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(54) Title: BICYCLONONENE DERIVATIVES

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

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Bicyclononene Derivatives

The invention relates to novel compounds of the formula (I). The invention also
5 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
10 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 AT1 and AT2. Whereas
AT1 seems to transmit most of the known functions of Ang II, the role of AT2 is
15 still unknown.

Modulation of the RAS represents a major advance in the treatment of
cardiovascular diseases. ACE inhibitors and AT1 blockers have been accepted to
treat hypertension (Waeber B. et al., "The renin-angiotensin system: role in
experimental and human hypertension", in Birkenhager W. H., Reid J. L. (eds):
20 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;
25 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).

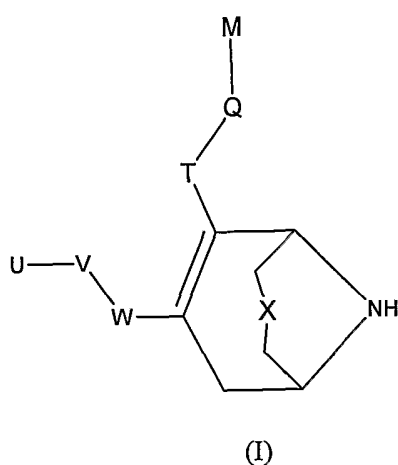
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, 1995, 9, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-
5 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
10 patients treated with ACE inhibitors. Blockade of the AT1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT2) to Ang II, whose concentration is significantly increased by the blockade of AT1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT1 blockers with regard to
15 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
20 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
25 first non-peptide renin inhibitors were described which show high in vitro activity (Oefner C. et al., *Chem. Biol.*, 1999, 6, 127; Patent Application WO97/09311; Märki H. P. et al., *Il Farmaco*, 2001, 56, 21). However, the development status of these compounds is not known.

The present invention relates to renin inhibitors of a non-peptidic nature and of
30 low molecular weight. Described are orally active renin inhibitors of long duration

of action 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
 5 describes these non-peptidic renin inhibitors of formula (I).

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



wherein

10 X represents -NH-, -N(L)-, -CH₂-, -CH(L)-, -O-, or -S-;

W represents a phenyl substituted by V in *para*-position;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-N(-R)-, -N(-R)-CH₂-CH₂-, -O-CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-CH₂-N(-R)-CH₂-CH₂-, -CH₂-N(-R)-CH₂-CH₂-O-, -CH₂-CH₂-CH₂-N(-R)-, -N(-R)-CH₂-CH₂-CH₂-, or -CH₂-CH₂-N(-R)-CO-;
 15

U represents phenyl; mono-, di-, tri-, or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, hydroxy-alkyl, halogen, -CF₃, -OCF₂O-, and cyano; a five-membered heteroaryl ring, wherein said heteroaryl ring is optionally mono-, di-, or tri-substituted,

wherein the substituents are independently selected from the group consisting of alkyl, hydroxy-alkyl, halogen and trifluoromethyl; or a quinolinyl;

T represents $-\text{CONR}^1-$;

Q represents methylene;

- 5 M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, alkoxy-alkyl, $-\text{OCF}_3$, $-\text{CF}_3$, and halogen; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from the group consisting of halogen, alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and alkoxy; with the proviso, that the halogen substituents are
10 not in 2- or 6-position of the pyridinyl ring;

L represents $-\text{R}^3$, $-\text{COR}^3$, $-\text{COOR}^3$, $-\text{CONR}^2\text{R}^3$, $-\text{SO}_2\text{R}^3$, or $-\text{SO}_2\text{NR}^2\text{R}^3$;

R represents hydrogen, alkyl, cycloalkyl, or $-\text{CH}_2\text{CF}_3$;

R^1 and $\text{R}^{1'}$ independently represent alkyl or cycloalkyl;

- R^2 and $\text{R}^{2'}$ independently represent hydrogen, alkyl, alkenyl, cycloalkyl, or
15 cycloalkyl-alkyl; and

- R^3 represents alkyl, cycloalkyl, or cycloalkyl-alkyl, wherein these groups may be unsubstituted or mono-, di- or tri-substituted, wherein the substituents are independently selected from hydroxy, $-\text{NH}_2$, $-\text{OCOR}^2$, $-\text{COOR}^2$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{CH}_3$, alkoxy, cyano, $-\text{CONR}^2\text{R}^{2'}$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^1\text{R}^{1'}$, tetrazolyl, and alkyl, with the
20 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, diastereomeric racemates, mixtures of diastereomeric racemates, and meso-forms, as well as salts and solvent complexes
25 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
5 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, diastereomeric racemates, mixtures of diastereomeric racemates, and meso-forms, as well as salts (especially
10 pharmaceutically acceptable salts) and solvent complexes (including hydrates) of such compounds, and morphological forms, as appropriate and expedient.

In the definitions of formula (I) – if not otherwise stated – the term **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.
15 Examples of 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-alkyl** refers to an HO-R group, wherein R is an alkyl group. Examples of hydroxy-alkyl groups are HO-CH₂-, HO-CH₂CH₂-, HO-
20 CH₂CH₂CH₂- and CH₃-CH(OH)-.

The term **alkoxy** refers to an R-O group, wherein R is an alkyl. Examples of alkoxy groups are methoxy, ethoxy, propoxy, iso-propoxy, iso-butoxy, sec-butoxy and tert-butoxy.

The term **alkenyl** means straight or branched chain groups comprising an olefinic
25 bond and consisting of two to seven carbon atoms, preferably two to four carbon atoms. Examples of alkenyl are vinyl, propenyl and butenyl.

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

The term **cycloalkyl** alone or in combination, means a saturated cyclic hydrocarbon ring system with 3 to 7 carbon atoms, e.g. cyclopropyl, cyclobutyl, 5 cyclopentyl, cyclohexyl or cycloheptyl.

The term **five-membered heteroaryl ring** means a five-membered aromatic ring containing two heteroatoms, especially independently selected from nitrogen, oxygen and sulfur, preferably a nitrogen and a sulfur atom, and especially represents an isothiazole ring.

10 Within the context of the present invention the beginning part of an asymmetric group V is linked to the group W of a compound of formula (I) (that means that for example the -O-CH₂ part of -O-CH₂-CH₂-N(R)- is linked to the group W of a compound of formula (I).

The term T within the present invention represents -CONR¹- which may be 15 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 -CONR¹- is linked to the bicyclononene core structure of formula (I)). Preferably, the term T within the present invention represents -CONR¹-, 20 wherein R¹ represents cycloalkyl, especially cyclopropyl.

The expression **pharmaceutically acceptable salts** encompasses either salts with inorganic acids or organic acids like hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, sulfamic acid, phosphoric acid, nitric acid, phosphorous acid, nitrous acid, citric acid, formic acid, acetic acid, oxalic acid, 25 maleic acid, lactic acid, tartaric acid, fumaric acid, benzoic acid, mandelic acid, cinnamic acid, palmoic acid, stearic acid, glutamic acid, aspartic acid, methanesulfonic acid, ethanesulfonic acid, ethanedisulfonic acid, *p*-toluenesulfonic acid, salicylic acid, succinic acid, trifluoroacetic acid, and the

like that are non toxic to living organisms or in case the compound of formula (I) is acidic in nature with an inorganic base like an alkali or earth alkali base, e.g. sodium hydroxide, potassium hydroxide, calcium hydroxide and the like. For other examples of pharmaceutically acceptable salts, reference can be made to
5 "Salt selection for basic drugs", *Int. J. Pharm.* (1986), **33**, 201-217.

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, diastereomeric racemates, mixtures of diastereomeric racemates, or meso-forms.

10 The present invention encompasses all these forms. Mixtures may be 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
15 condensation), sulfur (sulfhydryl 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 and 5,703,073; WO 97/27749; WO 98/19672; WO 98/21193; WO 99/00361 and Oae
20 et al., *Org. Prep. Proc. Int.*, 15(3): 165-198 (1983).

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

X represents -NH-;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-N(-R)-, -O-
25 CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-CH₂-N(-R)-, or -CH₂-CH₂-N(-R)-CO-;

U represents phenyl; mono-, di-, or tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, and halogen; or a five-membered heteroaryl ring, wherein said heteroaryl ring is optionally mono- or di-substituted, wherein the substituents are independently
5 selected from the group consisting of alkyl, hydroxy-alkyl, halogen and trifluoromethyl;

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-\text{OCF}_3$, $-\text{CF}_3$, and halogen; or mono- or di-substituted pyridinyl, wherein the substituents are
10 independently selected from the group consisting of halogen, alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring; and

R represents hydrogen, alkyl, or cycloalkyl;

and wherein the remaining substituents and symbols are as defined for formula (I)
15 above.

Preferred compounds of formula (I) are also those wherein X, W, V, U, Q and M are as defined in formula (I) and T represents $-\text{CONR}^1-$, wherein R^1 represents a cyclopropyl group.

More preferred compounds of formula (I) are those wherein X, W, U, T, Q and M
20 are as defined in formula (I) and V represents $-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{N}(-\text{CH}_2-\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-\text{CH}_2-$, $-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-\text{CH}_2-\text{O}-$, or $-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CO}-$.

Further preferred compounds of formula (I) are those wherein X, W, U, T, Q and M are as defined in formula (I) and V represents $-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$, $-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$, or $-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CO}-$.
25

Also more preferred compounds of formula (I) are those wherein X, W, U, T, Q and M are as defined in formula (I) and V represents $-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$ or $-\text{CH}_2-\text{CH}_2-\text{N}(-\text{CH}_3)-\text{CH}_2-$.

Preferred compounds of formula (I) are those wherein X, W, V, U, T and Q are as defined in formula (I) and M represents di-substituted phenyl.

Very preferred compounds of formula (I) are also those wherein X, U, T, Q, W and V are as defined in formula (I) and M represents phenyl di-substituted by methoxy and methyl .

Very preferred compounds of formula (I) are also those wherein X, U, T, Q, W and V are as defined in formula (I) and M represents 2,3-dichlorophenyl.

Very preferred compounds of formula (I) are also those wherein X, W, V, T, Q and M are as defined in formula (I) and U represents an isothiazole ring di-substituted by halogen.

Very preferred compounds of formula (I) are also those wherein X, W, V, Q, T and M are as defined in formula (I) and U represents a mono-, di- or tri-substituted phenyl, wherein the substituents are selected from halogen, methyl and methoxy, especially from halogen and methyl.

Very preferred compounds of formula (I) are also those wherein U, W, V, Q, T and M are as defined in formula (I) and X represents -NH-, -N(-COCH₃)-, or -N(-CONHCH₂C(CH₃)₂CONH₂)-, especially -NH-.

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

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

X represents -NH-;

W represents a phenyl substituted by V in *para*-position;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -O-CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-O-, -CH₂-CH₂-CH₂-N(-R)-, or -CH₂-CH₂-N(-R)-CO-;

U represents phenyl; mono-, di-, or tri-substituted phenyl, wherein the substituents
5 are independently selected from the group consisting of alkyl, alkoxy, halogen, -CF₃, -OCF₂O-, and cyano; or a quinolinyl;

T represents -CONR¹-;

Q represents methylene;

M represents di-substituted phenyl, wherein the substituents are independently
10 selected from the group consisting of alkyl, alkoxy, and halogen;

R represents alkyl, cycloalkyl, or -CH₂CF₃; and

R¹ represents cycloalkyl.

