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Thierry [FR/FR]; 6, rue de Thann, F-68116 Guewenheim (FR). **WELLER, Thomas** [CH/CH]; Hölzlistrasse 58, CH-4102 Binningen (CH).

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(74) Agent: **GSCHWEND, Thomas**; Actelion Pharmaceuticals Ltd, Gewerbstrasse 16, CH-4123 Allschwil (CH).

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(71) Applicant (*for all designated States except US*):
ACTELION PHARMACEUTICALS LTD [CH/CH];
Gewerbstrasse 16, CH-4123 Allschwil (CH).

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(72) Inventors; and

(75) Inventors/Applicants (*for US only*): **BEZENCON, Olivier** [CH/CH]; Äussere Baselstrasse 137, CH-4125 Riehen (CH). **BOSS, Christoph** [CH/CH]; Muesmattweg 98, CH-4123 Allschwil (CH). **BUR, Daniel** [CH/CH]; Im Rosengarten 24, CH-4106 Therwil (CH). **CORMIN-BOEUF, Olivier** [CH/CH]; Muesmattweg 102a, CH-4123 Allschwil (CH). **FISCHLI, Walter** [CH/CH]; Obertorweg 64, CH-4123 Allschwil (CH). **GRISOSTOMI, Corinna** [CH/CH]; Rebeggässli 11C, CH-4123 Allschwil (CH). **REMEN, Lubos** [SK/CH]; Kurzellängeweg 28, CH-4123 Allschwil (CH). **RICHARD, Sylvia** [FR/FR]; 12 Rue des Beaux Prés, F-68440 Dietwiller (FR). **SIFFERLEN,**

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(54) Title: BICYCLONONENE DERIVATIVES

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

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

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

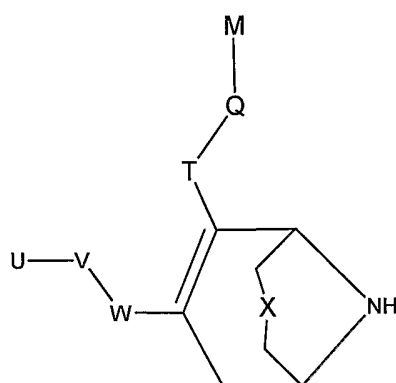
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D.,
25 *Cardiovasc. Drugs*, 1995, 9, 645). The only substrate known for renin is angiotensinogen,
which can only be processed (under physiological conditions) by renin. In contrast, ACE
can also cleave bradykinin besides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

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

Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, 1994, 12, 419; Neutel J. M. *et al.*, *Am. Heart*, 1991, 122, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, 1995, 9, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, 2000, 7, 493; Mealy N. E., *Drugs of the Future*, 2001, 26, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, 1999, 6, 127; Patent Application 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 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 describes these non-peptidic renin inhibitors of formula (I).

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



(I)

wherein

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

W represents 1,4-phenyl;

5 V represents a group of the formula -E¹-Z-E²-;

E¹ represents a bond or methylene;

E² represents oxygen or -CH₂-O-, wherein the -CH₂ part of -CH₂-O- is preferably connected to Z;

Z represents a pyrrolidine or azetidine ring, preferably a pyrrolidine ring;

10 U represents unsubstituted aryl (preferably phenyl); mono-, di-, tri- or tetra-substituted aryl (preferably mono-, di-, tri- or tetra-substituted phenyl), wherein the substituents are independently selected from the group consisting of halogen, -CF₃, -OCF₃, hydroxy-C₁₋₇-alkyl, R¹COO-C₁₋₇-alkyl and C₁₋₇-alkyl; or five-membered heteroaryl containing two heteroatoms independently selected from nitrogen, oxygen and sulfur (preferably pyrazolyl or isoxazolyl), wherein said heteroaryl radical is optionally mono-, di- or tri-substituted,
 15 wherein the substituents are independently selected from C₁₋₇-alkyl, C₁₋₇-alkoxy, -CF₃, -OCF₃ and halogen;

T represents -CONR¹-;

Q represents methylene;

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, -OCF₃, -CF₃, hydroxy-C₁₋₇-alkyl, halogen, C₁₋₇-alkyl-O-(CH₂)₀₋₄-CH₂-, C₁₋₇-alkyl-O-(CH₂)₂₋₄-O-, and
5 R⁴₂N-(CH₂)₀₋₄-CH₂-; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from the group consisting of halogen, C₁₋₇-alkyl, -OCF₃, -CF₃ and C₁₋₇-alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;

L represents -R³, -COR³, -COOR³, -CONR²R³, -SO₂R³, or -SO₂NR²R³;

10 R¹ and R^{1'} independently represent C₁₋₇-alkyl or cycloalkyl;

R² and R^{2'} independently represent hydrogen, C₁₋₇-alkyl, C₂₋₇-alkenyl, cycloalkyl, or cycloalkyl-C₁₋₇-alkyl;

R³ represents C₁₋₇-alkyl, cycloalkyl, or cycloalkyl-C₁₋₇-alkyl, wherein these groups may be unsubstituted or mono-, di-, or tri-substituted, wherein the substituents are independently
15 selected from hydroxy, -NH₂, -OCOR², -COOR², -SO₃H, -SO₂CH₃, C₁₋₇-alkoxy, cyano, -CONR²R^{2'}, -NH(NH)NH₂, -NR¹R^{1'}, tetrazolyl, and C₁₋₇-alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp³-hybridized; and

R⁴ represents hydrogen, C₁₋₇-alkyl, cyclopropyl, or -C(=O)-R' wherein R' is C₁₋₄-alkyl,
20 -CF₃, -CH₂-CF₃, or cyclopropyl;

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.

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

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

Any reference to a compound of formula (I) is to be understood as referring also to optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and meso-forms, as well as salts (especially pharmaceutically acceptable salts) and solvent complexes (including hydrates) of such compounds, and morphological forms, as appropriate and expedient.

In the definitions of formula (I) - if not otherwise stated - the term **C₁₋₇-alkyl**, alone or in combination with other groups, means saturated, straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms (i.e. C₁₋₄-alkyl). Examples of C₁₋₇-alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl and isopropyl groups are preferred.

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

The term **hydroxy-C₁₋₇-alkyl**, alone or in combination with other groups, refers to an HO-R group, wherein R is a C₁₋₇-alkyl. Examples of hydroxy-C₁₋₇-alkyl groups are HO-CH₂-, HO-CH₂CH₂-, HO-CH₂CH₂CH₂- and CH₃-CH(OH)-.

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

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

The term **aryl**, alone or in combination, relates to a phenyl, naphthyl or indanyl group, preferably a phenyl group. In a preferred embodiment the substituent U represents di-, tri-, or tetra-substituted aryl (preferably phenyl), wherein the substituents are selected from the group consisting of halogen, C₁₋₇-alkyl, hydroxy-C₁₋₇-alkyl and R¹COO-C₁₋₇-alkyl, wherein
5 R¹ is C₁₋₇-alkyl. In a further preferred embodiment the substituent U represents di-, or tri-substituted aryl (preferably phenyl), wherein the substituents are selected from the group consisting of fluorine, chlorine, bromine, CH₃CH(OH)-, HOCH₂CH₂-, and methyl. In a preferred embodiment the substituent M represents mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy,
10 -OCF₃, -CF₃, hydroxy-C₁₋₇-alkyl and halogen. In a further preferred embodiment the substituent M represents mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl and C₁₋₇-alkoxy. In a further preferred embodiment the substituent M represents di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy and halogen.

15 Five-membered heteroaryl containing two heteroatoms independently selected from nitrogen, oxygen and sulfur preferably stands for thiazolyl, isoxazolyl, pyrazolyl or oxazolyl, especially pyrazolyl or isoxazolyl.

If M represents mono- or di-substituted pyridinyl, the substituents are preferably selected from the group consisting of fluorine, chlorine, methyl, methoxy, -OCF₃ and -CF₃; with the
20 proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring.

The term V within the present invention represents a group of the formula -E¹-Z-E²- which may be connected in both possible ways to the group W and U of a compound of formula (I). In a preferred embodiment of the invention the beginning part of the group -E¹-Z-E²- is linked to the group W of the compound of formula (I) (that means that the -E¹-part of -E¹-
25 Z-E²- is linked to the group W of a compound of formula (I)). Preferably, the term V within the present invention represents (3*R*)-pyrrolidin-1-yl.

The term T within the present invention represents -CONR¹- which may be connected in both possible ways to the bicyclononene core structure of formula (I). In a preferred embodiment of the invention the beginning part of the group T is linked to the
30 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 $-\text{CONR}^1-$, wherein R^1 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, 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 "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.

The present invention encompasses all these forms. Mixtures are separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, HPLC or crystallization.

Compounds of the invention also include nitrosated compounds of formula (I) that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (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 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 a group of the formula -E¹-Z-E²-;

5 E¹ represents a bond or methylene;

E² represents oxygen;

Z represents a pyrrolidine ring;

U represents unsubstituted aryl; or mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are selected from the group consisting of halogen, -CF₃, -OCF₃, -CH₂OH and
10 C₁₋₇-alkyl; and

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, -OCF₃, -CF₃, hydroxy-C₁₋₇-alkyl, and halogen; or mono- or di-substituted pyridinyl, wherein the substituents are selected from the group consisting of halogen, C₁₋₇-alkyl, -OCF₃, -CF₃ and C₁₋₇-alkoxy; with the proviso,
15 that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;
and wherein the remaining substituents and symbols are as defined for formula (I) above.

In a preferred embodiment M represents phenyl or mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, -OCF₃, -CF₃, hydroxy-C₁₋₇-alkyl and halogen.

20 In a further preferred embodiment M represents mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C₁₋₇-alkyl and C₁₋₇-alkoxy.

In a further preferred embodiment M represents mono- or di-substituted phenyl, wherein the substituents are chlorine atoms.

In a further preferred embodiment R¹ represents a cyclopropyl group.

25 In a further preferred embodiment Z represents pyrrolidinyl, especially 1,3-pyrrolidinyl.

In a further preferred embodiment E² represents an oxygen atom.

In a further preferred embodiment E¹ represents a bond.

In a further preferred embodiment U represents a mono-, di-, tri or tetra-substituted phenyl wherein the substituents are independently selected from the group consisting of halogen, hydroxy-C₁₋₇-alkyl and C₁₋₇-alkyl.

- 5 In another preferred embodiment U represents a mono-, di-, or tri-substituted phenyl wherein the substituents are selected from the group consisting of halogen and C₁₋₇-alkyl.

In a further preferred embodiment X represents -NH-, -N(COCH₃)-, or -N(CONHCH₂C(CH₃)₂CONH₂)-, preferably -NH-.

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

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

- 15 X represents -NH-;

W represents 1,4-phenyl;

V represents a group of the formula -E¹-Z-E²-;

E¹ represents a bond or methylene;

E² represents oxygen or -CH₂-O-;

- 20 Z represents a pyrrolidine ring;

U represents di-, tri- or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, hydroxy-C₁₋₇-alkyl, R¹COO-C₁₋₇-alkyl and C₁₋₇-alkyl; or pyrazolyl or isoxazolyl, wherein these two heteroaryl radicals are di- or tri-substituted, wherein the substituents are independently selected from C₁₋₇-alkyl, -CF₃, and

- 25 halogen;

T represents -CONR¹-;

Q represents methylene;

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

R¹ represents C₁₋₇-alkyl or cycloalkyl.

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

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)-amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-

difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-

methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

5 a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

10 a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

15 a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

20 a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

25 a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
5
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
10
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
15
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- 20 a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- 25 a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

- a mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
5
- a mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
10
- a mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
15
- a mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
20
- a mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
25
- a mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

- a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)oxymethyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yl)oxymethyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]methyl}pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]methyl}pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy]methyl}pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, and (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy]methyl}pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (*1R*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]methyl}-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]methyl}pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (*1S*, *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*1R*, *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1R*, *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*1R*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1R*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

- (1*R*, 5*S*)-7-(4-((3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
- (1*S*, 5*R*)-7-(4-((3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-
 5 3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
- (1*R*, 5*S*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
- 10 (1*S*, 5*R*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
- acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-((1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl
 15 ester;
- acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-((1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester;
- acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-((1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl
 20 ester;
- acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-((1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester;
- 25 acetic acid (1*R*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-((1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

acetic acid (1*R*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

10 acetic acid (1*R*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;

acetic acid (1*R*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester; and

20 acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester.

