene and butenylene.

The term C_{1-7}-alkylenoxy refers to an -R-O- group, wherein R is a C_{1-7}-alkylene. Examples of C_{1-7}-alkylenoxy groups are methylenoxy, ethylenoxy, propylenoxy, iso-propylenoxy, iso-butylenoxy, sec-butylenoxy and tert-butylenoxy.

The term C_{1-7}-alkylenedioxy refers to an -O-R-O- group, wherein R is a C_{1-7}-alkylene. Examples are oxymethylenoxy, oxyethylenoxy, oxypropylenoxy, oxy-iso-propylenoxy, and oxy-tert-butylenoxy.

The term halogen means fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine.

The term C_3-C_6-cycloalkyl, alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 6 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, and cyclohexyl, which can be optionally mono- or multi-substituted, wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl, C_{2-7}-alkenyl, C_{2-7}-alkenylene, C_{1-7}-alkoxy, C_{1-7}-alkylenoxy, C_{1-7}-alkylenedioxy, C_{1-7}-alkoxy-C_{1-7}-alkyl, hydroxy, halogen, $-CF_3$, and $-OCF_3$.

Preferred meanings of Z are five-membered aromatic rings containing one oxygen and two nitrogen atoms; five-membered aromatic rings containing one nitrogen and one oxygen atom; five-membered aromatic rings containing two nitrogen atoms; five-membered aromatic rings containing three nitrogen atoms; and five-membered aromatic rings containing two nitrogen atoms and one sulfur atom. Examples of such ring systems are thiazolyl, isothiazolyl, oxazolyl, isoxazolyl, and oxadiazolyl. Especially preferred meanings of Z are oxazolyl, oxadiazolyl, and isoxazolyl.

The term V within the present invention represents a radical of the formula $-E^1-Z-E^2-$ which may be connected in both possible ways to the group W and U of formula (I). In a preferred embodiment of the invention the beginning part of the group $-E^1-Z-E^2-$ is linked to the group W of the compound of formula (I) (that means that the $-E^1$ part of $-E^1-Z-E^2-$ is linked to the group W of formula (I)).

The term T within the present invention represents $-CONR^1-$ which may be connected in both possible ways to the bicyclononene core structure of formula (I). In a preferred embodiment of the invention the beginning part of the group T is linked to the bicyclononene core structure of formula (I) (that means that the -C(=O)- part of

-$CONR^1$- is linked to the bicyclononene core structure of formula (I)). Preferably, the term T within the present invention represents -$CONR^1$-, wherein R^1 represents C_{1-7}-alkyl or C_3-C_6-cycloalkyl, especially and most preferred cyclopropyl.

E^1 preferably represents -O-CH_2- which may be connected in both possible ways to the group Z. In a preferred embodiment of the invention the CH_2 part of -O-CH_2- is linked to the group Z.

The expression pharmaceutically acceptable salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic 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.

The compounds of the formula (I) contain two or more asymmetric carbon atoms and may be prepared in form of optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, mixtures of enantiomers and diasteromers such as diastereomeric racemates, or meso-forms. The present invention encompasses all these forms. Mixtures are separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, HPLC 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 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).

In a preferred embodiment X represents -NH- or -N($COCH_3$)-.

In a further preferred embodiment M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and halogen.

In a further preferred embodiment M represents di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and chlorine.

In a further preferred embodiment R^1 represents a cyclopropyl group.

In a further preferred embodiment Z represents an oxazole ring.

In a further preferred embodiment Z represents an oxadiazole or isoxazole ring, especially an isoxazole ring.

In a further preferred embodiment U represents a mono-, di-, or tri-substituted phenyl, wherein the substituents are selected from the group consisting of halogen and C_{1-7}-alkyl.

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 an embodiment of formula (I), are replaced by their preferred meanings as defined herein, such as those defined above.

In one embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -N($COCH_3$)-, for example -NH-; E^1 represents -O-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a di- or tri-substituted phenyl, substituted with halogen; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl,

substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -N($COCH_3$)-, for example -NH-; E^1 represents -O-CH_2-; Z represents an isoxazole ring; E^2 represents a bond; U represents a di- or tri-substituted phenyl, substituted with halogen; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -N($COCH_3$)-, for example -NH-; E^1 represents -O-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a mono-substituted phenyl, substituted with halogen; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -N($COCH_3$)-, for example -NH-; E^1 represents -O-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a mono-substituted phenyl, substituted with chloro; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -N($COCH_3$)-, for example -NH-; E^1 represents -O-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a tri-substituted phenyl, substituted with halogen; T represents

-$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with chloro, such as especially 2,3-dichlorophenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -$N(COCH_3)$-, for example -NH-; E^1 represents -CH_2-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a di- or tri-substituted phenyl, substituted with halogen; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -$N(COCH_3)$-, for example -NH-; E^1 represents -CH_2-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a di- or tri-substituted phenyl, substituted with halogen; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl and C_1-C_4-alkoxy, preferably with methyl and methoxy, such as especially 3-methoxy-2-methyl-phenyl.

In another embodiment, the present invention relates to a compound of formula (I), wherein X represents -NH-, -N(L)-, -O-, or -S-, especially -NH- or -$N(COCH_3)$-, for example -NH-; E^1 represents -O-CH_2- or -CH_2-CH_2-; Z represents an oxadiazole ring; E^2 represents a bond; U represents a di- or tri-substituted phenyl, substituted with fluoro and chloro; T represents -$CONR^1$-, wherein R^1 represents cyclopropyl; and M represents di-substituted phenyl, substituted with C_1-C_4-alkyl, C_1-C_4-alkoxy, chloro, or -CF_3.

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

X represents -NH- or -N(L)-;

W represents phenyl, substituted by V in *para* position;

V represents a radical of the formula -E^1-Z-E^2-;

E^1 represents -O-CH_2- or -CH_2-CH_2-;

E^2 represents a bond;

Z represents a five-membered heteroaryl with one nitrogen and one oxygen heteroatom, or a five-membered heteroaryl with one oxygen and two nitrogen heteroatoms;

U represents mono-, di-, or tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, -CF_3, and C_{1-7}-alkyl; or (less preferred) a five-membered heteroaryl with two nitrogen heteroatoms, wherein said five-membered heteroaryl is tri-substituted, wherein the substituents are independently selected from the group consisting of halogen and C_{1-7}-alkyl;

T represents -$CONR^1$-;

Q represents methylene;

M represents di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and halogen;

L represents -COR^3;

R^1 represents cyclopropyl; and

R^3 represents C_{1-7}-alkyl.

In a more preferred embodiment the bicyclononene compounds formula (I) are those selected from the group consisting of:

(*1R**, *5S**)-7-{4-[5-(2-chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide,

(*1R**, *5S**)-7-{4-[5-(2-chlorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-(4-{2-[3-(2,3-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-(4-{2-[3-(2,6-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide, and

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide.

In another very preferred embodiment the bicyclononene compounds formula (I) are those selected from the group consisting of:

(*1R**, *5S**)-7-{4-[2-(2-chloro-3,6-difluorophenyl)oxazol-4-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[5-(2-chloro-3,6-difluorophenyl)isoxazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R*, *5S*)-3-acetyl-7-{4-[3-(2-chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(4-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-6-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,5-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-4-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,4-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,6-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,3,6-trichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,3-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-6-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-2-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(6-chloro-2-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

(*1R**, *5S**)-7-{4-[3-(3-chloro-2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-2,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-6-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,6-dimethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and

(*1R**, *5S**)-7-{4-[3-(2,5-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide.

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 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.

Suitable carrier materials are not only inorganic carrier materials, but also organic carrier materials. Thus, for example, lactose, corn starch or derivatives thereof, talc, stearic acid or its salts can be used as carrier materials for tablets, coated tablets, dragées and hard gelatine capsules. Suitable carrier materials for soft gelatine capsules are, for example, vegetable oils, waxes, fats and semi-solid and liquid polyols (depending on the nature of the active ingredient no carriers are, however, required in the case of soft gelatine capsules). Suitable carrier materials for the production of solutions and syrups are, for example, water, polyols, sucrose, invert sugar and the like. Suitable carrier materials for injections are, for example, water, alcohols, polyols, glycerols and vegetable oils. Suitable carrier materials for suppositories are, for example, natural or hardened oils, waxes, fats and semi-liquid or liquid polyols. Suitable carrier materials for topical preparations are glycerides, semi-synthetic and synthetic glycerides, hydrogenated oils, liquid waxes, liquid paraffins, liquid fatty alcohols, sterols, polyethylene glycols and cellulose derivatives.

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavor-improving agents, salts for varying the osmotic pressure, buffer substances, solubilizers, colorants and masking agents and antioxidants come into consideration as pharmaceutical adjuvants.

The dosage of compounds of formula (I) can vary within wide limits depending on the disease to be controlled, the age and the individual condition of the patient and the mode of administration, and will, of course, be fitted to the individual requirements in each particular case.

In a preferred embodiment, this amount is comprised between 2 mg and 1000 mg per day.

In a particular preferred embodiment, this amount is comprised between 1 mg and 500 mg per day.

In a more particularly preferred embodiment, this amount is comprised between 5 mg and 200 mg per day.

Another aspect of the invention is related to a process for the preparation of a pharmaceutical composition comprising a compound of the formula (I). According to said process, one or more active ingredients of the formula (I) are mixing with inert excipients in a manner known *per se*.

The 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 and/or other drugs beneficial for the prevention or the treatment of the above-mentioned diseases such as 11beta-hydroxysteroid dehydrogenase type 1 inhibitors and soluble guanylate cyclase activators.

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.

