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(54) Title: BICYCLONONENE DERIVATIVES

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

WO 2006/021403 A1

Bicyclononene Derivatives

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

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

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

The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D.,
Cardiovasc. Drugs, 1995, 9, 645). The only substrate known for renin is

angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be bypassed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing
5 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
10 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.

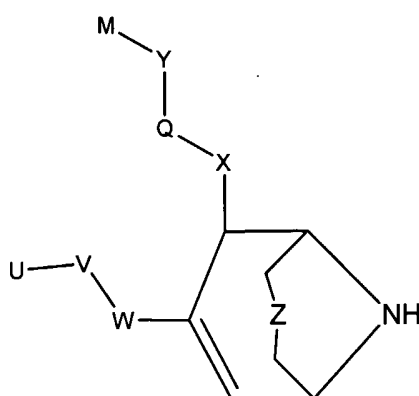
Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin
15 inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. 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
20 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;
25 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
30 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),

5



(I)

wherein

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

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

10 V represents oxy-alkylene or oxy-alkylene-oxy;

U represents unsubstituted aryl (preferably phenyl); or mono-, di-, tri- or tetra-substituted aryl (preferably mono-, di-, tri- or tetra-substituted phenyl), wherein the substituents are independently selected from halogen, -CF₃, -OCF₃, -CH₂OH and alkyl;

15 X and Y independently represent a bond or alkylene, preferably alkylene, especially methylene;

Q represents $-\text{CO}-\text{N}(\text{R}^1)-$;

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from alkyl, alkoxy, $-\text{OCF}_3$, $-\text{CF}_3$, hydroxy-alkyl, halogen, alkyl-O- $(\text{CH}_2)_{0.4}-\text{CH}_2-$, alkyl-O- $(\text{CH}_2)_{2.4}-\text{O}-$, and $\text{R}^4_2\text{N}-(\text{CH}_2)_{0.4}-\text{CH}_2-$; or mono-
5 or di-substituted pyridinyl, wherein the substituents are independently selected from halogen, alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;

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

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

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

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

R^4 represents hydrogen, alkyl, cyclopropyl, or $-\text{C}(=\text{O})-\text{R}'$ wherein R' is C_1 - C_4 -alkyl, $-\text{CF}_3$, $-\text{CH}_2-\text{CF}_3$, or cyclopropyl;

20 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.

The general terms used hereinbefore and hereinafter preferably have, within this
25 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
5 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.

10 In the definitions of formula (I) – if not otherwise stated – the term **alkyl**, alone or in combination with other groups, means saturated, straight or branched chain groups with one to seven carbon atoms, preferably one to four carbon atoms, i.e. C₁-C₄-alkyl. Examples of alkyl groups are methyl, ethyl, n-propyl, iso-propyl, n-butyl, iso-butyl, sec-butyl, tert-butyl, pentyl, hexyl and heptyl. The methyl, ethyl
15 and isopropyl groups are preferred.

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

The term **oxy-alkylene** refers to an -O-R- group, wherein R is alkylene. Examples
20 are oxymethylene, oxyethylene, oxypropylene, oxy-iso-propylene, oxy-tert-butylene etc..

The Term **oxy-alkylene-oxy** refers to an -O-R-O- group, wherein R is alkylene. Examples are oxymethylenoxy, oxyethylenoxy, oxypropylenoxy, oxy-iso-propylenoxy, oxy-tert.-butylenoxy etc..

25 The term **hydroxy-alkyl** refers to an HO-R group, wherein R is alkyl. Examples are hydroxymethyl, hydroxyethyl, hydroxypropyl, hydroxybutyl, CH₃CH(OH)-, etc..

The term **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 alkenyl are vinyl, propenyl and butenyl.

- 5 The term **alkylene**, alone or in combination with other groups, means straight or branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms.

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

- 10 The term **cycloalkyl**, alone or in combination with other groups, 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 with other groups, relates to a phenyl or naphthyl group, preferably a phenyl group.

- 15 The term V within the present invention represents oxy-alkylene or oxy-alkylene-oxy, wherein said bivalent groups, if asymmetric, 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 an asymmetric group V is linked to the group U of a compound of formula (I) (that means that the oxy part
20 of oxy-alkylene is linked to the group U of a compound of formula (I).

- The term Q within the present invention represents -CO-N(R¹)- which may be connected in both possible ways to the group X of formula (I). In a preferred embodiment of the invention the beginning part of the group Q is linked to the group X of formula (I) (that means that the -C(=O) part of -CO-N(R¹)- is linked to
25 the group X of formula (I)). Preferably, the term Q within the present invention represents -CO-N(R¹)- wherein R¹ represents cycloalkyl, preferably 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 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 may be separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, HPLC or crystallization.

Compounds of the invention also include nitrosated compounds of formula (I) that have been nitrosated through one or more sites such as oxygen (hydroxyl condensation), sulfur (sulfydryl condensation) and/or nitrogen.

The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758 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

Z represents -NH-; and

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

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

Preferred compounds are compounds of formula (I), wherein M represents phenyl
di-substituted independently with fluorine, chlorine, methyl or methoxy.

Preferred compounds are also compounds of formula (I), wherein M represents
15 phenyl di-substituted with methyl and methoxy or fluorine and methoxy or mono-
substituted with chlorine.

Preferred compounds are also compounds of formula (I), wherein M represents
pyridinyl di-substituted with methyl and methoxy or fluorine and methoxy or
mono-substituted with chlorine.

20 Very preferred compounds are also compounds of formula (I), wherein M
represents pyridinyl substituted in 2-position by methoxy and in 3-position by
methyl.

Preferred compounds are also compounds of formula (I), wherein X represents
methylene.

25 Preferred compounds are further compounds of formula (I), wherein Y represents
methylene.

Preferred compounds are in addition compounds of formula (I), wherein Q represents -CO-N(R¹)-, wherein R¹ represents cyclopropyl.

Preferred compounds are compounds of formula (I), wherein Q represents -CO-N(R¹)-, wherein R¹ represents alkyl.

- 5 Very preferred compounds are also compounds of formula (I), wherein U represents phenyl tri-substituted independently by methyl, fluorine and chlorine or by fluorine and chlorine.

Very preferred compounds are also compounds of formula (I), wherein U represents phenyl tri-substituted independently by methyl and chlorine.

- 10 Very preferred compounds are also compounds of formula (I), wherein V represents -O-CH₂-CH₂-CH₂-.

Very preferred compounds are also compounds of formula (I), wherein V represents -O-CH₂-CH₂-O-.

- 15 Very preferred compounds are also compounds of formula (I), wherein Z represents -NH-, -CH₂-, -N(COCH₃)-, or -N(CONHCH₂C(CH₃)₂CONH₂)-, especially -NH- or -CH₂-, very especially -NH-.

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

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

Z represents -NH- or -CH₂-;

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

- 25 V represents oxy-alkylene or oxy-alkylene-oxy;

U represents tri-substituted phenyl, wherein the substituents are independently selected from alkyl, especially methyl, and halogen;

X and Y independently represent alkylene;

Q represents -CO-N(R¹)-;

- 5 M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from alkyl, alkoxy and halogen; or di-substituted pyridinyl, wherein the substituents are independently selected from alkyl and alkoxy; and

R¹ represents alkyl or cycloalkyl.