Especially preferred derivatives of formula (I) are those selected from the group consisting of:

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

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(methylphenylamino)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methyl-
20 benzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(methyl-*m*-tolylamino)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(3-chloro-2,6-difluorobenzoyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(4,5-dichloroisothiazole-3-carbonyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluoro-3-methylbenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-3,6-difluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-4-fluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-6-fluoro-3-methylbenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-3,6-difluorobenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-6-fluorobenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

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

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

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chlorobenzyl)cyclopropylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

15 (*rac.*)-(1*R**, 5*S**)-7-[4-({methyl-[2-(2,3,6-trichlorophenyl)ethyl]amino}methyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

20 (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2,6-dimethylbenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[methyl-(2,3,6-trichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{{ethyl-(2,3,5-trifluorobenzyl)amino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{{ethyl-(2,3,6-trifluorobenzyl)amino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,2-difluorobenzo[1,3]dioxol-4-ylmethyl)ethylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{{ethyl-(2,3,6-trichlorobenzyl)amino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,6-difluorobenzyl)ethylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2,4,6-trifluorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

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

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

15 (*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2-fluoro-5-methoxybenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2-fluoro-6-trifluoromethylbenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(6-chloro-2-fluoro-3-methylbenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

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

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

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

20 (*rac.*)-(1*R**, 5*S**)-7-(4-{[cyclopropyl-(2,3,6-trichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-cyanobenzyl)cyclopropylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

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

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

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(2-fluoro-5-methylphenyl)methylamino]propyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(5-chloro-2-methylphenyl)methylamino]propyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

5 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(3-fluoro-2-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(5-fluoro-2-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(2-chloro-5-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(3-chloro-2,6-difluorobenzyl)-(2,2,2-trifluoroethyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
15 cyclopropyl-(2,3-dichlorobenzyl)amide; and

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(3-chloro-2-fluoro-6-trifluoromethylbenzyl)-(2,2,2-trifluoroethyl)amino]methyl}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
20 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
25 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 known to be 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
5 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
10 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
15 comprising a compound of formula (I) and a pharmaceutically acceptable carrier material. These pharmaceutical compositions may be used for the treatment 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,
20 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
25 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) and 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.

The pharmaceutical preparations conveniently contain about 1 - 500 mg, preferably 5 - 200 mg of a compound of formula (I).

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. For adult patients a daily dosage of about 1
5 mg to about 1000 mg, especially about 50 mg to about 500 mg, comes into consideration.

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
10 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*.

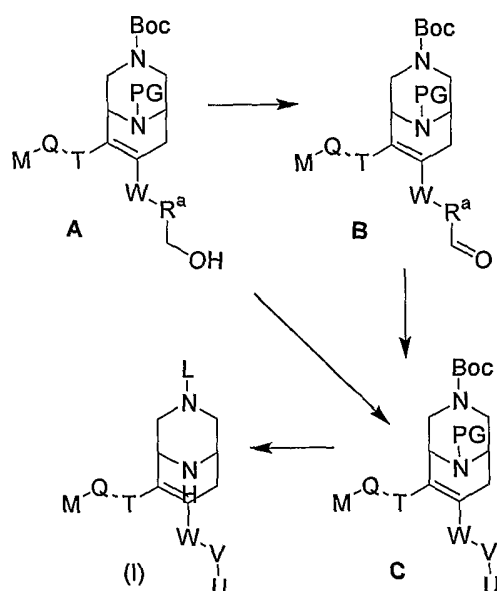
15 Compounds of formula (I) or the above-mentioned pharmaceutical compositions are also of use in combination with other pharmacologically active compounds such as ACE-inhibitors, neutral endopeptidase inhibitors, aldosterone antagonists, angiotensin II receptor antagonists, endothelin receptors antagonists,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

The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the
25 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.

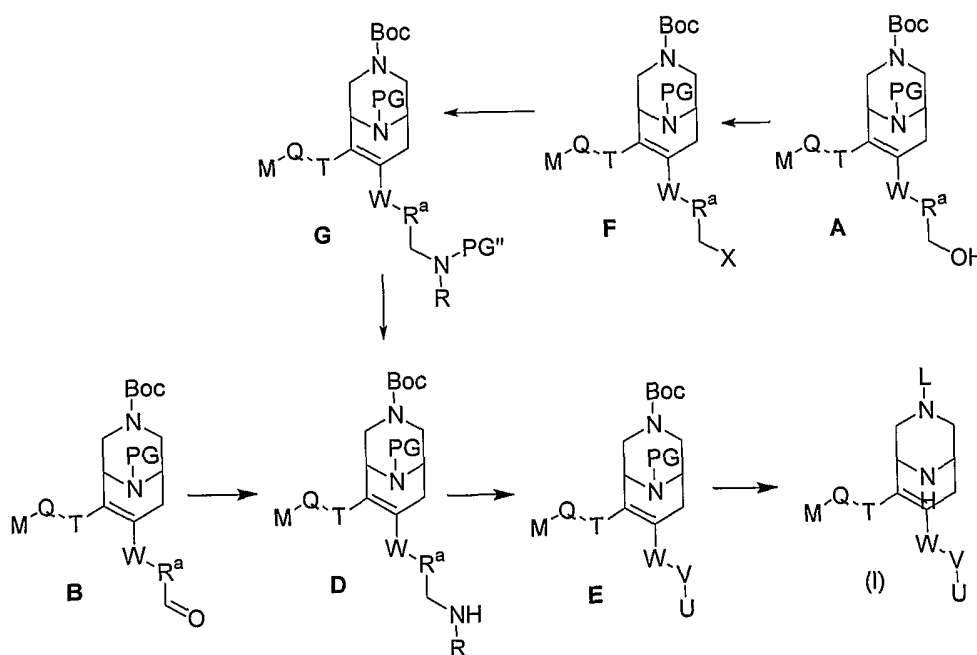
The chemistry is described hereby for the more complex diazabicyclononene moiety. The same chemistry can be used for the oxazabicyclononene and thiazabicyclononene moieties as included in formula (I), using also the preparations described in WO 2004/096366. For the azabicyclononene moiety, the chemistry described in WO 2004/096803 can be used.

Compounds of type A in Scheme 1 may be prepared as described in the patent application WO 03/093267, or using very similar chemistry (see experimental part for details). R^a represents a linker, which, together with its terminal substituent, will be completed and converted later into a U-V-substituent, as defined in formula (I). PG stands for a suitable protecting group. Compounds of type A can be oxidized to compounds of type B, following standard procedures (for instance: Swern oxidation, Dess-Martin oxidation, Ley oxidation). A reductive amination with the desired amine or aniline derivative leads to a compound of type C that is deprotected into a final compound of formula (I). Also, a compound of type A can be converted into a compound of type C directly, by nucleophilic substitution (see experimental part for details). Finally, deprotection step(s) will yield the desired final compound of formula (I).

Scheme 1

If a secondary amine or aniline derivative is necessary but is not commercially available, the corresponding primary amine or aniline derivative is prepared according to the literature, and is then *N*-alkylated by reductive amination.

A compound of type **B** is transformed into a compound of type **D** as well by reductive amination, as indicated in Scheme 2. An amide bond formation with a carboxylic acid or acyl chloride leads to a compound of type **E**. Finally, deprotection step(s) will yield the desired final compound of formula (I). Also a compound of type **A** is activated in a compound of type **F**, wherein X stands for a good leaving group, like a mesylate, a tosylate, or a triflate group, or an iodine or a bromine atom. A compound of type **F** is then transformed into a compound of type **G**, whereas PG'' stands for a suitable protecting group. A compound of type **G** is then deprotected to a compound of type **D**.



15

Scheme 2

Selective removal of the Boc protecting group on a compound of type **C** or **E**, then alkylation or acylation, allows the introduction of the L-substituent as defined

in formula (I). Also, a compound of formula (I) with X = NH can be acylated selectively at its 3-position.

The bicyclic core of oxaazabicyclononene derivatives (X = O in formula (I)), or thiaazabicyclononene derivatives (X = S in formula (I)) can be prepared as described in WO 2004/096366, using the chemistry described herein. The
5 azabicyclononene core (X = -CH₂- or -CH(L)- in formula (I)) can be prepared as described in WO 2004/096803, using the chemistry described herein.

It will be obvious to the person skilled in the art that many steps presented herein can be exchanged with each other under certain circumstances. Also some steps
10 can be omitted.

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

15 Abbreviations (as used herein)

AcOH	Acetic acid
Ang	Angiotensin
aq.	aqueous
Boc	<i>tert</i> -Butyloxycarbonyl
20 BSA	Bovine serum albumine
BuLi	<i>n</i> -Butyllithium
DIPEA	Diisopropylethylamine
DMAP	4- <i>N,N</i> -Dimethylaminopyridine
DMF	<i>N,N</i> -Dimethylformamide
25 DMSO	Dimethylsulfoxide
EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
EDTA	Ethylene diamine tetra acetate
EIA	Enzyme immunoassay
ELSD	Evaporating Light Scattering detection

	eq.	Equivalent(s)
	ES	Electrospray (in MS)
	Et	Ethyl
	EtOAc	Ethyl acetate
5	EtOH	Ethanol
	FC	Flash Chromatography
	h	hour(s)
	HOBt	Hydroxybenzotriazol
	HPLC	High Performance Liquid Chromatography
10	LC-MS	Liquid Chromatography – Mass Spectroscopy
	Me	Methyl
	MeOH	Methanol
	min	minute(s)
	MS	Mass Spectroscopy
15	NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
	OD	Optical density
	org.	organic
	<i>p</i>	<i>para</i>
	PG	protecting group
20	Ph	phenyl
	rt	room temperature
	sat.	saturated
	sol.	Solution
	TBAF	Tetra- <i>n</i> -butylammonium fluoride
25	TBDMS	<i>tert</i> -Butyldimethylsilyl
	TBME	<i>tert</i> -Butylmethylether
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	TLC	Thin Layer Chromatography
30	t_R	retention time (in HPLC or LC-MS)
	UV	Ultra violet

Vis visible

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

Analytic: Zorbax 59 SB Aqua column, 4.6 x 50 mm from Agilent Technologies.

5 Eluents: A: acetonitrile; B: H₂O + 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: H₂O + 0.05% ammonium hydroxide (25% aq.).

10 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% Et₃N. Eluent B: hexane. Isocratic conditions, 60% B, over 40 min, 1 mL/min. The isocratic mixture may vary, depending on the compounds.

15 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.

General procedures

General procedure A (reductive amination):

20 An aldehyde (0.08 mmol) was dissolved in CH₂Cl₂ (0.5 mL). The aniline (0.16 mmol) or amine (0.16 mmol), NaBH(OAc)₃ (35 mg, 0.167 mmol) and AcOH (20 µL, 0.33 mmol) were added. The mixture was stirred overnight and aq. 1M NaOH (0.200 mL) was added. The mixture was filtered through Isolute® (1 g) pre-washed with aq. 1M NaOH (0.7 mL). After 5 min. Isolute was rinsed with CH₂Cl₂
25 (3 x 1 mL). The combined org. filtrates were evaporated under reduced pressure, and the crude was directly used in the next step.

General procedure B (final compounds):

To a sol. of crude compound of type C or E in CH₂Cl₂ (1 mL) at 0 °C was added
30 4M HCl / dioxane (1 mL). The mixture was stirred at 0 °C until no more starting

material was visible by TLC or LC-MS. The solvents were rapidly removed under reduced pressure, and the residue was dried under high vacuum. Purification of the crude by HPLC yielded the final compounds.

5 *General procedure C (amide formation):*

A compound of type **D** (0.05mmol), Amberlyst A21 (100 mg), and the acid chloride (0.075 mmol) were stirred at rt in EtOAc overnight. Some water was added and the mixture was stirred for 1 h. The Amberlyst was filtered, and the mixture was evaporated under reduced pressure. The crude was used without
10 further purification.

General procedure D (reductive amination)

A compound of type **D** (0.05 mmol) was dissolved in CH₂Cl₂ (1 mL). NaBH(OAc)₃ (21 mg, 0.1 mmol) and the desired aldehyde (0.1 mmol) were
15 added. The mixture was stirred for 2 h. If the reaction was not complete, more aldehyde was added. Aq. 1M NaOH (0.200 mL) was added. The mixture was filtered through Isolute[®] (1 g) treated with aq. 1M NaOH (0.7 mL). After 5 min the Isolute[®] was rinsed with CH₂Cl₂ (3 x 1 mL). The combined org. filtrates were evaporated under reduced pressure, and the crude was directly used in the next
20 step.