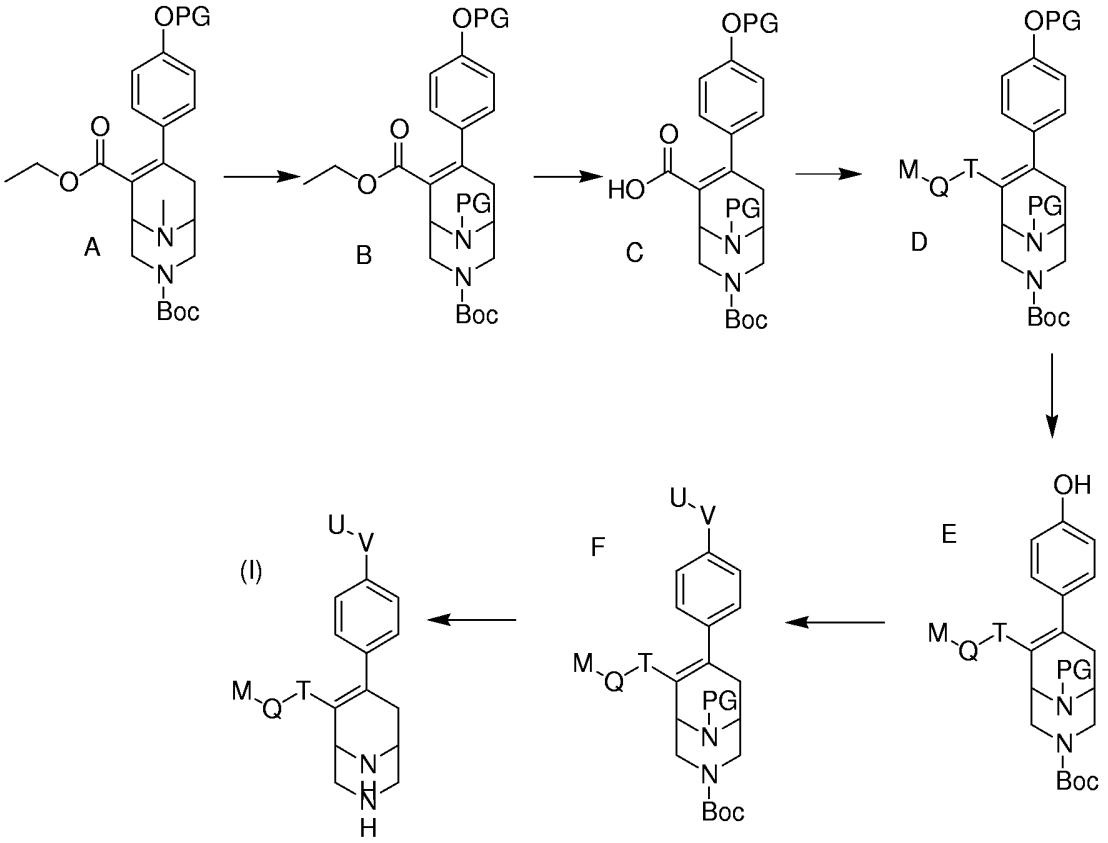
The compounds of formula (I) can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

The chemistry is hereby described for the more complex diazabicyclononene moiety. The same chemistry can be used for the oxaazabicyclononene and thiaazabicyclononene moieties as included in formula (I), using the preparation described in WO 2004/096366.

Compounds mentioned below, and not including W-V-U as a specific substituent, can be prepared by the chemistry described in the patent application WO 03/093267.

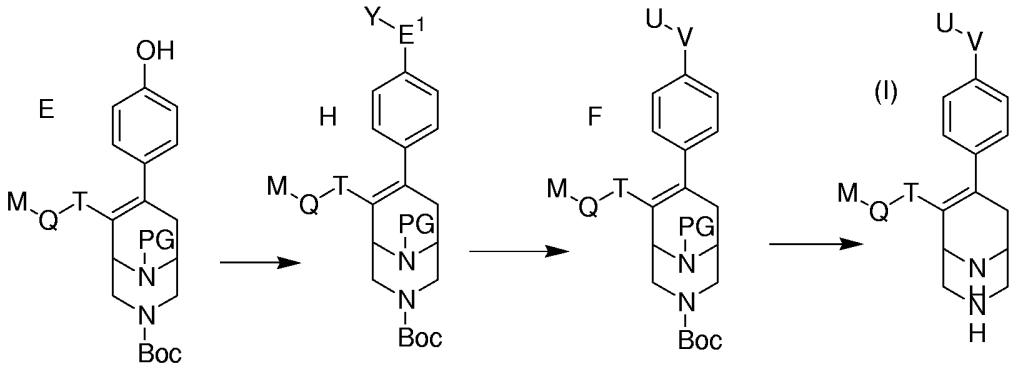
A compound of type A in Scheme 1, wherein PG stands for a protecting group, can be prepared from 9-methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267), and a protected 4-bromophenol derivative via a *Negishi* coupling, or any other coupling catalyzed by a palladium catalyst. A protecting group manipulation delivers a compound of type B, then a hydrolysis of the ethyl ester yields a compound of type C. An amide coupling, for instance, leads then to a compound of type E, and a subsequent ether formation, via a Mitsunobu reaction, for instance, delivers a compound of type F. The fragment necessary for the construction of the fragment U-V is prepared in parallel, very often following literature procedures. Final deprotection yields a compound of formula (I), wherein X represents -NH-. If another group X is desired, the Boc-protecting group can be cleaved selectively, and an alkylation or an acylation will allow the introduction of the desired L substituent. Final cleavage of the PG-protecting group leads to a compound of formula (I). Also, a compound of formula (I) with X = NH can be acylated selectively at its 3-position.

Scheme 1



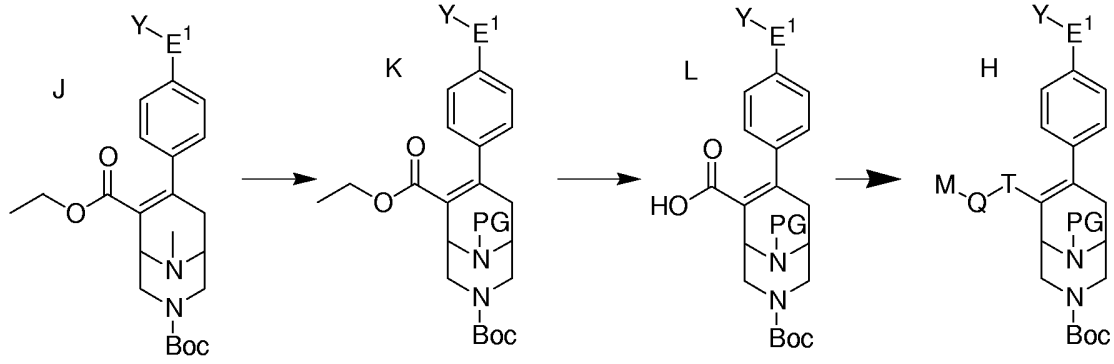
Otherwise the segment U-V- can be prepared directly on the template as described in Scheme 2. Starting from a compound of type E, a compound of type H can be prepared, wherein Y stands for a precursor of the radical V as described in formula (I). Y can be modified along the synthesis. Finally the whole segment U-V- is constructed to yield a compound of type F. Deprotection yields a compound of formula (I).

Scheme 2



Another possibility is sketched in Scheme 3. The Y-E^1 substituent can be present from the beginning on the phenyl moiety, and be introduced on 9-methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267) via a *Negishi* coupling to a compound of type J. Subsequent protecting group manipulations lead to a compound of type K, then hydrolysis to a compound of type L. An amide coupling, for instance, leads to a compound of type H. The synthesis can then follow the scheme 2.

Scheme 3



Other combinations of sequences are always possible, as long as the chemistry allows it. The skilled person in the art shall notice such possibilities as obvious variations of the sequences presented hereby.

An enantiomerically pure compound can be prepared by separation of an intermediate or of a final compound by HPLC, using a chiral column. Otherwise, an enantiomerically pure material can be prepared by enantioselective synthesis, as described in WO 03/093267.

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

Chemistry

Abbreviations (as used herein)

ACE	Angiotensin Converting Enzyme
AcOH	acetic acid
Ang	Angiotensin
aq.	aqueous
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
Bu	Butyl
BuLi	*n*-Butyllithium
conc.	concentrated
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
EIA	Enzyme immunoassay
ELSD	Evaporative light-scattering detection
eq.	Equivalent(s)
ES+	Electro spray, positive ionization
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FC	Flash Chromatography

h	hour(s)
HOBt	Hydroxybenzotriazol
HPLC	High performance liquid chromatography
LC-MS	Liquid chromatography – mass spectrometry
Me	methyl
MeOH	Methanol
min	minute(s)
MS	mass spectrometry
NMR	Nuclear magnetic resonance spectroscopy
NCS	*N*-chlorosuccinimide
org.	organic
PG	protecting group
Ph	Phenyl
rt	room temperature
sat.	saturated
sol.	Solution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
TFA	trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
t_R	retention time
UV	Ultra violet
Vis	visible

General remarks (Examples 1 to 6):

The compound is characterized at least by LC-MS and ^{1}H-NMR. Only the LC-MS data are given here (Zorbax SB-AQ column, 5 µm, 4.6x50 mm; eluent A: 0.04% trifluoroacetic acid in water; eluent B: acetonitrile; gradient 5% → 100% eluent B over 1.5 min, flow 1 mL/min).

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: H_2O + 0.5% TFA. Gradient: 90% B → 5% B over 2 min. Flow: 1 mL/min. Detection: UV/Vis + MS.

Preparative: Zorbax SB Aqua column, 20 x 500 mm from Agilent Technologies. Eluent: A: Acetonitrile; B: H_2O + 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: Regis Whelk column, 4.6 x 250 mm, 10 μm. Eluent A: EtOH + 0.05% Et_3N. Eluent B: hexane. Isocratic conditions, 65% B, over 40 min, 1 mL/min. The isocratic mixture may vary, depending on the compounds.

Chiral, preparative: As analytical conditions, but on a Regis Whelk 01 column, 50x250 mm and a flow of 100 mL/min.

All t_R are given in min.

Experimental part

General procedures:

General procedure A for the preparation of oximes:

The desired aldehyde (1.00 eq.) was dissolved in CH_3CN (1.7 mL for 1 mmol of aldehyde). $NaHCO_3$ (3.00 eq.) was added, and the mixture was stirred for 5 min. Water (same amount as CH_3CN), $NH_2OH{\cdot}HCl$ (2.00 eq.), and Bu_4NCl (0.05 eq.) were added. The mixture was stirred for 90 min, and AcOH was carefully added until a pH-value of 6 to 7 was reached. The mixture was extracted with Et_2O (3x). The combined org. extracts were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification of the crude residue by FC (CH_2Cl_2) yielded the title compound.

