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(54) **Title:** BICYCLIC FIVE-MEMBERED HETEROARYL DERIVATIVES AND THEIR USE AS RENIN INHIBITORS

(57) **Abstract:** The invention relates to novel five-membered heteroaryl 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 comprising one or more of those compounds and especially their use as inhibitors of renin.

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BICYCLIC FIVE-MEMEBERED HETEROARYL DERIVATIVES AND THEIR USE AS RENIN INHIBITORS

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

In the renin-angiotensin system (RAS) the biologically active angiotensin II (Ang II) is generated by a two-step mechanism. The highly specific enzyme renin cleaves angiotensinogen to angiotensin I (Ang I), which is then further processed to Ang II by the less specific angiotensin-converting enzyme (ACE). Ang II is known to work on at least two receptor subtypes called AT_1 and AT_2. Whereas AT_1 seems to transmit most of the known functions of Ang II, the role of AT_2 is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT_1 blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Birkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, **1986**, 489-519; Weber M. A., *Am. J. Hypertens.*, **1992**, *5*, 247S). In addition, ACE inhibitors are used for renal protection (Rosenberg M. E. *et al.*, *Kidney International*, **1994**, *45*, 403; Breyer J. A. *et al.*, *Kidney International*, **1994**, *45*, S156), in the prevention of congestive heart failure (Vaughan D. E. *et al.*, *Cardiovasc. Res.*, **1994**, *28*, 159; Fouad-Tarazi F. *et al.*, *Am. J. Med.*, **1988**, *84 (Suppl. 3A)*, 83) and myocardial infarction (Pfeffer M. A. *et al.*, *N. Engl. J. Med.*, **1992**, *327*, 669).

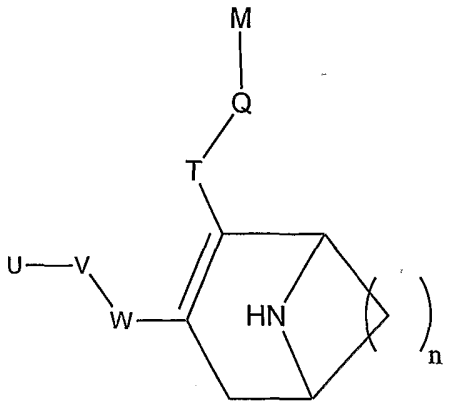
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by

renin. In contrast, ACE can also cleave bradykinin besides Ang I and can be by-passed by chymase, a serine protease (Husain A., *J. Hypertens.*, **1993**, *11*, 1155). In patients inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, **1992**, *117*, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT_1 receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT_2) to Ang II, whose concentration is significantly increased by the blockade of AT_1 receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT_1 blockers with regard to efficacy in blocking the RAS and in safety aspects.

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

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

The present invention relates to novel five-membered heteroaryl compounds of the formula (I)



(I)

wherein

W represents a five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, said heteroaryl being optionally substituted by alkyl;

V represents $-CH_2CH_2-O-$, $-CH_2CH_2CH_2-O-$, $-O-CH_2CH_2-O-$, $-O-CH_2CH_2CH_2-O-$, $-CH_2-O-CH_2CH_2-O-$, $-O-CH_2CH_2-O-CH_2-$, or $-O-CH_2CH_2CH_2-O-CH_2-$;

U represents unsubstituted aryl; mono-, di-, tri or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-CF_3$, $-OCF_3$, halogen and hydroxy-alkyl; unsubstituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S; or mono-, di- or tri-substituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-CF_3$, $-OCF_3$ and halogen;

T represents $-CONR^1-$ or $-CH_2CONR^1-$;

Q represents methylene;

M represents unsubstituted aryl; or mono- or di-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-OCF_3$, $-CF_3$, hydroxy-alkyl and halogen;

R^1 represents alkyl or cycloalkyl; and

n is the integer 2 or 3;

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 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.

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

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

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

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

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

The term **aryl**, alone or in combination with other groups, relates to a phenyl, naphthyl or indanyl group, preferably a phenyl group.