General procedure E (N-methylation of anilines)

The aniline (1.00 g) was dissolved in dimethylcarbonate (8.00 mL). Na-Y-zeolite (1.00 g) was added. The mixture was stirred at 90 °C for several weeks, while the
25 reaction was followed by LC-MS. When the conversion was complete, the mixture was filtered through *Celite*, the precipitate was washed with EtOAc, and the filtrate was evaporated under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:40) yielded the title compound.

[2-(4-Bromophenyl)ethoxy]-tert-butyldimethylsilane

TBDMS-Cl (10.50 g, 69.6 mmol) and imidazole (5.10 g, 76.6 mmol) were added to a sol. of 2-(4-bromophenyl)ethanol (7.00 g, 34.8 mmol) in DMF (0.12 L), and the mixture was stirred at rt overnight. The reaction mixture was partitioned
5 between EtOAc and aq. 1M HCl, the phases were separated, and the organic layer was washed again with aq. 1M HCl, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (EtOAc/heptane 1:1) yielded the title compound as a transparent oil (10.93 g, 99%). LC-MS: t_R = 1.18 min.

10 Benzylcyclopropylamine

Cyclopropylamine (6.61 mL, 94.23 mmol, 2.00 eq.) was added to a sol. of benzaldehyde (5.00 g, 47.11 mmol, 1.00 eq.) in MeOH (0.11 L), and the mixture was stirred at rt overnight. The reaction mixture was cooled to 0 °C, and portionwise was added NaBH₄ (2.32 g, 61.25 mmol). The reaction mixture was
15 stirred at rt over 6 h. The reaction mixture was quenched with ice, the solvents were removed under pressure, and the residue was extracted with EtOAc. The org. layer was washed with aq. 1M NaOH. The aq. layer was extracted again with EtOAc, the combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the title
20 compound (6.27 g, 90%), which was not further purified. LC-MS: t_R = 0.49 min, ES+: 148.20.

(4-Bromobenzyloxy)-tert-butyldimethylsilane

TBDMS-Cl (16.00 g, 0.11 mol) and imidazole (7.90 g, 0.12 mol) were added to a
25 stirred sol. of 4-bromobenzyloxyalcohol (10.00 g, 53.46 mmol) in DMF (0.20 L), and the mixture was stirred at rt over 72 h. The reaction mixture was partitioned between EtOAc and aq. 1M HCl, the phases were separated, and the org. layer was washed again with aq. 1M HCl, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (50% EtOAc in
30 heptane) yielded the title compound (13.52 g, 84 %). LC-MS: t_R = 1.18 min.

2-(2,4-Dimethylphenoxy)-N-methylacetamide

Carbonyldiimidazole (162 mg, 1.00 mmol) was added to a mixture of (2,4-dimethylphenoxy)acetic acid (180 mg, 1.00 mmol) in CH₂Cl₂ (4 mL). The mixture was stirred for 1 h at rt, and was cooled to 0 °C. MeNH₂ (41% in H₂O, 5 0.506 mL, 6.00 mmol) was added, and the mixture was stirred for 2 h at 0 °C. The mixture was washed with water. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (170 mg, 88%) that was used without further purification. LC-MS: t_R = 0.94 min, ES+: 235.13 (Eluent A: 10 water + 0.04% TFA; eluent B: acetonitrile; gradient: 5% → 95% B over 1.00 min, then 95% B over 0.55 min).

[2-(2,4-Dimethylphenoxy)ethyl]methylamine

LiAlH₄ (1M in THF, 3.00 mL, 3.00 mmol) was added to a sol. of 2-(2,4-dimethylphenoxy)-N-methylacetamide (170 mg, 0.88 mmol) in THF (3 mL). The 15 mixture was stirred for 30 min at rt, then for 4 h at 60 °C. The mixture was cooled to 0 °C, and water (0.114 mL) was added carefully. Aq. 15% NaOH (0.114 mL), then water (0.342 mL) were added, and the mixture was stirred overnight. The mixture was filtered, and the precipitate was washed with EtOAc. The filtrate was 20 evaporated under reduced pressure, and the residue was loaded on a FC-column filled with SCX-silica gel (*Varian*, Cat. No. 12213039). The FC was eluted with MeOH, then 7M NH₃/MeOH. After evaporation, the title compound was obtained (44 mg, 24%). LC-MS: t_R = 0.76 min, ES+: 180.18 (Eluent A: water + 0.04% TFA; eluent B: acetonitrile; gradient: 5% → 95% B over 1.00 min, then 95% B 25 over 0.55 min).

2,6-Dichloro-4-methylbenzaldehyde

MnO₂ (4.56 g, 52 mmol) was added to a sol. of (2,6-dichloro-4-methylphenyl)-methanol (Wigal, C. T.; McKinley, J. D.; Coyle, J.; Porter, D. J.; Lehman, D. E., 30 *J. Org. Chem.*, **1995**, *60*, 8421; 3.00 g, 15.7 mmol) in CH₂Cl₂ (100 mL). The mixture was stirred for 1 h, and MnO₂ (9.12 g, 104 mmol) was added again. The

mixture was stirred for 30 h at rt. The mixture was filtered through *Celite*, and the filtrate was evaporated under reduced pressure. Purification by FC (EtOAc/heptane 1:19 → 1:9) yielded the title compound (1.22 g, 42%). LC-MS: t_R = 0.99 min, ES+: 241.01.

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***N*-Methyl-2-(2,3,6-trichlorophenyl)acetamide**

Carbonyldiimidazole (200 mg, 1.23 mmol) was added to a sol. of (2,3,6-trichlorophenyl)acetic acid (294 mg, 1.23 mmol) in CH₂Cl₂ (5.00 mL). The mixture was stirred for 2 h at rt, and cooled to 0 °C. MeNH₂ (41% in water, 0.560 mL, 7.38 mmol) was added, and the mixture was stirred for 2 h at rt. The mixture was washed with water. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (266 mg, 85%) as a solid that was not purified further. LC-MS: t_R = 0.93 min, ES+: 294.93 (Eluent A: water + 0.04% TFA; eluent B: acetonitrile; gradient: 5% → 95% B over 1.00 min, then 95% B over 0.55 min).

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Methyl-[2-(2,3,6-trichlorophenyl)ethyl]amine

BH₃ (1M in THF, 7.37 mL, 7.37 mmol) was added to a sol. of *N*-methyl-2-(2,3,6-trichlorophenyl)acetamide (266 mg, 1.05 mmol) in THF (5.00 mL). The mixture was heated to reflux for 24 h. The mixture was allowed to cool to rt, and aq. 6M HCl (10 mL) was added. The mixture was heated to reflux for 1 h. The mixture was allowed to cool to rt, and diluted with EtOAc. The mixture was washed with aq. 10% NaOH (3x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by HPLC yielded the title compound (140 mg, 56%).

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(2-Fluoro-5-methylphenyl)methylamine

Prepared according to general procedure E, from 2-fluoro-5-methylaniline.

32 mg were obtained. LC-MS: t_R = 0.65 min, ES+: 140.13.

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(2,3-Dichlorophenyl)methylamine

Prepared according to general procedure E, from 2,3-dichloroaniline.
137 mg were obtained. LC-MS: $t_R = 0.97$ min, ES+: 176.12.

5 **(2,6-Difluorophenyl)methylamine**

Prepared according to general procedure E, from 2,6-difluoroaniline.
38 mg were obtained. LC-MS: $t_R = 0.72$ min.

(2,6-Dichlorophenyl)methylamine

10 Prepared according to general procedure E, from 2,6-dichloroaniline.
107 mg were obtained. LC-MS: $t_R = 0.89$ min, ES+: 176.08.

(2,5-Difluorophenyl)methylamine

Prepared according to general procedure E, from 2,5-difluoroaniline. 10 mg were
15 obtained. LC-MS: $t_R = 0.88$ min.

(5-Chloro-2-methylphenyl)methylamine

Prepared according to general procedure E, from 5-chloro-2-methylaniline.
10 mg were obtained. LC-MS: $t_R = 0.86$ min, ES+: 156.70.
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(2,5-Dichlorophenyl)methylamine

Prepared according to general procedure E, from 2,5-dichloroaniline. 86 mg were
obtained. LC-MS: $t_R = 0.98$ min, ES+: 176.02.

25 **(3-Fluoro-2-methylphenyl)methylamine**

Prepared according to general procedure E, from 3-fluoro-2-methylaniline.
39 mg were obtained. LC-MS: $t_R = 0.62$ min, ES+: 140.15.

(5-Fluoro-2-methylphenyl)methylamine

30 Prepared according to general procedure E, from 5-fluoro-2-methylaniline.
691 mg were obtained. LC-MS: $t_R = 0.74$ min, ES+: 140.14.

(2-Chloro-5-methylphenyl)methylamine

Prepared according to general procedure E, from 2-chloro-5-methylaniline. 87 mg were obtained. LC-MS: t_R = 0.92 min, ES+: 156.14.

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(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-hydroxypropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A1)**

To a suspension of NaHCO₃ (15.5 g, 184 mmol) and 7-{4-[2-(*tert*-butyldimethylsilyloxy)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 CH₂ClCH₂Cl (190 mL) was added 1-chloroethyl chloroformate (20.0 mL, 55.1 mmol). The mixture was heated and stirred at 80 °C for 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 CH₂Cl₂ (190 mL), DIPEA (15.7 mL, 91.8 mmol) and Boc₂O (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. NaHCO₃ (1x). The org. phase was dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC (50% EtOAc in heptane) yielded 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 (8.86 g, 91%). LC-MS: t_R = 1.04 min, ES+: 531.22.

1 M NaOH (198 mL) was added to a sol. of the former compound (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 partially 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 MgSO₄, filtered, and the solvents were removed under reduced pressure to yield 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 (13.3 g, 94%).

TBDMS-Cl (7.38 g, 48.7 mmol) and imidazole (5.32 g, 77.9 mmol) were added to a stirred sol. of the former compound (9.79 g, 19.5 mmol) in DMF (100 mL). The
5 reaction mixture was stirred at rt over 15 h. The solvents were removed *in vacuo*, the crude mixture partitioned between Et₂O and aq. sat. NH₄Cl. The org. extracts were dried over MgSO₄, 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 K₂CO₃ (1.46 g), and the mixture stirred at rt for 30
10 min. The mixture was then partitioned between Et₂O and aq. sat. NH₄Cl and the aq. layer extracted once more with Et₂O. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed *in vacuo* to yield 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 (12.2 g, quantitative yield) as a
15 yellow foam. LC-MS: *t*_R = 1.19 min, ES⁺: 617.48.

To a stirred sol. of the former compound (12.0 g, 19.4 mmol) in CH₂Cl₂ (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 (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.;
20 Brown, J. D., *J. Org. Chem.*, 1989, 54, 3730 and cyclopropylamine, 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 CH₂Cl₂, and the org. phase was washed with aq. sat. NaHCO₃. The org. extracts were dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC
25 (heptane/EtOAc 8/2) yielded 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 (8.20 g, 52%).
LC-MS: *t*_R = 1.32 min, ES⁺: 790.53.

To a sol. of the former compound (10.0 g, 12.7 mmol) in THF (225 mL) was
30 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. NH₄Cl and

EtOAc, the org. phase washed with brine, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC (0-10% MeOH in CH₂Cl₂) yielded the title compound (7.00 g, 82 %) as a yellow foam. LC-MS: t_R = 1.11 min, ES+: 676.54.

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(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A2)**

BuLi (1.60 M in hexane, 41.00 mL, 65.44 mmol) was added dropwise to a cooled (-78 °C) sol. of [2-(4-bromophenyl)ethoxy]-*tert*-butyldimethylsilane (16.00 g, 49.1 mmol) in THF (0.45 L). The reaction mixture was stirred at -78 °C for 1 h, and ZnCl₂ (1M in THF, 79.00 mL, 79.00 mmol) was added dropwise at -78 °C. The cooling bath was removed, and the reaction mixture was stirred for 1 h at rt. A sol. of (rac.)-(1*R**, 5*S**)-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, 15.00 g, 32.72 mmol) in THF (50.00 mL) was added dropwise, followed by Pd(PPh₃)₄ (0.94 g, 0.82 mmol). The reaction mixture was stirred at rt for 30 min, partitioned between EtOAc and aq. 1M NaOH, the layers were separated and the aq. layer was extracted with EtOAc. The combined org. phases were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc) yielded (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (17.00 g, 95%) as an orange oil. LC-MS: t_R = 0.97 min, ES+: 545.44.