- 10 Most preferred compounds are compounds of formula (I) above selected from the group consisting of:

(*rac.*)-*N*-(2-chlorobenzyl)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-acetamide;

- 15 (*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2-fluoro-5-methoxybenzyl)acetamide;

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxy-2-methyl-

- 20 benzyl)acetamide,

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2-methoxy-3-methylpyridin-4-ylmethyl)acetamide,

- a mixture of (*rac.*)-*N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)-2-((1*R**, 2*R**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-3-en-2-yl)acetamide and (*rac.*)-*N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)-2-((1*R**, 2*S**,
- 25

5*S*^{*})-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-aza-bicyclo[3.3.1]non-3-en-2-yl)acetamide,

(*rac.*)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxy-
5 benzyl)acetamide,

(*rac.*)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dichloro-benzyl)acetamide,

(*rac.*)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dimethyl-
10 benzyl)acetamide,

(*rac.*)-*N*-benzyl-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)-propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-methylacetamide,

(*rac.*)-*N*-(2-chlorobenzyl)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluoro-
15 phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-ethylacetamide,

(*rac.*)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,5-dimethoxy-benzyl)acetamide, and

(*rac.*)-2-((1*R*^{*}, 5*S*^{*}, 6*R*^{*})-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,4-dimethoxy-
20 benzyl)acetamide.

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,
25 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
5 related to the renin-angiotensin system.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

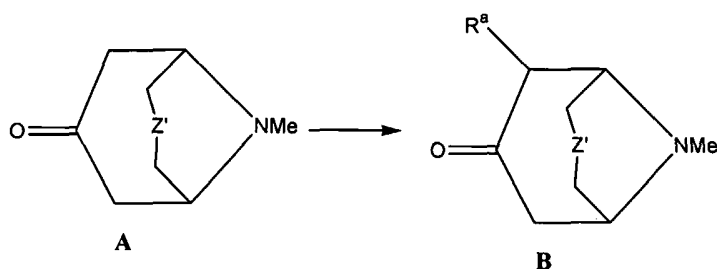
The compounds of formula (I) can be manufactured by the methods outlined below, by the methods described in the examples or by analogous methods.

Chemistry

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

A compound of type A (Scheme 1) can be prepared from (*rac.*)-(1*R**, 5*S**)-9-methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267) by ester hydrolysis and decarboxylation in acidic milieu, or as described in Jerchel, Weidmann, *Justus Liebigs Ann. Chem.*, **1957**, 607, 126. Z' stands for a precursor of the group Z as defined in general formula (I), or for this group Z itself. Compound A can be alkylated into a compound of type B, directly through an enolate, or through an enamine intermediate, or any other methodology known in the literature for the introduction of a substituent in α -position to a ketone. R^a stands for any precursor of the fragment M-Y-Q-X.

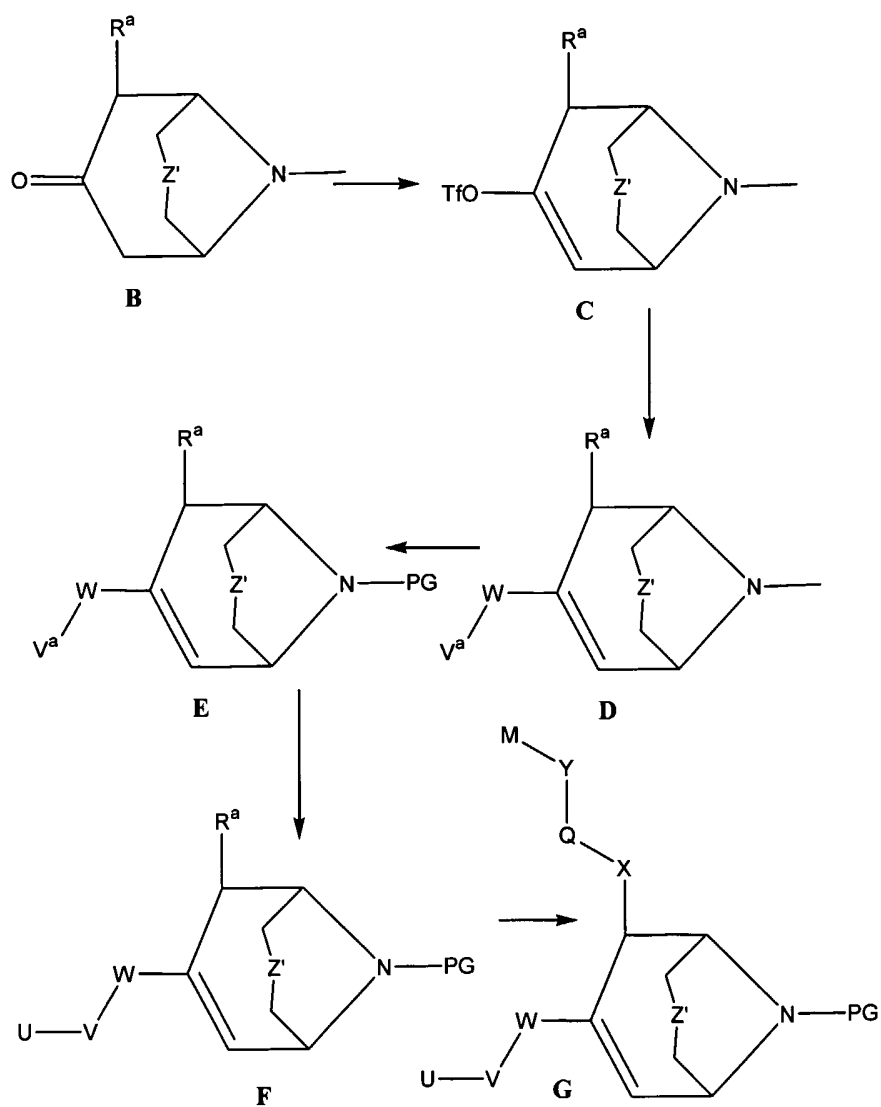
20 Scheme 1:



A compound of type B can be then transformed into a compound of type C (Scheme 2). A C-C coupling, typically catalyzed by a transition metal (*Negishi*

coupling, *Suzuki* coupling, or *Stille* coupling) can lead to a compound of type **D**, wherein V^a stands for a precursor of the substituent V as defined in formula (I). Protecting group manipulations lead to a compound of type **E**, wherein PG stands for a suitable protecting group. The fragment $U-V$ can then be put in place, leading to a compound of type **F**. Finally, the chain $X-Q-Y-M$ can be put in place, for instance by an amide coupling, leading to a compound of type **G**. Manipulating Z' , if necessary, and final deprotection can then lead to a compound of formula (I') with Z being $-NH-$.