V in formula (I) represents -CH_2CH_2-O-, -$CH_2CH_2CH_2$-O-, -O-CH_2CH_2-O-, -O-$CH_2CH_2CH_2$-O-, -CH_2-O-CH_2CH_2-O-, -O-CH_2CH_2-O-CH_2-, or -O-$CH_2CH_2CH_2$-O-CH_2-, wherein said groups, if asymmetric, may be connected in both possible ways to the groups W and U of formula (I). In a preferred embodiment of the invention the "beginning part" of an asymmetric group V is linked to the group W of formula (I) [that means that for example the -CH_2- part of -$CH_2CH_2CH_2$-O- is linked to the group W of formula (I)].

T in formula (I) represents -$CONR^1$- or -CH_2CONR^1-. The "beginning part" of the group T is linked to the core structure (bicyclic template) of formula (I) [that means that for example the -C(=O) part of -$CONR^1$- is linked to the core structure of formula (I)]. Preferably, T represents -$CONR^1$- (wherein R^1 represents alkyl or cycloalkyl, preferably cycloalkyl, most preferably cyclopropyl).

If U in formula (I) represents an optionally substituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, then U is preferably an optionally substituted pyrazolyl or isoxazolyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, -CF_3, -OCF_3 and halogen. Examples are 5-ethyl-4-fluoroisoxazol-3-yl, 4,5-dimethylisoxazol-3-yl and 4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yl.

Salts are preferably the pharmaceutically acceptable salts of the compounds of formula (I).

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 can be separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, high performance liquid chromatography (HPLC) or crystallization.

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

The nitrosated compounds of the present invention can be prepared using conventional methods known to one skilled in the art. For example, known methods for nitrosating compounds are described in U.S. Pat. Nos. 5,380,758, 5,703,073, 5,994,294, 6,242,432 and 6,218,417; WO 98/19672; and Oae et al., Org. Prep. Proc. Int., 15(3): 165-198 (1983).

Preferred embodiments of the invention:

Preferably, W represents a thiazolyl, an oxazolyl, or an isoxazolyl ring wherein said rings are optionally substituted by alkyl. More preferably, W represents a thiazolyl ring or a methyl-substituted thiazolyl ring. In an especially preferred embodiment, W represents a thiazolyl ring, particularly a thiazolyl ring substituted by V in position 2 and attached in position 5 to the bicyclic template of formula (I).

In a preferred embodiment of the invention T represents -$CONR^1$-.

In another preferred embodiment of the invention R^1 represents a cyclopropyl group.

In another preferred embodiment of the invention M represents phenyl; or mono- or di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy and halogen.

In another especially preferred embodiment of the invention M represents 2,3-dichlorophenyl.

In another preferred embodiment of the invention V represents -$CH_2CH_2CH_2$-O-, -O-CH_2CH_2-O- or -CH_2-O-CH_2CH_2-O-.

In another preferred embodiment of the invention U represents unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, halogen and hydroxy-alkyl; unsubstituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S; or mono-, di- or tri-substituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, wherein the substituents are independently selected from the group consisting of alkyl, -CF_3 and halogen.

The present invention thus also 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 herein, such as those defined for the above-given preferred embodiments.

Another preferred embodiment of the invention relates to compounds of formula (I), wherein

W represents a thiazolyl ring, preferably substituted by V at position 2 and attached in position 5 to the bicyclic template of formula (I);

V represents $-CH_2CH_2CH_2-O-$, $-O-CH_2CH_2-O-$, or $-CH_2-O-CH_2CH_2-O-$;

U represents di-, tri or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, halogen and hydroxy-alkyl; or isoxazol-3-yl or 1H-pyrazol-3-yl, wherein these two heteroaryl radicals are di- or tri-substituted with substituents independently selected from the group consisting of alkyl, $-CF_3$, and halogen;

T represents $-CONR^1-$;

Q represents methylene;

M represents di-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, and halogen and especially represents 2,3-dichloro-phenyl or 2-methyl-3-methoxy-phenyl;

R^1 represents cyclopropyl; and

n is the integer 2 or 3.