The compounds of formula (I) are useful for the treatment and/or prophylaxis of diseases such as or related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction,

hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

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

In one embodiment, the invention relates to a method for the treatment and/or prophylaxis
10 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, dragées, hard and soft gelatine capsules, solutions,
20 emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

The invention also relates to the use of a compound of formula (I) for the preparation of
25 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
30 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.

5 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
10 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
15 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,
20 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
25 particular case.

In a preferred embodiment, the amount administered to a patient of a pharmaceutically active amount of a compound of formula (I) 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
30 per day.

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

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

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
10 antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists and/or other drugs beneficial for the prevention or the treatment of the above-mentioned diseases.

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

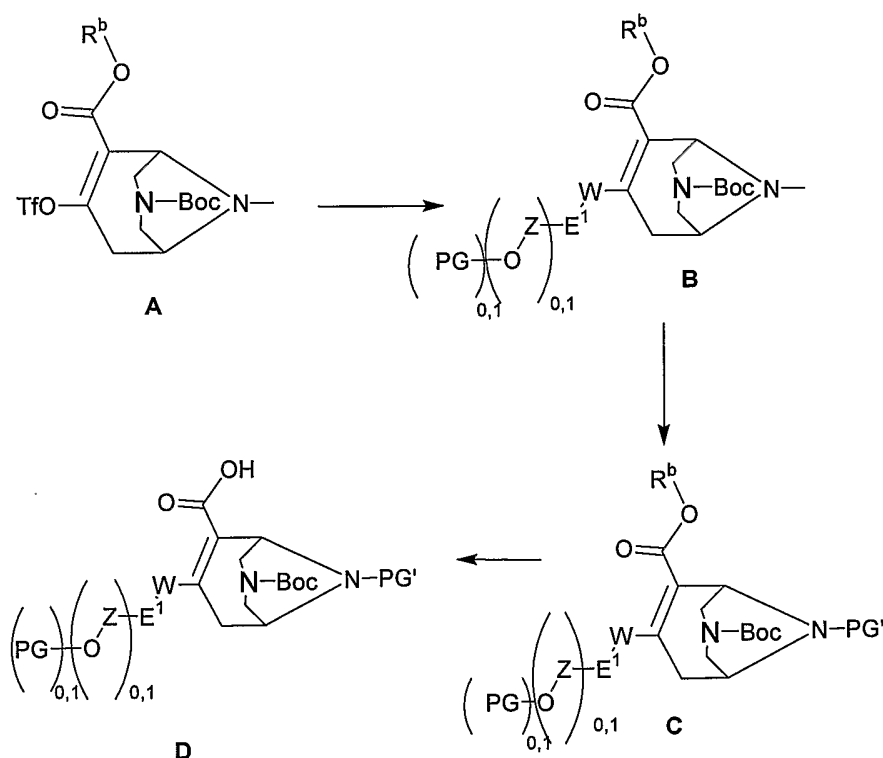
The compounds of formula (I) can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

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

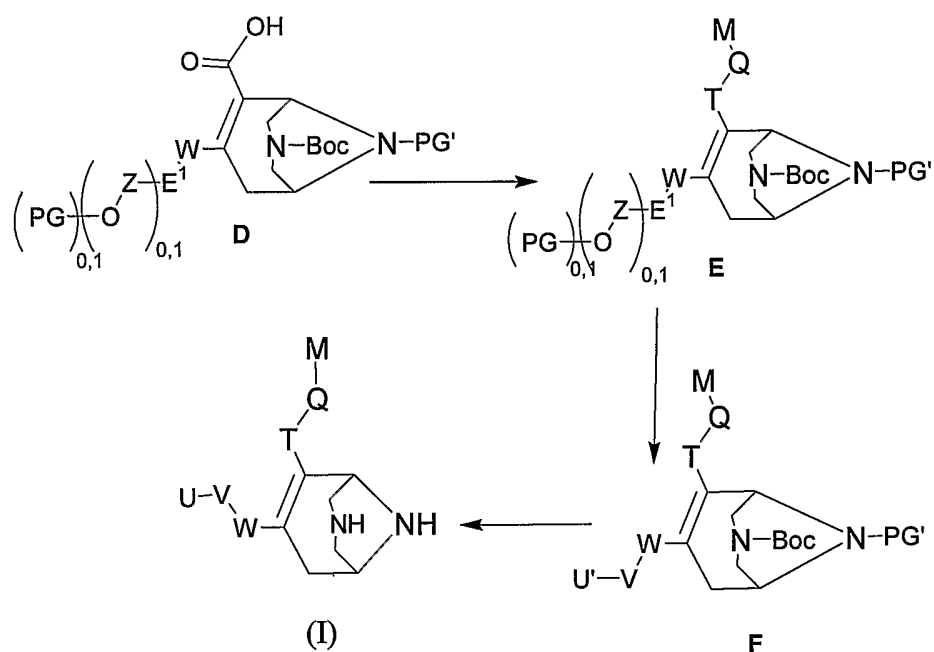
Compounds mentioned below, and not including U-V-W- as a specific substituent, can be
25 prepared by the chemistry described in the patent application WO 03/093267. A compound of type A (WO 03/093267) in Scheme 1a is transformed into a compound of type B, whereas R^b is a typical substituent for an ester, for instance a methyl, ethyl, or benzyl group. R^b can be modified along the synthesis using elementary chemical steps, like a transesterification. The protecting group PG, as well as the group -O-Z-, may or

may not be present. These substituents can be introduced whenever necessary along the synthesis. The transformation of **A** into **B** can be performed typically by a *Negishi* coupling, a *Suzuki* coupling, or a *Stille* coupling, or more generally by a coupling between two sp^2 -hybridized carbon atoms, catalyzed by a transition metal complex. After protecting group manipulations a compound of type **C** is obtained, whereas PG' stands for a suitable protecting group. Then the ester functionality is cleaved to the corresponding acid carboxylic to a compound of type **D**. An amide coupling yields a compound of type **E**, which is then transformed into a compound of type **F** (Scheme 1b). U' can represent U as defined in formula (I), or a substituent close to U (with a protecting group still attached, for instance) that is transformed into a group U in the subsequent step. Removal of the protecting group PG' and Boc leads to a final compound as defined in formula (I), wherein X represents NH.

Scheme 1a

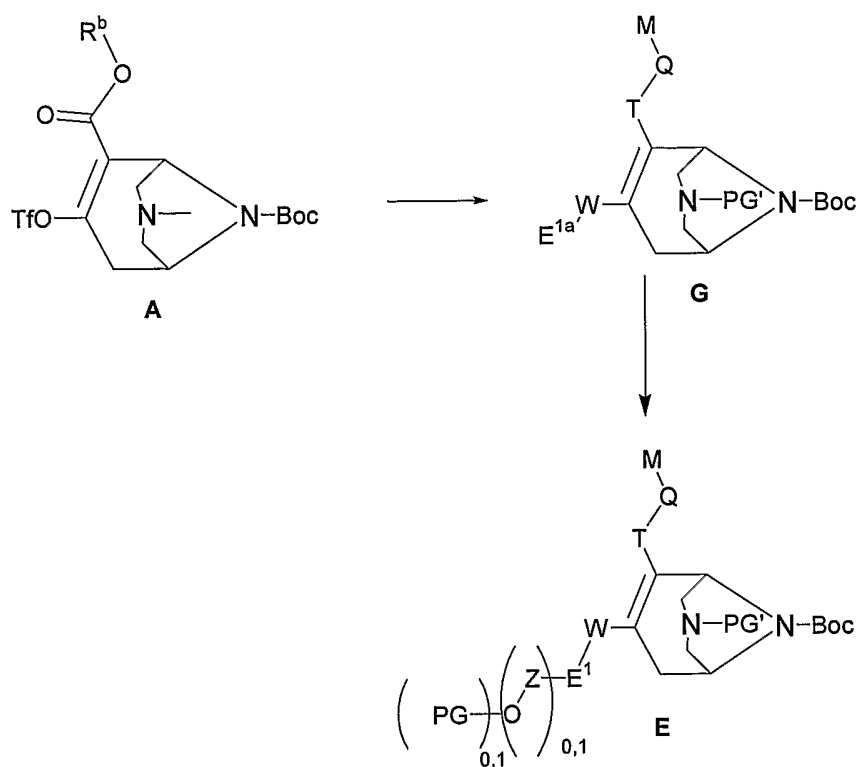


Scheme 1b



Also, if another substituent than a hydrogen atom is desired for L, the protecting group PG' can be cleaved selectively first. The resulting secondary amine is then alkylated, or acylated. Final cleavage of the Boc-protecting group leads to a compound of formula (I), with X being $-\text{N}(\text{L})-$. Also, a compound of formula (I) with X = NH can be acylated selectively at its 3-position.

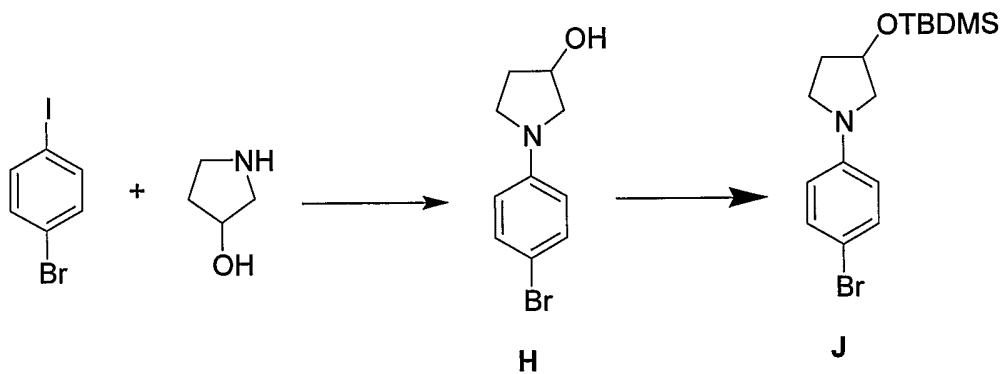
Under certain circumstances the group W may be built on the template itself. In such a case, a compound of type A can be transformed into a compound of type G in several steps, as described in Scheme 2, following similar chemistry as described herein above (see also examples for details). The substituent E^{1a} stands for any intermediate substituent constructed from a compound of type A, which can lead to a definitive substituent E^1 in compound B. The substituent E^{1a} can be modified in successive steps toward the substituent W.

Scheme 2

In other cases the substituent $W^1-E^{1a}-Z-PG$ must be prepared separately in several steps.

For instance compounds **H** and **J** as shown in Scheme 3, must be prepared separately.

5

Scheme 3

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

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

Enantiomerically pure compounds can be prepared by enantioselective synthesis (see WO 03/093267 for the diazabicyclononene template; see for instance Maczka, W. K., Mironowicz, A, *Tetrahedron Asymmetry*, **2004**, *15*, 1965; Wu, X., Li, X., Hems, W., King, F., Xiao, J, *Org. Biomol. Chem.*, **2004**, *2*, 1818; Genov, D. G., Ager, D. J., *Angew. Chem. Intern. Ed.*, **2004**, *43*, 2816; Comasseto, J. V., Andrade, L. H., Omori, A. T., Assis, L. F., Porto, A. L. M., *J. Mol. Cat. B: Enzymatic*, **2004**, *29*, 55; Degni, S., Wilen, C.-E., Rosling, A., *Tetrahedron Asymmetry*, **2004**, *15*, 1495 for the chiral secondary alcohol). They can be prepared by separation of a mixture of stereoisomers by HPLC, using a chiral column.