1-Chloroethyl chloroformate (29.00 mL, 0.26 mol) was added dropwise to a suspension of NaHCO₃ (22.00 g, 0.26 mol) and (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (14.30 g, 26.25 mmol) in 1,2-dichloroethane (0.17 L), and the mixture was heated to reflux for 2 h. The reaction mixture was allowed to cool to rt, filtered, and the solvents were

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thoroughly removed *in vacuo*. MeOH (0.17 L) was added, and the mixture was stirred at 50 °C for 60 min. The solution was allowed to cool to rt and the solvents were removed *in vacuo*. The residue was dissolved in CH₂Cl₂ (190 mL), DIPEA (22 mL, 0.13 mol) was added, followed by Boc₂O (17.00 g, 78.75 mmol),
5 and the mixture was stirred at rt for 60 min. The mixture was washed with aq. 1M HCl, and aq. sat. NaHCO₃. The org. phase was dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (EtOAc/heptane 1:1) yielded (*rac.*)-(1*R**, 5*S**)-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (9.00 g, 66%). LC-MS: *t_R* = 1.02 min, ES+: 517.37.
10 A sol. of (*rac.*)-(1*R**, 5*S**)-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (9.23 g, 17.86 mmol) in EtOH (0.18 L) was treated with aq. 1M NaOH (180 mL). The resulting mixture was stirred at 70 °C for 5 h, cooled to rt, and the solvents were
15 removed *in vacuo*. The crude mixture was partitioned between TBME and aq. sat. NH₄Cl. The aq. layer was extracted once more with TBME, then acidified (pH ~ 4) with aq. 2M HCl, and extracted again with TBME. The combined org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield (*rac.*)-(1*R**, 5*S**)-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester, as
20 a pale brown foam, which was not further purified (6.61 g, 76%). LC-MS: *t_R* = 0.90 min, ES+: 489.41.
TBDMS-Cl (6.61 g, 33.82 mmol) and imidazole (4.00 g, 54.12 mmol) were added to a stirred sol. of (*rac.*)-(1*R**, 5*S**)-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (6.61
25 g, 13.53 mmol) in DMF (50.00 mL). The reaction mixture was stirred at rt over 15 h. The solvents were removed *in vacuo*, and the crude mixture was partitioned between Et₂O and water. The org. layer was washed with aq. sat. NaHCO₃, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. To
30 a sol. of the crude residue in THF (120.00 mL) were added MeOH (23.00 mL), water (23.00 mL) and K₂CO₃ (1.00 g, 7.23 mmol), and the mixture was stirred at

rt for 1 h. The mixture was then partitioned between Et₂O and aq. sat. NH₄Cl, the layers were separated, and the aq. layer was extracted once more with Et₂O. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed *in vacuo* to yield (*rac.*)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (7.65 g, 94% yield), which was not further purified, as a yellow foam. LC-MS: t_R = 1.16 min, ES⁺: 603.48.

To a stirred sol. of the (*rac.*)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (7.65 g, 12.7 mmol) in CH₂Cl₂ (77.0 mL) were added EDC•HCl (6.10 g, 31.7 mmol), HOBt (2.30 g, 15.2 mmol), DMAP (0.39 g, 3.17 mmol), 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, 3.60 g, 19.03 mmol), and DIPEA (10.00 mL, 57.10 mmol). The mixture was stirred at rt for 6 days. Twice were added EDC•HCl (2.44 g, 12.7 mmol), HOBt (1.92 g, 12.7 mmol), DMAP (0.39 g, 3.17 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (2.40 g, 12.7 mmol), and DIPEA (2.22 mL, 12.7 mmol). The reaction mixture was partitioned between aq. 1M HCl and CH₂Cl₂, and the phases were separated. The org. phase was washed with aq. sat. NaHCO₃, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (heptane/EtOAc = 8/2) yielded (*rac.*)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)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 (5.70 g, 58%). LC-MS: t_R = 1.31 min, ES⁺: 776.51.

TBAF (5.00 g, 15.74 mmol, 2.00 eq.) was added to a sol. of (*rac.*)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)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 (6.11 g, 7.87 mmol) in THF (60.00 mL), and the mixture was stirred at rt for 60 min. The reaction mixture was partitioned between water and EtOAc, the phases were separated and the aq. phase extracted once more with

EtOAc. The combined org. phases were washed with brine, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (0-10% MeOH in CH₂Cl₂) resulted in the title compound as a yellow foam (4.45 g, 85%). LC-MS: t_R = 1.09 min, ES+: 662.48.

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(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A3)**

To a suspension of NaHCO₃ (29.2 g, 0.347 mol) and (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]phenyl}-9-methyl-3,9-diazabicyclo-
10 [3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (prepared as described in WO 03/093267, 19.4 g, 34.7 mmol) in 1,2-dichloroethane (400 mL) was added dropwise 1-chloroethyl chloroformate (37.8 mL, 0.347 mol). The mixture was heated to 80 °C. After 2 h, the reaction mixture was allowed to cool
15 to rt, filtered, and the solvents were thoroughly removed *in vacuo*. MeOH (400 mL) was added and the mixture was stirred at 50 °C for 15 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 CH₂Cl₂ (400 mL), and cooled to 0 °C. DIPEA (30.0 mL, 0.174 mol) and Boc₂O (11.4 g, 52 mmol) were
20 added. The mixture was stirred at 0 °C for 1 h, then at rt for 3 h. The mixture was washed with aq. 1M HCl (1x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC (EtOAc/heptane 1:5 → 1:1 → MeOH/AcOEt 1:9) yielded 7-[4-(2-hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,6,9-tricarboxylic
25 acid 3,9-di-*tert*-butyl ester 6-ethyl ester (14.1 g, 76%). LC-MS: t_R = 1.02 min, ES+: 533.38.

Aq. 1 M NaOH (550 mL) was added to a sol. of the former compound (17.8 g, 33.4 mmol) in EtOH (1000 mL). The resulting mixture was stirred at 80 °C overnight, cooled to rt and the solvents were partially removed *in vacuo*. The
30 crude mixture was partitioned between EtOAc and aq. 1M HCl. The aq. phase was extracted again with EtOAc. The combined org. extracts were dried over

MgSO₄, filtered, and the solvents were removed under reduced pressure to yield 7-[4-(2-hydroxyethoxy)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (6.61 g, 76%). LC-MS: t_R = 0.89 min, ES+: 505.32.

- 5 TBDMS-Cl (15.5 g, 92 mmol) and imidazole (9.28 g, 166 mmol) were added to a stirred sol. of the former compound (6.61 g, 32.8 mmol) in DMF (115 mL). The reaction mixture was stirred at rt overnight. The solvents were removed *in vacuo*, and the crude mixture partitioned between heptane and aq. sat. NH₄Cl. The aq. phase was extracted with heptane. The combined org. extracts were dried over
- 10 MgSO₄, filtered, and the solvents were removed under reduced pressure. To a sol. of the residue in THF (100 mL) were added MeOH (40 mL), water (40 mL) and K₂CO₃ (1.30 g), and the mixture stirred at rt for 2 h. It was then partitioned between Et₂O and aq. sat. NH₄Cl and the aq. layer extracted once more with Et₂O. The combined org. extracts were dried over MgSO₄, filtered, and the solvents
- 15 were removed *in vacuo* to yield 7-{4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (23.05 g, quantitative yield). LC-MS: t_R = 1.15 min, ES+: 619.41.

- To a stirred sol. of the former compound (8.66g, 12.7 mmol) in CH₂Cl₂ (210 mL)
- 20 were added EDC•HCl (9.33 g, 49.0 mmol), HOBt (2.08 g, 15.4 mmol), DMAP (0.428 g, 3.5 mmol), 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, 8.03 g, 42 mmol) and DIPEA (9.54 mL, 56 mmol). The mixture was stirred at rt for 3 days.
- 25 The reaction mixture was partitioned between aq. 1M HCl and CH₂Cl₂, and the org. phase was washed with aq. sat. NaHCO₃. The org. extracts were dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC (EtOAc/heptane 1:9 → 2:8 → 3:7 → 4:6 → 1:1) yielded 7-{4-[2-(*tert*-butyldimethylsilyloxy)ethoxy]phenyl}-6-[cyclopropyl-(3-methoxy-2-
- 30 methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (6.42 g, 57%). LC-MS: t_R = 1.31 min, ES+: 776.51.

To a sol. of the former compound (6.42 g, 8.10 mmol) in THF (90 mL) at 0 °C was added TBAF (1M in THF, 12.2 mL, 12.2 mmol) and the mixture was stirred at 0 °C over 60 min. The reaction mixture was partitioned between water and EtOAc, the org. phase was washed with brine, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification by FC (EtOAc/heptane 1:3 → 1:1 → EtOAc) yielded the title compound (4.75 g, 93 %). LC-MS: *t_R* = 1.09 min, ES+: 678.33.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-(2-hydroxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A4)**

To a stirred sol. of the (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (24.71 g, 41 mmol) in CH₂Cl₂ (0.34 L) were added EDC•HCl (19.65 g, 0.10 mol), HOBt (9.41 g, 61.5 mmol), DMAP (1.25 g, 10.25 mmol), cyclopropyl-(2,3-dichlorobenzyl)amine (prepared by reductive amination from 2,3-dichlorobenzaldehyde and cyclopropylamine, 17.72 g, 82.00 mmol), and DIPEA (32.14 mL, 0.18 mol). The mixture was stirred at rt for 5 days. On day 4 were added EDC•HCl (4.00 g, 20.86 mmol), HOBt (3.00 g, 19.60 mmol), cyclopropyl-(2,3-dichlorobenzyl)amine (5.00 g, 23.163 mmol), and DIPEA (6.00 mL, 34.44 mol). The reaction mixture was partitioned between aq. sat. NaHCO₃ and EtOAc, and the phases were separated. The org. phase was washed with aq. 1M HCl, dried over MgSO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (heptane/EtOAc = 8/2) yielded (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (25.79 g, 78%). LC-MS: *t_R* = 1.33 min, ES+: 800.53.

p-Toluene sulfonic acid (11.09 g, 64.40 mmol) was added to a stirred sol. of (rac.)-(1*R**, 5*S**)-7-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-

3,9-dicarboxylic acid di-*tert*-butyl ester (25.79 g, 32.20 mmol) in MeOH (320 mL), and the mixture was stirred at rt for 30 min. The reaction mixture was quenched with aq. 10% Na₂CO₃ and the solvents were removed under pressure. To the resulting suspension was added EtOAc (200 mL), the precipitate was
5 filtered, and the phases were separated. The org. layer was washed with Na₂CO₃, brine, dried over Na₂SO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (20-100% EtOAc/Heptane) resulted in the title compound as a yellow foam (13.36 g, 60%). LC-MS: t_R = 1.13 min, ES⁺: 648.49.

10 **(*rac.*)-(1*R**, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A5)**

BuLi (1.60 M in hexane, 34.00 mL, 53.87 mmol) was added dropwise to a cooled (-78 °C) sol. of (4-bromobenzyloxy)-*tert*-butyldimethylsilane (15.30 g, 51.05
15 mmol) in THF (0.47 L). The reaction mixture was stirred at -78 °C for 1 h, and ZnCl₂ (1M in THF, 68.0 mL, 68.0 mmol) was added dropwise at -78 °C. The cooling bath was removed, and the reaction stirred for 1 h at rt. A sol. of (*rac.*)-(1*R**, 5*S**)-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, 13.00
20 g, 28.36 mmol) in THF (50.0 mL) was added dropwise, followed by Pd(PPh₃)₄ (0.95 g, 0.82 mmol). The reaction mixture was stirred at rt for 1 h, partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced
25 pressure. Purification of the residue by FC (EtOAc) yielded (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)phenyl]-9-methyl-3,9-diazabicyclo[3.3.1]-non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (17.85 g, >99%) as an orange oil. LC-MS: t_R = 0.95 min, ES⁺: 531.34.