General procedure B for the preparation of isoxazoles:

To a sol. of NCS (2.50 eq.) and pyridine (0.50 eq.) in DMF (2.00 mL for 1 mmol of NCS) was added dropwise a sol. of the desired oxime (2.50 eq.) in DMF (0.60 mL for 1 mmol of oxime). The mixture was stirred for 1 h at rt, and *tert*-butyldimethylprop-2ynyloxysilane (1.00 eq.) in DMF (0.80 mL for 1 mmol of the alkyne) was added. The

mixture was heated to 85 °C, and a sol. of Et_3N (2.50 eq.) in DMF (0.80 mL for 1 mmol of Et_3N) was added slowly. The mixture was stirred at 85 °C for 15 min, and was allowed to cool to rt. The mixture was diluted with water (half of the *total* volume of DMF), and was extracted with heptane (2x). The combined org. extracts were washed with water, brine, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4) yielded the title compound.

General procedure C for the cleavage of a silyl ether:

To a sol. of the desired isoxazole (1.00 eq.) in MeOH (3.22 mL for 1 mmol of isoxazole) was added TBAF (1.10 eq.). The mixture was stirred for 3 h, and aq. sat. $NaHCO_3$ was added. The mixture was partially evaporated under reduced pressure. The remaining aq. mixture was extracted with EtOAc (2x). The combined org. extracts were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 3:7) yielded the title compound.

General procedure D for a Mitsunobu coupling:

A mixture of a desired phenol (1.00 eq.), of the desired alcohol (1.5 eq.), azodicarboxylic dipiperidide (2.00 eq.) and PBu_3 (3.00 eq.). The reaction mixture was stirred at 100 °C for 1 h, and allowed to cool to rt. The mixture was diluted with Et_2O, and the resulting mixture was filtered. The filtrate was diluted with EtOAc, and the mixture was washed with aq. 1M NaOH. The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by preparative TLC (0.5 mm plates, EtOAc/heptane 1:1) yielded the title compound.

General procedure E for the Boc-deprotection:

A compound of type F is dissolved in CH_2Cl_2 (15 mL for 1 mmol of compound of type F). The mixture was cooled to 0 °C, and HCl (4M in dioxane, 5 mL for 1 mmol of compound of type F) was added. The mixture was stirred for 1 h at 0 °C, and 1 h at rt.

The solvents were removed under reduced pressure, and the residue was purified by HPLC to yield the title compound.

General procedure F for the oxime preparation:

A mixture of the aldehyde (3.1 mmol) and $NaHCO_3$ (9.3 mmol, 778 mg,) in water (13.5 mL) was treated at rt with $NH_2OH{\cdot}HCl$ (6.2 mmol, 429 mg) and tetrabutylammonium chloride (0.16 mmol, 43 mg). The mixture was stirred at rt for 4 h. Acetic acid (1.0 mL) was then added and the mixture was stirred for 30 min at rt. The mixture was poured in water (50 mL) and extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to afford the desired oxime.

General procedure G for the oxime cyclization:

A solution of NCS (0.25 mmol, 33 mg) in DMF (1.0 mL) was treated with one drop of pyridine followed by the oxime (0.25 mmol). After 1 h, compound H7 (0.10 mmol, 70 mg) was added and the mixture was heated to 85 °C. Et_3N (0.25 mmol, 0.04 mL) was then added dropwise, and the mixture was stirred for 1 h at 85 °C. Water (3.0 mL) was added at rt and the mixture was extracted with EtOAc, washed with 10% $KHSO_4$, water and brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the desired isoxazole. Purification via HPLC afforded the desired isoxazole.

Preparation of the aryl-heterocyclyl derivatives:

2-Chloro-3,6-difluorobenzaldehyde oxime

A mixture of 2-chloro-3,6-difluorobenzaldehyde (1.13 mmol, 200 mg) and $NaHCO_3$ (3.4 mmol, 286 mg) in water (1.9 mL) was treated at rt with $H_2NOH{\cdot}HCl$ (2.3 mmol, 160 mg) and Bu_4NCl (0.06 mmol, 16 mg). Acetonitrile (1.2 mL) was then added and the mixture was stirred at rt for 90 min. AcOH (0.2 mL) was then added and the mixture was stirred for 30 min at rt. The mixture was extracted with EtOAc, washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced

pressure. Purification of the residue by FC (EtOAc/heptane 3:7) yielded the title compound (170 mg, 78%). LC-MS: t_R = 0.84 min; ES+: CH_3CN: 233.81.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2-chloro-3,6-difluorophenyl)isoxazole

A solution of 2-chloro-3,6-difluoro-benzaldehyde oxime (0.834 mmol, 170 mg) in DMF (0.53 mL) was added dropwise at rt to a solution of NCS (0.83 mmol, 111 mg) and pyridine (2 drops) in DMF (1.8 mL). After 1 h, *tert*-butyldimethylprop-2-ynyloxysilane (0.33 mmol, 0.07 mL) was added and the mixture was heated to 85 °C. Et_3N (0.83 mmol, 0.12 mL, 2.5 eq.) in DMF (0.7 mL) was then added over 35 min. At the end of the addition, the mixture was stirred for 1 h at 85 °C. Water was added at rt and the mixture was extracted with EtOAc. The org. extracts were washed with aq. 10% $KHSO_4$, water, and brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 5:95) yielded the title compound (94 mg, 79%). LC-MS: t_R = 1.16 min; ES+: 360.05.

[3-(2-Chloro-3,6-difluorophenyl)isoxazol-5-yl]methanol

A sol. of 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2-chloro-3,6-difluorophenyl)-isoxazole (0.25 mmol, 94 mg) in THF (6.8 mL) at 0 °C was treated with TBAF (0.50 mmol, 0.50 mL of a 1 M solution in THF). After 1 h at rt, aq. sat. NH_4Cl was added. The mixture was extracted with EtOAc, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 3:7) yielded the title compound (60 mg, 98%). LC-MS: t_R = 0.84 min; ES+: CH_3CN: 287.14.

2-Chloro-3,6-difluorobenzonitrile

2-Chloro-3,6-difluorobenzamide (0.80 g, 4.18 mmol) in $POCl_3$ (12 mL) was heated for 2 h at 95 °C. The sol. was cooled and the excess of $POCl_3$ was removed by distillation under reduced pressure. The residue was diluted with EtOAc and aq. 10% K_2CO_3 was cautiously added. The layers were separated and the org. phase was washed with water (2x), and brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the title compound (0.46 g) that was not further purified.

2,3-dichloro-*N*-hydroxybenzamidine

To 2-chloro-3,6-difluorobenzonitrile (0.36 g, 2.08 mmol) in 95 % EtOH (4 mL) was added $H_2NOH{\cdot}HCl$ (0.32 g, 4.56 mmol) and Et_3N (0.66 mL, 4.77 mmol). The mixture was stirred at 75 °C for 18 h. After cooling to rt, the mixture was filtered. The filtrate was diluted with water (3 mL), and neutralized to pH 7 with aq. conc. HCl. The solvents were partially evaporated under reduced pressure, and the residue was filtered, washed with water, and dried under vacuum. The residue (0.41 g) was used in the next step without further purification. LC-MS: t_R = 0.34 min, ES+ = 207.02.

2-(2-Chloro-3,6-difluorophenyl)-4-chloromethyloxazole

A mixture of 2-chloro-3,6-difluorobenzamide and 1,3-dichloroacetone was stirred for 24 h at 130 °C. Purification of the residue by FC (EtOAc/heptane 10:90) yielded the title compound (0.30 g, 43%). LC-MS: t_R = 0.97 min; ES+: 264.07.

(*rac.*)-1-(2-Chloro-3,6-difluorophenyl)ethanol

To a sol. of 2-chloro-3,6-difluorobenzaldehyde (5.00 g, 28.32 mmol) in dry Et_2O (60 mL) at 0 °C was added dropwise MeMgBr (3M in Et_2O, 40 mL, 120 mmol). The mixture was stirred overnight at rt. Aq. sat. NH_4Cl was added and the mixture was extracted with EtOAc (2x). The org. layer was washed with brine, dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The residue was used in the next step without further purification.

1-(2-Chloro-3,6-difluorophenyl)ethanone

To a sol. of (*rac.*)-1-(2-chloro-3,6-difluorophenyl)ethanol (5.00 g, 28 mmol) in acetone (150 mL) at 0 °C was added dropwise CrO_3 (3.5 g CrO_3) in H_2O (11.5 mL) and H_2SO_4 (3.00 mL). After stirring for 30 min at 0 °C, the reaction mixture was added to water (150 mL) and extracted with EtOAc (3x). The org. layers were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 5/95 → 2/8) yielded the title compound (3.05g, 57 % for 2 steps). ^{1}H-NMR ($CDCl_3$) δ 7.12-7.22 (m, 1H), 7.0-7.1 (m, 1H), 2.60 (s, 3H).

4-(2-Chloro-3,6-difluorophenyl)-2,4-dioxobutyric acid ethyl ester

To a sol. of 1-(2-chloro-3,6-difluorophenyl)ethanone (1.00 g, 5.25 mmol) in anhydrous toluene (12 mL) was added portionwise NaH (60% in oil, 0.023 g, 5.77 mmol). After stirring for 1 h at rt, a sol. of diethyl oxalate (1.15 g, 7.87 mmol) in toluene (5 mL) was added, and the mixture was refluxed for 90 min. Aq. sat. NH_4Cl was added, and the mixture was extracted with EtOAc (2x). The org. layer was washed with water (2x), dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:9) yielded the title compound (1.00 g, 66%). ^{1}H-NMR ($CDCl_3$) δ 7.00-7.15 (m, 1H), 6.80-6.95 (m, 1H), 6.35 (s, 1H), 4.40 (q, 2H), 1.40 (t, 3H).

5-(2-Chloro-3,6-difluorophenyl)isoxazole-3-carboxylic acid ethyl ester

To a sol. of 4-(2-chloro-3,6-difluorophenyl)-2,4-dioxobutyric acid ethyl ester (1.00 g, 3.46 mmol) in MeOH (10 mL) were added $NH_2OH{\cdot}HCl$ (0.17 g, 5.20 mmol) and a catalytic amount of *para*-toluenesulfonic acid. The reaction mixture was refluxed for two days. The solvents were evaporated, and the crude mixture was purified by FC (EtOAc/heptane 2:8→ EtOAc) to yield the title compound (0.08 g, 8%). ^{1}H-NMR ($CDCl_3$) δ 7.25-7.35 (m, 1H), 7.10-7.20 (m, 1H), 7.05 (s, 1H), 4.50 (q, 2H), 1.45 (t, 3H).