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

Chemistry

Abbreviations (as used herein)

AcOH	Acetic acid
Ang	Angiotensin
aq.	aqueous
Boc	<i>tert</i> -Butyloxycarbonyl
Bu	Butyl
BSA	Bovine serum albumine
BuLi	<i>n</i> -Butyllithium

	conc.	concentrated
	DDQ	2,3-Dichloro-5,6-dicyano- <i>para</i> -benzoquinone
	DIPEA	Diisopropylethylamine
	DMAP	4- <i>N,N</i> -Dimethylaminopyridine
5	DMF	<i>N,N</i> -Dimethylformamide
	DMSO	Dimethylsulfoxide
	EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	Enzyme immunoassay
	ELSD	Evaporating Light Scattering Detection
10	ES	Electrospray
	Et	Ethyl
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	FC	Flash Chromatography
15	h	hour(s)
	LC-MS	Liquid Chromatography – Mass Spectrometry
	HOBt	Hydroxybenzotriazol
	HPLC	High performance Liquid Chromatography
	Me	methyl
20	MeOH	Methanol
	min	minute(s)
	MS	Mass Spectrometry
	org.	organic
	<i>p</i>	<i>para</i>
25	PG	protecting group
	Ph	Phenyl
	PPTS	<i>p</i> -Toluene sulfonic acid
	R _f	retention index (TLC)
	rt	room temperature
30	sat.	saturated
	sol.	Solution
	TBAF	Tetra- <i>n</i> -butylammonium fluoride

	TBDMS	<i>tert</i> -Butyldimethylsilyl
	TBME	<i>tert</i> -Butylmethylether
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
5	TLC	Thin Layer Chromatography
	t_R	retention time (LC-MS)
	UV	Ultra violet
	Vis	visible

10 Experimental part

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

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

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

Chiral analytic: Regis Whelk column, 4.6 x 250 mm, 10 μ m. Eluent A: EtOH + 0.05% Et₃N. Eluent B: hexane. Isocratic conditions, 60% B, over 40 min, 1 mL/min. The
20 isocratic mixture may vary, depending on the compounds.

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

All t_R are given in min.

General procedures

25 General procedure A (Mitsunobu reaction)

A compound of type E (0.05 mmol) was dissolved in toluene (2 mL) under nitrogen. The phenol or the hydroxy heterocycle (0.10 mmol), azodicarboxylic dipiperidide (for phenol derivatives, 0.10 mmol) or diethylazodicarboxylate (for hydroxyheterocyclic derivatives, 0.10 mmol), and PBu₃ (0.15 mmol) were added. The mixture was stirred for 2 h at rt, 2 h
30 reflux, then at rt overnight. Water was added, and the mixture was extracted with EtOAc.

The org. extracts were separated, and the solvents were evaporated. The crude material was used without further purification.

General procedure B (Boc-deprotection):

- 5 To a sol. of a compound of type F (about 0.05 mmol) in CH_2Cl_2 (1 mL) at 0 °C was added 4M HCl / dioxane (0.5 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.

10

2,6-Dichloro-4-hydroxymethylphenol

- BH_3 (1M in THF, 250 mL, 250 mmol) was added dropwise to a cooled sol. of 3,5-dichloro-4-hydroxybenzoic acid (20 g, 96.6 mmol) in THF (200 mL) at 0 °C. The resulting mixture was stirred at 0 °C for 15 min, and then at rt for 13 h. The milky mixture
15 was cooled to 0 °C and MeOH (150 mL), then water (100 mL), were added dropwise. The mixture was further stirred at 0 °C for 15 min, and then at rt for 5 h. The mixture was then partially concentrated under reduced pressure. EtOAc (200 mL) and water (50 mL) were added to the residue, and the phases were shaken and separated. The aq. phase was further extracted with EtOAc. The combined org. extracts were washed with brine, dried over
20 MgSO_4 , filtered, and concentrated under reduced pressure. Purification by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$, 100:1) led to the title compound as a slightly beige solid (17.86 g, 96%).
LC-MS: t_R = 0.69 min.

3,5-Dichloro-4-hydroxybenzaldehyde

- 25 2,6-Dichloro-4-hydroxymethylphenol (3.56 g, 18.4 mmol) was dissolved in dioxane, and DDQ (4.19 g, 18.4 mmol) was added. The reaction mixture was stirred at rt overnight. The solvents were removed under reduced pressure. The residue was diluted with CH_2Cl_2 , and the mixture was filtered. The filtrate was dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Crystallization from EtOAc yielded the title
30 compound (0.77g, 22%). LC-MS: t_R = 0.82 min.

(rac.)-2,6-Dichloro-4-(1-hydroxyethyl)phenol

A sol. of 2,6-dichloro-4-hydroxybenzaldehyde (1.635 g, 8.56 mmol) in Et₂O (30 mL) was cooled to -78 °C. MeMgBr (3M in Et₂O, 7.15 mL, 21.5 mmol) was added dropwise to the cooled reaction mixture over 18 min. Et₂O (20 mL) was added again during the addition of MeMgBr. Stirring was continued at -78 °C for 1 h, and then the reaction mixture was allowed to warm up to rt over 1 h. The mixture was cooled to 0 °C, and aq. sat. NH₄Cl (10 mL) was added dropwise. The mixture was allowed to warm up to rt, and additional aq. sat. NH₄Cl (35 mL) and water (35 mL) were added. The phases were then separated and the aq. phase was extracted with Et₂O. The combined org. extracts were then washed with brine (50 mL), dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (EtOAc/heptane, 1:1) yielded the title compound (1.683 g, 95%). LC-MS: t_R = 0.74 min.

(rac.)-2-(tert-Butyldimethylsilyloxy)-5-[1-(tert-butyldimethylsilyloxy)ethyl]-1,3-dichlorobenzene

To a sol. of (rac.)-2,6-dichloro-4-(1-hydroxyethyl)phenol (100 mg, 0.483 mmol) in DMF (5.5 mL) were added TBDMS-Cl (175 mg, 1.16 mmol), and imidazole (145 mg, 2.42 mmol). The sol. was stirred at rt overnight. The sol. was cooled to 0 °C, and aq. sat. NH₄Cl was added. The mixture was extracted with heptane/Et₂O (1/1, 4x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (CH₂Cl₂) yielded the title compound (188 mg, 90%). LC-MS: t_R = 1.35 min, ES+: 435.20.

(rac.)-4-[1-(tert-Butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol

A sol. of (rac.)-2-(tert-butyldimethylsilyloxy)-5-[1-(tert-butyldimethylsilyloxy)ethyl]-1,3-dichlorobenzene (188 mg, 0.432 mmol) and Cs₂CO₃ (76.2 mg, 0.126 mmol) in a mixture of DMF (0.50 mL) and water (50 µL) was stirred at rt overnight. Et₂O (75 mL) was added. The sol. was washed with brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (CH₂Cl₂) yielded the title compound (122 mg, 88%). LC-MS: t_R = 1.15 min.

2,6-Dichloro-3,4-dimethylphenol

To a sol. of 3,4-dimethylphenol (3.00 g, 24.6 mmol) in CH₂Cl₂ (5 mL) was added SO₂Cl₂ (4.98 mL, 61.3 mmol). The resulting sol. was heated to 50 °C for 4 h. The mixture was poured onto ice-water. CH₂Cl₂ (200 mL) was added, the layers were separated, and the org. layer was washed with water, then with aq. sat. NaHCO₃. The org. layer was dried
5 over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:4) yielded the title compound (1.174 g, 25%). LC-MS: t_R = 0.97 min. R_f = 0.38 (EtOAc/heptane 1:4).

2-(2-Ethyl-[1,3]dioxolan-2-yl)fluoroacetic acid methyl ester

10 2-Fluoro-3-oxopentanoic acid methyl ester (2.21 g, 14.9 mmol), ethylene glycol (4.15 mL, 74.5 mmol), and BF₃·Et₂O (0.189 mL, 1.49 mmol) were mixed in cyclohexane (10 mL). The mixture was heated to reflux for 5 h, and allowed to cool to rt. The mixture was diluted with EtOAc, and washed with brine, water, aq. sat. NaHCO₃, and brine again. The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under
15 reduced pressure. The title compound was obtained as an oil (1.88 g, 52%).

2-(2-Ethyl-[1,3]dioxolan-2-yl)-2-fluoro-N-hydroxyacetamide

A mixture of 2-(2-ethyl-[1,3]dioxolan-2-yl)fluoroacetic acid methyl ester (1.50 g, 7.80 mmol) and hydroxylamine hydrochloride (1.07 g, 15.6 mmol) were dissolved in pyridine
20 (8 mL). MeONa (30% in MeOH, 3.94 mL, 15.6 mmol) was dropped slowly over 15 min. More pyridine (8 mL) was added. The mixture was stirred for 30 min, then filtered. AcOH (1 mL) was added to the filtrate. The mixture was stirred for 5 min, then the solvents were removed under reduced pressure. Purification by FC (MeOH/CH₂Cl₂ 1:10) yielded the title compound (502 mg, 40%).

25

5-Ethyl-4-fluoroisoxazol-3-ol

A sol. of 2-(2-ethyl-[1,3]dioxolan-2-yl)-2-fluoro-N-hydroxyacetamide (502 mg, 2.60 mmol) in conc. H₂SO₄ (1.2 mL) was stirred for 2 h at rt, then for 2 other hours at 50 °C. The mixture was poured onto ice, and this mixture was extracted with EtOAc. The
30 combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (280 mg, 82%). LC-MS: t_R = 0.66, ES⁺: not visible.

(3,5-Dichloro-4-hydroxyphenyl)acetic acid

A mixture of 4-hydroxyphenylacetic acid (5.00 g, 32.9 mmol) in SO_2Cl_2 (11.1 mL, 82.2 mmol) was heated at 50 °C for 1 h. The mixture turned solid, and SO_2Cl_2 (2.00 mL) was added. The mixture was stirred at 50 °C for 1 h again. The reaction mixture was poured onto ice-water, and the title compound was filtered off as pure compound (3.14 g, 43%). LC-MS: t_R = 0.74 min, ES+: 222.07.

2,6-Dichloro-4-(2-hydroxyethyl)phenol

To an ice-cooled sol. of (3,5-dichloro-4-hydroxyphenyl)acetic acid (3.14 g, 14.2 mmol) in THF (140 mL) was added dropwise BH_3 (1M in THF, 43.0 mL, 43.0 mmol). The sol. was stirred overnight while warming up to rt. The reaction mixture was cooled to 0 °C, and MeOH (10 mL) was carefully added, followed by water (100 mL). The solvents were partially removed under reduced pressure, and the residue was extracted with EtOAc (3x). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 50/1) yielded the title compound (2.94 g, quantitative yield). LC-MS: t_R = 0.74 min, ES+: 207.01.

2-(*tert*-Butyldimethylsilyloxy)-5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,3-dichlorobenzene

To a sol. of 2,6-dichloro-4-(2-hydroxyethyl)phenol (2.40 g, 14.2 mmol) in DMF (134 mL) were added imidazole (4.27 g, 71.0 mmol) and TBDMS-Cl (5.14 g, 34.1 mmol). The sol. was stirred at rt overnight. The sol. was cooled to 0 °C, and aq. sat. NH_4Cl was added. The mixture was extracted with Et_2O (3x). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification by FC (CH_2Cl_2) yielded the compound (4.94 g, 80%). LC-MS: t_R = 1.34 min, ES+: 435.18.

4-[2-(*tert*-Butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol

A sol. of 2-(*tert*-butyldimethylsilyloxy)-5-[2-(*tert*-butyldimethylsilyloxy)ethyl]-1,3-dichlorobenzene (4.94 g, 11.3 mmol) and Cs_2CO_3 (2.00 g, 5.67 mmol) in DMF (15 mL) and water (1.5 mL) was stirred at rt for 2 h. Et_2O was added, and the mixture was washed

with brine (3x), dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH₂Cl₂) yielded the title compound (3.5 g, 96%). LC-MS: t_R = 1.13 min, ES+: 321.11.

5 Intermediates and building blocks

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(*tert*-Butyldimethylsilanyloxy)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(*tert*-butyldimethylsilanyloxy)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo-
10 [3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B1)

BuLi (1.6 M in hexane, 31.5 mL, 50.5 mmol) was added to a sol. of compound J1 (17.3 g, 48.5 mmol) in THF (500 mL) at -78 °C. The sol. was stirred for 30 min at -78 °C, and ZnCl₂ (1M in THF, 58.2 mL, 58.2 mmol) was added. The mixture was allowed to warm to rt, and (rac.)-(1*R**, 5*S**)-9-methyl-7-trifluoromethanesulfonyloxy-3,9-
15 diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267, 8.90 g, 19.4 mmol) and Pd(PPh₃)₄ (560 mg, 0.49 mmol) were added. The mixture was heated quickly to 55 °C and stirred at this temperature for 45 min. The mixture was allowed to cool to rt, and aq. sat. NH₄Cl (250 mL) was added. The mixture was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over MgSO₄,
20 filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:30 → 1:15) yielded the title compound (12.0 g, quantitative yield). LC-MS: t_R = 0.99 min, ES+: 586.31.