1-Chloroethyl chloroformate (37.00 mL, 0.33 mol) was added dropwise to a
30 suspension of (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)phenyl]-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-

butyl ester 6-ethyl ester (17.85 g, 33.63 mmol) and NaHCO_3 (28.00 g, 0.33 mol) in 1,2-dichloroethane (0.23 L). The mixture was heated to reflux for 3 h, then allowed to cool to rt, filtered, and the solvents were thoroughly removed *in vacuo*. MeOH (0.23 L) was added and the mixture was stirred at 50 °C for 60 min. The
5 sol. was allowed to cool to rt, and the solvents were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (0.23 L), DIPEA (29.00 mL, 0.17 mol, 5.00 eq.) was added, followed by Boc_2O (22.00 g, 0.10 mol), and the mixture was stirred at rt for 45 min. The mixture was washed with aq. 1M HCl, and aq. sat. NaHCO_3 . The organic phase was dried over MgSO_4 , filtered, and the solvents were removed
10 *in vacuo*. Purification of the crude by FC (50% EtOAc in heptane) yielded (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (11.62 g, 69%). LC-MS: t_R = 1.01 min, ES+: 503.24.

Aq. 1M NaOH (162.00 mL) was added to a sol. of the (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid
15 3,9-di-*tert*-butyl ester 6-ethyl ester (8.20 g, 16.31 mmol) in EtOH (0.32 L). The resulting mixture was stirred at 70 °C for 3 h, cooled to rt, and the solvents were removed *in vacuo*. The crude mixture was partitioned between TBME and aq. sat. 1M HCl. The aq. layer was extracted twice more with TBME, the combined org.
20 extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure to yield (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (5.80 g, 75%), which was not further purified. LC-MS: t_R = 0.88 min, ES+: 475.05.

TBDMS-Cl (4.51 g, 29.92 mmol) and imidazole (3.26 g, 47.87 mmol) were added
25 to a stirred sol. of the (*rac.*)-(1*R**, 5*S**)-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (5.68 g, 11.96 mmol) in DMF (50 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 water. The aq. phase was extracted again with Et_2O . The combined org.
30 extracts were washed with aq. sat. NaHCO_3 , brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The residue was

- dissolved in THF (100.00 mL), MeOH (21.00 mL), and water (21.00 mL), and K_2CO_3 (0.83 g, 6.00 mmol) was added. The mixture was stirred at rt for 1 h. The mixture was partitioned between Et_2O and aq. sat. NH_4Cl , the phases were separated, and the aq. layer was extracted once more with Et_2O . The combined
5 org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* to yield (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)-phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (7.53 g, >99% yield) as a yellow foam. No further purification. LC-MS: t_R = 1.14 min, ES+: 589.53.
- 10 To a stirred sol. of the (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (7.53 g, 11.96 mmol) in CH_2Cl_2 (0.10 L) were added EDC•HCl (5.73 g, 29.90 mmol), HOBt (2.19 g, 14.35 mmol), DMAP (0.36 g, 2.99 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (prepared by
15 reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*, 1989, 54, 3730 and cyclopropylamine, 3.43 g, 17.94 mmol) and DIPEA (9.37 mL, 53.82 mmol). The mixture was stirred at rt for 5 days. The reaction mixture was partitioned between aq. sat. $NaHCO_3$ and EtOAc, the phases were separated, and the aq. layer was extracted once more with EtOAc.
- 20 The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (10-30% EtOAc in heptane) yielded (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)-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 (7.74 g, 85%).
25 LC-MS: t_R = 1.29 min, ES+: 762.61.
- TBAF (6.42 g, 20.34 mmol) was added to a sol. of (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)-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 (7.74 g, 10.16 mmol) in THF (70.0 mL) and stirred at rt for 2 h.
- 30 The reaction mixture was partitioned between water and EtOAc, the phases were separated, and the aq. layer was extracted again with EtOAc. The combined org.

extracts were washed with brine, dried over MgSO_4 , filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (0-100% EtOAc in heptane followed by 10% MeOH in CH_2Cl_2) yielded the title compound (6.53 g, 99 %). LC-MS: t_R = 1.09 min, ES+: 648.58.

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(rac.)-(1R*, 5S*)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-hydroxymethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (A6)

To a stirred sol. of (rac.)-(1R*, 5S*)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (32.3 g, 54.8 mmol), EDC•HCl (26.28 g, 0.14 mol), HOBt (10.07 g, 65.86 mmol), DMAP (1.67 g, 13.71 mmol), and DIPEA (42.30 mL, 0.246 mol) in CH_2Cl_2 (0.46 L) was added after 15 min cyclopropyl-(2,3-dichlorobenzyl)amine (17.78 g, 82.27 mmol). The mixture was stirred at rt for 7 days. After 36 h HOBt (7.00 g, 45.74 mmol), cyclopropyl-(2,3-dichlorobenzyl)amine (prepared by reductive amination from 2,3-dichlorobenzaldehyde and cyclopropylamine, 10.00 g, 46.27 mmol), and DMAP (1.67 g, 13.71 mmol) were added. On the third day only cyclopropyl-(2,3-dichlorobenzyl)amine was added (5.00 g, 23.13 mmol). On the fourth day, EDC•HCl (5.00 g, 26.08 mmol), HOBt (4.00 g, 26.14 mmol), DIPEA (5.00 mL, 28.70 mmol,) and cyclopropyl-(2,3-dichlorobenzyl)amine (5.00 g, 23.13 mmol, 0.42 eq.) were added. The reaction mixture was partitioned between EtOAc and aq. 1M HCl. The layers were separated, and the aq. phase was extracted again with EtOAc (2x 100mL). The combined org. extracts were washed with aq. sat. NaHCO_3 , brine, dried over MgSO_4 , filtered, and the solvents were removed *in vacuo* to yield an orange oil. Purification of the crude by FC (30% EtOAc in heptane) yielded (rac.)-(1R*, 5S*)-7-[4-(*tert*-butyldimethylsilanyloxymethyl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (25.04 g, 58%) as a yellow oil. LC-MS: t_R = 1.32 min, ES+: 786.48.

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p-Toluene sulfonic acid (12.28 g, 64.60 mmol) was added to a sol. of (*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-butyldimethylsilyloxymethyl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (25.40 g, 32.30 mmol) in MeOH (330 mL). The mixture was stirred at rt over 30 min. The reaction mixture was treated with aq. 10% Na₂CO₃ (50 mL), and the solvents were removed under pressure. The resulting suspension was treated with EtOAc (0.20 L), filtered, and washed with aq. 10% Na₂CO₃ (0.10 L) and brine (0.10 L), dried over Na₂SO₄, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (20 – 40% EtOAc in heptane followed by EtOAc then 10% MeOH in CH₂Cl₂) yielded the title compound (8.18 g, 38%) as a white foam. LC-MS: *t*_R = 1.12 min, ES+: 672.40.

(*rac.*)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(3-oxopropyl)phenyl]-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (B1)**

Compound A1 (101 mg, 0.15 mmol) was dissolved in CH₂Cl₂ (1 mL). 4Å Molecular sieve (75 mg), NMO (26.4 mg, 0.225 mmol), and tetrapropylammonium perruthenate (2.64 mg, 0.0075 mmol) were added. The mixture was stirred overnight. The mixture was filtered through Isolute® (1 g) pre-washed with aq. water (1.8 mL). After 5 min the Isolute® was rinsed with CH₂Cl₂ (2 x 1 mL). The combined org. filtrates were evaporated under reduced pressure, and the crude was directly used in the next step. LC-MS: *t*_R = 1.11 min, ES+: 674.49.

(*rac.*)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-formylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (B2)**

Anhydrous DMSO (0.44 mL, 6.17 mmol) in CH₂Cl₂ (4.00 mL) was added dropwise over 10 min to a cooled (-63 °C) sol. of oxalyl chloride (0.392 mL, 3 mmol) in CH₂Cl₂ (8.00 mL). After additional 30 min at -63 °C, the reaction mixture was treated dropwise over 20 min with compound A5 (1.00 g, 1.54 mmol)

in CH₂Cl₂ (8.00 mL), and the mixture was stirred for 30 min at –63 °C, followed by warming to –30 °C for 1 h, and finally cooled back to –63 °C. Et₃N (1.29 mL, 9.26 mmol, 6.00 eq.) was added dropwise over 20 min, and the mixture was stirred for additional 30 min at –63 °C. The reaction mixture was allowed to
5 warm up to rt, and poured onto aq. 10% citric acid (10 mL). The org. layer was separated, and the aq. layer was extracted with EtOAc (3 x 20 mL). The combined org. extracts were washed with aq. sat. NaHCO₃ (10 mL), brine (10 mL), dried over MgSO₄, and filtered. The solvents were removed under reduced pressure to yield the title compound as a white crystalline foam, which was not
10 further purified (0.99 g, 99%). LC-MS: t_R = 1.16 min, ES+: 646.43.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-formyl-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (B3)**

15 Anhydrous DMSO (0.85 mL, 11.89 mmol, 4.00 eq.) in CH₂Cl₂ (8.00 mL) was added dropwise over 10 min to a cooled (–63 °C) sol. of oxalyl chloride (0.75 mL, 8.92 mmol, 3.00 eq.) in CH₂Cl₂ (8.00 mL). After additional 30 min at –63 °C, the reaction mixture was treated dropwise over 20 min with compound A6 (2.00 g, 2.974 mmol) in CH₂Cl₂ (8.00 mL), and the mixture was stirred for 30 min at –63
20 °C, warmed to –30 °C for 1 h, and finally cooled back to –63 °C. Et₃N (2.48 mL, 17.84 mmol, 6.00 eq.) was added dropwise over 20 min, and the mixture was stirred for 30 min at –63 °C. The reaction mixture was allowed to warm up to rt, quenched with aq. 10% citric acid, and the org. layer was separated. The aq. layer was extracted with EtOAc (3 x 50.00 mL). The combined org. extracts were
25 washed with aq. sat. NaHCO₃ (50.00 mL), brine (50.00 mL), dried over MgSO₄ and filtered. The solvents were removed under reduced pressure to yield the title compound as a white foam, which was not further purified (2.00 g, 99%). LC-MS: t_R = 1.18 min, ES+: 670.43.

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

A sol. of glacial AcOH (0.50 mL) and compound **G1** (1.69 g, 2.21 mmol) in EtOAc (20.00 mL) was treated with 10% Pd/C (50% H₂O, 0.17 g) and submitted to a hydrogen atmosphere for two days. 10% Pd/C (50% H₂O, 0.05 g) was added, and the reaction mixture set again under a hydrogen atmosphere overnight. The mixture was filtered through *Celite*, washed thoroughly with EtOAc, and the solvents were removed *in vacuo* to yield the title compound as a transparent foam (1.35 g, 91%), which was not further purified. LC-MS: *t_R* = 0.92 min, ES⁺: 675.62.

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

A sol. of glacial AcOH (0.35 mL) and compound **G2** (1.10 g, 1.41 mmol) in EtOAc (14.00 mL) was treated with 10% Pd/C (0.11 g) and submitted to a hydrogen atmosphere for three days. 10% Pd/C (0.05 g) was added together with glacial AcOH (4 mL), and the reaction mixture was set under a 3 bar hydrogen atmosphere over 2 h. The mixture was then filtered through *Celite*, washed thoroughly with EtOAc, and the solvents were removed *in vacuo* to yield the title compound as a yellow foam (0.973 g, 97%), which was not further purified. LC-MS: *t_R* = 0.94 min, ES⁺: 689.53.