[5-(2-Chloro-3,6-difluorophenyl)isoxazol-3-yl]methanol

To a sol. of 5-(2-chloro-3,6-difluorophenyl)isoxazole-3-carboxylic acid ethyl ester (53 mg, 0.18 mmol) in anhydrous THF (1.8 mL) was added a sol. of $LiAlH_4$ (1M in THF, 0.28 mL) and the reaction mixture was stirred for 30 min at 40 °C. Aq. 10% NaOH (2 mL) was added, and the solid formed was filtered and washed with EtOAc. The phases were separated and the aq. phase was extracted with EtOAc. The combined org. phases were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8→ EtOAc) yielded the title compound (50 mg, quantitative yield). LC-MS: t_R = 0.85 min, ES+: 246.17.

4-Fluoro-2-trifluoromethylbenzaldehyde oxime

According to general procedure A, from 4-fluoro-2-trifluoromethylbenzaldehyde (5.00 g, 26 mmol). The title product was obtained as a colourless solid (4.96 g, 92%). LC-MS: t_R = 0.88 min; ES+: 208.13.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(4-fluoro-2-trifluoromethylphenyl)-isoxazole

According to general procedure B, from 4-fluoro-2-trifluoromethylbenzaldehyde oxime (4.96 g, 23.95 mmol), the title product was obtained (2.33 g, 64%). LC-MS: t_R = 1.16 min; ES+: 376.22.

[3-(4-Fluoro-2-trifluoromethylphenyl)isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(4-fluoro-2-trifluoromethylphenyl)-isoxazole (2.33 g, 6.21 mmol), the title product was obtained (1.38 g, 85%). LC-MS: t_R = 0.86 min; ES+: 262.08.

2,5-Difluorobenzaldehyde oxime

According to general procedure A, from 2,5-difluorobenzaldehyde (3.00 g), the title product was obtained (1.50 g, 45%). LC-MS: t_R = 0.80 min; ES+: 212.06.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2,5-difluorophenyl)isoxazole

According to general procedure B, from 2,5-difluorobenzaldehyde oxime (1.50 g), the title product was obtained (0.82 g, 66%). LC-MS: t_R = 1.16 min; ES+: 326.17.

[3-(2,5-Difluorophenyl)isoxazol-5-yl]-methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2,5-difluorophenyl)isoxazole (0.82 g), the title product was obtained (0.57 g, quantitative yield). LC-MS: t_R = 0.80 min; ES+: 212.06.

2-Chloro-4-fluorobenzaldehyde oxime

According to general procedure A, from 2-chloro-4-fluorobenzaldehyde (2.00 g), the title product was obtained (2.19 g, quantitative yield). LC-MS: t_R = 0.84 min; ES+: 174.60.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2-chloro-4-fluorophenyl)isoxazole

According to general procedure B, from 2-chloro-4-fluorobenzaldehyde oxime (2.19 g), the title product was obtained (1.09 g, 26%). LC-MS: t_R = 1.18 min; ES+: 343.12.

[3-(2-Chloro-4-fluorophenyl)isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2-chloro-4-fluorophenyl)isoxazole (1.09 g), the title product was obtained (0.34 g, 47%). LC-MS: t_R = 0.83 min; ES+: 228.05.

5-Chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde oxime

According to general procedure A, from 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde (1.00 g), the title product was obtained (1.10 g, quantitative yield). LC-MS: t_R = 0.67 min; ES+: 174.60.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)-isoxazole

According to general procedure B, from 5-chloro-1,3-dimethyl-1H-pyrazole-4-carbaldehyde oxime (1.10 g), the title product was obtained (0.60 g, 67%). LC-MS: t_R = 1.17 min; ES+: 343.12.

[3-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)-isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)isoxazole (0.60 g), the title product was obtained (0.17 g, 18%). LC-MS: t_R = 0.70 min; ES+: 228.65.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2-chloro-6-fluorophenyl)isoxazole

According to general procedure B, from 2-chloro-6-fluorobenzaldehyde oxime (5.00 g), the title product was obtained (2.41 g, 62%). LC-MS: t_R = 1.15 min; ES+: 342.18.

[3-(2-Chloro-6-fluorophenyl)isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2-chloro-6-fluorophenyl)isoxazole (2.41 g), the title product was obtained (1.30 g, 81%). LC-MS: t_R = 0.81 min; ES+: 228.06.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2,6-dichlorophenyl)isoxazole

According to general procedure B, from 2,6-dichlorobenzaldehyde oxime (5.00 g), the title product was obtained (2.88 g, 76%). LC-MS: t_R = 1.16 min; ES+: 358.17.

[3-(2,6-Dichlorophenyl)isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2,6-dichlorophenyl)isoxazole (2.88 g), the title product was obtained (1.13 g, 58%). LC-MS: t_R = 0.84 min; ES+: 244.02.

5-(*tert*-Butyldimethylsilanyloxymethyl)-3-(2,4-dichlorophenyl)isoxazole

According to general procedure B, from 2,4-dichlorobenzaldehyde oxime (5.00 g), the title product was obtained (2.49 g, 66%). LC-MS: t_R = 1.20 min; ES+: 358.14.

[3-(2,4-Dichlorophenyl)isoxazol-5-yl]methanol

According to general procedure C, from 5-(*tert*-butyldimethylsilanyloxymethyl)-3-(2,4-dichlorophenyl)isoxazole (2.49 g), the title product was obtained (1.66 g, 98%). LC-MS: t_R = 0.88 min; ES+: 243.99.

3-Chloro-2-fluoro-benzaldehyde oxime

According to the general procedure F, 3-chloro-2-fluorobenzaldehyde (492 mg, 3.10 mmol) was used to prepare the title compound (550 mg, 100%). LC-MS: t_R = 0.85 min.

6-Chloro-2-fluoro-3-methylbenzaldehyde oxime

According to the general procedure F, 6-chloro-2-fluoro-3-methylbenzaldehyde (535 mg, 3.10 mmol) was used to prepare the title compound (582 mg, 100%). LC-MS: t_R = 0.87 min; ES+: 229.14.

3-Chloro-2-fluoro-6-trifluoromethylbenzaldehyde oxime

According to the general procedure F, 3-chloro-2-fluoro-6-trifluoromethylbenzaldehyde (702 mg, 1.50 mmol) was used to prepare the title compound (155 mg, 43%). LC-MS: t_R = 0.92 min; ES+: 242.35.

3-Chloro-2,6-difluorobenzaldehyde oxime

According to the general procedure F, 3-chloro-2,6-difluorobenzaldehyde (500 mg, 2.80 mmol) was used to prepare the title compound (460 mg, 87%). LC-MS: t_R = 0.84 min; ES+: 233.16.

3-Chloro-6-fluoro-2-trifluoromethylbenzaldehyde oxime

According to the general procedure F, 3-chloro-6-fluoro-2-trifluoromethylbenzaldehyde (700 mg, 3.10 mmol) was used to prepare the title compound (710 mg, 95%). LC-MS: t_R = 0.93 min.

2,6-Dimethylbenzaldehyde oxime

According to the general procedure F, 2,6-dimethylbenzaldehyde (403 mg, 3.00 mmol) was used to prepare the title compound (380 mg, 85%). LC-MS: t_R = 0.82 min.

2,5-Dichlorobenzaldehyde oxime

According to the general procedure F, 2,5-dichlorobenzaldehyde (530 mg, 3.00 mmol) was used to prepare the title compound (558 mg, 98%). LC-MS: t_R = 0.89 min.

2,3,6-Trichlorobenzaldehyde oxime

According to the general procedure F, 2,3,6-trichlorobenzaldehyde (648 mg, 3.00 mmol) was used to prepare the title compound (610 mg, 91%). LC-MS: t_R = 0.91 min.

2-Fluoro-6-trifluoromethylbenzaldehyde oxime

According to the general procedure F, 2-fluoro-6-trifluoromethylbenzaldehyde (506 mg, 2.60 mmol) was used to prepare the title compound (380 mg, 72%). LC-MS: t_R = 0.87 min.

2,3-Dichlorobenzaldehyde oxime

According to the general procedure F, 2,3-dichlorobenzaldehyde (1.00 g, 5.70 mmol) was used to prepare the title compound (1.10 g, 100%). LC-MS: t_R = 0.89 min.

2-Chloro-6-fluoro-3-methyl-benzaldehyde oxime

According to the general procedure F, 2-chloro-6-fluoro-3-methylbenzaldehyde (500 mg, 2.81 mmol) was used to prepare the title compound (470 mg, 89%). LC-MS: t_R = 0.86 min; ES+: 229.12.

(*rac.*)-(*1R**, *5S**)-9-Methyl-7-(4-triisopropylsilanyloxyphenyl)-3,9-diazabicyclo[3.3.1]-non-6-ene-3,6-dicarboxylic acid3-*tert*-butyl ester 6-ethyl ester (A1)

A sol. of (4-bromophenoxy)triisopropylsilane (P. Wipf *et al.*, *Org. Lett.* 2000, *2*, 26, 4213-4216; 18.6 g; 56.4 mmol) in THF (215 mL) was cooled to –78 °C. BuLi (1.6M in hexane, 36.8 mL; 58.8 mmol) was added dropwise over 15 min. After completion of the addition, the resulting solution was stirred further at –75 °C for 30 min. $ZnCl_2$ (1.06 M in THF; 58.8 mL, 62.3 mmol) was added dropwise over 20 min, and the reaction mixture was allowed to warm up to rt. A mixture of 9-methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267, 10.78 g; 23.5 mmol) and $Pd(PPh_3)_4$ (1.36 g; 1.18 mmol) in THF (25 mL) was added. The resulting sol. was stirred at rt for 5 min, then at 45 °C for 50 min. The reaction mixture was cooled to 0 °C, and aq. sat. $NaHCO_3$ was added to this reaction mixture, followed by EtOAc. The phases were shaken, separated and the aq. phase was extracted with EtOAc (2 x 100 mL). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (CH_2Cl_2/CH_3OH 20/1) yielded the title compound (10.99 g, 84%). LC-MS: t_R = 1.03 min.