A group of especially preferred compounds is represented by:

(*1R**, *5S**)-3-{2-[2-(2-chloro-3,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichlorophenoxy)ethoxymethyl]-thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(3-chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2-chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(4,5-dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(5-ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichlorophenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-6-fluoro-3-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)-phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)-phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R, 5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R, 5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2-chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(4,5-dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(5-ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-propyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichlorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(3-chloro-2,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-6-fluoro-3-methylphenoxy)propyl]-thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

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(*1R**, *5S**)-3-{2-[2-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichlorophenoxy)ethoxymethyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-fluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(3-chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2-chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]-non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-(2-{2-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxy-ethyl)phenoxy]-propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{2-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R*, 5S**)-3-{2-[2-(2,6-dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[2-(2-chloro-3,6-difluorophenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, and

(*1R*, 5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide.

The compounds of formula (I) are useful for the treatment and/or prophylaxis of diseases such as or related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases known to be related to the renin-angiotensin system.

The compounds of formula (I) are especially useful for the treatment and/or prophylaxis of hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac 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 or prophylaxis of diseases, which are associated with a dysregulation of the renin-angiotensin system, in particular to a method for the treatment or prophylaxis of the above-mentioned diseases, said methods comprising administering to a patient a pharmaceutically active amount of a compound of formula (I).

Compounds of formula (I) and their pharmaceutically acceptable (acid addition) salts can be used as medicaments, e.g. in the form of pharmaceutical compositions. A further aspect of the present invention therefore relates to pharmaceutical compositions comprising at least one compound of formula (I) and a pharmaceutically acceptable carrier material. These pharmaceutical compositions may be used for the treatment and/or prophylaxis of the above-mentioned diseases. The present invention further also relates to the use of a compound of formula (I) for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of the above-mentioned diseases.

The pharmaceutical compositions can be used for enteral, parenteral, or topical administration. They can be administered, for example, perorally, e.g. in the form of

tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions, rectally, e.g. in the form of suppositories, parenterally, e.g. in the form of injection solutions or infusion solutions, or topically, e.g. in the form of ointments, creams or oils.

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

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

Usual stabilizers, preservatives, wetting and emulsifying agents, consistency-improving agents, flavour-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.

Another aspect of the invention relates 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 mixed 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 antagonists, endothelin receptors antagonists, vasodilators, calcium antagonists, potassium activators, diuretics, sympatholitics, beta-adrenergic antagonists, alpha-adrenergic antagonists and/or other drugs beneficial for the prevention or the treatment of the above-mentioned diseases such as 11beta-hydroxysteroid dehydrogenase type 1 inhibitors and soluble guanylate cyclase activators.

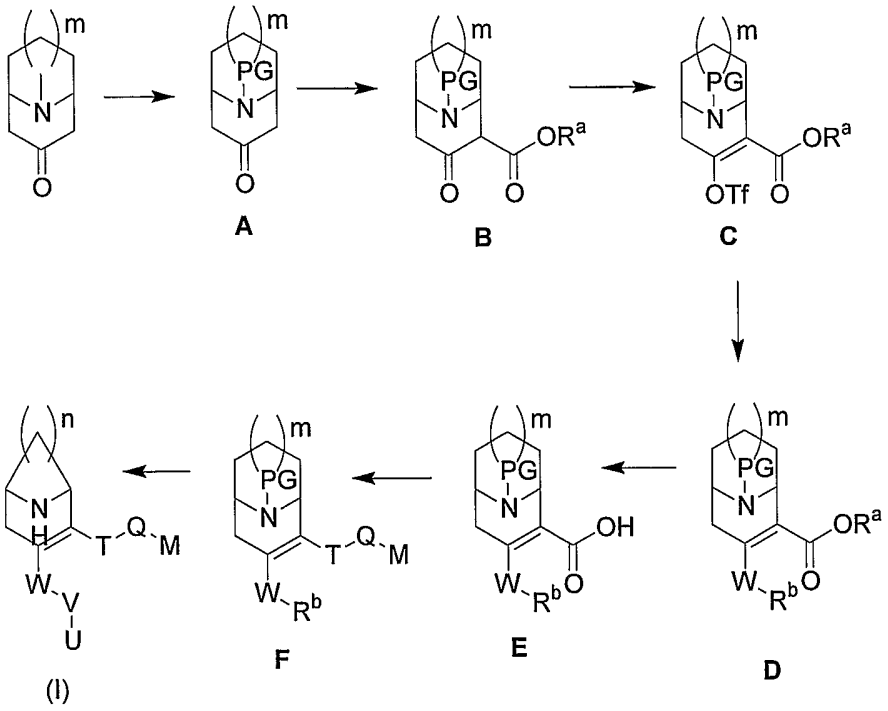
The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-drugs of the compound of formula (I), as appropriate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