(rac.)-(1R*, 5S*)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-isopropylaminoethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D3)

A sol. of glacial AcOH (0.16 mL) and compound **G3** (0.50 g, 0.63 mmol) in EtOAc (6.00 mL) was treated with 10% Pd/C (0.05 g). The reaction mixture was submitted to a 3 bar hydrogen atmosphere overnight. 10% Pd/C (0.05 g) was added, and the reaction mixture submitted to a 3 bar hydrogen atmosphere again

overnight. The mixture was then filtered through *Celite*, washed thoroughly with EtOAc, and the solvents were removed *in vacuo* to yield the title compound as a yellow foam (0.44 g, >99%), which was not further purified. LC-MS: t_R = 0.95 min, ES+: 703.52.

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(rac.)-(1*R, 5*S**)-7-[4-(2-Cyclopropylaminoethyl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D4)**

A sol. of glacial AcOH (0.54 mL), 1,2-dichlorobenzene (2.50 mL) and compound
10 **G4** (2.00 g, 2.45 mmol) in EtOAc (25.0 mL) was treated with 10% Pd/C (0.20 g), and submitted to a hydrogen atmosphere for 8 h. The mixture was filtered through *Celite*, washed thoroughly with EtOAc, and the solvents were removed *in vacuo*. Purification of the residue by FC (10% MeOH in CH₂Cl₂) yielded the title compound (1.40 g, 79%), as a transparent foam. LC-MS: t_R = 0.96 min, ES+:
15 725.47.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-(4-methylaminomethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D5)**

20 Compound **B2** (5.00 g, 7.74 mmol) and *N*-methyl-amine (20 mL, 41% aq. sol.) were mixed in MeOH (20 mL), and the mixture was heated to reflux under N₂ for 4 h. The mixture was cooled to rt, and carefully treated with solid NaBH₄ (1.10 g, 28.40 mmol). The reaction was stirred for 30 min and partitioned between EtOAc and H₂O. The phases were separated, and the aq. phase was extracted with
25 EtOAc. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the crude title compound (4.33 g, 85%) as a white foam. No further purification was necessary. LC-MS: t_R = 0.91 min, ES+: 661.66.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(isopropylaminomethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D6)**

Compound **B2** (2.00 g, 3.10 mmol) and isopropyl amine (0.53 mL, 6.20 mL) were
5 mixed in MeOH (40 mL) and heated to reflux overnight. The mixture was cooled
to 0 °C, and carefully treated with solid NaBH₄ (0.23 g, 6.20 mmol, 2.00 eq.). The
reaction mixture was stirred for 60 min, and partitioned between EtOAc and aq.
1M NaOH. The phases were separated, and the aq. phase was extracted with
EtOAc. The combined org. extracts were washed with brine, dried over MgSO₄,
10 filtered, and the solvents were removed under reduced pressure to yield the crude
title product (2.02 g, 95%) as a white foam. No further purification was
undertaken. LC-MS: t_R = 0.95 min, ES+: 689.56.

(rac.)-(1*R, 5*S**)-7-(4-Aminomethylphenyl)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D7)**

Compound **A5** (0.674 g, 1.041 mmol) was dissolved in toluene (20 mL) and THF
(20 mL). *N*-phthalimide (0.23 g, 1.56 mmol), polymer bound-PPh₃ (0.654 g), and
di-*tert*-butyl azodicarboxylate (0.36g, 1.56 mmol) were added, and the reaction
20 mixture was heated to 50 °C overnight. The mixture was filtered through *Celite*,
washed with THF, and the filtrate was reduced *in vacuo* to yield a cream colored
foam. Purification of the residue by FC (30-50% EtOAc in heptane) yielded
(rac.)-(1*R**, 5*S**)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-
(1,3-dioxo-1,3-dihydroisindol-2-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-
25 ene-3,9-dicarboxylic acid di-*tert*-butyl ester as a white powder (0.57 g, 71%). LC-
MS: t_R = 1.18 min, ES+: 777.41.

Methylamine (41% in H₂O, 9.27 mL) was added to a sol. of (rac.)-(1*R**, 5*S**)-6-
[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(1,3-dioxo-1,3-
dihydroisindol-2-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-
30 dicarboxylic acid di-*tert*-butyl ester (0.57 g) in EtOH (10.0 mL), and the mixture
was stirred at rt over 4 h. The reaction mixture was partitioned between EtOAc

(50.0 mL) and aq. sat. NaHCO₃ (30 mL), and the aq. layer was extracted again with EtOAc (2x 20 mL). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed *in vacuo* to yield a yellow oil. Purification over HPLC yielded the title compounds as a white foam
5 (0.195, 41%). LC-MS: t_R = 0.90 min, ES+: 648.60.

(rac.)-(1R*, 5S*)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-ethylaminomethylphenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D8)

10 Compound **B3** (5.00 g, 7.74 mmol) and *N*-ethyl-amine (2.70 mL, 70% aq. sol.) were mixed in MeOH (18.0 mL) and the mixture was heated to reflux overnight. The mixture was cooled to rt, and carefully treated with solid NaBH₄ (0.20 g, 5.37 mmol). The reaction was stirred for 30 min and partitioned between EtOAc and NaHCO₃. The phases were separated, and the aq. phase was extracted with
15 EtOAc (3x 30 mL). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the title compound (1.90 g, quantitative yield) as a white foam. No further purification was undertaken. LC-MS: t_R = 0.95 min, ES+: 699.49.

20 **(rac.)-(1R*, 5S*)-7-(4-Cyclopropylaminomethylphenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D9)**

Compound **B3** (1.60 g, 2.39 mmol) and *N*-cyclopropyl-amine (0.50 mL, 7.16 mmol) were mixed in MeOH (25.0 mL), and the mixture was heated to reflux for
25 4 h in an autoclave. The mixture was cooled to rt and carefully treated with solid NaBH₄ (0.22 g, 5.96 mmol). The reaction was stirred overnight, then partitioned between EtOAc and NaHCO₃. The phases were separated and the aq. phase was extracted with EtOAc (3x 30 mL). The combined org. extracts were washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced
30 pressure to yield the title compound (1.61 g, 95%) as a white foam. No further purification was undertaken. LC-MS: t_R = 0.96 min, ES+: 711.40.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-{4-[(2,2,2-trifluoroethylamino)methyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D10)**

- 5 Compound **B3** (2.00 g, 2.98 mmol) and *N*-(2,2,2-trifluoroethyl)amine (0.469 mL, 5.96 mmol) were mixed in MeOH (30.0 mL), and the mixture was heated to reflux in an autoclave overnight. The mixture was cooled to rt and carefully treated with solid NaBH₄ (0.225 g, 5.96 mmol). The mixture was stirred for 60 min and partitioned between EtOAc and H₂O. The phases were separated, and the aq.
- 10 phase was extracted with EtOAc. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield crude product (1.57 g) as a mixture of aldehyde and amine. The reaction was restarted in the autoclave, with the addition of an excess of *N*-(2,2,2-trifluoroethyl)amine (2.34 mL, 29.82 mmol), and
- 15 the mixture was heated to reflux in MeOH (20.0 mL) overnight. The mixture was allowed to cool to rt and treated with NaBH₄ (0.28 g, 7.54 mmol). The mixture was stirred for 60 min and partitioned between EtOAc and H₂O. The phases were separated, and the aq. phase was extracted with EtOAc. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered,
- 20 and the solvents were removed under reduced pressure to yield the title compound (1.57 g, 70%, 82% pure) as a white foam, which was not further purified. LC-MS: *t*_R = 1.06 min, ES⁺: 753.33.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(3-methylaminopropyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (D11)**

- 25 Compound **B1** (3.40 g, 5.04 mmol) and *N*-methylamine (35.0 mL, 41% aq. sol.) were mixed in MeOH (70.0 mL), and the mixture was heated to reflux under N₂ for 4 h. The mixture was cooled to rt and carefully treated with solid NaBH₄ (0.57 g, 15.14 mmol). The reaction was stirred for 60 min and partitioned between
- 30 EtOAc and H₂O. The phases were separated, and the aq. phase was extracted with

EtOAc. The combined org. extracts were washed with aq. sat. NaHCO₃, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the title compound (3.60 g, 87%) as a white foam. No further purification was undertaken. LC-MS: t_R = 0.92 min, ES+: 689.55.

5

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-(2-methanesulfonyloxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F1)**

Et₃N (2.53 mL, 18.1 mmol, 3.00 eq.) and methane sulfonyl chloride (0.71 mL, 9.07 mmol, 1.50 eq.) were added to a cooled (0 °C) sol. of compound **A2** (4.00 g, 5.83 mmol) in CH₂Cl₂ (36.00 mL). The reaction mixture was stirred at 0 °C for 15 min, quenched with ice water, and the aq. layer was extracted with CH₂Cl₂ (2 x 40.00 mL). The combined org. layers were washed with aq. 1M HCl, (2x), aq. sat. NaHCO₃ (50.00 mL), and brine (50.00 mL). The org. layer was dried over Na₂SO₄, filtered, and the solvents were removed *in vacuo* to yield 4.40 g (99%) of the title compound, which was not further purified. LC-MS: t_R = 1.13 min, ES+: 740.50.

(rac.)-(1*R, 5*S**)-6-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-(2-methanesulfonyloxyethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F2)**

Et₃N (2.43 mL, 17.48 mmol) and methane sulfonyl chloride (0.68 mL, 8.74 mmol) were added to a cooled (0 °C) sol. of compound **A4** (4.00 g, 5.82 mmol) in CH₂Cl₂ (30.0 mL). The reaction mixture was stirred at 0 °C for 15 min, quenched with ice water, and the aq. layer was extracted with CH₂Cl₂ (2 x 40 mL). The combined org. extracts were washed with aq. 1M HCl, (2x 40 mL), aq. sat. NaHCO₃ (50.00 mL), brine (50.00 mL), dried over MgSO₄, filtered, and the solvents were removed *in vacuo* to yield of the title compound (4.40 g, 99%) as a white foam, which was not further purified. LC-MS: t_R = 1.16 min, ES+: 764.29.

30

(rac.)-(1*R, 5*S**)-7-{4-[2-(Benzylmethylamino)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 (G1)**

Compound F1 (0.55 g, 0.74 mmol) and *N*-benzyl-methylamine (0.38 mL, 2.97 mmol, 4.00 eq.) were mixed in EtOH (4.00 mL), and the mixture was heated to reflux for 3 h. The mixture was diluted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (5-10% MeOH in CH₂Cl₂) resulted in the title compound as a white foam (0.29 g, 51%). LC-MS: *t*_R = 0.96 min, ES+: 765.71.

10

(rac.)-(1*R, 5*S**)-7-{4-[2-(Benzylethylamino)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 (G2)**

Compound F1 (2.20 g, 2.97 mmol) and *N*-benzyl-ethyl-amine (2.65 mL, 17.84 mmol, 6.00 eq.) were stirred in EtOH (18.00 mL) and heated to reflux overnight. EtOH was removed *in vacuo*, the residue was dissolved in CH₂Cl₂, and washed with brine. The aq. layer was extracted with CH₂Cl₂, the combined org. extracts dried over Na₂SO₄, and the solvents were removed under reduced pressure to yield an oil (4.82 g). Purification of the residue by FC (1-20% 7M NH₃/MeOH in CH₂Cl₂) yielded the title compound as a white foam (1.10 g, 47%). LC-MS: *t*_R = 1.00 min, ES+: 779.51.

20

(rac.)-(1*R, 5*S**)-7-{4-[2-(Benzylisopropylamino)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 (G3)**

25

Compound F1 (2.20 g, 2.97 mmol) and *N*-benzyl-isopropylamine (2.704 mL, 17.84 mmol) were stirred in EtOH (18.00 mL) and heated to reflux overnight. *N*-benzyl-isopropylamine (0.9 mL, 5.94 mmol, 2.00 eq.) was added, and the reaction mixture was stirred for additional 4 h at reflux. EtOH was removed *in vacuo*, the residue was dissolved in CH₂Cl₂, and the mixture was washed with brine. The aq. layer was extracted with CH₂Cl₂, and the combined org. extracts were dried over

30

Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (1-20% 7M NH₃/MeOH in CH₂Cl₂) yielded the title compound a white foam (0.5 g, 21%). LC-MS: t_R = 1.01 min, ES+: 793.52.