(rac.)-(1*R**, 5*S**)-7-[4-(*tert*-Butyldimethylsilanyloxymethyl)phenyl]-9-methyl-3,9-
25 diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B2)
BuLi (1.6 M in hexane, 30.0 mL, 47 mmol) was added to a sol. of (4-bromobenzyloxy)-*tert*-butyldimethylsilane (Sessler, J. L.; Wang, B.; Harriman, A., *J. Am. Chem. Soc.*, **1995**, *117*, 704; Nassal, M., *Liebigs Ann. Chem.*, **1983**, 1510; 15.8 g, 52 mmol) in THF (220 mL) at -78 °C. The sol. was stirred for 60 min at -78 °C, and ZnCl₂ (1.09 M in THF, 50.5
30 mL, 65 mmol) was added. The mixture was allowed to warm to rt, and (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, 8.90 g, 19.4 mmol) in

THF (110 mL) and Pd(PPh₃)₄ (1.26 g, 1.1 mmol) were added. The mixture was stirred at rt for 60 min, and aq. sat. NH₄Cl was added. The mixture was extracted with EtOAc (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:99
5 → 2:98 → 3:97 → 5:95) yielded the title compound (28.05 g, 57%). LC-MS: t_R = 0.98 min; ES+: 572.21.

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(*tert*-Butyldimethylsilanyloxy)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(*tert*-butyldimethylsilanyloxy)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B3)

BuLi (1.6 M in hexane, 16 mL, 25.5 mmol) was added to a sol. of compound J2 (8.1 g, 20.1 mmol) in THF (160 mL) at -78 °C. The sol. was stirred for 30 min at -78 °C, and
15 ZnCl₂ (1.09 M in THF, 29.5 mL, 29.5 mmol) was added. The mixture was allowed to warm to rt, and (*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, 4.5 g, 9.82 mmol) in THF (50 mL), and Pd(PPh₃)₄ (0.28 g, 0.25 mmol) were added. The mixture was stirred at 45 °C for 20 min, and aq. sat. NH₄Cl was added. The
20 mixture was extracted with EtOAc (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:25) yielded the title compound (5.7 g, 99%). LC-MS: t_R = 0.98 min; ES+: 586.49.

25 Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]phenyl}-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (B4)

30 BuLi (1.6 M in hexane, 5.7 mL, 9.1 mmol) was added to a sol. of compound J3 (3.14 g, 8.48 mmol) in THF (44 mL) at -78 °C. The sol. was stirred for 30 min at -78 °C, and ZnCl₂ (1.0 M in THF, 13.0 mL, 13.0 mmol) was added. The mixture was allowed to warm

to rt, and (*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, 2.99 g, 6.52 mmol) in THF (8 mL) and Pd(PPh₃)₄ (0.19 g, 0.16 mmol) were added. The mixture was stirred at rt for 45 min, and aq. sat. NH₄Cl was added. The mixture was
5 extracted with Et₂O (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:25) yielded the title compound (3.66 g, 94%). LC-MS: t_R = 1.02 min; ES+: 600.50.

10 **Mixture of (1*R*, 5*S*)-7-[4-((3*S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester and (1*S*, 5*R*)-7-[4-((3*S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (C1)**

NaHCO₃ (4.30 g, 51.2 mmol) and 1-chloroethyl chloroformate (5.58 mL, 51.2 mmol) were
15 added to a sol. of compound B1 (3.00 g, 5.12 mmol) in CH₂ClCH₂Cl (50 mL). The mixture was heated to 85 °C and stirred at this temperature for 3 h. The mixture was allowed to cool to rt, and was filtered. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was dissolved in MeOH (50 mL), and the mixture was stirred at 50 °C for 30 min. The mixture was allowed to cool to
20 rt, and CH₂Cl₂ was added. The mixture was washed with aq. sat. NH₄Cl, and with brine (2x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum. The residue was dissolved in CH₂Cl₂ (100 mL), and DIPEA (4.13 mL, 41.0 mmol) was added. The mixture was cooled to 0 °C, and Boc₂O (5.58 g, 25.6 mmol) was added. The mixture was stirred
25 overnight while warming up to rt. The mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:30 → 1:20) yielded the title compound (2.42 g, 85%). LC-MS: t_R = 1.03 min, ES+: 558.28.

30 **(*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 (C2)**

NaHCO₃ (44.8 g, 534 mmol) and 1-chloroethyl chloroformate (67.0 mL, 534 mmol) were added to a sol. of compound **B2** (28.3 g, 53 mmol) in CH₂ClCH₂Cl (480 mL). The mixture was heated to 80 °C and stirred at this temperature for 3 h. The mixture was allowed to cool to rt, and was filtered. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was dissolved in MeOH (480 mL), and the mixture was stirred at 50 °C for 60 min. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (580 mL). DIPEA (27.4 mL, 160 mmol) and Boc₂O (58.2 g, 267 mmol) were added. The mixture was stirred overnight while warming up to rt. The mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:30 → 1:20) yielded the title compound (16.6 g, 62%). LC-MS: t_R = 1.01 min, ES+: 503.24.

Mixture of (1*R*, 5*S*)-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester and (1*S*, 5*R*)-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (C3)

NaHCO₃ (8.36 g, 99.6 mmol) and 1-chloroethyl chloroformate (10.8 mL, 99.6 mmol) were added under nitrogen to a sol. of compound **B3** (5.83 g, 10.0 mmol) in CH₂ClCH₂Cl (80 mL). The mixture was heated to 85 °C, and stirred at this temperature for 3 h. The mixture was allowed to cool to rt, and was filtered. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was dissolved in MeOH (80 mL), and the mixture was stirred at 50 °C for 60 min. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (150 mL) and extracted with aq. NH₄OH (ca.12%) (30 mL). The aq. phase was extracted with CH₂Cl₂ (3x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (80 mL). DIPEA (8.5 mL, 49.8 mmol) and Boc₂O (6.5 g, 29.9 mmol) were added. The mixture was stirred overnight at rt. The mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue

by FC (MeOH/CH₂Cl₂ 1:30) yielded the title compound (0.62 g, 11%). LC-MS: t_R = 1.03 min; ES+: 558.44.

Mixture of (*1R*, *5S*)-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester and (*1S*, *5R*)-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester 6-ethyl ester (C4)

NaHCO₃ (5.2 g, 61 mmol) and 1-chloroethyl chloroformate (6.8 mL, 61 mmol) were added under nitrogen to a sol. of compound B4 (3.66 g, 6.10 mmol) in CH₂ClCH₂Cl (55 mL). The mixture was heated to 85 °C and stirred at this temperature for 60 min. The mixture was allowed to cool to rt, and was filtered. The solvents were removed under reduced pressure, and the residue was dried under high vacuum. The residue was dissolved in MeOH (55 mL), and the mixture was stirred at 50 °C for 60 min. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dissolved in CH₂Cl₂ (70 mL). DIPEA (4.3 mL, 24.4 mmol) and Boc₂O (3.40 g, 15.2 mmol) were added. The mixture was stirred overnight at rt. The mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (MeOH/CH₂Cl₂ 1:35 → 1:30) yielded the title compound (2.7 g, 78%). LC-MS: t_R = 1.03 min; ES+: 572.43.

Mixture of (*1R*, *5S*)-7-[4-((*3S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1S*, *5R*)-7-[4-((*3S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (D1)

A mixture of compound C1 (4.20 g, 7.53 mmol) in EtOH (150 mL) and aq. 1M NaOH (70 mL) was stirred at 85 °C for 3.5 h. The mixture was allowed to cool to rt, and the solvents were partially removed under reduced pressure. The residue was diluted with CH₂Cl₂, and acidified with aq. 1M HCl to pH 2. The phases were separated, and the aq. phase was extracted with CH₂Cl₂. The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying under high vacuum yielded the

crude title compound (3.98 g, quantitative yield) that was used without further purification. LC-MS: t_R = 0.90 and 0.93 min, ES+: 530.41.

(rac.)-(1*R, 5*S**)-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 (D2)**

A mixture of compound C2 (16.6 g, 33 mmol) in EtOH (460 mL) and aq. 1M NaOH (230 mL) was stirred at 80 °C for 3 h. The mixture was allowed to cool to rt, and the solvents were partially removed under reduced pressure. The residue was diluted with Et₂O, and acidified with aq. 1M HCl to pH 2. The phases were separated, and the aq. phase was extracted with Et₂O (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The residue was dried under high vacuum and dissolved in DMF (110 mL). Imidazole (5.93 g, 88 mmol) and TBDMS-Cl (10.0 g, 66 mmol) were added, and the mixture was stirred at rt overnight. Et₂O was added, and the mixture was washed with water (2x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The residue was dissolved in THF (265 mL), MeOH (50 mL), and water (50 mL). K₂CO₃ (2.07 g) was added, and the mixture was stirred at rt for 3 h. Aq. sat. NH₄Cl was added, and the mixture was extracted with TBME (2x). The combined org. extracts were washed with brine, dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the crude title compound (19.5 g, 89%) that was used further without purification. LC-MS: t_R = 1.14 min, ES+: 589.30.

Mixture of (1*R*, 5*S*)-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (1*S*, 5*R*)-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (D3)

A mixture of compound C3 (7.10 g, 12.1 mmol) in EtOH (110 mL) and aq. 1M NaOH (256 mL) was stirred at 85 °C for 3.5 h. The mixture was allowed to cool to rt, and the solvents were partially removed under reduced pressure. The residue was acidified with aq. 1M HCl to pH 2. The aq. phase was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the crude title compound (3.35 g,

58%) that was used further without purification. LC-MS: t_R = 0.90 and 0.93 min, ES+: 530.37.

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1S*, *5R*)-7-{4-[(*3R*)-3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (D4)

The mixture of compound D3 (16.6g, 31.3 mmol), imidazole (8.53g, 125.3 mmol) and TBDMS-Cl (11.8g, 78.3 mmol) in DMF (300 mL) was stirred at rt overnight. The mixture was diluted with aq. sat. NH_4Cl , and extracted with heptane (3x). The org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure. The crude product was dissolved in THF (300 mL). To this sol. were added MeOH (100 mL), H_2O (100 mL) and K_2CO_3 (2.7 g), and the mixture was stirred at rt for 1 h. Aq. sat. NH_4Cl was added, and the mixture was extracted with Et_2O (3x). The org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure. The crude title product was used in the next step without purification. LC-MS: t_R = 1.17 and 1.19 min, ES+: 644.32.

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1S*, *5R*)-7-{4-[(*3S*)-3-(*tert*-Butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (D5)

The mixture of compound D1 (16.0 g, 30.2 mmol), imidazole (8.20 g, 121 mmol) and TBDMS-Cl (11.4 g, 75.5 mmol) in DMF (160 mL) was stirred at rt overnight. The mixture was diluted with aq. sat. NH_4Cl , and extracted with heptane (3x). The org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure. The crude product was dissolved in THF (295 mL). To this sol. MeOH (98 mL), H_2O (98 mL), and K_2CO_3 (1.96 g) were added, and the mixture was stirred at rt for 2.5 h. Aq. sat. NH_4Cl was added, and the mixture was extracted with heptane (3x). The org. extracts were dried over Na_2SO_4 , filtered, and the solvents were removed under reduced pressure. The crude title compound was used in the next step without purification. LC-MS: t_R = 1.17 and 1.19 min, ES+: 644.41.

Mixture of (*1R*, *5S*)-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1S*, *5R*)-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (**D6**)

A mixture of compound **C4** (2.7 g, 4.7 mmol) in EtOH (55 mL) and aq. 1M NaOH (20 mL) was stirred at 90 °C for 4.5 h. The mixture was allowed to cool to rt, and the solvents were partially removed under reduced pressure. The residue was acidified with aq. 1M HCl to pH 2. The aq. phase was extracted with EtOAc (2x). The combined org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the crude title compound (2.56 g, quantitative) that was used further without purification. LC-MS: *t*_R = 0.90 and 0.93 min, ES+: 544.43.

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester and (*1S*, *5R*)-7-{4-[(*3R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,6,9-tricarboxylic acid 3,9-di-*tert*-butyl ester (**D7**)

The mixture of compound **D6** (2.56 g, 4.71 mmol), imidazole (1.31 g, 19.3 mmol) and TBDMS-Cl (1.81 g, 12.0 mmol) in DMF (50 mL) was stirred at rt overnight. The mixture was diluted with aq. sat. NH₄Cl, and extracted with heptane (3x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The crude product was dissolved in THF (50 mL). To this sol. were added MeOH (17 mL), H₂O (17 mL) and K₂CO₃ (0.5 g), and the mixture was stirred at rt for 1 h. Aq. sat. NH₄Cl was added, and the mixture was extracted with Et₂O (3x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. The crude title compound (3.37 g) was used in the next step without purification. LC-MS: *t*_R = 1.18 and 1.20 min, ES+: 658.49.