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

A compound of type **A** as described in Scheme 1 can be prepared by protecting group (PG) manipulations from the commercially available pseudopelletierine (m = 1) or tropinone (m = 0). An acylation leads then to a compound of type **B**, wherein R^a stands for a standard ester substituent, like for instance methyl or benzyl. The formation of the corresponding vinylic triflate **C** occurs from **B** using standard reagents like *N*-

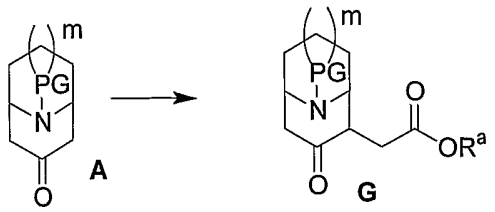
phenyl-bis(trifluoromethanesulfonimide) or *N*-(5-chloro-2-pyridyl)-bis(trifluoromethane-sulfonimide). A coupling catalyzed by a transition metal, preferentially palladium, between a compound of type **C** and a suitable thiazoyl precursor (see examples), leads to a compound of type **D**, wherein R^b stands for a substituent that can be transformed later on into the U-V chain as defined for formula (I). R^b can be modified during the synthesis. Hydrolysis of the ester following standard conditions, like saponification or hydrogenolysis, leads to a compound of type **E**. An amide coupling for instance completes the formation of the T-Q-M chain as defined for formula (I) to a compound of type **F**. Completion of the U-V chain and removal of the protecting group yield the desired compound of formula (I).

Scheme 1



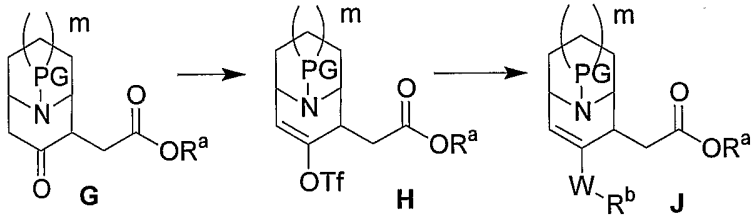
Also compound **A** (Scheme 2) can be alkylated into a compound of type **G** through the corresponding enolate and using an alkyl bromoacetate.

Scheme 2



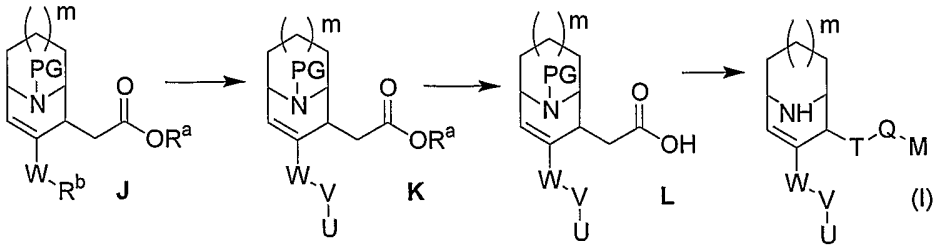
The compound of type **G** can then be transformed into a compound of type **H** (Scheme 3) using standard reagents like *N*-phenyl-bis(trifluoromethanesulfonimide) or *N*-(5-chloro-2-pyridyl)-bis(trifluoromethane-sulfonimide). A coupling catalyzed by a transition metal, preferentially palladium, between a compound of type **H** and a suitable thiazoyl precursor, leads to a compound of type **J**.

Scheme 3



A compound of type **J** can be transformed into a compound of type **K** (Scheme 4), typically using a *Mitsunobu* type reaction. A compound of type **K** can be transformed into a compound of type **L**, then an amide coupling and final removal of the protecting group leads to a desired compound of formula (I).