5 **(rac.)-(1*R**, 5*S**)-7-{4-[2-(Benzylcyclopropylamino)ethyl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G4)**

Compound F2 (2.20 g, 2.88 mmol) and benzylcyclopropylamine (1.67 mL, 11.50 mmol) were stirred in EtOH (18.00 mL) and heated to reflux overnight. The
10 reaction mixture was diluted with CH₂Cl₂, washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (20-30% EtOAc in heptane) yielded the title compound as a white foam (2.00 g, 85%). LC-MS: t_R = 1.02 min, ES+: 815.41.

15 **Examples**

Example 1

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

20 From compound B1 and (2,4-difluorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.80 min; ES+: 601.30.

Example 2

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

From compound B1 and *N*-methylaniline, according to the general procedures A and B. LC-MS: t_R = 0.70 min; ES+: 579.34.

30 **Example 3**

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(Methyl-*m*-tolylamino)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

From compound **B1** and (3-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.67 min; ES+: 579.38.

Example 4

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(Methyl-*o*-tolylamino)propyl]phenyl}-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

From compound **B1** and (2-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.67 min; ES+: 579.36.

Example 5

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

From compound **B1** and (2-chlorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.79 min; ES+: 599.30.

Example 6

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

From compound **B1** and (3-chlorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.85 min; ES+: 599.30.

Example 7

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

A mixture of compound A3 (68 mg), DIPEA (0.027 mL) and *N*-methylaniline (0.020 mL) was stirred in propionitrile (1 mL). Cyanomethyltrimethylphosphonium iodide (F. Zaragoza, H. Stephensen, *J. Org. Chem.*, **2001**, *66*, 2518, 36 mg) was added, and the mixture was stirred at 90 °C overnight. The mixture
5 was filtered through Isolute® (1 g) pre-washed with aq. 1M NaOH (0.7 mL). After 5 min the Isolute® was rinsed with CH₂Cl₂ (3 x 1 mL). The combined org. filtrates were evaporated under reduced pressure. The crude was directly used in general procedure B. LC-MS: *t_R* = 0.74 min; ES+: 581.30.

10 Example 8

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

From compound D1 and 3-chloro-2,6-difluorobenzoyl chloride, according to the
15 general procedures C and B. LC-MS: *t_R* = 0.80 min; ES+: 649.38.

Example 9

(rac.)-(1*R, 5*S**)-7-(4-{2-[(4,5-Dichloroisothiazole-3-carbonyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-**
20 **(3-methoxy-2-methylbenzyl)amide**

From compound D1 and 4,5-dichloroisothiazole-3-carbonyl chloride, according to the general procedures C and B. LC-MS: *t_R* = 0.78 min; ES+: 654.37.

Example 10

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

From compound D5 and 2,4-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: *t_R* = 0.70 min; ES+: 619.43.

30

Example 11

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

From compound **D5** and 2-chloro-6-fluoro-3-methylbenzaldehyde, according to
5 the general procedures D and B. LC-MS: t_R = 0.69 min; ES+: 617.45.

Example 12

(rac.)-(1R*, 5S*)-7-(4-{[(2-Chloro-3,6-difluorobenzyl)methyl-amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide
10

From compound **D5** and 2-chloro-3,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.68 min; ES+: 621.41.

Example 13

(rac.)-(1R*, 5S*)-7-(4-{[(2-Chloro-4-fluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide
15

From compound **D5** and 2-chloro-4-fluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.68 min; ES+: 603.44.

20

Example 14

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

25 From compound **D5** and 2-chloro-6-fluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.67 min; ES+: 603.48.

Example 15

(rac.)-(1R*, 5S*)-7-(4-{[(2,3-Dichlorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide
30

From compound **D5** and 2,3-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.69 min; ES+: 619.38.

Example 16

5 (rac.)-(1*R**, 5*S**)-7-(4-[(2-Chlorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

From compound **D5** and 2-chlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.68 min; ES+: 585.46.

10

Example 17

(rac.)-(1*R**, 5*S**)-7-(4-[(2,6-Dichlorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

15 From compound **D5** and 2,6-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.68 min; ES+: 619.47.

Example 18

20 (rac.)-(1*R**, 5*S**)-7-(4-{2-[(2-Chloro-6-fluoro-3-methylbenzyl)methylamino]ethyl}phenyl)-3,9-diaza-bicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

From compound **D1** and 2-chloro-6-fluoro-3-methylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 631.49.

25 Example 19

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

30 From compound **D1** and 2-chloro-3,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.69 min; ES+: 635.49.

Example 20

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

- 5 From compound **D1** and 2-chloro-6-fluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.68 min; ES+: 617.51.

Example 21

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

From compound **D1** and 2,3-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 633.42.

- 15 **Example 22**

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

- 20 From compound **D1** and 2-chlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.69 min; ES+: 599.42.

Example 23

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

From compound **D1** and 2,6-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.70 min; ES+: 633.39.

Example 24

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

From compound **B2** and [2-(2,4-dimethylphenoxy)ethyl]methylamine, according to the general procedures A and B. LC-MS: t_R = 0.73 min; ES+: 609.46.

Example 25

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

From compound **D5** and 2,6-dichloro-4-methylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.74 min; ES+: 633.37

Example 26

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

From compound **B2** and *N*-(2-chlorobenzyl)(cyclopropyl)amine (WO 2003/093267), according to the general procedures A and B. LC-MS: t_R = 0.70 min; ES+: 611.35.

Example 27

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

From compound **B2** and methyl-[2-(2,3,6-trichlorophenyl)ethyl]amine, according to the general procedures A and B. LC-MS: t_R = 0.73 min; ES+: 667.30.

Example 28

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

From compound **D1** and 3-chlorobenzaldehyde, according to the general
5 procedures D and B. LC-MS: t_R = 0.69 min; ES+: 599.34.

Example 29

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

From compound **D1** and 2,6-dimethylbenzaldehyde, according to the general
10 procedures D and B. LC-MS: t_R = 0.71 min; ES+: 593.42.

Example 30

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

From compound **D1** and 2,3,6-trichlorobenzaldehyde, according to the general
15 procedures D and B. LC-MS: t_R = 0.71 min; ES+: 667.27.

20

Example 31

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

From compound **D5** and 2,3,6-trichlorobenzaldehyde, according to the general
25 procedures D and B. LC-MS: t_R = 0.703 min; ES+: 655.24.

Example 32

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

30

From compound **D8** and 3-chloro-2,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.72 min; ES+: 659.36.

Example 33

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

From compound **D8** and 3-chlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 625.29.

10

Example 34

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

15 From compound **D8** and 2,3,5-trifluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 643.31.

Example 35

20 (rac.)-(1*R**, 5*S**)-7-(4-{[Ethyl-(2,3,6-trifluorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

From compound **D8** and 2,3,6-trifluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.70 min; ES+: 643.29.

25 Example 36

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

30 From compound **D8** and 2-chloro-3,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 659.38.

Example 37

(*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,2-Difluorobenzo[1,3]dioxol-4-ylmethyl)ethylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

- 5 From compound **D8** and 2,2-difluorobenzo[1,3]dioxole-4-carbaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.75 min; ES+: 669.41.

Example 38

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

From compound **D8** and 2,3,6-trichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.74 min; ES+: 693.27.

15 **Example 39**

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

- From compound **D8** and 2-cyanobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.69 min; ES+: 614.42.

Example 40

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

From compound **D8** and 2,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.70 min; ES+: 625.34.

Example 41

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

From compound **D8** and 2,4,6-trifluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.70 min; ES+: 643.32.

Example 42

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

From compound **D8** and 2-chloro-6-fluoro-3-methylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.72 min; ES+: 657.35.

Example 43

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

From compound **D8** and 2,4-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.74 min; ES+: 659.32.

Example 44

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

From compound **D8** and 2-chloro-6-fluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 643.25.

Example 45

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

From compound **D8** and 2-fluoro-5-methoxybenzaldehyde, according to the general procedures D and B. LC-MS: $t_R = 0.71$ min; ES+: 637.33.

Example 46

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

From compound **D8** and 2-fluoro-6-trifluoromethylbenzaldehyde, according to the general procedures D and B. LC-MS: $t_R = 0.73$ min; ES+: 675.36.

10

Example 47

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

15 From compound **D8** and 2,5-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: $t_R = 0.73$ min; ES+: 659.31.

Example 48

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

From compound **D5** and 2,6-dimethylbenzaldehyde, according to the general procedures D and B. LC-MS: $t_R = 0.69$ min; ES+: 579.31.

25 Example 49

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

30 From compound **D5** and 2-chloro-6-fluoro-3-methylbenzaldehyde, according to the general procedures D and B. LC-MS: $t_R = 0.69$ min; ES+: 617.29.

Example 50

(rac.)-(1*R, 5*S**)-7-(4-[(2,3-difluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide**

- 5 From compound **D5** and 2,3-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.67 min; ES+: 587.33.

Example 51

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

From compound **D4** and 3-chloro-2,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.75 min; ES+: 685.33.

- 15 **Example 52**

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

- 20 From compound **D6** and 3-chloro-2-fluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.71 min; ES+: 649.43.

Example 53

- 25 **(rac.)-(1*R**, 5*S**)-7-(4-[(3-Chloro-2,6-difluorobenzyl)cyclopropylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

From compound **D9** and 3-chloro-2,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.79 min; ES+: 671.33.

Example 54

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

From compound **D9** and 2,6-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.77 min; ES+: 671.31.

Example 55

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

From compound **D9** and 2,3-dichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.77 min; ES+: 671.37.

Example 56

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

From compound **D9** and 2,3,6-trichlorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.84 min; ES+: 705.29.

Example 57

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

From compound **D9** and 2,6-dimethylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.75 min; ES+: 629.45.

Example 58

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

From compound **D9** and 2-cyanobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.76 min; ES+: 626.39.

Example 59

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

From compound **D9** and quinoline-4-carbaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.74 min; ES+: 652.45.

10

Example 60

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

15 From compound **D9** and 6-chloro-2-fluoro-3-methylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.76 min; ES+: 667.37.

Example 61

20 (rac.)-(1*R**, 5*S**)-7-(4-{[Cyclopropyl-(2-fluoro-6-trifluoromethylbenzyl)-amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

From compound **D9** and 2-fluoro-6-trifluoromethylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.81 min; ES+: 687.41.

25 Example 62

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

30 From compound **B1** and (2-fluoro-5-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.77 min; ES+: 597.51.

Example 63

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

- 5 From compound **B1** and (2,3-dichlorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.87 min; ES+: 633.42.

Example 64

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

From compound **B1** and (2,6-difluorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.84 min; ES+: 601.47.

15 **Example 65**

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

- 20 From compound **B1** and (2,6-dichlorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.89 min; ES+: 633.46.

Example 66

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

From compound **B1** and (2,5-difluorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.86 min; ES+: 601.50.

Example 67

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

From compound **B1** and (5-chloro-2-methylphenyl)methylamine, according to the
5 general procedures A and B. LC-MS: t_R = 0.79 min; ES+: 613.49.

Example 68

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

10 From compound **B1** and (2,5-dichlorophenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.88 min; ES+: 633.44.

Example 69

15 **(rac.)-(1R*, 5S*)-7-(4-{3-[(3-Fluoro-2-methylphenyl)methylamino]propyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide**

From compound **B1** and (3-fluoro-2-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.76 min; ES+: 597.53.

20

Example 70

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

25 From compound **B1** and (5-fluoro-2-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.76 min; ES+: 597.52.

Example 71

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

From compound **B1** and (2-chloro-5-methylphenyl)methylamine, according to the general procedures A and B. LC-MS: t_R = 0.80 min; ES+: 613.51.