Mixture of (*1R*, *5S*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((*3S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-

dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3*S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E1)

Cyclopropyl-(2-methoxy-3-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, 4.31 g, 22.5 mmol), DIPEA (7.70 mL, 45.1 mmol), DMAP (230 mg, 1.88 mmol), HOBt (1.22 g, 9.02 mmol), and EDC·HCl (5.76 g, 30.1 mmol) were added to a sol. of compound **D1** (3.98 g, 7.51 mmol) in CH₂Cl₂ (200 mL). The mixture was stirred at rt for 4 days. More CH₂Cl₂ was added, and the mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1) yielded the title compound (1.63 g, 31%).

(*rac.*)-(1*R**, 5*S**)-7-[4-(*tert*-Butyldimethylsilanyloxymethyl)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 (E2)

Cyclopropyl-(2-methoxy-3-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, 4.27 g, 22 mmol), DIPEA (11.5 mL, 67 mmol), DMAP (450 mg, 4 mmol), HOBt (2.41 g, 18 mmol), and EDC·HCl (7.13 g, 37 mmol) were added to a sol. of compound **D2** (9.42 g, 15 mmol) in CH₂Cl₂ (240 mL). The mixture was stirred at rt overnight. More CH₂Cl₂ was added, and the mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 4:1) yielded the title compound (22.5 g, 92%). LC-MS: *t*_R = 1.29 min, ES⁺: 762.35.

(*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 (E3)

A mixture of compound **E2** (24.5 g, 32 mmol) and TBAF (20.3 g, 64 mmol) in THF (225 mL) was stirred at rt for 2 h. The mixture was diluted with Et₂O (250 mL), and washed

with water (2x), and brine (1x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH₂Cl₂ 1:49) yielded the title compound (13.0 g, 62%). LC-MS: t_R = 1.09 min, ES+: 648.44.

5 **(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 (E4)**

Dess-Martin reagent (1.70 g, 4.01 mmol) was added to a sol. of compound E3 (2.00 g, 3.08 mmol) in CH₂Cl₂ (70 mL). The mixture was stirred at rt for 45 min, and aq. 1M NaOH was added. The mixture was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying under high vacuum yielded the crude title compound (2.13 g, quantitative yield) that was used further without purification. LC-MS: t_R = 1.15 min, ES+: 646.46.

15 **Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)-carbamoyl]-7-[4-((3*R*)-3-hydroxypyrrolidin-1-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3*R*)-3-hydroxy-pyrrolidin-1-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E5)**

20 A mixture of compound E4 (2.13 g, 2.84 mmol), (*R*)-3-pyrrolidinol (0.490 mL, 5.68 mmol), NaBH(OAc)₃ (1.20 g, 5.68 mmol) and AcOH (0.650 mL) in CH₂Cl₂ (40 mL) was stirred at rt overnight. Aq. 1M NaOH was added, and the mixture was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/ CH₂Cl₂ 1:15
25 → 1:10) yielded the title compound (1.80 g, 88%).

Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diaza-
30 **bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E6)**

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, 2.99 g, 15.6 mmol), DIPEA (5.3 mL, 31.2 mmol), DMAP (159 mg, 1.3 mmol), HOBt (840 mg, 6.24 mmol), and EDC·HCl (3.99 g, 20.8 mmol) were added to a sol. of compound **D3** (3.35 g, 5.2 mmol) in CH₂Cl₂ (50 mL). The mixture was stirred at rt for 4 days. The solution was diluted with CH₂Cl₂ (50 mL), and the mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (CH₂Cl₂/MeOH 30:1 → 20:1) yielded the title compound (0.293 g, 8%). LC-MS: t_R = 1.11 min, ES⁺: 703.47.

Mixture of (1R, 5S)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3S)-3-hydroxypyrrolidin-1-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-tert-butyl ester and (1S, 5R)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((3S)-3-hydroxypyrrolidin-1-ylmethyl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-tert-butyl ester (E7)

A mixture of compound **E4** (1.04 g, 1.60 mmol), (S)-3-pyrrolidinol (0.26 mL, 3.2 mmol), NaBH(OAc)₃ (0.68 g, 3.22 mmol) and AcOH (0.37 mL) in CH₂Cl₂ (20 mL) was stirred at rt for 1.5 h. Aq. 1M NaOH was added, and the mixture was extracted with CH₂Cl₂ (2x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH / CH₂Cl₂ 1:15) yielded the title compound (0.92 g, 80%). LC-MS: t_R = 0.90 min; ES⁺: 717.56.

Mixture of (1R, 5S)-7-{4-[(3R)-3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-tert-butyl ester and (1S, 5R)-7-{4-[(3R)-3-(tert-butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-tert-butyl ester (E8)

Cyclopropyl-(2,3-dichlorobenzyl)amine (prepared by reductive amination from 2,3-dichlorobenzaldehyde and cyclopropylamine, 20.31 g, 94.0 mmol), DIPEA (21.5 mL, 125.3 mmol), DMAP (957 mg, 7.8 mmol), HOBt (5.08 g, 37.6 mmol), and EDC·HCl (15.0

g, 78.3 mmol) were added to a sol. of compound **D4** (20.2 g, 31.3 mmol) in CH₂Cl₂ (480 mL). The mixture was stirred at rt for 5.5 days. Additional cyclopropyl-(2,3-dichlorobenzyl)amine (13.5 g, 62.5 mmol) was added, and the mixture was stirred for 3 days. The sol. was diluted with CH₂Cl₂ (50 mL), and the mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 1:2) yielded the title compound (9.5 g, 36%). LC-MS: t_R = 1.34 min; ES+: 841.46.

10 **Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-((3*R*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E9)**

15 A mixture of compound **E8** (9.00 g, 10.7 mmol) and TBAF (21.4 g, 21.4 mmol) in THF (180 mL) was stirred at 0 °C for 1 h. The mixture was diluted with Et₂O (100 mL), and washed with aq. sat. NH₄Cl (2x). The org. phase was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH₂Cl₂ 1:45 → 1:40 → 1:30) yielded the title compound (5.83 g, 75%). LC-MS: t_R = 1.14 min; ES+: 727.39.

20 **Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(*tert*-butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(*tert*-butyldimethylsilyloxy)pyrrolidin-1-yl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E10)**

25 Cyclopropyl-(2,3-dichlorobenzyl)amine (prepared by reductive amination from 2,3-dichlorobenzaldehyde and cyclopropylamine, 12.8 g, 59 mmol), DIPEA (30.4 mL, 178 mmol), DMAP (906 mg, 7.4 mmol), HOBt (4.8 g, 35.6 mmol), and EDC·HCl (22.7 g, 118.6 mmol) were added to a sol. of compound **D5** (19.1 g, 29.7 mmol) in CH₂Cl₂ (420 mL). The mixture was stirred at rt for 2 days. Additional cyclopropyl-(2,3-

dichlorobenzyl)amine (12.8 g, 59 mmol) was added and the mixture was stirred for 7 days. The sol. was diluted with CH₂Cl₂ (50 mL), and the mixture was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4 → 1:3 → 1:2) yielded the title compound (7.0 g, 28%). LC-MS: t_R = 1.34 min; ES⁺: 841.43.

Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-((3*S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-[4-((3*S*)-3-hydroxypyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E11)

A mixture of compound **E10** (7.0 g, 8.3 mmol) and TBAF (16.6 mL, 16.6 mmol) in THF (180 mL) was stirred at 0°C for 1 h. The mixture was diluted with Et₂O (100 mL), and washed with aq. sat. NH₄Cl (2x). The org. phase was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH₂Cl₂ 1:50 → 1:40 → 1:30) yielded the title compound (4.50 g, 74%). LC-MS: t_R = 1.14 min; ES⁺: 727.37.

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]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 and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(*tert*-butyldimethylsilanyloxymethyl)pyrrolidin-1-yl]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 (E12)

Cyclopropyl-(2-methyl-3-methoxybenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*, **1989**, *54*, 3730 and cyclopropylamine, 2.94 g, 15.4 mmol), DIPEA (3.5 mL, 20.5 mmol), DMAP (156 mg, 1.3 mmol), HOBt (830 mg, 6.1 mmol), and EDC·HCl (2.45 g, 12.8 mmol) were added to a sol. of compound **D7** (3.37 g, 5.1 mmol) in CH₂Cl₂ (80 mL). The mixture was stirred at rt for 6 days. The mixture was diluted with CH₂Cl₂ (50 mL), and was washed with aq. 1M HCl (2x), and aq. sat. NaHCO₃ (1x). The org. extracts were dried over

Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:4) yielded the title compound (0.95 g, 23%). LC-MS: t_R = 1.32 min; ES+: 831.55.

5 Mixture of (*1R*, *5S*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (*1S*, *5R*)-6-[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-7-[4-((*3R*)-3-hydroxymethylpyrrolidin-1-yl)phenyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E13)

10 A mixture of compound E12 (945 mg, 1.14 mmol) and TBAF (2.3 mL, 2.27 mmol) in THF (17 mL) was stirred at 0 °C for 1 h. The mixture was diluted with Et₂O (100 mL), and washed with aq. sol. of NH₄Cl (2x). The org. phase was dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH₂Cl₂ 1:30) yielded the title compound (780 mg, 96%). LC-MS: t_R = 1.12 min; ES+: 717.48.

Mixture of (*1R*, *5S*)-7-[4-((*3S*)-3-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester
20 and (*1S*, *5R*)-7-[4-((*3S*)-3-{4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F1)

A sol. of compound E9 (1.11 g, 1.53 mmol), 4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol (0.74 g, 2.29 mmol), azodicarboxylic dipiperidide (0.58 g, 2.29 mmol), and PBu₃ (1.13 mL, 4.59 mmol) in toluene (30 mL) was refluxed for 2 h. The reaction mixture was allowed to cool to rt, was diluted with EtOAc, and washed with water (3x) and brine. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8 → 1:1) led to the
30 title compound (1.50 g, 95%). LC-MS: t_R = 1.44 min, ES+ = 1031.63.

Mixture of (*1R*, *5S*)-7-[4-((*3S*)-3-{4-[(*1R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1S*, *5R*)-7-[4-((*3S*)-3-{4-[(*1R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1R*, *5S*)-7-[4-((*3S*)-3-{4-[(*1S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, and (*1S*, *5R*)-7-[4-((*3S*)-3-{4-[(*1S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F2)

A sol. of compound E9 (2.18 g, 3.00 mmol), (*rac.*)-4-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol (1.44 g, 4.50 mmol), azodicarboxylic dipiperidide (1.13 g, 4.50 mmol), and PBu₃ (2.22 mL, 9.00 mmol) in toluene (30 mL) was refluxed for 2 h. The reaction mixture was allowed to cool to rt, was diluted with EtOAc, and washed with water (3x) and brine. The org. layer was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8 → 1:0) yielded the title compound (2.55 g, 82%). LC-MS: t_R = 1.45 min, ES⁺: 1031.65.

Mixture of (*1R*, *5S*)-7-[4-((*3R*)-3-{4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (*1S*, *5R*)-7-[4-((*3R*)-3-{4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F3)

A sol. of compound E11 (1.02 g, 1.40 mmol), 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol (0.67 g, 2.10 mmol), azodicarboxylic dipiperidide (0.53 g, 2.10 mmol), and PBu₃ (1.036 mL, 4.20 mmol) in toluene (30 mL) was refluxed for 2 h. The reaction mixture was allowed to cool to rt, was diluted with EtOAc, and was washed with water (3x) and brine. The org. layer was dried over MgSO₄, filtered, and the solvents were

removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8 → 1:0) yielded the title compound (1.29 g, 89%). LC-MS: t_R = 1.44 min, ES+: 1031.63.