Scheme 2:



If Z represents -N(L)-, as defined in general formula (I), selective removal of the Boc protecting group on a compound of type G, then alkylation or acylation, allows the introduction of the L-substituent as defined in formula (I). Also, a compound of formula (I) with Z = NH can be acylated selectively at its 3-position.

- 5 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 oxazabicyclononene derivatives (X = -CH₂- or -CH(L)- in formula (I)) can be prepared as described in WO 2004/096803, using the
10 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
15 (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
20 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.

- 25 They are, however, not intended to limit its scope in any manner.

Experimental part

Abbreviations (as used herein)

Ang Angiotensin

	aq.	aqueous
	Boc	<i>tert</i> -Butyloxycarbonyl
	BSA	Bovine serum albumine
	Bu	Butyl
5	BuLi	<i>n</i> -Butyllithium
	DIBAL	Diisobutyl aluminium hydride
	DIPEA	Diisopropylethylamine
	DMAP	4- <i>N,N</i> -Dimethylaminopyridine
	DMSO	Dimethylsulfoxide
10	EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	Enzyme immunoassay
	ELSD	Evaporating light scattering detection
	eq.	Equivalent(s)
	ES	Electrospray
15	Et	Ethyl
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	FC	Flash Chromatography
	h	hour(s)
20	HOBt	Hydroxybenzotriazol
	HPLC	High Performance Liquid Chromatography
	LC-MS	Liquid Chromatography Mass Spectroscopy
	LDA	Lithium diisopropylamide
	LiHMDS	Lithium hexamethyldisilazide
25	MeOH	Methanol
	min	minute(s)
	MS	Mass Spectroscopy
	NaHMDS	Sodium hexamethyldisilazide
	org.	organic
30	PG	protecting group
	Ph	phenyl

	R_t	retention time (LC-MS, HPLC)
	rt	room temperature
	sat.	saturated
	sol.	Solution
5	TBME	<i>tert</i> -Butylmethylether
	Tf	Trifluoromethylsulfonyl
	TFA	Trifluoroacetic acid
	THF	Tetrahydrofuran
	UV	Ultra violet
10	Vis	visible

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

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

Eluents: A: acetonitrile; B: H₂O + 0.5% TFA. Gradient: 90% B → 5% B over 2
15 min. Flow: 1 mL/min. Detection: UV/Vis + MS.

Preparative: Zorbax SB Aqua column, 20 x 500 mm from Agilent Technologies.

Eluent: A: Acetonitrile; B: H₂O + 0.05% ammonium hydroxide (25% aq.).
Gradient: 80% B → 10% B over 6 min. Flow: 40 mL/min. Detection: UV + MS,
or UV + ELSD.

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

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

25 All t_R are given in min.

General procedures

General procedure A for amide coupling

The acid of type F (0.05 mmol) in CH₂Cl₂ (2.0 mL) was treated with the desired
30 amine (3.0 eq.) followed by DIPEA (4.0 eq.), DMAP (0.25 eq.), HOBt (1.2 eq.)
and EDC·HCl (2.5 eq.). The reaction mixture was then stirred for 48 h at rt. The

mixture was then filtered through Isolute® preactivated with aq. 1M HCl and eluted with CH₂Cl₂, concentrated, and used further without purification.

General procedure B for Boc-deprotection

- 5 A sol. of the desired Boc-protected amine of type G (0.05 mmol) in CH₂Cl₂ (1.0 mL) was treated with 4.0M HCl/dioxane (1.0 mL) and the mixture was stirred for 2 h at 0 °C. The sol. was then concentrated and purified by preparative HPLC followed by treatment with 1.0M HCl (0.1 mmol) to give the hydrochloride salt.

10 **Preparation of cyclopropyl-(2-methoxy-3-methylpyridin-4-ylmethyl)amine**

a) 2-Chloro-3,*N*-dimethyl-*N*-phenylisonicotinamide

- To the sol. of 2-chloro-*N*-phenylisonicotinamide (Epszajn, J.; Bieniek, A.; Plotka, M. W.; Suwald, K., *Tetrahedron*, **1989**, 45, 7469, 139.8 g, 601 mmol) in THF (1 L) was added at –78 °C BuLi (1.6 M in hexane, 826 mL, 1321 mmol) over 2 h, while the temperature of the reaction mixture was kept below –65 °C. The mixture was then stirred for 30 min at this temperature. Methyl iodide (123 mL, 1.98 mol) was added and the mixture was stirred for 1 h at –78 °C. The mixture was allowed to warm up slowly to 33 °C and was stirred at this temperature for 30 min. Water (300 mL) was added dropwise, then aq. 10% NH₄OH (300 mL) was added, and the mixture was extracted with Et₂O (3 x 300 mL). The combined org. phases were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the product as a pale yellow amorphous material (124.92 g, 80%).

b) 2-Chloro-3-methylpyridine-4-carbaldehyde

- 25 To a sol. of 2-chloro-3,*N*-dimethyl-*N*-phenylisonicotinamide (124.9 g, 479 mmol) in CH₂Cl₂ (1300 mL) was added at –78 °C DIBAL (1M in THF, 719 mL, 719 mmol) over 1 h, and the mixture was stirred for 2 h at this temperature. DIBAL (1M in THF, 281 mL, 281 mmol) was added again, and the reaction mixture was stirred at –60 °C for 30 min. Aq. sat. potassium sodium tartrate (500 mL) was added over 30 min, the cooling bath was removed, and the mixture was stirred overnight at rt. Water was added (100 mL), the org. phase was separated, and the

water phase was extracted with CH_2Cl_2 (2x100 mL). The combined org. phases were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the product (58.35 g, 78%) as pale yellow crystals.

5 c) (2-Chloro-3-methylpyridin-4-ylmethyl)cyclopropylamine

A mixture of 2-chloro-3-methylpyridine-4-carbaldehyde (58.35 g, 375 mmol) and cyclopropylamine (52.6 mL, 750 mmol) in MeOH (800 mL) was stirred overnight at rt. The mixture was cooled to 0 °C and NaBH_4 (18.4 g, 488 mmol) was added portionwise. The mixture was stirred overnight at rt. Aq. 1M NaOH (250 mL) was
10 added and the solvents were partially removed under reduced pressure. The aq. phase was extracted with EtOAc (3x). The combined org. phases were washed with brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification by FC yielded the compound (54.56 g, 74%) as a pale yellow liquid.

15 d) Cyclopropyl-(2-methoxy-3-methylpyridin-4-ylmethyl)amine

A mixture of (2-chloro-3-methylpyridin-4-ylmethyl)cyclopropylamine (10.0 g, 50.8 mmol) and sodium methoxide (13.73g, 254 mmol) in dioxane (40 mL) was heated to reflux for 48 h. The reaction mixture was filtered through *Celite*, and the remaining solid was washed with Et_2O (2x). The solvents were removed under
20 reduced pressure. Purification by FC yielded the title compound (8.8 g, 90%) as a pale, yellow liquid.