Example 72

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

From compound **D10** and 3-chloro-2,6-difluorobenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.91 min; ES+: 715.34.

10

Example 73

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

15 From compound **D10** and 3-chloro-2-fluoro-3,6-trifluoromethylbenzaldehyde, according to the general procedures D and B. LC-MS: t_R = 0.93 min; ES+: 763.40.

Biological Assays

20

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

1.1 Preparation of AngI-BSA conjugate

25 1.3 mg (1 μ mol) of AngI [1-10 (Bachem, H-1680)] and 17 mg (0.26 μ mol) of BSA (Fluka, 05475) were dissolved in 4 mL of 0.1M phosphate buffer, pH 7.4, after which 2 mL of a 1:100 dilution of glutaraldehyde in H₂O (Sigma G-5882) was added dropwise. The mixture was incubated overnight at 4 °C, then dialyzed against 2 liters of 0.9% NaCl, twice for 4 h at rt, followed by dialysis against 2
30 liters of PBS 1X overnight at rt. The solution was then filtered with a Syringe filter, 0.45 μ m (Nalgene, Cat. No. 194-2545). The conjugate can be stored in polypropylene tubes in 0.05% sodium azide at 4 °C for at least 12 months.

1.2 Preparation of BSA-AngI coated MTP

Microtiter plates (MPT384, MaxiSorp™, Nunc) were incubated overnight at 4 °C with 80 µl of AngI (1-10)/BSA conjugate, diluted 1:100'000 in PBS 1X in a teflon beaker (exact dilution dependent on batch of conjugate), emptied, filled with 90 µl of blocking solution [0.5% BSA (Sigma A-2153) in PBS 1X, 0.02% NaN₃], 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.

10 The plates can be stored in blocking solution at 4 °C for 1 month.

1.3 AngI-EIA in 384 well MTP

The AngI (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-AngI antiserum, pre-diluted 1:10 in horse serum), diluted to a final concentration of 1:100'000 in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4). 5 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.

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

30

2. Primary renin inhibition assay: IC₅₀ 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 (AngI). In the
5 second step, the accumulated AngI 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
10 primary assay down to low pM concentration.

2.1 Methodology

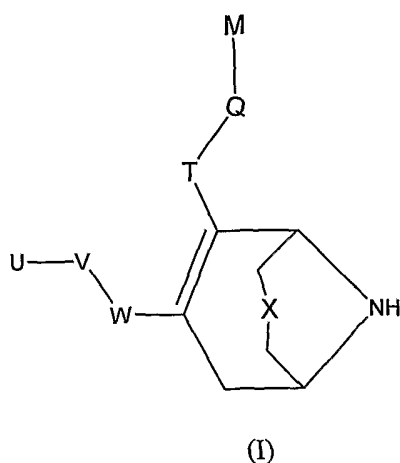
Recombinant human renin (3 pg/ μ l) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μ M
15 in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H₂O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 μ l per well of this premix was transferred into polypropylene plates (MTP384, Nunc). Test compounds were dissolved and diluted in 100% DMSO and 2.5 μ l added to the premix, then incubated at 37 °C for 3 h. At the end of the incubation period, 5 μ l
20 of the renin reaction (or standards in assay buffer) were transferred into EIA assays (as described above) and AngI produced by renin was quantified. The percentage of renin inhibition (AngI decrease) was calculated for each concentration of compound and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC₅₀). The IC₅₀-values of
25 all compounds tested are below 300 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.	IC₅₀ values [nM]		Compound of Example No.	IC₅₀ values [nM]
1	68		40	10
2	36		46	37
3	29		53	22
19	2.4		58	17
24	26		66	7.2
31	7		71	8.3

Claims

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



5

wherein

X represents -NH-, -N(L)-, -CH₂-, -CH(L)-, -O-, or -S-;

W represents a phenyl substituted by V in *para*-position;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-N(-R)-, -N(-R)-CH₂-CH₂-, -O-CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-CH₂-N(-R)-CH₂-CH₂-, -CH₂-N(-R)-CH₂-CH₂-O-, -CH₂-CH₂-CH₂-N(-R)-, -N(-R)-CH₂-CH₂-CH₂-, or -CH₂-CH₂-N(-R)-CO-;

U represents phenyl; mono-, di-, tri-, or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, hydroxy-alkyl, halogen, -CF₃, -OCF₂O-, and cyano; a five-membered heteroaryl ring, wherein said heteroaryl ring is optionally mono-, di-, or tri-substituted, wherein the substituents are independently selected from the group consisting of alkyl, hydroxy-alkyl, halogen and trifluoromethyl; or a quinolinyl;

15

T represents $-\text{CONR}^1-$;

Q represents methylene;

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, alkoxy-alkyl, $-\text{OCF}_3$, $-\text{CF}_3$, and halogen; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from the group consisting of halogen, alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;

L represents $-\text{R}^3$, $-\text{COR}^3$, $-\text{COOR}^3$, $-\text{CONR}^2\text{R}^3$, $-\text{SO}_2\text{R}^3$, or $-\text{SO}_2\text{NR}^2\text{R}^3$;

R represents hydrogen, alkyl, cycloalkyl, or $-\text{CH}_2\text{CF}_3$;

R^1 and $\text{R}^{1'}$ independently represent alkyl or cycloalkyl;

R^2 and $\text{R}^{2'}$ independently represent hydrogen, alkyl, alkenyl, cycloalkyl, or cycloalkyl-alkyl; and

R^3 represents alkyl, cycloalkyl, or cycloalkyl-alkyl, wherein these groups may be unsubstituted or mono-, di- or tri-substituted, wherein the substituents are independently selected from hydroxy, $-\text{NH}_2$, $-\text{OCOR}^2$, $-\text{COOR}^2$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{CH}_3$, alkoxy, cyano, $-\text{CONR}^2\text{R}^{2'}$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^1\text{R}^{1'}$, tetrazolyl, and 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, diastereomeric racemates, mixtures of 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 $-\text{NH}-$;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-N(-R)-, -O-CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-CH₂-N(-R)-CH₂-CH₂-, -CH₂-CH₂-CH₂-N(-R)-, or -CH₂-CH₂-N(-R)-CO-;

U represents phenyl; mono-, di-, or tri-substituted phenyl, wherein the substituents
5 are independently selected from the group consisting of alkyl, alkoxy, and halogen; or a five-membered heteroaryl ring, wherein said heteroaryl ring is optionally mono- or di-substituted, wherein the substituents are independently selected from the group consisting of alkyl, hydroxy-alkyl, halogen and trifluoromethyl;

10 M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, -OCF₃, -CF₃, and halogen; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from the group consisting of halogen, alkyl, -OCF₃, -CF₃ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-
15 position of the pyridinyl ring; and

R represents hydrogen, alkyl, or cycloalkyl.

3. A compound according to claim 1 or 2, wherein R¹ represents a cyclopropyl group.
20

4. A compound according to any one of claims 1 to 3, wherein V represents -CH₂-N(-CH₃)-CH₂-, -CH₂-CH₂-N(-CH₃)-CH₂-, or -CH₂-CH₂-N(-CH₃)-CO-.

5. A compound according to any one of claims 1 to 4, wherein M represents di-
25 substituted phenyl.

6. A compound according to claim 5, wherein M represents phenyl di-substituted by methoxy and methyl.

30 7. A compound according to claim 5, wherein M represents 2,3-dichlorophenyl.

8. A compound according to any one of claims 1 to 7, wherein U represents a mono-, di- or tri-substituted phenyl, wherein the substituents are independently selected from halogen and methyl.

5

9. A compound according to any one of claims 1 to 7, wherein U represents an isothiazole ring di-substituted by halogen.

10. A compound according to claim 1, wherein

10 X represents -NH-;

V represents -CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-, -O-CH₂-CH₂-N(-R)-, -CH₂-CH₂-N(-R)-CH₂-, -CH₂-N(-R)-CH₂-CH₂-O-, -CH₂-CH₂-CH₂-N(-R)-, or -CH₂-CH₂-N(-R)-CO-;

15 U represents phenyl; mono-, di-, or tri-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, halogen, -CF₃, -OCF₂O-, and cyano; or a quinolinyl;

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

R represents alkyl, cycloalkyl, or -CH₂CF₃; and

20 R¹ represents cycloalkyl.

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

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

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

- (*rac.*)-(1*R**, 5*S**)-7-{4-[3-(methyl-*m*-tolylamino)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-{4-[3-(methyl-*o*-tolylamino)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 5 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(2-chlorophenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 10 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(3-chlorophenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-{4-[2-(methylphenylamino)ethoxy]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 15 (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(3-chloro-2,6-difluorobenzoyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(4,5-dichloroisothiazole-3-carbonyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 20 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2,4-dichlorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluoro-3-methylbenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluoro-3-methylbenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-3,6-difluorobenzyl)methylamino]methyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

5 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-4-fluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2,3-dichlorobenzyl)methylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

20 (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-6-fluoro-3-methylbenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-3,6-difluorobenzyl)methylamino]ethyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chloro-6-fluorobenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(2-chlorobenzyl)methylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide; and

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

10

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

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

15 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2,6-dichloro-4-methylbenzyl)methylamino]methyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

20

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

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

25

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

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

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

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(3-chlorobenzyl)ethylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-
15 amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2,3,5-trifluorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2,3,6-trifluorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
20

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

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[(2,2-difluorobenzo[1,3]dioxol-4-ylmethyl)ethylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2,3,6-trichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

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

10 (*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2,4,6-trifluorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluoro-3-methylbenzyl)ethylamino]-methyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
15

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(2-chloro-6-fluorobenzyl)ethylamino]methyl}phenyl)-
20 3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2-fluoro-5-methoxybenzyl)amino]methyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

25 (*rac.*)-(1*R**, 5*S**)-7-(4-{[ethyl-(2-fluoro-6-trifluoromethylbenzyl)amino]methyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

- (*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,5-dichlorobenzyl)ethylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,6-dimethylbenzyl)methylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{{(6-chloro-2-fluoro-3-methylbenzyl)methylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- 10 (*rac.*)-(1*R**, 5*S**)-7-(4-{{(2,3-difluorobenzyl)methylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{2-[(3-chloro-2,6-difluorobenzyl)cyclopropylamino]ethyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- 15 (*rac.*)-(1*R**, 5*S**)-7-(4-{{(3-chloro-2-fluorobenzyl)isopropylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{{(3-chloro-2,6-difluorobenzyl)cyclopropylamino}methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- 20 (*rac.*)-(1*R**, 5*S**)-7-(4-{{[cyclopropyl-(2,6-dichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- (*rac.*)-(1*R**, 5*S**)-7-(4-{{[cyclopropyl-(2,3-dichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- 25 (*rac.*)-(1*R**, 5*S**)-7-(4-{{[cyclopropyl-(2,3-dichlorobenzyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

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

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

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

10 (*rac.*)-(1*R**, 5*S**)-7-{4-[(cyclopropyl-quinolin-4-ylmethylamino)methyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(6-chloro-2-fluoro-3-methylbenzyl)cyclopropylamino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-
15 (2,3-dichlorobenzyl)amide;

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

20 (*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(2-fluoro-5-methylphenyl)methylamino]propyl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

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

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

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(5-chloro-2-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

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

(*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(3-fluoro-2-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(5-fluoro-2-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{3-[(2-chloro-5-methylphenyl)methylamino]propyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(3-chloro-2,6-difluorobenzyl)-(2,2,2-trifluoroethyl)amino]methyl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide; and

(*rac.*)-(1*R**, 5*S**)-7-(4-{[(3-chloro-2-fluoro-6-trifluoromethylbenzyl)-(2,2,2-trifluoroethyl)amino]methyl}phenyl)-3,9-diazabicyclo[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.

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

15 15. Use of a compound according to any one of claims 1 to 12 for the preparation of a pharmaceutical composition for the treatment 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 known to be related to the renin-angiotensin system.