Scheme 4



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

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

Examples

Abbreviations (as used herein)

AcOH	Acetic acid
Ang / AngI	Angiotensin / Angiotensin I
aq.	aqueous
Boc	*tert*-Butyloxycarbonyl
BSA	Bovine serum albumine
Bu	Butyl
BuLi	*n*-Butyllithium
conc.	concentrated
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DIPEA	Diisopropylethylamine
DMAP	4-*N,N*-Dimethylaminopyridine
DMF	*N,N*-Dimethylformamide
DMSO	Dimethylsulfoxide
EDC•HCl	Ethyl-*N,N*-dimethylaminopropylcarbodiimide hydrochloride
ES	Electrospray
Et	Ethyl
EtOAc	Ethyl acetate
EtOH	Ethanol
FC	Flash Chromatography
h	hour(s)
HMDS	Hexamethyldisilyl amide
HMPA	Hexamethyl phosphoramide
HOBt	Hydroxybenzotriazol
HPLC	High Performance Liquid Chromatography
LC-MS	Liquid Chromatography – Mass Spectrometry

Me	methyl
MeOH	Methanol
min	minute(s)
MTP	Micro Titer Plates
OD	Optical Density
org.	organic
p	para
PBS	Phosphate Buffered Saline
PG	Protecting Group
Ph	phenyl
rt	room temperature
sat.	saturated
sol.	Solution
TBAF	Tetra-*n*-butylammonium fluoride
TBDMS	*tert*-Butyldimethylsilyl
Tf	Trifluoromethylsulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
TLC	Thin Layer Chromatography
t_R	Retention time

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

Analytic: Zorbax SB-AQ column, 5 µm, 4.6x50 mm; eluent A: 0.04% trifluoroacetic acid in water; eluent B: acetonitrile; gradient 5% → 100% eluent B over 1.5 min, flow 1 mL/min. The retention times (t_R) are given in minutes.

Preparative: Waters XTerra®PrepMS-C_{18} column, 5 µm, 19x50 mm; eluent A: H_2O with 0.5% of aq. 25% NH_4OH; eluent B: acetonitrile; gradient: 90% eluent B to 100% eluent A over 5 min.

Experimental Part

*Procedure (A) for the formation of an aryl ether (*Mitsunobu *reaction):*

The bicyclononene (0.10 mmol) was dissolved or suspended in toluene (1.00 mL). The phenol derivative (0.15 mmol) in toluene (0.50 mL) was added. Azodicarboxylic dipiperidide (0.30 mmol) in toluene (0.50 mL) was added, followed by PPh_3 (0.30 mmol). The reaction mixture was stirred for 2 h at rt and then 3 h at 80 °C, then overnight at rt. Water (1 mL) was added, and the mixture was shaken vigorously. The mixture was transferred to syringes containing dry diatomaceous earth (0.8 g) (Isolute Sorbent Technology, Johnson, C.R., *et al.*, Tetrahedron, 1998, *54*, 4097). The product was eluted with CH_2Cl_2 and the solvents were removed under reduced pressure. The residue was purified by HPLC.

Procedure (B) for the removal of a Boc-protecting group:

To a sol. of the above product in CH_2Cl_2 (1 mL), cooled to 0°C, was added HCl (4M in dioxane, 0.5 mL to 1.0 mL). The ice bath was removed and the sol. was stirred for 1 h to 4 h, following the reaction by LC-MS. The reaction mixture was quenched with aq. 2M NaOH (2 mL to 4 mL), and poured on a syringe containing dry diatomaceous earth (0.8g) (Isolute Sorbent Technology, Johnson, C.R., *et al.*, Tetrahedron, **1998**, *54*, 4097). The product was eluted with CH_2Cl_2 and the solvents were removed under reduced pressure. Purification of the residue by HPLC yielded the title compound.

Preparation of heterocyclic precursors:

2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]thiazole

NaH (50% suspension in oil, 2.98 g, 62.1 mmol) was suspended in hexane and washed twice. THF (20 mL) was then added followed by a solution of 2-(*tert*-butyldimethylsilanyloxy)ethanol (McDougal, P. G.; Rico, J. G.; Oh, Y. I.; Condon, B. D., *J. Org. Chem.*, **1986**, *51*, 3388, 9.49 g, 53.8 mmol) in THF (30 mL) over 30 min. The mixture was then stirred for 2 h at rt. 2-Bromothiazole (6.79 g, 41.4 mmol) was then added dropwise and the reaction mixture was then stirred at reflux for 20 h. Aq. sat. NH_4Cl was added carefully and the product 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 of the residue by FC (Et_2O/hexane 5:95) yielded the title compound (3.80 g, 35%).