2-(4-Bromophenoxy)ethanol

To a sol. of 4-bromophenol (40 g, 231 mmol) in EtOH (140 mL) was added
25 NaOH (10.2 g, 254 mmol). The resulting mixture was stirred at 70 °C for 30 min until the whole amount of NaOH had dissolved. A sol. of 2-bromoethanol (17.3 mL, 231 mmol) in EtOH (40 mL) was added dropwise at 70°C. The sol. rapidly turned milky. The mixture was heated to reflux overnight. The solvents were removed under reduced pressure, and the residue was dissolved in EtOAc. The
30 mixture was washed with water and brine, dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC

(EtOAc/heptane 1:5 → 1:4 → 1:3 → 1:2 → EtOAc) yielded the title compound (39.2 g, 78%) as a pale brown oil that crystallized when placed at -18 °C. R_f = 0.3 in (EtOAc/heptane 1:1).

5 **1-Bromo-4-(2-iodoethoxy)benzene**

To a sol. of 2-(4-bromophenoxy)ethanol (39.2 g, 181 mmol) in dry toluene (500 mL) was added imidazole (61.5 g, 903 mmol), PPh_3 (90 g, 343 mmol), and iodine (87.1 g, 343 mmol). This mixture was stirred at 60 °C for 2 h. The mixture was filtered over *Celite*, and the filtrate was concentrated under reduced pressure.

10 Purification of the residue by FC (EtOAc/heptane 1:5 → 1:4 → 1:3 → 1:2 → 1:1) yielded the title compound (39.9 g, 67%).

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

In a 500-mL 3-necked flask equipped with a mechanical stirrer and a reflux
15 condenser were mixed 1-bromo-4-(2-iodoethoxy)benzene (39.9 g, 122 mmol) and 2,6-dichloro-*p*-cresol (21.6 g, 122 mmol) in dry acetone (1200 mL). To this mixture was added K_2CO_3 (16.86 g, 122 mmol), and the resulting suspension was heated to reflux for 20 h. The reaction mixture was concentrated under reduced pressure, the residue was dissolved in EtOAc and this org. phase was washed with
20 water (2x), and with brine (1x). The org. layer was dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification of the residue by a short FC (EtOAc/heptane 1:9) yielded the title compound (44.4 g, 96%).

Preparation of intermediates

25 **9-Methyl-3,9-diazabicyclo[3.3.1]nonan-7-one hydrochloride (A1)**

9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3,6-dicarboxylic acid 3-*tert*-butyl ester 6-ethyl ester (WO 03/093267, 1.50 g, 4.60 mmol) was dissolved in aq. 6.0M HCl (8.0 mL) and the solution was heated to reflux for 2 days. The suspension was concentrated to give 1.40 g of a brown solid which was used for the next step
30 without further purification. LC-MS: R_t = 0.12 min, ES+: 155.18.

9-Methyl-7-oxo-3,9-diazabicyclo[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (A2)

Compound A1 (4.80 g, 31.13 mmol) was dissolved in EtOH (62 mL) and the pH of the solution was adjusted to 12 using Et₃N. A solution of Boc₂O (7.63 g, 34.24 mmol) in EtOH (15 mL) was then added and the reaction was stirred for 1 h at rt. The suspension was then concentrated and the residue purified by FC on silica gel (95:5 CH₂Cl₂:MeOH) to give the title compound (5.89 g, 74%, 2 steps) as a solid. LC-MS: R_t = 0.51 min, ES⁺: 296.20.

3-Oxo-9-azabicyclo[3.3.1]nonane-9-carboxylic acid *tert*-butyl ester (A')

A sol. of the hydrochloride salt of 9-methyl-9-azabicyclo[3.3.1]nonan-3-one (35.82 g, 188.8 mmol) in MeOH (300 mL) was treated with Et₃N (34.2 mL, 245.5 mmol) and the mixture was stirred at rt for 15 min. The solvent was then removed under reduced pressure. The resulting material was triturated in Et₂O, filtrated and the mother liquor was concentrated to dryness. This procedure was repeated three times. A sol. of the resulting solid in 1,2-dichloroethane (400 mL) was prepared, and 1-chloroethyl chloroformate (38.0 mL, 349 mmol) was added. The resulting sol. was stirred at reflux for 2 h, cooled to rt and concentrated to dryness under reduced pressure. A sol. of the resulting oil in MeOH (900 mL) was stirred at reflux for 1 h, and concentrated under reduced pressure. The resulting material was triturated in toluene and concentrated under reduced pressure. This procedure was repeated twice. A sol. of the resulting solid in dioxane (225 mL) and aq. 1M KOH (225 mL) was treated at rt with Boc₂O (49.1 g, 225 mmol), and the mixture was stirred overnight at rt. The resulting sol. was extracted with Et₂O (5x), and the combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Cyclohexane (45 mL) was then added, and the mixture was stirred for 20 min at 0 °C, filtrated, and the filtrate was dried under reduced pressure to yield the title compound as a white powder (32.4 g, 72%). LC-MS: t_R = 0.86 min; ES⁺: 281.29.

(rac.)-(1*R, 5*S**, 6*S**)-6-Methoxycarbonylmethyl-9-methyl-7-oxo-3,9-diazabicyclo-[3.3.1]nonane-3-carboxylic acid *tert*-butyl ester (B)**

Compound A2 (3.26 g, 12.82 mmol) in dry THF (50 mL) at -78 °C was treated with LiHMDS (12.82 mL of a 1.0 M THF solution, 12.82 mmol). The mixture was stirred for 1 h at -78 °C and then methyl bromoacetate (1.30 mL, 14.10 mmol) was added. The mixture was stirred overnight at -78 °C. MeOH (10 mL) was then carefully added and the mixture was allowed to warm to rt and concentrated. The residue was purified by FC on silica gel (95:5 CH₂Cl₂:MeOH) to give recovered compound A2 (1.22 g, 4.79 mmol) and the title compound (1.60 g, 38%). LC-MS: R_t = 0.61 min, ES⁺: 368.24.

Mixture of (rac.)-(1*R, 2*R**, 5*S**)-2-methoxycarbonylmethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-carboxylic acid *tert*-butyl ester and (rac.)-(1*R**, 5*S**, 2*S**)-2-methoxycarbonylmethyl-3-oxo-9-azabicyclo[3.3.1]nonane-9-**

carboxylic acid *tert*-butyl ester (B')

A sol. of compound A' (3.80 g, 15.7 mmol) in THF (50 mL) at -78 °C was treated with LDA (15.7 mL of a 1.0M THF sol., 15.7 mmol), and the mixture was stirred for 1 h at -78 °C. Methyl bromoacetate (1.60 mL, 17.3 mmol) was added, and the mixture was then allowed to warm slowly to rt overnight. MeOH (4.4 mL) was then added, and the mixture was concentrated under reduced pressure. The residue was dissolved in CH₂Cl₂, washed twice with water, the org. phase was dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 40:60) yielded the title compounds as a mixture of diastereomers (1.03 g, 21%). LC-MS: t_R = 0.90 min and 0.92min; ES⁺: 312.27.