Mixture of (*1R*, *5S*)-7-[4-((*3R*)-3-{4-[(*1R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)-
 5 carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1S*, *5R*)-7-[4-((*3R*)-3-{4-[(*1R*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1R*, *5S*)-7-[4-
 10 ((*3R*)-3-{4-[(*1S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}-pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, and (*1S*, *5R*)-7-[4-((*3R*)-3-{4-[(*1S*)-1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenoxy}-pyrrolidin-1-yl)phenyl]-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-
 15 diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F4)

A sol. of compound E11 (2.18 g, 3.00 mmol), (*rac.*)-4-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol (1.16 g, 3.60 mmol), azodicarboxylic dipiperidide (1.13 g, 4.50 mmol), and PBu₃ (2.22 mL, 9.00 mmol) in toluene (45 mL) was refluxed for 2 h. The reaction mixture was allowed to cool to rt, was diluted with EtOAc, and was washed with water (3x) and brine. The org. layer was dried over MgSO₄, filtered,
 20 and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8 → 1:0) yielded the title compound (3.1 g, 100%). LC-MS: t_R = 1.44 min, ES+: 1031.63.

Mixture of (*1R*, *5S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-{(*3R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]-
 25 non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (*1S*, *5R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-{(*3R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid di-
 30 *tert*-butyl ester (F5)

PPTS (0.412 g, 1.64 mmol) was added to a sol. of compound F3 (1.30 g, 1.26 mmol) in MeOH (12 mL), under N₂. The reaction mixture was stirred for 18 h, then PPTS (0.316 g,

1.26 mmol) was added again, and stirring was continued for 5 h. The reaction mixture was diluted with EtOAc, and was washed with water (3x) and brine. The org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 3:7→ 6:4) yielded the title compound
5 (0.796 g, 69%). LC-MS: t_R = 1.27, ES+: 917.51.

Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)-
10 phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, and (1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)-phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo-[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F6)
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TBAF (0.78 g, 2.47 mmol) was added to a sol. of compound F2 (2.55 g, 2.47 mmol) in THF (40 mL), at 0°C and under N₂. The reaction mixture was stirred for 1 h at 0°C, then
20 aq. sat. NH₄Cl (50 mL) was added. The reaction mixture was diluted with EtOAc. The resulting mixture was washed with water and brine. The org. extracts were dried over MgSO₄, filtered, and the solvents removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8→ 1:0) yielded the title compound (2.25 g, 99%). LC-MS: t_R = 1.26, ES+: 917.11.

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Mixture of (1*R*, 5*S*)-7-(4-((3*S*)-3-[4-((1*R*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*S*, 5*R*)-7-(4-((3*S*)-3-[4-((1*R*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*R*, 5*S*)-7-(4-((3*S*)-3-[4-((1*S*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester,
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and (1*S*, 5*R*)-7-(4-((3*S*)-3-[4-((1*S*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F7)

To a sol. of compound F6 (1.10 g, 1.20 mmol), Et₃N (0.28 mL, 2.04 mmol) and DMAP (0.015 g, 0.12 mmol) in CH₂Cl₂ (10 mL) was added acetic acid anhydride (0.17 mL, 1.80 mmol). After 1 h at rt, aq. 1M HCl and EtOAc were added. The phases were separated. The org. phase was washed with water, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8→1:0) yielded the title compound (1.00 g, 87%). LC-MS: t_R = 1.31, ES+: 959.55.

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Mixture of (1*R*, 5*S*)-7-(4-((3*R*)-3-[4-(2-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}-phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-7-(4-((3*R*)-3-[4-(2-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F8)

To a sol. of compound F5 (0.45 g, 0.49 mmol), Et₃N (0.089 mL, 0.639 mmol) and DMAP (0.006 g, 0.05 mmol) in CH₂Cl₂ (5 mL) was added acetic acid anhydride (0.056 mL, 0.59 mmol). After 1 h at rt, aq. 1M HCl and EtOAc were added. The phases were separated. The org. phase was washed with water, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:1) yielded the title compound (0.44 g, 93%). LC-MS: t_R = 1.31, ES+: 959.56.

Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F9)

As described for compound F6 but from compound F1 (1.49 g, 1.45 mmol), TBAF (0.46 g, 1.45 mmol) and THF (15 mL). Purification by FC yielded the title compound (1.08 g, 81%). LC-MS: t_R = 1.26; ES+: 917.17.

Mixture of (1*R*, 5*S*)-7-(4-((3*S*)-3-[4-(2-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester and (1*S*, 5*R*)-7-(4-((3*S*)-3-[4-(2-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]-non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F10)

To a sol. of compound F9 (0.50 g, 0.55 mmol), Et₃N (0.13 mL, 0.93 mmol) and DMAP (0.007 g, 0.055 mmol) in CH₂Cl₂ (10 mL) was added acetic acid anhydride (0.078 mL, 0.82 mmol). After 1 h at rt, aq. 1M HCl and EtOAc were added. The phases were separated. The org. phase was washed with water, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8→ 1:0) yielded the title compound (0.51 g, 97%). LC-MS: t_R = 1.30, ES+: 959.11.

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Mixture of (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)-phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)-phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-7-(4-((3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)-phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F11)

As described for compound F6 but from compound F4 (3.50 g, 3.06 mmol), TBAF (0.96 g, 3.06 mmol) and THF (20 mL). Purification by FC yielded the title compound (2.70 g, 96%). LC-MS: t_R = 1.26; ES+: 917.56.

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Mixture of (1*R*, 5*S*)-7-(4-((3*R*)-3-[4-((1*R*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl}phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diaza-

bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1S*, *5R*)-7-(4-((*3R*)-3-[4-((*1R*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl)phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, (*1R*, *5S*)-7-(4-((*3R*)-3-[4-((*1S*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl)phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester, and (*1S*, *5R*)-7-(4-((*3R*)-3-[4-((*1S*)-1-acetoxyethyl)-2,6-dichlorophenoxy]pyrrolidin-1-yl)phenyl)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F12)

To a sol. of compound F11 (1.10 g, 1.20 mmol), Et₃N (0.28 mL, 2.04 mmol) and DMAP (0.015 g, 0.12 mmol) in CH₂Cl₂ (10 mL) was added acetic acid anhydride (0.17 mL, 1.80 mmol). After 1 h at rt, aq. 1M HCl and EtOAc were added. The phases were separated. The org. phase was washed with water, brine, dried over MgSO₄, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 2:8→ 1:0) yielded the title compound (1.00 g, 86%). LC-MS: t_R = 1.31, ES⁺: 959.55.

(*S*)-1-(4-Bromophenyl)pyrrolidin-3-ol (H1)

1-Bromo-4-iodobenzene (21.5 g, 76.0 mmol), K₃PO₄·H₂O (35.0 g, 152 mmol), and CuI (5.79 g, 30.4 mmol) were added to a sol. of (*S*)-hydroxypyrrolidine (13.3 g, 152 mmol) in *N,N*-dimethylaminoethanol (72 mL) under nitrogen at rt. The mixture was stirred at 55 °C over 3 days. The mixture was allowed to cool to rt, and water (250 mL) was added. The mixture was extracted with Et₂O (4x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:4 → EtOAc) yielded the title compound (14.0 g, 76%). R_f = 0.4 (EtOAc/heptane 1:1).

(*S*)-1-(4-Bromophenyl)-3-(*tert*-butyldimethylsilyloxy)pyrrolidine (J1)

Compound H1 (14.0 g, 57.7 mmol) was dissolved in DMF (100 mL), and TBDMS-Cl (10.4 g, 69.2 mmol) and imidazole (9.81 g, 144 mmol) were added. The mixture was stirred at rt overnight. Aq. sat. NH₄Cl (100 mL) was added, and the mixture was extracted with heptane (2x). The combined org. extracts were dried over MgSO₄, filtered, and the

solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 1:15 → 1:4) yielded the title compound (17.3 g, 84%).

(R)-1-(4-Bromophenyl)pyrrolidin-3-ol (H2)

5 A mixture of 1-bromo-4-iodobenzene (22.6 g, 79.8 mmol), (R)-hydroxypyrrolidine (16.9 g, 160 mmol), K₃PO₄·H₂O (36.7 g, 160 mmol), and CuI (2.0 g, 32 mmol) in *N,N*-dimethylaminoethanol (75 mL) was heated at 55 °C for 60 h. The mixture was allowed to cool to rt, water was added, and the mixture was extracted with Et₂O (2x). The combined org. extracts were washed with aq. sat. NH₄OH (2x), dried over Na₂SO₄, filtered, and the
10 solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:4) yielded the title compound (13.3 g, 69%). LC-MS: t_R = 0.87 min; ES⁺: 242.01.

(R)-1-(4-Bromophenyl)-3-(tert-butyldimethylsilyloxy)pyrrolidine (J2)

A mixture of compound **H2** (12.9 g, 53.5 mmol), imidazole (9.1 g, 134 mmol) and
15 TBDMS-Cl (9.70 g, 64.2 mmol) in DMF (100 mL) was stirred at rt overnight. The mixture was diluted with aq. sat. NH₄Cl, and extracted with heptane (3x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:4) yielded the title compound (17.7 g, 93%). LC-MS: t_R = 1.23 min; ES⁺: 356.13.

(R)-[1-(4-Bromophenyl)pyrrolidin-3-yl]methanol (H3)

A mixture of 1-bromo-4-iodobenzene (5.5 g, 19.5 mmol), (R)-hydroxymethylpyrrolidine (3.9 g, 38.9 mmol), K₃PO₄·H₂O (9.0 g, 39 mmol) and CuI (742 mg, 3.9 mmol) in *N,N*-dimethylaminoethanol (50 mL) was heated at 55 °C for 96 h. The mixture was allowed to
25 cool to rt, water was added, and the mixture was extracted with CH₂Cl₂ (2x). The combined org. extracts were washed with aq. sat. NH₄OH (2x), dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:3) yielded the title compound (2.36 g, 47%). LC-MS: t_R = 0.88 min; ES⁺: 256.11.

(R)-1-(4-Bromophenyl)-3-(tert-butyldimethylsilyloxymethyl)pyrrolidine (J3)

A mixture of compound **H3** (2.36 g, 9.2 mmol), imidazole (1.60 g, 23.1 mmol) and TBDMS-Cl (1.70 g, 11.1 mmol) in DMF (30 mL) was stirred at rt overnight. The mixture was diluted with water, and extracted with heptane (3x). The org. extracts were dried over Na₂SO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:15 → 1:10) yielded the title compound (3.1 g, 90%). LC-MS: t_R = 1.24 min; ES+: 370.22.

Examples

Example I

Mixture of (*1R*, *5S*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

Compound **F5** (0.40 g, 0.44 mmol) was dissolved in CH₂Cl₂ (10 mL), and the sol. was cooled to 0 °C. 4M HCl in dioxane (3.27 mL, 13.10 mmol) was added and the reaction mixture was stirred for 1 h at 0 °C. The reaction mixture was diluted with CH₂Cl₂, washed with aq. 1M NaOH, water, brine, dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by HPLC (gradient acetonitrile/H₂O (0.05% NH₄OH) yielded the title compound (0.20 g, 64%). LC-MS: t_R = 0.83, ES+: 717.40.

Example II

Mixture of (*1R*, *5S*)-7-(4-((3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-7-(4-((3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-7-(4-((3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-7-(4-((3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-

yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

As described for **Example I** but from compound **F6** (1.15 g, 1.25 mmol), 4M HCl in dioxane (9.41 mL, 37.63 mmol) and CH₂Cl₂ (10 mL). Purification of the residue by HPLC
5 (gradient acetonitrile/H₂O (0.05% NH₄OH) yielded the title compound (0.65 g, 72%). LC-MS: t_R = 0.84, ES⁺: 717.43.

Example III

Mixture of (*1R*, *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
10 cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

As described for **Example I** but from compound **F9** (0.54 g, 0.59 mmol), 4M HCl in dioxane (4.42 mL, 17.67 mmol) and CH₂Cl₂ (10 mL). Purification of the residue by HPLC
15 (gradient acetonitrile/H₂O (0.05% NH₄OH) yielded the title compound (0.28 g, 66%). LC-MS: t_R = 0.84, ES⁺: 717.35.

Example IV

Mixture of (*1R*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
20 cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo-
25 [3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

As described for **Example I** but from compound **F11** (1.15 g, 1.25 mmol), 4M HCl in dioxane (9.41 mL, 37.63 mmol) and CH₂Cl₂ (10 mL). Purification of the residue by HPLC
30

(gradient acetonitrile/H₂O (0.05% NH₄OH) yielded the title compound. LC-MS: t_R = 0.83, ES+: 717.43.

Example 1

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 2,3,6-trifluorophenol. LC-MS: t_R = 0.71 min; ES+: 647.43.

Example 2

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 2,6-dichlorophenol. LC-MS: t_R = 0.72 min; ES+: 663.16.

Example 3

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.72 min; ES+: 663.49.