(*rac.*)-(*1R**, *5S**)-7-(4-Triisopropylsilanyloxyphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (B1)

A mixture compound A1 (3.5 g, 6.26 mmol), $NaHCO_3$ (5.26 g, 62.64 mmol) and 1-chloroethyl chloroformate (6.80 mL, 62.4 mmol) in CH_2ClCH_2Cl (69 mL) was heated

to reflux for 1 h. The reaction mixture was allowed to cool to rt, and was filtered. The precipitate was washed with 1,2-dichloroethane, and the filtrate was concentrated under reduced pressure. The residue was dissolved in MeOH (69 mL), and the resulting sol. was stirred at 40 °C for 1 h. The solvents were removed under reduced pressure, and the residue was dried under high vacuum for 1 h. The dried residue was dissolved in CH_2Cl_2 (69 mL). The resulting sol. was cooled to 0 °C. DIPEA (6.45 mL, 37.67 mmol) was added dropwise, followed by the addition at once of Boc_2O (4.10 g, 18.79 mmol). After further stirring at 0 °C for 30 min, the mixture was stirred at rt for 3 h. Aq. 1M HCl (35 mL) was added dropwise to the reaction mixture at 0 °C. The phases were shaken and separated. The org. phase was washed with aq. sat. $NaHCO_3$. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (CH_2Cl_2/CH_3OH 100/1) yielded the title product as a yellow foam (3.64 g, 90%). LC-MS : t_R = 1.30 min.

(*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (C1)

To a sol. of compound B1 (8.78 g, 13.6 mmol) in EtOH (100 mL) was added aq. 1M NaOH (41 mL, 41 mmol). The resulting mixture was stirred at 80°C for 20 h. The solvents were partially removed under reduced pressure. EtOAc, then aq. 1M HCl were added. The mixture was shaken, and the phases were separated. The aq. phase was extracted with EtOAc (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum, and dissolved in DMF (155 mL). Imidazole (4.51 g; 66.2 mmol) and TBDMS-Cl (6.24 g, 41.4 mmol) were added. The reaction mixture was stirred at rt for 5 h. The reaction mixture was cooled to 0 °C, and aq. sat. NH_4Cl (155 mL) was slowly added. The resulting mixture was extracted with heptane/Et_2O (1/1, 5x), and the combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The resulting residue was dissolved in THF (315 mL). MeOH (32 mL), water (32 mL) and K_2CO_3 (1.56 g) were added. The reaction mixture was stirred at rt for 30 min. The reaction mixture was cooled to 0 °C, and aq. sat. NH_4Cl (300 mL) was slowly added. The phases were separated and the aq. phase was extracted with Et_2O. The combined org. extracts were dried over $MgSO_4$, filtered, and

the solvents were removed under reduced pressure. Purification of the residue by FC (CH_2Cl_2/CH_3OH 40/1) yielded a mixture of the title compound with (*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-butyldimethylsilanyloxy)phenyl]-3,9-diazabicyclo[3.3.1]-non-7-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (5.57 g, 71%). LC-MS: t_R = 1.14 min and 1.15 min (minor isomer).

(*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]-6-[cyclopropyl-(3-meth-oxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D1)

To a sol. of compound C1 with its regioisomer (1.64 g; 2.853 mmol; 1 eq.) in CH_2Cl_2 (32 mL) were added at rt cyclopropyl-(3-methoxy-2-methylbenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*, 1989, *54*, 3730 and cyclopropylamine, 1.64 g, 8.56 mmol), DIPEA (1.95 mL, 11.39 mmol) DMAP (87 mg, 0.71 mmol), HOBt (578 mg, 4.28 mmol), and EDC·HCl (2.19 g, 11.413 mmol). The mixture was stirred at rt for 3 days. CH_2Cl_2 (50 mL) was added to the reaction mixture, and the sol. was washed with aq. 1M HCl (3x). The combined aq. layers were extracted with CH_2Cl_2 (25 mL). The combined org. extracts were washed with aq. sat. $NaHCO_3$ (25 mL). The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (CH_2Cl_2/CH_3OH 100/3) yielded the title compound (1.45 g, 68%). LC-MS: t_R = 1.29 min.

(*rac.*)-(*1R**, *5S**)-7-[4-(*tert*-Butyldimethylsilanyloxy)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D2)

A sol. of compound C1 (3.48 mmol, 2.0 g) in CH_2Cl_2 (28 mL) was treated with DMAP (0.87 mmol, 106 mg), HOBt (4.18 mmol, 0.56 g), EDC·HCl (8.70 mmol, 1.67 g), and DIPEA (13.92 mmol, 2.38 mL). After 30 min at rt, cyclopropyl-(2,3-dichlorobenzyl)-amine (WO 2004/096366; 10.4 mmol, 2.30 g) was added and the mixture was stirred for 5 days at rt. The reaction was then diluted with CH_2Cl_2, washed with aq. 1M HCl, dried over MgSO4, filtered, and the solvents were removed under reduced pressure.

Purification of the residue by FC (EtOAc/heptane 30:70) yielded the title compound (1.2 g, 45%). LC-MS: t_R = 1.31 min; ES+: 772.55.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-hydroxyphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E1)

To a sol. of compound D1 (2.13 g, 2.85 mmol) in THF (32 mL) at 0 °C was added dropwise a sol. of TBAF (899 mg 2.85 mmol) in THF (9 mL). The reaction mixture was stirred at 0°C for 40 min. Aq. sat. NH_4Cl was added. EtOAc was then added and the phases were shaken before being separated. The org. phase was washed with aq. sat. NH_4Cl and with brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were reduced under reduced pressure. Purification of the residue by FC (CH_2Cl_2/CH_3OH 100/3) yielded the title compound (1.73 g, 96%). LC-MS: t_R = 1.09 min.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-hydroxy-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E2)

A sol. of compound D2 (1.55 mmol, 1.2 g) in THF (31 mL) at 0 °C was treated with TBAF (3.3 mmol, 3.3 mL of a 1M solution in THF). After 4 h at rt, aq. sat. NH_4Cl was added. The mixture was extracted with EtOAc, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 50:50) yielded the title compound (0.85 g, 83%). LC-MS: t_R = 1.12 min; ES+: 658.47.

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]-phenyl}-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F1)

To a sol. of compound H2 (0.07 g, 0.1 mmol) in pyridine (1 mL) was added 2-chloro-3,6-difluorobenzoyl chloride (0.025 g, 0.12 mmol) and the reaction mixture was refluxed for 4 h. EtOAc was added and the mixture was washed with aq. 1M HCl (3x), water and brine. The org. phase was dried over Na_2SO_4, filtered, and the solvents were

removed under reduced pressure. The residue was used in the next step without further purification. LC-MS: t_R = 1.23 min, ES+: 862.51.

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chlorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]phenyl}-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F2)

To a sol. of compound H2 (0.07 g, 0.1 mmol) in pyridine (1 mL) was added 2-chloro-benzoyl chloride (0.025 g, 0.12 mmol) and the reaction mixture was refluxed for 4 h. EtOAc was added and the mixture was washed with aq. 1M HCl (3x), water and brine. The org. phase was dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The residue was used in the next step without further purification. LC-MS: t_R = 1.23 min, ES+ : 826.46.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-{2-[3-(2,3-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F3)

A sol. of compound H5 (0.52 g, 0.05 mmol), 2,3-dichloro-*N*-hydroxybenzamidine (0.011 g, 0.055 mmol), DMAP (0.002 g, 0.012 mmol), DIPEA (0.035 mL, 0.2 mmol), HOBt (0.042 g, 0.062 mmol) and EDC·HCl (0.014 g, 0.075 mmol) in toluene (2 mL) was stirred for 72 h. The mixture was then heated at 110 °C for 6 h. After being cooled, the mixture was diluted with CH_2Cl_2 and poured on a syringe containing diatomaceous earth pretreated with aq. 1M HCl (Isolute Sorbent Technology, Johnson, C.R., *et al.*, Tetrahedron, 1998, *54*, 4097). The product was eluted with CH_2Cl_2 and the solvent was removed under reduced pressure. The residue was used in the next step without further purification. LC-MS: t_R = 1.25 min, ES+: 858.41.

(*rac.*)-(*1R**, *5S**)-7-(4-{2-[3-(2-Chlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F4)

A sol. of compound H5 (0.52 g, 0.05 mmol), 2-chloro-*N*-hydroxybenzamidine (0.011 g, 0.055 mmol), DMAP (0.002 g, 0.012 mmol), DIPEA (0.035 mL, 0.2 mmol), HOBt (0.042 g, 0.062 mmol) and EDC·HCl (0.014 g, 0.075 mmol) in toluene (2 mL) was

stirred for 72 h. The mixture was then heated at 110 °C for 6 h. After being cooled, the mixture was diluted with CH_2Cl_2 and poured on a syringe containing diatomaceous earth pretreated with aq. 1M HCl (Isolute Sorbent Technology, Johnson, C.R., *et al.*, Tetrahedron, 1998, *54*, 4097). The product was eluted with CH_2Cl_2 and the solvent was removed under reduced pressure. The residue was used in the next step without further purification. LC-MS: t_R = 1.24 min, ES+: 858.50.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F5)

A solution of compound E2 (0.08 mmol, 50 mg) in toluene (1 mL) was treated with [3-(2-chloro-3,6-difluorophenyl)isoxazol-5-yl]methanol (0.11 mmol, 28 mg) followed by azodicarboxylic dipiperidide (0.15 mmol, 38 mg) and tributylphosphine (0.27 mmol, 0.06 mL). The mixture was stirred at 110 °C for 1 h, cooled to rt, and filtered on Isolute. The solvents were removed under reduced pressure. Purification of the residue by HPLC yielded the title compound (33 mg, 47%). LC-MS: t_R = 1.24 min; ES+: 887.25.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F6)

A sol. of compound H6 (0.30 g, 0.43 mmol), 2-chloro3,6-difluoro-*N*-hydroxybenzamidine (0.17 g, 0.85 mmol), DMAP (0.005 g, 0.04 mmol), DIPEA (0.22 mL, 1.28 mmol), HOBt (0.065 g, 0.43 mmol) and EDC·HCl (0.12 g, 0.64 mmol) in CH_2Cl_2 (4 mL) was stirred for 48 h. The mixture was diluted with CH_2Cl_2, washed with aq. 1 HCl, water, and finally brine. The org. layer was dried over $MgSO_4$, filtered, and the solvent was evaporated under reduced pressure. Pyridine (1 mL) was added to the residue and the mixture was then heated at 110 °C for 4 h. After being cooled, the mixture was diluted with CH_2Cl_2, washed with aq. 1M HCl, water, and brine. The org. extracts were evaporated under reduced pressure. The residue (0.28 g) was used in the next step without further purification. LC-MS: t_R = 1.24 min, ES+: 888.38.