(rac.)-(1*R, 5*S**, 8*R**)-8-Methoxycarbonylmethyl-9-methyl-7-trifluoromethanesulfonyloxy-3,9-diazabicyclo[3.3.1]non-6-ene-3-carboxylic acid *tert*-butyl ester (C)**

Compound B (0.52 g, 1.59 mmol) in dry THF (8.0 mL) at -78 °C was treated with NaHMDS (0.92 mL of a 2.0M THF solution, 1.83 mmol). The mixture was stirred

for 1 h at -78°C and then a solution of Ti_2NPh (0.64 g, 1.75 mmol) in THF (3.5 mL) was added dropwise and the mixture was stirred for 2 h at -78°C . MeOH (1.0 mL) was then carefully added and the mixture was allowed to warm to rt and concentrated. The residue was purified by FC on silica gel (98:2 CH_2Cl_2 :MeOH) to give the title compound (0.43 g, 59%). LC-MS: $R_t = 0.82$ min, ES+: 459.11.

Mixture of (*rac.*)-(1*R**, 2*R**, 5*S**)-2-methoxycarbonylmethyl-3-trifluoromethanesulfonyloxy-9-azabicyclo[3.3.1]nonane-9-carboxylic acid *tert*-butyl ester and (*rac.*)-(1*R**, 5*S**, 2*S**)-2-methoxycarbonylmethyl-3-trifluoromethanesulfonyloxy-9-azabicyclo[3.3.1]nonane-9-carboxylic acid *tert*-butyl ester (C')

A sol. of compound B' (1.03 g, 3.30 mmol) in dry THF (15.0 mL) at -78°C was treated with NaHMDS (1.9 mL of a 2.0M THF sol., 3.8 mmol). The mixture was stirred for 1 h at -78°C , and a sol. of Ti_2NPh (1.30 g, 3.63 mmol) in THF (7.0 mL) was added dropwise. The mixture was allowed to warm to rt. MeOH (2.0 mL) was then carefully added and the mixture was diluted with Et_2O , washed with brine, the org. phase was dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 50:50) yielded the title compounds as a mixture of diastereomers (0.9 g, 61%). LC-MS: $t_R = 1.10$ min; ES+: 444.30.

(*rac.*)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(*tert*-Butyldimethylsilyloxy)propyl]phenyl}-8-methoxycarbonylmethyl-9-methyl-3,9-diazabicyclo[3.3.1]non-6-ene-3-carboxylic acid *tert*-butyl ester (D)

[3-(4-Bromophenyl)propoxy]-*tert*-butyldimethylsilane (WO 03/093267, 0.78 g, 2.36 mmol) in dry THF (8.0 mL) at -78°C was treated with BuLi (1.65 mL of a 1.6M hexane sol., 2.64 mmol). The mixture was stirred for 1 h at -78°C , then ZnCl_2 (2.90 mL of a 1.0M THF sol., 2.90 mmol) was added, and the cooling bath was removed. After 1.5 h, a sol. of compound C (0.43 g, 0.94 mmol) in dry THF (4.0 mL) was added, followed by $\text{Pd}(\text{PPh}_3)_4$ (0.05 g, 0.05 mmol), and the mixture was warmed to 50°C for 45 min. The sol. was allowed to cool to rt, and was

diluted with EtOAc. Aq. sat. NH_4Cl was added. The aq. layer was extracted with EtOAc and the combined org. extracts were dried over MgSO_4 , filtered, and concentrated. The residue was purified by FC on silica gel (95:5 CH_2Cl_2 :MeOH) to give the title compound (0.38 g, 72%). LC-MS: $R_t = 1.00$ min, ES+: 559.25.

5

(rac.)-(1*R, 5*S**, 8*S**)-7-[4-(3-Hydroxypropyl)phenyl]-8-methoxycarbonylmethyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (E)**

Compound **D** (0.38 g, 0.68 mmol) in 1,2-dichloroethane (7.0 mL) at rt was treated with NaHCO_3 (0.57 g, 6.82 mmol) followed by 1-chlorethyl chloroformate (0.74 mL, 6.82 mmol). After 30 min at reflux, the mixture was concentrated. The residue was dissolved in MeOH (5.0 mL), stirred for 15 min at rt, and then heated for 30 min at 75 °C. The mixture was then concentrated to dryness. The residue was dissolved in CH_2Cl_2 (7.0 mL), DIPEA (0.58 mL, 3.41 mmol) was added, and the mixture was cooled to 0 °C. Boc_2O (0.45 g, 2.05 mmol) in CH_2Cl_2 (2.5 mL) was added and the mixture was stirred overnight at rt. The sol. was diluted with CH_2Cl_2 and washed twice with aq. 1.0M HCl and twice with brine. The org. layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by FC on silica gel (90:10 CH_2Cl_2 :MeOH) to give the title compound (0.26 g, 71%). LC-MS: $R_t = 1.03$ min, ES+: 531.07.

20

(rac.)-(1*R, 5*S**, 8*S**)-7-[4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl]-8-methoxycarbonylmethyl-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F1)**

Compound **E** (0.26 g, 0.48 mmol) in dry THF (4.0 mL) was treated with 2-chloro-3,6-difluorophenol (0.16 g, 0.96 mmol), azodicarboxylic dipiperidide (0.18 g, 0.72 mmol) and PBU_3 (0.29 g, 1.45 mmol). The mixture was then heated overnight at 50 °C. The sol. was diluted with EtOAc and the org. layer was washed twice with aq. 1.0M NaOH, and brine. The org. layer was dried over MgSO_4 , filtered, and concentrated. The residue was purified by FC on silica gel (40:60 EtOAc/heptane) to give the title compound (0.30 g, 92%). LC-MS: $R_t = 1.22$ min, ES+: 677.47.

30

(rac.)-(1*R, 5*S**, 8*S**)-8-Carboxymethyl-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (F2)**

5 Compound F1 (0.24 g, 0.35 mmol) in MeOH (3.5 mL) was treated with aq. 1.0M NaOH (3.5 mL) and the mixture was stirred at 70 °C for 5 h. The resulting sol. was partitioned between TBME (25 mL) and a 1:1 mixture of aq. 1.0M HCl and brine (25 mL). The org. layer was washed with brine and the aq. layer was extracted back twice with TBME. The combined org. extracts were dried on
10 MgSO₄, filtered, and concentrated to give the title compound (0.23 g, 98%) which was used for the next step without further purification. LC-MS: R_t = 1.15 min, ES+: 663.06.