Example 4

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-

methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 2,6-dichloro-4-fluorophenol. LC-MS: t_R = 0.72 min; ES+: 679.42.

Example 5

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo-[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.72 min; ES+: 663.48.

Example 6

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E5 and 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.73 min; ES+: 659.56.

Example 7

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E1 and 2,3-dichlorophenol. LC-MS: t_R = 0.84 min; ES+: 647.37.

Example 8

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E1 and 2-chloro-4-methylphenol. LC-MS: t_R = 0.85 min; ES+: 627.44.

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Example 9

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E1 and 2-bromo-5-fluorophenol. LC-MS: t_R = 0.84 min; ES+: 677.41.

20 **Example 10**

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E1 and 2,6-dichloro-4-methylphenol. LC-MS: t_R = 0.87 min; ES+: 661.44.

Example 11

30 Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(3-chloro-2,6-

difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]-non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E1 and 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.84 min; ES+: 649.46.

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Example 12

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

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According to general procedures A and B, starting from compound E1 and 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.85 min; ES+: 645.40.

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Example 13

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

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According to general procedures A and B, starting from compound E1 and 2-chloro-4,5-dimethylphenol. LC-MS: t_R = 0.86 min; ES+: 641.49.

Example 14

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

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According to general procedures A and B, starting from compound E1 and 2,6-difluorophenol. LC-MS: t_R = 0.82 min; ES+: 615.43.

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Example 15

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E6 and 2-chloro-4,5-dimethylphenol. LC-MS: t_R = 0.86 min; ES+: 641.49.

Example 16

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-difluorophenoxy)pyrrolidin-1-ylmethyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E7 and 2,3-difluorophenol. LC-MS: t_R = 0.71 min; ES+: 629.55.

Example 17

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.87 min; ES+: 675.31.

Example 18

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-

yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 5-ethyl-4-fluoroisoxazol-3-ol. LC-MS: t_R = 0.84 min; ES+: 640.37.

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Example 19

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

10

According to general procedures A and B, starting from compound E9 and 4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-ol (EP 304409 A1). LC-MS: t_R = 0.88 min; ES+: 711.33.

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Example 20

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

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According to general procedures A and B, starting from compound E9 and 2,6-dichlorophenol. LC-MS: t_R = 0.88 min; ES+: 673.30.

Example 21

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

25

According to general procedures A and B, starting from compound E9 and 2,6-dichloro-4-fluorophenol. LC-MS: t_R = 0.89 min; ES+: 691.28.

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Example 22

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.88 min; ES+: 673.22.

Example 23

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.90 min; ES+: 687.31.

Example 24

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)-pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.89 min; ES+: 671.38.

Example 25

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)-

pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 6-chloro-2-fluoro-3-methylphenol. LC-MS: t_R = 0.89 min; ES+: 671.32.

5

Example 26

Mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

10

According to general procedures A and B, starting from compound E9 and 2-chloro-*p*-cresol. LC-MS: t_R = 0.88 min; ES+: 653.37.

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Example 27

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

20

According to general procedures A and B, starting from compound E11 and 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.88 min; ES+: 673.31.

Example 28

Mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

25

According to general procedures A and B, starting from compound E11 and 4,5-dimethylisoxazol-3-ol (Katritzky, A. R.; Oeksne, S., *Proc. Chem. Soc.*, **1961**, 387). LC-MS: t_R = 0.82 min; ES+: 622.36.

30

Example 29

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E11 and 5-ethyl-4-fluoroisoxazol-3-ol. LC-MS: t_R = 0.85 min; ES+: 641.35.

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Example 30

A mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

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According to general procedures A and B, starting from compound E11 and 4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-ol (EP 304409 A1). LC-MS: t_R = 0.87 min; ES+: 711.33.

20

Example 31

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

25

According to general procedures A and B, starting from compound E11 and 2,6-dichlorophenol. LC-MS: t_R = 0.88 min; ES+: 671.29.

Example 32

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-

30

yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E11 and 2,6-dichloro-4-fluorophenol. LC-MS: t_R = 0.89 min; ES+: 691.26.

5

Example 33

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

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According to general procedures A and B, starting from compound E11 and 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.87 min; ES+: 673.36.

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Example 34

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

20

According to general procedures A and B, starting from compound E11 and 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.90 min; ES+: 687.34.

Example 35

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

25

According to general procedures A and B, starting from compound E11 and 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.89 min; ES+: 669.32.

30

Example 36

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)-pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E11 and 6-chloro-2-fluoro-3-methylphenol. LC-MS: t_R = 0.89 min; ES+: 671.35.

Example 37

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E11 and 2-chloro-*p*-cresol. LC-MS: t_R = 0.88 min; ES+: 653.35.

Example 38

Mixture of (*1R*, *5S*)-7-(4-{(*3S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(*3S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.84 min; ES+: 717.31.

Example 39

Mixture of (*1R*, *5S*)-7-{4-[(*3S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-{4-[(*3S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)-

pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E9 and 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 0.92 min; ES+: 715.32.

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Example 40

Mixture of (*1R*, *5S*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-((3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)-
10 phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

According to general procedures A and B, starting from compound E11 and 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.84 min; ES+: 717.32.

15

Example 41

Mixture of (*1R*, *5S*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluoro-
20 phenoxy)methyl]pyrrolidin-1-yl}-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.87 min; ES+: 663.43.

Example 42

25 Mixture of (*1R*, *5S*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl}-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

30 According to general procedures A and B, starting from compound E13 and 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 0.91 min; ES+: 689.44.

Example 43

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxymethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxymethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound **E13** and 4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-ol (EP 304409 A1). LC-MS: t_R = 0.87 min; ES+: 622.42.

Example 44

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichlorophenoxyethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichlorophenoxyethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound **E13** and 2,6-dichlorophenol. LC-MS: t_R = 0.88 min; ES+: 661.51.

Example 45

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-fluorophenoxyethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-fluorophenoxyethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound **E13** and 2,6-dichloro-4-fluorophenol. LC-MS: t_R = 0.88 min; ES+: 679.42.

Example 46

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(3-chloro-2,6-difluorophenoxyethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-

methoxy-2-methylbenzyl)amide and (*1S*, *5RS*)-7-{4-[(*3R*)-3-(3-chloro-2,6-difluorophenoxymethyl)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.87 min; ES⁺: 663.43.

Example 47

Mixture of (*1R*, *5S*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy-methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (*1S*, *5R*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy-methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (*1R*, *5S*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy-methyl]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, and (*1S*, *5R*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy-methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and (*rac.*)-4-[1-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.83 min; ES⁺: 705.46.

Example 48

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy-methyl)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2,6-dichloro-4-methylphenoxy-methyl)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.90 min; ES⁺: 659.51.

Example 49

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]-pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.88 min; ES+: 659.51.

Example 50

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]-pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 6-chloro-2-fluoro-3-methylphenol. LC-MS: t_R = 0.88 min; ES+: 659.5.

Example 51

Mixture of (*1R*, *5S*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-{4-[(*3R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 2-chloro-*p*-cresol. LC-MS: t_R = 0.87 min; ES+: 641.49.

Example 52

Mixture of (*1R*, *5S*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy)methyl]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (*1S*, *5R*)-7-(4-{(*3R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide

According to general procedures A and B, starting from compound E13 and 4-[2-(*tert*-butyldimethylsilyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.83 min; ES+: 705.47.

Example 53

- 5 Mixture of (*1S*, *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide
- 10 The mixture from Example II was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title mixture was obtained (240 mg). Analytical chiral HPLC: t_R = 25.72 min.

Example 54

- 15 Mixture of (*1R*, *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1R*, *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxy-ethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide
- 20 The mixture from Example II was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title mixture was obtained (200 mg). Analytical chiral HPLC: t_R = 43.30 and 46.97 min (not completely separated).

Example 55

- 25 Mixture of (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*1S*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide
- 30 The mixture from Example IV was separated by preparative HPLC using a chiral column (isocratic conditions, 40% A and 60% B). The title mixture was obtained (139 mg). Analytical chiral HPLC: t_R = 26.70 min.

Example 56

Mixture of (*1R*, *5S*)-7-(4-{{(3*R*)-3-[2,6-dichloro-4-((*1R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid
5 cyclopropyl-(2,3-dichlorobenzyl)amide and (*1R*, *5S*)-7-(4-{{(3*R*)-3-[2,6-dichloro-4-((*1S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

The mixture from **Example IV** was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title mixture was obtained (133 mg).

10 Analytical chiral HPLC: $t_R = 42.38$ min.

Example 57

(*1R*, *5S*)-7-(4-{{(3*S*)-3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-
15 dichlorobenzyl)amide

The mixture from **Example III** was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title compound was obtained (41 mg).

Analytical chiral HPLC: $t_R = 23.35$ min.

Example 58

(*1S*, *5R*)-7-(4-{{(3*S*)-3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-
20 dichlorobenzyl)amide

The mixture from **Example III** was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title compound was obtained (67 mg).

25 Analytical chiral HPLC: $t_R = 37.32$ min.

Example 59

(*1R*, *5S*)-7-(4-{{(3*R*)-3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-
30 dichlorobenzyl)amide

The mixture from **Example I** was separated by preparative HPLC using a chiral column (isocratic conditions, 50% A and 50% B). The title compound was obtained (51 mg). Analytical chiral HPLC: t_R = 24.35 min.

5 **Example 60**

(*IS*, *5R*)-7-(4-((3*R*)-3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl)-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

The mixture from **Example I** was separated by preparative HPLC using a chiral column
10 (isocratic conditions, 50% A and 50% B). The title compound was obtained (43 mg). Analytical chiral HPLC: t_R = 36.50 min.

Example 61

Acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-((*IR*, *5S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-
15 carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester

Compound **F8** was separated by preparative HPLC using a chiral column (isocratic conditions, 55% A and 45% B). The intermediate compound was obtained (160 mg). Analytical chiral HPLC: t_R = 19.45 min. The intermediate compound was treated
20 according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (129 mg). LC-MS: t_R = 0.88 min; ES+: 759.15.

Example 62

Acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-((*IS*, *5R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-
25 carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}-ethyl ester

Compound **F8** was separated by preparative HPLC using a chiral column (isocratic conditions, 55% A and 45% B). The intermediate compound was obtained (106 mg). Analytical chiral HPLC: t_R = 31.17 min. The intermediate compound was treated
30 according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (81 mg). LC-MS: t_R = 0.88 min; ES+: 759.15.

Example 63

Acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-{(*IR*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}-ethyl ester

- 5 Compound **F10** was separated by preparative HPLC using a chiral column (isocratic conditions, 55% A and 45% B). The intermediate compound was obtained (163 mg). Analytical chiral HPLC: t_R = 20.20 min. The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (115 mg). LC-MS: t_R = 0.88 min; ES+: 759.18.

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Example 64

Acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-{(*IS*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}-ethyl ester

- 15 Compound **F10** was separated by preparative HPLC using a chiral column (isocratic conditions, 55% A and 45% B). The intermediate compound was obtained (170 mg). Analytical chiral HPLC: t_R = 32.45 min. The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (137 mg). LC-MS: t_R = 0.86 min; ES+: 759.15.

20

Example 65

Acetic acid (*IR*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(*IR*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

- 25 Compound **F7** was separated by preparative HPLC using a chiral column (isocratic conditions, 85% A and 15% B). The intermediate compound was obtained (188 or 195 mg). Analytical chiral HPLC: t_R = 12.17 or 51.28 min (with example 66). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (153 or 144 mg, together with example
30 66). LC-MS: t_R = 0.88 min; ES+: 759.18.

Example 66

Acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

Compound **F7** was separated by preparative HPLC using a chiral column (isocratic conditions, 85% A and 15% B). The intermediate compound was obtained (188 or 195 mg). Analytical chiral HPLC: t_R = 12.17 or 51.28 min (with example 65). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (153 or 144 mg, together with example 65). LC-MS: t_R = 0.88 min; ES+: 759.18.

10

Example 67

Acetic acid (1*R*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

Compound **F7** was separated by preparative HPLC using a chiral column (isocratic conditions, 85% A and 15% B). The intermediate compound was obtained (195 or 130 mg). Analytical chiral HPLC: t_R = 18.20 or 67.90 min (with example 68). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (137 or 150 mg, together with example 68). LC-MS: t_R = 0.88 min; ES+: 759.18.