(*rac.*)-(*1R**, *5S**)-7-{4-[2-(2-Chloro-3,6-difluorophenyl)oxazol-4-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F7)

A sol. of compound E2 (0.08 mmol; 50 mg) and 2-(2-chloro-3,6-difluorophenyl)-4-chloromethyloxazole (0.38 mmol; 100 mg) in DMF (1.5 mL) was treated with K_2CO_3 (0.76 mmol; 105 mg). The reaction mixture was heated at 100 °C for 2 h, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 50:50) yielded the title compound (40 mg, 60%). LC-MS: t_R = 1.25 min; ES+: 887.21.

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chloro-3,6-difluorophenyl)isoxazol-3-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F8)

To a sol. of compound E2 (0.26 g, 0.39 mmol), [5-(2-chloro-3,6-difluorophenyl)isoxazol-3-yl]methanol (0.08 g, 0.33 mmol) and azodicarboxyl dipiperidide (0.123 g, 0.49 mmol) in toluene (3.5 mL) was added PBu_3 (0.16 mL, 0.65 mmol) at 0 °C . The reaction mixture was heated to 65 °C for 2 h. After cooling the reaction mixture to rt, it was diluted with EtOAc, and washed with water. The org. phase was dried over Na_2SO_4, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 3/7) yielded the title compound (0.32 g, quantitative yield). LC-MS: t_R = 1.26 min, ES+: 885.13.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(4-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F10)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(4-fluoro-2-trifluoromethyl-phenyl)-isoxazol-5-yl]-methanol.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-6-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F11)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(2-chloro-6-fluorophenyl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,5-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F12)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(2,5-difluorophenyl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-4-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F13)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(2-chloro-4-fluorophenyl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)-isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F14)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,4-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F15)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(2,4-dichlorophenyl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,6-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F16)

Prepared according to general procedure D, from compound E2 (200 mg), and [3-(2,6-dichlorophenyl)isoxazol-5-yl]methanol.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,3,6-trichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F17)

According to the general procedure G, from 2,3,6-trichlorobenzaldehyde oxime (56 mg, 0.25 mmol) and compound H7 (100 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (57 mg, 62%). LC-MS: t_R = 1.27 min; ES+: 919.28.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F18)

According to the general procedure G, from 2-fluoro-6-trifluoromethylbenzaldehyde oxime (52 mg, 0.25 mmol) and compound H7 (100 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (63 mg, 70%). LC-MS: t_R = 1.24 min; ES+: 901.37.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,3-dichloro-phenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F19)

According to the general procedure G, from 2,3-dichloro-benzaldehyde oxime (48 mg, 0.25 mmol) and compound H7 (100 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (60 mg, 68%). LC-MS: t_R = 1.27 min; ES+: 885.38.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-6-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F20)

According to the general procedure G, from 2-chloro-6-fluoro-3-methyl-benzaldehyde oxime (47 mg, 0.25 mmol) and compound H7 (100 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (64 mg, 73%). LC-MS: t_R = 1.26 min; ES+: 883.31.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F21)

According to the general procedure G, from 3-chloro-2-fluorobenzaldehyde oxime (44 mg, 0.25 mmol) and compound H7 (70 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (35 mg, 41%). LC-MS: t_R = 1.27 min; ES+: 867.31.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(6-Chloro-2-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F22)

According to the general procedure G, from 6-chloro-2-fluoro-3-methylbenzaldehyde oxime (47 mg, 0.25 mmol) and compound H7 (70 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (55 mg, 62%). LC-MS: t_R = 1.26 min; ES+: 883.40.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F23)

According to the general procedure G, from 3-chloro-2-fluoro-6-trifluoromethyl-benzaldehyde oxime (60 mg, 0.25 mmol) and compound H7 (70 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (75 mg, 80%). LC-MS: t_R = 1.26 min; ES+: 937.36.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F24)

According to the general procedure G, from 3-chloro-2,6-difluorobenzaldehyde oxime (48 mg, 0.25 mmol) and compound H7 (70 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (67 mg, 76%). LC-MS: t_R = 1.25 min; ES+: 885.40.

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-6-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F25)

According to the general procedure G, from 3-chloro-6-fluoro-2-trifluoromethylbenzaldehyde oxime (60 mg, 0.25 mmol) and compound H7 (70 mg, 0.10 mmol). Purification of the residue by HPLC yielded the title compound (71 mg, 76%). LC-MS: t_R = 1.26 min; ES+: 935.40.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,6-dimethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F26)

According to the general procedure G, from 2,6-dimethylbenzaldehyde oxime (54 mg, 0.36 mmol) and compound H7 (100 mg, 0.14 mmol). Purification of the residue by HPLC yielded the title compound (101 mg, 83%). LC-MS: t_R = 1.24 min; ES+: 843.37.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[3-(2,5-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F27)

According to the general procedure G, from 2,5-dichlorobenzaldehyde oxime (68 mg, 0.36 mmol) and compound H7 (100 mg, 0.14 mmol). Purification of the residue by HPLC yielded the title compound (110 mg, 87%). LC-MS: t_R = 1.27 min; ES+: 885.25.

(*rac.*)-(*1R**, *5S**)-7-(4-Cyanomethoxyphenyl)-6-[cyclopropyl-(3-methoxy-2-methyl-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H1)

To a sol. of compound E1 (1.40 g 2.20 mmol) in anhydrous acetone (16 mL) were added successively K_2CO_3 (381 mg, 2.76 mmol), NaI (63 mg, 0.42 mmol), and chloroacetonitrile (208 mg, 2.75 mmol). The mixture was heated to reflux for 4 h. The crude reaction mixture was allowed to cool to rt, and was filtered. The filtrate was

concentrated under reduced pressure, and was purified by FC (CH_2Cl_2/CH_3OH 100/3). This yielded the title compound (1.35 g, 91%). LC-MS: t_R = 1.14 min.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(*N*-hydroxycarbamimidoylmethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H2)

To a sol. of compound H1 (1.39 g, 2.07 mmol) in EtOH (25 mL) were added successively water (6 mL), $H_2NOH{\cdot}HCl$ (531 mg, 7.64 mmol) and K_2CO_3 (485 mg, 3.51 mmol). The mixture was heated to reflux for 3.5 h. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. Water and CH_2Cl_2 were added. The layers were shaken and separated, and the aq. layer was extracted with CH_2Cl_2, until the aq. layer did not contain any product. The combined org. layers were evaporated under reduced pressure. Drying the solid residue under high vacuum yielded the title compound (1.45 g), which was used without further purification. LC-MS t_R = 0.92 min.

(*rac.*)-(*1R**, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H3)

To a stirred sol. of the compound L2 (12.0 g, 19.4 mmol) in CH_2Cl_2 (158 mL) were added EDC·HCl (9.34 g, 48.7 mmol), HOBt (3.18 g, 23.4 mmol), DMAP (0.596 g, 4.87 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (11.2 g, 58.4 mmol) and DIPEA (13.4 mL, 77.9 mmol). The mixture was stirred at rt for 5 days. The reaction mixture was partitioned between aq. 1M HCl and CH_2Cl_2, and the org. phase was washed with aq. sat. $NaHCO_3$. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification by FC (heptane/EtOAc 8/2) yielded the title compound (8.20 g, 52%).

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-di-carboxylic acid di-*tert*-butyl ester (H4)

To a sol. of the compound H3 (10.0 g, 12.7 mmol) in THF (225 mL) was added TBAF (1M in THF, 25.3 mL, 25.3 mmol) and the mixture was stirred at 0 °C for 4 h. The reaction mixture was partitioned between aq. sat. NH_4Cl and EtOAc, the org. phase washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification by FC (0-10% MeOH in CH_2Cl_2) yielded the title compound (7.00 g, 82 %) as a yellow foam.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-methoxy-carbonylmethoxyphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H5)

To a sol. of compound E2 (0.33 g, 0.5 mmol) in anhydrous CH_3CN (3 mL) was added K_2CO_3 (0.15 g, 1.1 mmol) and methyl bromoacetate (0.046 mL, 0.5 mmol). The reaction mixture was refluxed for 18 h. After cooling to rt, CH_2Cl_2 was added, the solid was filtered, and washed with CH_2Cl_2. The solvents were removed under reduced pressure, and the residue was dissolved in CH_2Cl_2, washed with water, and brine. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure to yield the title compound (0.35 g) that was not further purified. LC-MS: t_R = 1.17 min, ES+: 730.29.

(*rac.*)-(*1R**, *5S**)-7-(4-Carboxymethoxyphenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H6)

To a sol. of compound H5 (0.35 g, 0.48 mmol) in THF (1 mL) was added a solution of NaOH 1M (1 mL), and the reaction mixture was stirred for 1 h. CH_2Cl_2 (20 mL) was added, as well as aq. 0.5M HCl (6 mL). The org. layer was separated and dried over $MgSO_4$, filtered, and the solvents were evaporated under reduced pressure. The obtained title compound (0.31 g) was not further purified. LC-MS: t_R = 1.10 min, ES+ = 716.40.

(*rac.*)-(*1R**, *5S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-prop-2-ynyloxyphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (H7)

A solution of compound E2 (5.00 g, 7.59 mmol) in DMF (75.0 mL) was treated with K_2CO_3 (1.15 g, 8.35 mmol), followed by propargyl bromide (0.90 mL, 8.35 mmol). The suspension was stirred for 3 h at 80 °C. Once at rt, EtOAc (200 mL) was added and the org. layer was washed twice with Na_2CO_3 and twice with brine. The org. phase was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 40:60) yielded the title compound (4.77 g, 90%). LC-MS: t_R = 1.18 min; ES+: 696.26.

(*rac.*)-(*1R**, *5S**)-7-[4-(2-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (K1)

To a suspension of $NaHCO_3$ (15.5 g, 184 mmol) and 7-{4-[2-(*tert*-butyl-dimethylsilanyloxy)propyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester WO 03/093267, 10.3 g, 18.4 mmol) in CH_2ClCH_2Cl (190 mL) was added 1-chloroethyl chloroformate (20.0 mL, 55.1 mmol). The mixture was heated and stirred to 80 °C. After 3 h, the reaction mixture was allowed to cool to rt, filtered, and the solvents were thoroughly removed *in vacuo*. The residue was dried under high vacuum for 15 min. MeOH (130 mL) was added and the mixture was stirred at 50 °C for 20 min. The sol. was allowed to cool to rt, and the solvents were removed *in vacuo*. The residue was dried under high vacuum. The residue was dissolved in CH_2Cl_2 (190 mL). DIPEA (15.7 mL, 91.8 mmol) and Boc_2O (12.0 g, 55.1 mmol) were added, and the mixture was stirred at rt for 30 min. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. phase was dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification by FC (50% EtOAc in heptane) yielded the title compound (8.86 g, 91%).