Mixture of (rac.)-(1*R, 4*R**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-4-methoxycarbonylmethyl-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester and (rac.)-(1*R**, 4*S**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-4-methoxycarbonylmethyl-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F1')**

A sol. of 1-bromo-4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]benzene (1.06 g; 2.82 mmol) in THF (10.8 mL) at -78 °C was treated dropwise over 5 min with BuLi (1.6M in hexane, 1.98 mL, 3.16 mmol). After completion of the addition, the resulting sol. was stirred at -78 °C for 1 h. ZnCl₂ (3.5 mL of a 1.0M THF sol., 3.5 mmol) was added dropwise over 5 min, and the reaction mixture was allowed to warm up to rt, and stirred for 1.5 h. A sol. of compound C' (500 mg, 2.5
25 1.13 mmol) in THF (5.5 mL) was added, followed by Pd(PPh₃)₄ (65 mg, 0.06 mmol). The resulting sol. was stirred at 50 °C for 2 h. The reaction mixture was cooled to rt, and EtOAc (25 mL) was added. The mixture was then poured in aq. sat. NH₄Cl (25 mL). The phases were shaken, separated, and the aq. phase was extracted with EtOAc (2 x 25 mL). The combined org. phases were dried over
30 MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/heptane 15:85) yielded the title

compounds as a mixture of diastereoisomers, contaminated with 4-[2-(2,6-dichloro-4-methyl-phenoxy)-ethoxy]-benzene (1.12 g). LC-MS: t_R = 1.23 min; ES+: 590.38.

5 Mixture of (*rac.*)-(1*R**, 4*R**, 5*S**)-4-carboxymethyl-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester and (*rac.*)-(1*R**, 4*S**, 5*S**)-4-carboxymethyl-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F2')

10 A solution of compound F1' (1.12 g, contaminated with 4-[2-(2,6-dichloro-4-methyl-phenoxy)ethoxy]benzene) in MeOH (15.0 mL) and aq. 1M NaOH (9.0 mL) was heated at 80 °C for 2.5 h. The reaction mixture was then allowed to cool to rt, and the solvents were removed under reduced pressure. Water and Et₂O were added, and the aq. phase was washed with Et₂O (2x). The pH of the aq. phase was
15 adjusted to 2 with aq. 2M HCl, and the mixture was extracted with Et₂O (2x). The combined org. phases were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure to yield the title compounds as a mixture of diastereomers (374 mg, 58% over two steps). LC-MS: t_R = 1.15 min; ES+: 576.37.

20

(*rac.*)-(1*R**, 5*S**, 8*S**)-8-[[2-(2-Chlorobenzyl)-cyclopropylcarbamoyl]methyl]-7-{4-[3-(2-chloro-3,6-difluorophenoxy)-propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G1)

Prepared according to general procedure A with compound F2 and (2-chloro-
25 benzyl)cyclopropylamine (WO 03/093267). LC-MS: R_t = 1.27 min, ES+: 826.18.

(*rac.*)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)propyl]-phenyl}-8-[[cyclopropyl-(2-fluoro-5-methoxybenzyl)-carbamoyl]methyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G2):

Prepared according to general procedure A with compound **F2** and cyclopropyl-(2-fluoro-5-methoxybenzyl)amine (WO 03/093267). LC-MS: R_t = 1.26 min, ES+: 840.22.

- 5 (rac.)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)propyl]-phenyl}-8-[[cyclopropyl-(3-methoxy-2-methylbenzyl)-carbamoyl]methyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (**G3**)

Prepared according to general procedure A with compound **F2** and cyclopropyl-(3-methoxy-2-methylbenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*,
10 1989, 54, 3730 and cyclopropylamine). LC-MS: R_t = 1.27 min, ES+: 836.23.

- (rac.)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)-propyl]-phenyl}-8-[[cyclopropyl-(2-methoxy-3-methyl-pyridin-4-yl-methyl)-
15 carbamoyl]methyl]-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (**G4**)

Prepared according to general procedure A with compound **F2** and cyclopropyl-(2-methoxy-3-methylpyridin-4-ylmethyl)amine. LC-MS: R_t = 1.26 min, ES+: 837.24.

20

- Mixture of (rac.)-(1*R**, 4*R**, 5*S**)-4-[[cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]methyl]-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]-phenyl}-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester and
(rac.)-(1*R**, 4*S**, 5*S**)-4-[[cyclopropyl-(3-methoxy-2-methylbenzyl)-
25 carbamoyl]methyl]-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (**G5**)

A solution of compound **F2'** (55.0 mg, 0.096 mmol) in CH₂Cl₂ (1.0 mL) was treated with DMAP (2.9 mg, 0.024 mmol), HOBt (15.5 mg, 0.12 mmol), EDC·HCl (45.7 mg, 0.24 mmol), and DIPEA (0.07 mL, 0.038 mmol). After 30
30 min at rt, cyclopropyl-(3-methoxy-2-methylbenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D.,

J. Org. Chem., 1989, 54, 3730 and cyclopropylamine, 54.7 mg, 0.29 mmol) was added and the mixture was stirred for 2 h at rt. The reaction was then concentrated under reduced pressure. Purification of the residue by HPLC yielded the title compounds as a mixture of diastereomers (32.0 mg, 45%). LC-MS: t_R =
5 1.28 min; ES+: 749.49.

(rac.)-(1*R, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-[[cyclopropyl-(3-methoxybenzyl)carbamoyl]-methyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G6)**

10 Prepared according to general procedure A with compound F2 and cyclopropyl-(3-methoxybenzyl)amine. LC-MS: R_t = 1.26 min, ES+: 862.63.

(rac.)-(1*R, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-[[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]methyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G7)**

15 Prepared according to general procedure A with compound F2 and (2,3-dichlorobenzyl)cyclopropylamine. LC-MS: R_t = 1.30 min, ES+: 860.52.

(rac.)-(1*R, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-8-[[cyclopropyl-(2,3-dimethylbenzyl)carbamoyl]methyl]-3,9-diaza-bicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G8)**

20 Prepared according to general procedure A with compound F2 and cyclopropyl-(2,3-dimethylbenzyl)amine (WO 2003093267). LC-MS: R_t = 1.28 min, ES+: 820.61.

25

(rac.)-(1*R, 5*S**, 8*S**)-8-[(Benzylmethylcarbamoyl)methyl]-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G9)**

30 Prepared according to general procedure A with compound F2 and benzylmethylamine. LC-MS: R_t = 1.24 min, ES+: 766.57.

(*rac.*)-(1*R**, 5*S**, 8*S**)-8-{[(2-Chlorobenzyl)ethylcarbamoyl]methyl}-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G10)

Prepared according to general procedure A with compound F2 and (2-chlorobenzyl)ethylamine (WO 2003093267). LC-MS: R_t = 1.27 min, ES+: 814.55.

(*rac.*)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-{[cyclopropyl-(3,5-dimethoxybenzyl)carbamoyl]methyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G11)

Prepared according to general procedure A with compound F2 and cyclopropyl-(2,5-dimethoxybenzyl)amine (WO 2003093267). LC-MS: R_t = 1.26 min, ES+: 852.67.

(*rac.*)-(1*R**, 5*S**, 8*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-8-{[cyclopropyl-(3,4-dimethoxybenzyl)carbamoyl]methyl}-3,9-diazabicyclo[3.3.1]non-6-ene-3,9-dicarboxylic acid di-*tert*-butyl ester (G12)

Prepared according to general procedure A with compound F2 and cyclopropyl-(3,4-dimethoxybenzyl)amine (WO 2003093267). LC-MS: R_t = 1.25 min, ES+: 852.64.