3-Thiazol-2-ylprop-2-yn-1-ol

Propargylic alcohol (0.72 mL, 12.1 mmol) and 2-bromothiazole (2.00 g, 12.2 mmol) were added to a suspension of cupric acetate monohydrate (122 mg, 0.61 mmol), PPh_3 (0.32 g, 1.22 mmol) and bis(benzonitrile) dichloropalladium (58 mg, 0.512 mmol) in diisopropylamine (6 mL). The reaction mixture was heated to 45°C overnight, then partitioned between aq. sat. NH_4Cl and Et_2O. The aq. layer was extracted again with Et_2O. The combined org. layers were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (EtOAc) yielded the desired product as an orange oil (1.06 g, 62%). LC-MS: t_R = 0.55 min, ES+ = 140.15.

3-Thiazol-2-ylpropan-1-ol

10% Pd/C (0.5 g) was added to a sol. of 3-thiazol-2-yl-prop-2-yn-1-ol (2.31 g, 16.6 mmol) in EtOH (85 mL), and the mixture was subjected to an atmosphere of H_2 overnight. The reaction mixture was filtered through *Celite*, thoroughly washed with EtOH, and the solvents were removed under reduced pressure to yield the title compound as an orange oil (2.16 g, 91%) that was not purified further. LC-MS: t_R = 0.30 min, ES+ =144.14.

Thiazole-2-carbaldehyde

A sol. of 2-bromothiazole (10.00 g, 60.96 mmol) in Et_2O (43 mL) was added dropwise over 1 h to a cooled sol. (-78 °C) of BuLi (1.6M in hexane, 46 mL, 73.5 mmol). The resulting mixture was stirred at –70 °C for 20 min, then DMF (7.50 mL, 97.5 mmol) was added over 1 h, while the temperature was kept below –65 °C. The reaction mixture was allowed to reach –40 °C during 1 h, then stirred at that temperature for one additional hour. The reaction mixture was allowed to warm to 0 °C, quenched with aq. 4M HCl, and the two layers were separated. The org. layer was washed with aq. 4M HCl, then discarded. The combined aq. layers were neutralized with K_2CO_3, and extracted with Et_2O (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* to give a brown oil as the title compound (6.88 g, 99%) that was not further purified.

Thiazol-2-yl-methanol

A stirred and cooled (-60 °C) sol. of thiazole-2-carbaldehyde (3.97 g, 35.1 mmol) in MeOH (35 mL) was treated with $NaBH_4$ (1.33 g, 35.1 mmol). The reaction mixture was stirred at –60 °C for 2 h, then carefully quenched with acetone (2.7 mL), warmed to rt, and the solvents were removed *in vacuo*. Purification of the crude by FC (EtOAc) yielded the title compound (3.00 g, 74%) as an orange oil that crystallized at –20 °C and remained a solid upon warming to rt.

(Thiazol-2-ylmethoxy)acetic acid methyl ester

NaH (55% dispersion in oil, 1.40 g, 33.0 mmol) was added to a stirred solution of thiazol-2-ylmethanol (3.55 g, 30.82 mmol) in THF (155 mL). The suspension was then heated to 45 °C for 1 h, and methyl bromoacetate (3.40 mL, 37.0 mmol) was added. Stirring was continued at 45 °C for 4 h. The reaction mixture was partitioned between EtOAc and H_2O, the phases separated, and the aq. layer was extracted with EtOAc (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC ($MeOH/CH_2Cl_2$ 1:9) yielded the title compound (5.50 g, 95%). LC-MS: t_R = 0.62 min, ES+ = 188.14.

2-(Thiazol-2-ylmethoxy)ethanol

A cooled (0 °C) sol. of (thiazol-2-ylmethoxy)acetic acid methyl ester (31.00 g, 165.6 mmol) in MeOH (830 mL) was treated portionwise with $NaBH_4$ (31.00 g, 1.656 mol). The reaction mixture was allowed to warm up to rt over 1 h, and was quenched with water. The mixture was extracted with CH_2Cl_2 (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* to give the title compound as an orange oil (22.9 g, 87%) that was not further purified. LC-MS: t_R = 0.44 min, ES+ = 160.19.