(*rac.*)-(*1R**, *5S**)-7-[4-(2-Hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (L1)

1 M NaOH (198 mL) was added to a sol. of compound K1 (15.0 g, 28.3 mmol) in EtOH (396 mL). The resulting mixture was stirred at 80 °C for 3 h, cooled to rt and the solvents were removed *in vacuo*. The crude mixture was partitioned between EtOAc and aq. 1M HCl. The aq. layer was extracted once more with EtOAc. The combined

org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to yield the title compound (13.3 g, 94%).

(*rac.*)-(*1R**, *5S**)-7-{4-[2-(*tert*-Butyldimethylsilanyloxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (L2)

TBDMS-Cl (7.38 g, 48.7 mmol) and imidazole (5.32 g, 77.9 mmol) were added to a stirred sol. of compound L1 (9.79 g, 19.5 mmol) in DMF (100 mL). The reaction mixture was stirred at rt over 15 h. The solvents were removed *in vacuo*, the crude mixture partitioned between Et_2O and aq. sat. NH_4Cl. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. To a sol. of the reaction mixture in THF (190 mL) were added MeOH (63 mL), water (33 mL) and K_2CO_3 (1.46 g), and the mixture was stirred at rt for 30 min. The mixture was then partitioned between Et_2O and aq. sat. NH_4Cl and the aq. layer was extracted once more with Et_2O. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* to yield the title compound (12.2 g, quantitative yield) as a yellow foam.

Examples

Example 1

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

To a sol. of the compound F1 (0.1 mmol) in CH_2Cl_2 (1 mL), cooled to 0 °C was added 4M HCl/dioxane (1 mL). The ice bath was removed and the sol. was stirred for 90 min. The solvents were evaporated under reduced pressure without heating. Purification of the residue by HPLC (H_2O, MeOH, NH_4OH) yielded the title compound (14 mg). LC-MS: t_R = 0.83 min, ES+: 662.47.

Example 2

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chlorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide

To a sol. of the compound F2 (0.1 mmol) in CH_2Cl_2 (1 mL), cooled to 0 °C was added 4M HCl/dioxane (1 mL). The ice bath was removed and the sol. was stirred for 90 min. The solvents were evaporated under reduced pressure without heating. Purification of the residue by HPLC (H_2O, MeOH, NH_4OH) yielded the title compound (14 mg). LC-MS: t_R = 0.82 min, ES+: 626.50.

Example 3

(*rac.*)-(*1R**, *5S**)-7-(4-{2-[3-(2,3-Dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide

To a sol. of compound F3 (0.05 mmol) in CH_2Cl_2 (0.5 mL), cooled to 0 °C, was added 4M HCl/dioxane (0.5 mL). The ice bath was removed and the sol. was stirred for 90 min. The solvents were evaporated under reduced pressure without heating. Purification of the residue by HPLC (H_2O, MeOH, NH_4OH) yielded the title compound (9 mg). LC-MS: t_R = 0.85 min, ES+: 658.38.

Example 4

(*rac.*)-(*1R**, *5S**)-7-(4-{2-[3-(2,6-Dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide

To a sol. of compound F4 (0.05 mmol) in CH_2Cl_2 (0.5 mL), cooled to 0 °C, was added 4M HCl/dioxane (0.5 mL). The ice bath was removed and the sol. was stirred for 90 min. The solvents were evaporated under reduced pressure without heating. Purification of the residue by HPLC (H_2O, MeOH, NH_4OH) yielded the title compound (9 mg). LC-MS: t_R = 0.83 min, ES+: 658.38.

Example 5

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

To a sol. of the compound F6 (0.074 g, 0.08 mmol) in CH_2Cl_2 (1 mL), cooled to 0 °C, was added 4M HCl in dioxane (1 mL). The ice bath was removed and the sol. was stirred for 2 h. The reaction mixture was quenched with aq. 2M NaOH (2 mL) and poured on a syringe containing diatomaceous earth (4 g, Isolute Sorbent Technology, Johnson, C.R., *et al.*, Tetrahedron, 1998, *54*, 4097). The product was eluted with CH_2Cl_2, and the solvents were removed under reduced pressure. The residue was purified by HPLC (H_2O, MeOH, NH_4OH) to yield the title product (0.026g). LC-MS: t_R = 0.86 min, ES+ = 688.28.

Example 6

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

To a sol. of compound F5 (0.05 mmol) in CH_2Cl_2 (0.5 mL), cooled to 0 °C, was added 4M HCl/dioxane (0.5 mL). The ice bath was removed and the sol. was stirred for 90 min. The solvents were evaporated under reduced pressure without heating. Purification of the residue by HPLC (H_2O, MeOH, NH_4OH) yielded the title compound (15 mg). LC-MS: t_R = 0.86 min; ES+: 685.29.

Example 7

(*rac.*)-(*1R**, *5S**) 7-{4-[2-(2-Chloro-3,6-difluorophenyl)oxazol-4-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide (C)

A sol. of compound F7 (0.08 mmol, 50 mg) in CH_2Cl_2 (1.0 mL) was treated with HCl (4M in dioxane, 1.0 mL), and the mixture was stirred for 2 h at 0 °C. Purification of the residue by preparative HPLC yielded the title compound (14 mg, 24%). LC-MS: t_R = 0.86 min; ES+: 687.27.

Example 8

(*rac.*)-(*1R**, *5S**)-7-{4-[5-(2-Chloro-3,6-difluorophenyl)isoxazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

To a sol. of compound F8 (0.31 g, 0.33 mmol) in CH_2Cl_2 (7 mL), cooled to 0 °C, was added 4M HCl in dioxane (7 mL). The ice bath was removed, and the sol. was stirred for 2 h. The solvents were removed under reduced pressure. The residue was purified by HPLC (H_2O, MeOH, NH_4OH) to yield the title product (0.062g). LC-MS: t_R = 0.86 min, ES+ = 687.15.

Example 9

(*1R*, *5S*)-3-Acetyl-7-{4-[3-(2-chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

The enantiomers of the racemate described in Example 6 (450 mg) were separated by HPLC using a chiral column. (*1R*, *5S*)-7-{4-[3-(2-Chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide was obtained (110 mg). HPLC: t_R = 11.53 min. This compound (45 mg, 0.066 mmol) was dissolved in THF 82 mL), and cooled to 0 °C. Acetyl chloride (5 μL, 0.066 mmol) was added dropwise, and the mixture was allowed to warm up to rt. The mixture was stirred at rt for 2 h, and the solvents were removed under reduced pressure. Purification by FC (CH_2Cl_2 → MeOH/CH_2Cl_2 1:9 as continuous gradient) yielded the title compound (43 mg, 90%). LC-MS: t_R = 0.91 min, ES+ = 729.17.

Example 10

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(4-Fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

Prepared according to general procedure E, from compound F10, the title compound was obtained (96 mg, 41% over 2 steps). LC-MS: t_R = 0.86; ES+: 701.22.

Example 11

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-6-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

Prepared according to general procedure E, from compound F11, the title compound was obtained (88 mg, 39% over 2 steps). LC-MS: t_R = 0.84; ES+: 667.22.

Example 12

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,5-Difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Prepared according to general procedure E, from compound F12, the title compound was obtained (69 mg, 32% over 2 steps). LC-MS: t_R = 0.85; ES+: 651.28.

Example 13

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-4-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Prepared according to general procedure E, from compound F13, the title compound was obtained (91 mg, 41% over 2 steps). LC-MS: t_R = 0.84; ES+: 669.23.

Example 14

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(5-Chloro-1,3-dimethyl-1H-pyrazol-4-yl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Prepared according to general procedure E, from compound F14, the title compound was obtained (53 mg, 24% over 2 steps). LC-MS: t_R = 0.79; ES+: 669.26.

Example 15

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,4-Dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Prepared according to general procedure E, from compound F15, the title compound was obtained (113 mg, 50% over 2 steps). LC-MS: t_R = 0.85; ES+: 685.19.

Example 16

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,6-Dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Prepared according to general procedure E, from compound F16, the title compound was obtained (97 mg, 42% over 2 steps). LC-MS: t_R = 0.84; ES+: 685.17.

Example 17

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,3,6-Trichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

According to the general procedure E, compound F17 (92 mg, 0.10 mmol) was used to prepare the title compound (41 mg, 57%). LC-MS: t_R = 0.89 min; ES+: 721.24.

Example 18

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

According to the general procedure E, compound F18 (90 mg, 0.10 mmol) was used to prepare the title compound (52 mg, 74%). LC-MS: t_R = 0.87 min; ES+: 701.39.

Example 19

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,3-Dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to the general procedure E, compound F19 (88 mg, 0.10 mmol) was used to prepare the title compound (50 mg, 73%). LC-MS: t_R = 0.88 min; ES+: 683.30.

Example 20

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-Chloro-6-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

According to the general procedure E, compound F20 (88 mg, 0.10 mmol) was used to prepare the title compound (53 mg, 77%). LC-MS: t_R = 0.87 min; ES+: 683.33.

Example 21

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

According to the general procedure E, from compound F21 (87 mg, 0.10 mmol), the title compound was obtained (23 mg, 35%). LC-MS: t_R = 0.87 min; ES+: 669.35.

Example 22

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(6-Chloro-2-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

According to the general procedure E, from compound F22 (88 mg, 0.10 mmol), the title compound was obtained (43 mg, 60%). LC-MS: t_R = 0.87 min; ES+: 681.36.

Example 23

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to the general procedure E, from compound F23 (94 mg, 0.10 mmol), the title compound was obtained (63 mg, 85%). LC-MS: t_R = 0.89 min; ES+: 735.33.

Example 24

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-2,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

According to the general procedure E, compound F24 (89 mg, 0.10 mmol) was used to prepare the title compound (56 mg, 82%). LC-MS: t_R = 0.87 min; ES+: 685.33.

Example 25

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(3-Chloro-6-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to the general procedure E, compound F25 (94 mg, 0.10 mmol) was used to prepare the title compound (56 mg, 77%). LC-MS: t_R = 0.89 min; ES+: 735.35.

Example 26

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,6-Dimethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

According to the general procedure E, compound F26 (84 mg, 0.10 mmol) was used to prepare the title compound (90 mg, 97%). LC-MS: t_R = 0.85 min; ES+: 643.33.