20

Example 68

Acetic acid (1*S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(1*S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

25

Compound **F7** was separated by preparative HPLC using a chiral column (isocratic conditions, 85% A and 15% B). The intermediate compound was obtained (195 or 130 mg). Analytical chiral HPLC: t_R = 18.20 or 67.90 min (with example 67). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (137 or 150 mg, together with example 67). LC-MS: t_R = 0.88 min; ES+: 759.18.

30

Example 69

Acetic acid (*IR*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*IR*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

5 Compound **F12** was separated by preparative HPLC using a chiral column (isocratic conditions, 75% A and 25% B). The intermediate compound was obtained (150 or 140 mg). Analytical chiral HPLC: $t_R = 12.65$ or 49.12 min (with example 70). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (138 or 130 mg, together with example
10 70). LC-MS: $t_R = 0.88$ min; ES+: 759.19.

Example 70

Acetic acid (*IS*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*IR*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

15 Compound **F12** was separated by preparative HPLC using a chiral column (isocratic conditions, 75% A and 25% B). The intermediate compound was obtained (150 or 140 mg). Analytical chiral HPLC: $t_R = 12.65$ or 49.12 min (with example 69). The intermediate compound was treated according to general procedure B, but without HPLC
20 purification. The bis-hydrochloride was obtained (138 or 130 mg, together with example 69). LC-MS: $t_R = 0.88$ min; ES+: 759.19.

Example 71

Acetic acid (*IR*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*IS*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

25 Compound **F12** was separated by preparative HPLC using a chiral column (isocratic conditions, 75% A and 25% B). The intermediate compound was obtained (148 or 100 mg). Analytical chiral HPLC: $t_R = 18.23$ or 68.63 min (with example 72). The
30 intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (140 or 95 mg, together with example 72). LC-MS: $t_R = 0.88$ min; ES+: 759.19.

Example 72

Acetic acid (*1S*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*1S*, 5*R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester

Compound **F12** was separated by preparative HPLC using a chiral column (isocratic conditions, 75% A and 25% B). The intermediate compound was obtained (148 or 100 mg). Analytical chiral HPLC: t_R = 18.23 or 68.63 min (with example 71). The intermediate compound was treated according to general procedure B, but without HPLC purification. The bis-hydrochloride was obtained (140 or 95 mg, together with example 71). LC-MS: t_R = 0.88 min; ES+: 759.19.

Biological Assays**1. Enzyme immuno assay (EIA) to estimate AngI accumulation and renin inhibition****1.1 Preparation of AngI-BSA conjugate**

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

1.2 Preparation of BSA-AngI coated MTP

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

and blocked with 250 µl blocking solution as above, except that the blocking solution contained 3% BSA. The plates can be stored in blocking solution at 4 °C for 1 month.

1.3 AngI-EIA in 384 well MTP

5 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
10 incubated overnight at 4 °C. After the incubation the plates were washed 3 times with wash buffer and incubated with secondary antibody [anti-rabbit IgG, linked to horseradish peroxidase (Amersham Bioscience, NA 934V), diluted 1:2'000 in wash buffer] for 2 h at rt. The plates were washed 3 times with wash buffer and then incubated for 1 h at rt with substrate solution [1.89mM ABTS (2,2'-azino-di-(3-ethyl-benzthiazolinsulfonate)] (Roche
15 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.

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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
25 substrate) to create the product Angiotensin I (AngI). In the second step, the accumulated AngI is measured by an immunological assay (enzyme immuno assay, EIA). The detailed 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
30 this primary assay down to low pM concentration.

2.1 Methodology

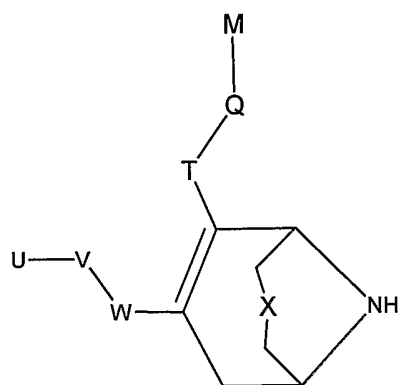
Recombinant human renin (3 pg/ μ l) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μ M in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H₂O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 μ l 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 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 compounds of formula (I) exhibit IC₅₀ values between 0.1 nM to 300 nM, especially between 1 nM to 30 nM.

Examples of inhibition:

Compound of Example No.	IC ₅₀ values [nM]	Compound of Example No.	IC ₅₀ values [nM]
1	38	33	14
2	38	39	5.6
10	1.1	47	23
15	17	56	11
20	2.9	61	13
27	2.8	69	17

Claims

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



(I)

wherein

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

W represents 1,4-phenyl;

V represents a group of the formula -E¹-Z-E²-;

10 E¹ represents a bond or methylene;

E² represents oxygen or -CH₂-O-;

Z represents a pyrrolidine or azetidine ring;

U represents unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of halogen, -CF₃, -OCF₃, hydroxy-C₁₋₇-alkyl, R¹COO-C₁₋₇-alkyl and C₁₋₇-alkyl; or five-membered heteroaryl containing two heteroatoms independently selected from nitrogen, oxygen and sulfur (preferably pyrazolyl or isoxazolyl), wherein said heteroaryl radical is optionally mono-, di- or tri-substituted, wherein the substituents are independently selected from C₁₋₇-alkyl, C₁₋₇-alkoxy, -CF₃, -OCF₃ and halogen;

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 C_{1-7} -alkyl, C_{1-7} -alkoxy, $-\text{OCF}_3$, $-\text{CF}_3$,
5 hydroxy- C_{1-7} -alkyl, halogen, C_{1-7} -alkyl- $\text{O}-(\text{CH}_2)_{0-4}-\text{CH}_2-$, C_{1-7} -alkyl- $\text{O}-(\text{CH}_2)_{2-4}-\text{O}-$, and $\text{R}^4\text{N}-(\text{CH}_2)_{0-4}-\text{CH}_2-$; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from the group consisting of halogen, C_{1-7} -alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and C_{1-7} -alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;

10 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^1 and $\text{R}^{1'}$ independently represent C_{1-7} -alkyl or cycloalkyl;

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

R^3 represents C_{1-7} -alkyl, cycloalkyl, or cycloalkyl- C_{1-7} -alkyl, wherein these groups may be
15 unsubstituted or mono-, di-, or tri-substituted, wherein the substituents are independently selected from hydroxy, $-\text{NH}_2$, $-\text{OCOR}^2$, $-\text{COOR}^2$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{CH}_3$, C_{1-7} -alkoxy, cyano, $-\text{CONR}^2\text{R}^{2'}$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^1\text{R}^{1'}$, tetrazolyl, and C_{1-7} -alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp^3 -hybridized; and

20 R^4 represents hydrogen, C_{1-7} -alkyl, cyclopropyl, or $-\text{C}(=\text{O})-\text{R}'$ wherein R' is C_{1-4} -alkyl, $-\text{CF}_3$, $-\text{CH}_2-\text{CF}_3$, or cyclopropyl;

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,
25 and morphological forms.

2. A compound according to claim 1, wherein

X represents $-\text{NH}-$;

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

E^1 represents a bond or methylene;

E^2 represents oxygen;

Z represents a pyrrolidine ring;

- 5 U represents unsubstituted aryl; or mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are selected from the group consisting of halogen, $-CF_3$, $-OCF_3$, $-CH_2OH$ and C_{1-7} -alkyl; and

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7} -alkyl, C_{1-7} -alkoxy, $-OCF_3$, $-CF_3$, hydroxy- C_{1-7} -alkyl, and
10 halogen; or mono- or di-substituted pyridinyl, wherein the substituents are selected from the group consisting of halogen, C_{1-7} -alkyl, $-OCF_3$, $-CF_3$ and C_{1-7} -alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring.

3. A compound according to claim 1 or 2, wherein M represents phenyl or mono- or di-
15 substituted phenyl, wherein the substituents are selected from the group consisting of C_{1-7} -alkyl, C_{1-7} -alkoxy, $-OCF_3$, $-CF_3$, hydroxy- C_{1-7} -alkyl and halogen.

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

5. A compound according to claim 3, wherein M represents mono- or di-substituted phenyl, wherein the substituents are chlorine atoms.

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

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

- 30 8. A compound according to any one of claims 1 to 7, wherein E^2 represents an oxygen atom.

9. A compound according to any one of claims 1 to 8, wherein E¹ represents a bond.
10. A compound according to claim 1, wherein U represents a mono-, di-, tri- or tetra-
5 substituted phenyl wherein the substituents are independently selected from the group consisting of halogen, hydroxy-C₁₋₇-alkyl and C₁₋₇-alkyl.
11. A compound according to claim 1, wherein
- X represents -NH-;
- 10 Z represents a pyrrolidine ring;
- U represents di-, tri- or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of halogen, hydroxy-C₁₋₇-alkyl, R¹COO-C₁₋₇-alkyl and C₁₋₇-alkyl; or pyrazolyl or isoxazolyl, wherein these two heteroaryl radicals are di- or tri-substituted, wherein the substituents are independently selected from C₁₋₇-alkyl, -CF₃, and
15 halogen;
- M represents di-substituted phenyl, wherein the substituents are independently selected from the group consisting of C₁₋₇-alkyl, C₁₋₇-alkoxy, and halogen; and
- R¹ represents C₁₋₇-alkyl or cycloalkyl.
- 20 12. A compound according to claim 1 selected from the group consisting of:
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,3,6-trifluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-
25 methoxy-2-methylbenzyl)amide;
- a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-
30 methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-bromo-5-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)-amide; and

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide.

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

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-

3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4,5-dimethylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,3-Difluoro-phenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,3-difluorophenoxy)pyrrolidin-1-ylmethyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

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

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-

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

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4,5-dimethylisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(5-ethyl-4-fluoroisoxazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]-

pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*S*)-3-(2,6-dichloro-3,4-dimethylphenoxy)pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-3,6-difluorophenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-3,4-dimethylphenoxy)methyl]pyrrolidin-1-yl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(4-chloro-1-methyl-5-trifluoromethyl-1*H*-pyrazol-3-yloxy)methyl]pyrrolidin-1-yl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichlorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-fluorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(3-chloro-2,6-difluorophenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, and (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2,6-dichloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]-pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-6-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]-pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(6-chloro-2-fluoro-3-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-{4-[(3*R*)-3-(2-chloro-4-methylphenoxy)methyl]pyrrolidin-1-yl}phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy)methyl]-pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy)methyl]pyrrolidin-1-yl}phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide;

a mixture of (1*S*, 5*R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*S*, 5*R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (1*R*, 5*S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((1*R*)-1-hydroxyethyl)phenoxy]-pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (1*R*, 5*S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-((1*S*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*IS*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*IR*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*IS*, *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*IS*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic
5 acid cyclopropyl-(2,3-dichlorobenzyl)amide;

a mixture of (*IR* *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*IR*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide and (*IR*, *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-((*IS*)-1-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic
10 acid cyclopropyl-(2,3-dichlorobenzyl)amide;

(*IR* *5S*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;

(*IS* *5R*)-7-(4-{(3*S*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
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(*IR* *5S*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;

(*IS* *5R*)-7-(4-{(3*R*)-3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]pyrrolidin-1-yl}-phenyl)-3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide;
20

acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-{(*IR*, *5S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl
25 ester;

acetic acid 2-{3,5-dichloro-4-[(3*R*)-1-(4-{(*IS*, *5R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester;

- acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester;
- acetic acid 2-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)-carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]phenyl}ethyl ester;
- acetic acid (*1R*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- 10 acetic acid (*1S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- acetic acid (*1R*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- 15 acetic acid (*1S*)-1-{3,5-dichloro-4-[(3*S*)-1-(4-{(*1S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- acetic acid (*1R*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- 20 acetic acid (*1S*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- acetic acid (*1S*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*1R*, 5*S*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester;
- 25 acetic acid (*1R*)-1-{3,5-dichloro-4-[(3*R*)-1-(4-{(*1S*, 5*R*)-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester; and

acetic acid (*1S*)-1-{3,5-dichloro-4-[(*3R*)-1-(4-{(*1S*, *5R*)-6-[cyclopropyl-(2,3-dichloro-benzyl)carbamoyl]-3,9-diazabicyclo[3.3.1]non-6-en-7-yl}phenyl)pyrrolidin-3-yloxy]-phenyl}ethyl ester.

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

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

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16. Use of a compound according to any one of claims 1 to 13, 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
15 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
20 of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.