2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazole

TBDMS-Cl (2.4 g, 15.7 mmol) and imidazole (1.10 g, 16.9 mmol) were added to a sol. of 2-(thiazol-2-ylmethoxy)ethanol (2.45 g, 15.39 mmol) in THF (80 mL). The reaction mixture was stirred at rt over 15 h, partitioned between aq. sat. NH_4Cl and Et_2O. The phases were separated and the aq. layer was extracted with Et_2O (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under

reduced pressure to give the title compound as an orange oil (22.93 g, 87%) that was not further purified. LC-MS: t_R = 1.06 min, ES+ = 274.24.

2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazole

TBDMS-Cl (10.7 g, 71.2 mmol) and imidazole (5.22 g, 76.8 mmol) were added to a sol. of 3-thiazol-2-ylpropan-1-ol (10.0 g 69.8 mmol) in THF (350 mL). Stirring was continued at rt overnight. The reaction mixture was partitioned between aq. sat. NH_4Cl and Et_2O. The aq. layer was extracted again with Et_2O. The combined org. layers were dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (CH_2Cl_2/MeOH 95:5) yielded the desired product as an orange oil (13.00 g, 72%). LC-MS: t_R = 1.05 min, ES+ = 258.24.

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

2-Fluoro-3-oxopentanoic acid methyl ester (2.21 g, 14.9 mmol), ethylene glycol (4.15 mL, 74.5 mmol), and $BF_3 \cdot Et_2O$ (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. $NaHCO_3$, and brine again. The org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under 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-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 (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/CH_2Cl_2 1:10) yielded the title compound (502 mg, 40%).

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. H_2SO_4 (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 combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the title compound (280 mg, 82%).

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 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 $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by FC (CH_2Cl_2/CH_3OH, 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

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 compound (0.77 g, 22%). LC-MS: t_R = 0.82 min.

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

A sol. of 3,5-dichloro-4-hydroxybenzaldehyde (1.635 g, 8.56 mmol) in Et_2O (30 mL) was cooled to –78 °C. MeMgBr (3M in Et_2O, 7.15 ml, 21.5 mmol) was added dropwise to the cooled reaction mixture over 18 min. Et_2O (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. NH_4Cl (10 mL) was added dropwise. The mixture was allowed to warm up to rt, and additional aq. sat. NH_4Cl (35 mL) and water (35 mL) were added. The phases were then separated and the aq. phase was extracted with Et_2O. The combined org. extracts were then washed with brine (50 ml), dried over $MgSO_4$, filtered, and concentrated under reduced pressure. Purification by FC (EtOAc/heptane, 1:1) yielded the title compound (1.68 g, 95%). LC-MS: t_R = 0.74 min.

(*rac.*)-2-(*tert*-Butyldimethylsilanyloxy)-5-[1-(*tert*-butyldimethylsilanyloxy)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. NH_4Cl was added. The mixture was extracted with a heptane/Et_2O (1/1, 4x). 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 title compound (188 mg, 90%).

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

A sol. of (*rac.*)-2-(*tert*-butyldimethylsilanyloxy)-5-[1-(*tert*-butyldimethylsilanyloxy)ethyl]-1,3-dichlorobenzene (188 mg, 0.432 mmol) and Cs_2CO_3 (76.2 mg, 0.126 mmol) in DMF (0.50 mL) and water (50 µL) was stirred at rt overnight. Et_2O (75 mL) was added. The sol. was washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (CH_2Cl_2) yielded the title compound (122 mg, 88%). LC-MS: t_R = 1.15 min.

(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 (3.14g, 43%).

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 (CH_2Cl_2/MeOH 50:1) yielded the title compound (2.94 g, quantitative yield).

2-(*tert*-Butyldimethylsilanyloxy)-5-[2-(*tert*-butyldimethylsilanyloxy)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%).

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

A sol. of 2-(*tert*-butyldimethylsilanyloxy)-5-[2-(*tert*-butyldimethylsilanyloxy)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 $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH_2Cl_2) yielded the title compound (3.5 g, 96%).