Examples

Example 1

(*rac.*)-*N*-(2-Chlorobenzyl)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropylacetamide

Prepared according to general procedure B from compound G1. LC-MS: R_t = 0.85 min, ES+: 626.43.

Example 2

(rac.)-(2-((1*R, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclo-propyl-*N*-(2-fluoro-5-methoxybenzyl)acetamide**

Prepared according to general procedure B from compound G2. LC-MS: R_t = 0.84 min, ES+: 640.53.

Example 3

(rac.)-(2-((1*R, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluoro-phenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxy-2-methylbenzyl)acetamide hydrochloride**

Prepared according to general procedure B compound G3. LC-MS: R_t = 0.84 min, ES+: 636.52.

Example 4

(rac.)-(2-((1*R, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclo-propyl-*N*-(2-methoxy-3-methylpyridin-4-ylmethyl)acetamide hydrochloride**

Prepared according to general procedure B from compound G4. LC-MS: R_t = 0.82 min, ES+: 637.52.

Example 5

Mixture of (rac.)-*N*-cyclopropyl-2-((1*R, 2*R**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-3-en-2-yl)-*N*-(3-methoxy-2-methylbenzyl)acetamide and (rac.)-*N*-Cyclopropyl-2-((1*R**, 2*S**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-aza-bicyclo[3.3.1]non-3-en-2-yl)-*N*-(3-methoxy-2-methyl-benzyl)acetamide**

A sol. of compound G5 (32.0 mg, 0.04 mmol) in CH₂Cl₂ (1.0 mL) at 0 °C was treated with HCl (1.0 mL of 4.0M dioxane sol., 4.0 mmol), and the mixture was stirred for 1 h at rt. The solvents were removed under reduced pressure. Purification of the residue by HPLC yielded the title compounds as a mixture of diastereomers (17.3 mg, 62%). LC-MS: t_R = 1.03 min; ES+: 649.42.

Example 6

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxy-
5 benzyl)acetamide

Prepared according to general procedure B compound G6. LC-MS: R_t = 0.83 min, ES+: 622.33.

Example 7

10 (*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dichloro-benzyl)acetamide

Prepared according to general procedure B compound G7. LC-MS: R_t = 0.86 min, ES+: 662.20.

15

Example 8

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dimethyl-benzyl)acetamide

20 Prepared according to general procedure B compound G8. LC-MS: R_t = 0.85 min, ES+: 620.34.

Example 9

25 (*rac.*)-*N*-Benzyl-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)-propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-methylacetamide

Prepared according to general procedure B compound G9. LC-MS: R_t = 0.81 min, ES+: 566.30.

Example 10

(*rac.*)-*N*-(2-Chlorobenzyl)-2-((*1R**, *5S**, *6R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-ethyl-acetamide

Prepared according to general procedure B compound G10. LC-MS: R_t = 0.84 min, ES+: 614.27.

Example 11

(*rac.*)-2-((*1R**, *5S**, *6R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,5-dimethoxy-benzyl)acetamide

Prepared according to general procedure B compound G11. LC-MS: R_t = 0.83 min, ES+: 652.31.

Example 12

(*rac.*)-2-((*1R**, *5S**, *6R**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,4-dimethoxy-benzyl)acetamide

Prepared according to general procedure B compound G12. LC-MS: R_t = 0.81 min, ES+: 652.31.

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 μm (Nalgene, Cat. No. 194-2545). The conjugate can be stored in polypropylene tubes in 0.05% sodium azide at 4 °C for at least 12 months.

1.2 Preparation of BSA-AngI coated MTP

5 Microtiter plates (MPT384, MaxiSorp™, Nunc) were incubated overnight at 4 °C with 80 μl of AngI (1-10)/BSA conjugate, diluted 1:100'000 in PBS 1X in a teflon beaker (exact dilution dependent on batch of conjugate), emptied, filled with 90 μl of blocking solution [0.5% BSA (Sigma A-2153) in PBS 1X, 0.02% NaN_3], and incubated for at least 2 h at rt, or overnight at 4 °C. 96 well MTP
10 (MaxiSorp™, Nunc) were coated with 200 μl conjugate and blocked with 250 μl blocking solution as above, except that the blocking solution contained 3% BSA. The plates can be stored in blocking solution at 4 °C for 1 month.

1.3 AngI-EIA in 384 well MTP

15 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
20 primary antibody solution and the plates were incubated overnight at 4 °C. After the incubation the plates were washed 3 times with wash buffer and incubated with secondary antibody [anti-rabbit IgG, linked to horseradish peroxidase (Amersham Bioscience, NA 934V), diluted 1:2'000 in wash buffer] for 2 h at rt. The plates were washed 3 times with wash buffer and then incubated for 1 h at rt
25 with substrate solution [1.89mM ABTS (2,2'-azino-di-(3-ethyl-benzthiazolinsulfonate)] (Roche Diagnostics, 102 946) and 2.36mM H_2O_2 [30%, (Fluka, 95300)] in substrate buffer (0.1M sodium acetate, 0.05M sodium dihydrogen phosphate, pH 4.2). The OD of the plate was read at 405 nm in a microplate reader (FLUOStar Optima from BMG). The production of AngI during
30 the renin reaction was quantified by comparing the OD of the sample with the OD of a standard curve of AngI(1-10), measured in parallel.

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

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, 5 recombinant human renin is incubated with its substrate (commercial human tetradecapeptide renin substrate) to create the product Angiotensin I (AngI). In the second step, the accumulated AngI is measured by an immunological assay (enzyme immuno assay, EIA). The detailed description of this assay is found below. The EIA is very sensitive and well suited for renin activity measurements 10 in buffer or in plasma. Due to the low concentration of renin used in this assay (2 fmol per assay tube or 10 pM) it is possible to measure inhibitor affinities in this primary assay down to low pM concentration.

2.1 Methodology

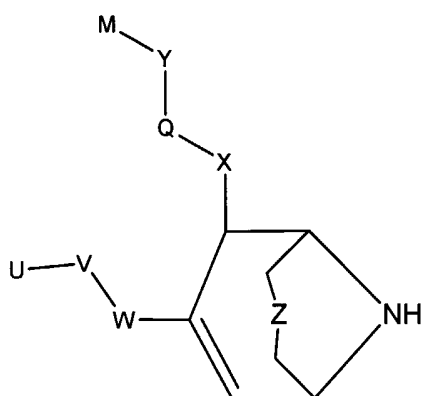
15 Recombinant human renin (3 pg/μl) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μM in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H₂O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 μl per well of this premix was transferred into polypropylene plates (MTP384, Nunc). Test 20 compounds were dissolved and diluted in 100% DMSO and 2.5 μl added to the premix, then incubated at 37 °C for 3 h. At the end of the incubation period, 5 μl of the renin reaction (or standards in assay buffer) were transferred into EIA assays (as described above) and AngI produced by renin was quantified. The percentage of renin inhibition (AngI decrease) was calculated for each 25 concentration of compound and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC₅₀). The IC₅₀-values of all compounds tested are below 100 nM. However, selected compounds exhibit a very good bioavailability and are metabolically more stable than prior art compounds.