Example 27

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2,5-Dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to the general procedure E, compound F26 (127 mg, 0.14 mmol) was used to prepare the title compound (89 mg, 91%). LC-MS: t_R = 0.87 min; ES+: 685.23.

Biological Assays

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

1.1 Preparation of Ang I-BSA conjugate

1.3 mg (1 µmol) of Ang I [1-10 (Bachem, H-1680)] and 17 mg (0.26 µmol) 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 H_2O (Sigma G-5882) was added dropwise.

The mixture was incubated overnight at 4 °C, then dialyzed against 2 liters of 0.9% NaCl, twice 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 µm (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.

1.2 Preparation of BSA-Ang I coated MTP

Microtiter plates (MPT384, MaxiSorp™, Nunc) were incubated overnight at 4 °C with 80 µl of Ang I (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 µl of blocking solution [0.5% BSA (Sigma A-2153) in PBS 1X, 0.02% NaN_3], and incubated for at least 2 h at rt, or overnight at 4 °C. 96 well MTP (MaxiSorp™, Nunc) were coated with 200 µl conjugate and blocked with 250 µl 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 Ang I-EIA in 384 well MTP

The Ang I (1-10)/BSA coated MTP were washed 3 times with wash buffer (PBS 1X, 0.01% Tween 20) and filled with 75 µl of primary antibody solution (anti-Ang I 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 µl of the renin reaction (or standards in assay buffer) (see below) were added to the primary antibody solution and the plates were 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 H_2O_2 [30%, (Fluka, 95300] in substrate buffer (0.1M sodium acetate, 0.05M sodium dihydrogen phosphate, pH 4.2). The OD of the plate was read at 405 nm in a microplate reader (FLUOStar Optima from BMG). The production of Ang I during the renin

reaction was quantified by comparing the OD of the sample with the OD of a standard curve of Ang I(1-10), measured in parallel.

2. Primary renin inhibition assay: IC_{50} in buffer, 384 well MTP

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 (Ang I). In the second step, the accumulated Ang I is measured by an immunological assay (enzyme immuno assay, EIA). The detailed 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.

2.1 Methodology

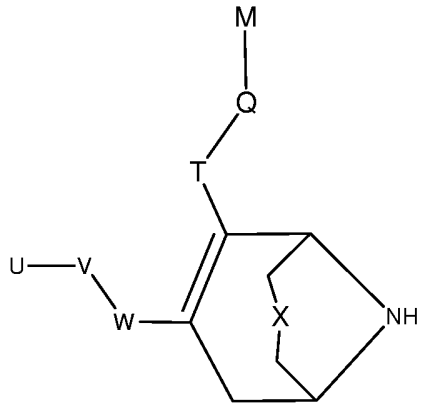
Recombinant human renin (3 pg/µl) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 µM in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H_2O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 µl per well of this premix was transferred into 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 Ang I produced by renin was quantified. The percentage of renin inhibition (Ang I decrease) was calculated for each concentration of compound and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50}-values of all compounds tested are below 100 nM. However, selected compounds exhibit a very good bioavailability and are metabolically more stable than prior art compounds.

Examples of inhibition:

Compound of Example No.	IC_{50} values [nM]
1	4
5	3.2
6	0.8
11	3.2
16	3.6
20	3.5
24	2.0

Claims

1. A compound selected from the group consisting of bicyclononene compounds of the formula (I)



(I)

wherein

X represents -NH-, -N(L)-, -O-, or -S-;

W represents phenyl, substituted by V in *para* position;

V represents a radical of the formula $-E^1-Z-E^2-$;

E^1 represents $-O-CH_2-$ or $-CH_2-CH_2-$;

E^2 represents a bond, -O-, or $-CH_2-$;

Z represents a five-membered heteroaryl with 2 or 3 heteroatoms independently selected from oxygen, nitrogen and sulfur;

U represents phenyl or mono-, di-, tri- or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, $-CF_3$, C_{1-7}-alkyl and hydroxy-C_{1-7}-alkyl; or five-membered heteroaryl with two heteroatoms independently selected from nitrogen, oxygen and sulfur, wherein said five-membered heteroaryl can optionally be mono, di, or tri-substituted, wherein the substituents are

independently selected from the group consisting of halogen, -CF_3, C_{1-7}-alkyl and hydroxy-C_{1-7}-alkyl;

T represents -$CONR^1$-;

Q represents methylene;

M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, -OCF_3, -CF_3, hydroxy-C_{1-7}-alkyl and halogen;

L represents -R^3, -COR^3, -$COOR^3$, -$CONR^2R^3$, -SO_2R^3, or -$SO_2NR^2R^3$;

R^1 and $R^{1'}$ independently represent C_{1-7}-alkyl or C_3-C_6-cycloalkyl;

R^2 and $R^{2'}$ independently represent hydrogen, C_{1-7}-alkyl, C_{2-7}-alkenyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-C_{1-7}-alkyl; and

R^3 represents C_{1-7}-alkyl, C_3-C_6-cycloalkyl, or C_3-C_6-cycloalkyl-C_{1-7}-alkyl, wherein these groups may be unsubstituted or mono-, di- or tri-substituted, wherein the substituents are independently selected from the group consisting of hydroxy, -NH_2, -$OCOR^2$, -$COOR^2$, -SO_3H, -SO_2CH_3, C_{1-7}-alkoxy, cyano, -$CONR^2R^{2'}$, -$NH(NH)NH_2$, -$NR^1R^{1'}$, tetrazolyl, 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;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, mixtures of enantiomers and diasteromers such as diastereomeric racemates, and meso-forms, as well as salts and solvent complexes of such compounds, and morphological forms.

2. A compound according to claim 1, wherein X represents -NH- or -$N(COCH_3)$-.

3. A compound according to claim 2, wherein

X represents -NH-; and

U represents phenyl or mono-, di-, tri- or tetra-substituted phenyl, wherein the substituents are selected from the group consisting of halogen, $-CF_3$, C_{1-7}-alkyl, and hydroxy-C_{1-7}-alkyl.

4. A compound according to any one of claims 1 to 3, wherein M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and halogen.

5. A compound according to any one of claims 1 to 3, wherein M represents di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and chlorine.

6. A compound according to any one of claims 1 to 5, wherein R^1 represents a cyclopropyl group.

7. A compound according to any one of claims 1 to 6, wherein Z represents an oxazole ring.

8. A compound according to any one of claims 1 to 6, wherein Z represents an oxadiazole or isoxazole ring.

9. A compound according to any one of claims 1 to 8, wherein U represents a mono-, di-, or tri-substituted phenyl, wherein the substituents are selected from the group consisting of halogen and C_{1-7}-alkyl.

10. A compound according to claim 1, wherein

X represents -NH- or -N(L)-;

V represents a radical of the formula $-E^1-Z-E^2-$;

E^1 represents $-O-CH_2-$ or $-CH_2-CH_2-$;

E^2 represents a bond;

Z represents a five-membered heteroaryl with one nitrogen and one oxygen heteroatom, or a five-membered heteroaryl with one oxygen and two nitrogen heteroatoms;

U represents mono-, di-, or tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, $-CF_3$, and C_{1-7}-alkyl; or a five-membered heteroaryl with two nitrogen heteroatoms, wherein said five-membered heteroaryl is tri-substituted, wherein the substituents are independently selected from the group consisting of halogen and C_{1-7}-alkyl;

T represents $-CONR^1-$, wherein R^1 represents cyclopropyl;

M represents di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C_{1-7}-alkyl, C_{1-7}-alkoxy, and halogen; and

L represents $-COR^3$, wherein R^3 represents C_{1-7}-alkyl.

11. A compound according to claim 1 selected from the group consisting of:

(*1R**, *5S**)-7-{4-[5-(2-chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide,

(*1R**, *5S**)-7-{4-[5-(2-chlorophenyl)-[1,2,4]oxadiazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-(4-{2-[3-(2,3-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-(4-{2-[3-(2,6-dichlorophenyl)-[1,2,4]oxadiazol-5-yl]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenyl)-[1,2,4]oxadiazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and

(*rac.*)-(*1R**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide.

12. A compound according to claim 1 selected from the group consisting of:

(*1R**, *5S**)-7-{4-[2-(2-chloro-3,6-difluorophenyl)oxazol-4-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[5-(2-chloro-3,6-difluorophenyl)isoxazol-3-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R*, *5S*)-3-acetyl-7-{4-[3-(2-chloro-3,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(4-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-6-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,5-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-4-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(5-chloro-1,3-dimethyl-1H-pyrazol-4-yl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,4-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,6-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,3,6-trichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,3-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2-chloro-6-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-2-fluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(6-chloro-2-fluoro-3-methylphenyl)isoxazol-5-ylmethoxy]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide

(*1R**, *5S**)-7-{4-[3-(3-chloro-2-fluoro-6-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-2,6-difluorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R**, *5S**)-7-{4-[3-(3-chloro-6-fluoro-2-trifluoromethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-7-{4-[3-(2,6-dimethylphenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and

(*1R**, *5S**)-7-{4-[3-(2,5-dichlorophenyl)isoxazol-5-ylmethoxy]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide.

13. A pharmaceutical composition comprising a compound according to any one of claims 1 to 12 and a pharmaceutically acceptable carrier material.

14. A compound according to any one of claims 1 to 12, or composition according to claim 13, for use as a medicament.

15. Use of a compound according to any one of claims 1 to 12 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, 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2005/054276

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D471/08 A61K31/495 A61P9/00

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K

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

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

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/105762 A (ACTELION PHARMACEUTICALS LTD.) 9 December 2004 (2004-12-09) claims 1-18	1-15
A	WO 2004/096804 A (ACTELION PHARMACEUTICALS LTD.) 11 November 2004 (2004-11-11) claims 1-11	1-15
A	WO 2004/096366 A (ACTELION PHARMACEUTICALS LTD.) 11 November 2004 (2004-11-11) claims 1-10	1-15
A	WO 2004/096116 A (ACTELION PHARMACEUTICALS LTD.) 11 November 2004 (2004-11-11) claims 1-12	1-15

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

[X] See patent family annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

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"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
27 April 2006	08/05/2006

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INTERNATIONAL SEARCH REPORT

International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/093267 A (ACTELION PHARMACEUTICALS LTD.) 13 November 2003 (2003-11-13) cited in the application claims 1-12	1-15

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/IB2005/054276

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