Examples of inhibition:

Compound of Example No.	IC₅₀ values [nM]
1	1.4
2	15
3	8.6
7	33
8	23
11	42

Claims

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



(I)

5

wherein

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

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

V represents oxy-alkylene or oxy-alkylene-oxy;

- 10 U represents unsubstituted aryl; or mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are independently selected from halogen, -CF₃, -OCF₃, -CH₂OH and alkyl;

X and Y independently represent a bond or alkylene, preferably alkylene;

Q represents -CO-N(R¹)-;

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from alkyl, alkoxy, $-\text{OCF}_3$, $-\text{CF}_3$, hydroxy-alkyl, halogen, alkyl-O-(CH₂)₀₋₄-CH₂-, alkyl-O-(CH₂)₂₋₄-O-, and R⁴N-(CH₂)₀₋₄-CH₂-; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from halogen, alkyl, $-\text{OCF}_3$, $-\text{CF}_3$ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring;

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

R¹ and R^{1'} independently represent alkyl or cycloalkyl;

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

R³ represents alkyl, cycloalkyl, or cycloalkyl-alkyl, wherein these groups may be unsubstituted or mono-, di- or tri-substituted, wherein the substituents are independently selected from hydroxy, $-\text{NH}_2$, $-\text{OCOR}^2$, $-\text{COOR}^2$, $-\text{SO}_3\text{H}$, $-\text{SO}_2\text{CH}_3$, alkoxy, cyano, $-\text{CONR}^2\text{R}^{2'}$, $-\text{NH}(\text{NH})\text{NH}_2$, $-\text{NR}^1\text{R}^{1'}$, tetrazolyl, and alkyl, with the proviso that a carbon atom is attached at the most to one heteroatom in case this carbon atom is sp³-hybridized;

R⁴ represents hydrogen, alkyl, cyclopropyl, or $-\text{C}(=\text{O})-\text{R}'$ wherein R' is C₁-C₄-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, and morphological forms.

2. A compound according to claim 1, wherein

Z represents $-\text{NH}-$; and

M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from alkyl, alkoxy, $-\text{OCF}_3$, $-\text{CF}_3$, hydroxy-alkyl, and

halogen; or mono- or di-substituted pyridinyl, wherein the substituents are independently selected from halogen, alkyl, -OCF₃, -CF₃ and alkoxy; with the proviso, that the halogen substituents are not in 2- or 6-position of the pyridinyl ring.

5

3. A compound according to claim 1 or 2, wherein M represents phenyl di-substituted independently with fluorine, chlorine, methyl or methoxy.

4. A compound according to claim 1 or 2, wherein M represents phenyl di-substituted with methyl and methoxy or fluorine and methoxy or mono-substituted with chlorine.

10

5. A compound according to claim 1 or 2, wherein M represents pyridinyl di-substituted with methyl and methoxy.

15

6. A compound according to claim 5, wherein M represents pyridinyl substituted in 2-position by methoxy and in 3-position by methyl.

7. A compound according to any one of claims 1 to 6, wherein X represents methylene.

20

8. A compound according to any one of claims 1 to 7, wherein Y represents methylene.

9. A compound according to any one of claims 1 to 8, wherein Q represents -CO-N(R¹)-, wherein R¹ represents cyclopropyl.

25

10. A compound according to any one of claims 1 to 8, wherein Q represents -CO-N(R¹)-, wherein R¹ represents alkyl.

30

11. A compound according to any one of claims 1 to 10, wherein U represents phenyl tri-substituted independently by fluorine, chlorine, and methyl.
12. A compound according to any one of claims 1 to 11, wherein V represents
 5 -O-CH₂-CH₂-CH₂- or -O-CH₂-CH₂-O-.
13. A compound according to claim 1, wherein
 Z represents -NH- or -CH₂-;
 V represents oxy-alkylene or oxy-alkylene-oxy;
 10 U represents tri-substituted phenyl, wherein the substituents are independently selected from alkyl and halogen;
 X and Y independently represent alkylene; and
 M represents phenyl; mono- or di-substituted phenyl, wherein the substituents are independently selected from alkyl, alkoxy and halogen; or di-substituted
 15 pyridinyl, wherein the substituents are independently selected from alkyl and alkoxy.
14. A compound according to claim 1 selected from the group consisting of:
- (*rac.*)-*N*-(2-chlorobenzyl)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluoro-
 20 phenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-
 acetamide;
- (*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-
 3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2-fluoro-5-methoxy-
 benzyl)acetamide;
- 25 (*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-
 3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxy-2-methyl-
 benzyl)acetamide, and

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2-methoxy-3-methylpyridin-4-ylmethyl)acetamide.

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

a mixture of (*rac.*)-*N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)-2-((1*R**, 2*R**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-azabicyclo[3.3.1]non-3-en-2-yl)acetamide and (*rac.*)-*N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)-2-((1*R**, 2*S**, 5*S**)-3-{4-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]phenyl}-9-aza-

10 bicyclo[3.3.1]non-3-en-2-yl)acetamide,

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3-methoxybenzyl)acetamide,

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dichlorobenzyl)acetamide,

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(2,3-dimethylbenzyl)acetamide,

20 (*rac.*)-*N*-benzyl-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-methylacetamide,

(*rac.*)-*N*-(2-chlorobenzyl)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-ethylacetamide,

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,5-dimethoxybenzyl)acetamide, and

25

(*rac.*)-2-((1*R**, 5*S**, 6*R**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]-phenyl}-3,9-diazabicyclo[3.3.1]non-7-en-6-yl)-*N*-cyclopropyl-*N*-(3,4-dimethoxybenzyl)acetamide.

- 5 16. A pharmaceutical composition comprising a compound according to any one of claims 1 to 15 and a pharmaceutically acceptable carrier material.

17. A compound according to any one of claims 1 to 15, or composition according to claim 16, for use as a medicament.

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18. Use of a compound according to any one of claims 1 to 15 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
15 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,
20 lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2005/009050

A. CLASSIFICATION OF SUBJECT MATTER
C07D471/08 A61K31/439 A61P9/10

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
C07D A61K A61P

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 03/093267 A (ACTELION PHARMACEUTICALS INC.) 13 November 2003 (2003-11-13) page 1, line 5 - page 3, line 10; claims; examples	1-18
P, Y	WO 2004/096366 A (ACTELION PHARMACEUTICALS INC.) 11 November 2004 (2004-11-11) page 10, line 22 - page 12, line 7; claims; examples	1-18
P, Y	WO 2004/096803 A (ACTELION PHARMACEUTICALS INC.) 11 November 2004 (2004-11-11) page 13, line 13 - page 14, line 31; claims; examples	1-18
P, Y	WO 2004/096116 A (ACTELION PHARMACEUTICALS INC.) 11 November 2004 (2004-11-11) page 1, line 5 - page 3, line 10; claims; examples	1-18

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/009050

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WO 2004096366 A	11-11-2004	NONE	
WO 2004096803 A	11-11-2004	NONE	
WO 2004096116 A	11-11-2004	NONE	