2,6-Dichloro-3,4-dimethylphenol

To a sol. of 3,4-dimethylphenol (3.00 g, 24.6 mmol) in CH_2Cl_2 (5 mL) was added SO_2Cl_2 (4.98 mL, 61.3 mmol). The resulting sol. was heated to 50 °C for 4 h. The mixture was poured onto ice-water. CH_2Cl_2 (200 mL) was added, the layers were separated, and the org. layer was washed with water, then with aq. sat. $NaHCO_3$. The org. layer was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (EtOAc/heptane 1:4) yielded the title compound (1.17 g, 25%).

3-Oxo-9-azabicyclo[3.3.1]nonane-9-carboxylic acid *tert*-butyl ester (A1)

Et_2O (800 mL) and Et_3N (22.0 mL, 0.158 mol) were added to pseudopelletierine hydrochloride (30.00 g, 0.158 mol). The suspension was stirred for 15 min, filtered and the filtrate reduced *in vacuo* to yield the free amine (23.00 g, 150.1 mmol). To a suspension of the free amine (23.00 g, 150.1 mmol) and $NaHCO_3$ (22.0 g, 0.263 mol) in 1,2-dichloroethane (800 mL) was added dropwise 1-chloroethyl chloroformate (82 mL, 0.750 mol). The mixture was heated to reflux. After 2 h, the reaction mixture was allowed to cool to rt, filtered, and the solvents were thoroughly removed *in vacuo*. MeOH (800 mL) was added and the mixture was stirred at 50 °C for 60 min. The sol. was allowed to cool to rt, and the solvents were removed *in vacuo*. The residue was dissolved in CH_2Cl_2 (400 mL), DIPEA (64 mL, 0.375 mol) was added followed by Boc_2O (39.0 g, 0.180 mol), and the mixture was stirred at rt overnight. The mixture was washed with aq. 1M HCl (1x), and aq. sat. $NaHCO_3$ (1x). The org. phase was dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Recrystallization from EtOAc yielded the title compound (31.7 g, 88%). LC-MS: t_R = 0.86 min, ES+ = 240.29.

3-Oxo-8-azabicyclo[3.2.1]octane-8-carboxylic acid *tert*-butyl ester (A2)

A mixture of tropinone (100 g, 718 mmol), and 1-chloroethyl chloroformate (308 g, 2.16 mol) in CH_2ClCH_2Cl (1.00 L) was heated to reflux for 5 h. The mixture was allowed to cool to rt, and the solvents were removed under reduced pressure. The residue was dried under high vacuum for 15 min, and was dissolved in MeOH (500 mL). The mixture was stirred at 75 °C for 1 h, and allowed to cool to rt. The residue was triturated with Et_2O (500 mL), and put in an ultrasound bath for 15 min. The

mixture was stirred then for 30 min, and was filtered. The precipitate was washed with Et_2O (250 mL), and dried under reduced pressure. The precipitate was diluted with dioxane (800 mL), and the mixture was cooled to 0 °C. Aq. 1M NaOH (800 mL, 800 mmol), and Boc_2O (165 g, 754 mmol) were added. The mixture was stirred overnight while warming up to rt. The mixture was extracted with Et_2O (2x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. The pure title compound (109 g, 67%) crystallized spontaneously, and was dried under high vacuum.

(*rac.*)-(*1R, *5S**)-3-Oxo-9-azabicyclo[3.3.1]nonane-2,9-dicarboxylic acid 2-benzylester 9-*tert*-butyl ester (B1)**

BuLi (1.6M in hexane, 33,5 mL, 53.6 mmol) was added dropwise to a cooled (0 °C) sol. of diisopropylamine (7.7 mL, 54.62 mmol) in THF (170 mL). The sol. was stirred at 0 °C for 20 min, cooled to –78 °C and a sol. of compound **A1** (11.67 g, 48.77 mmol) in THF (70 mL) was added dropwise. The reaction mixture was stirred for 1 h at –78 °C. Benzylcyanoformate was added dropwise, and the reaction mixture was allowed to reach rt overnight. The mixture was cooled again to 0°C, and EtOAc was added. The mixture was allowed to warm to rt, and was washed with brine. The aq. layer was extracted again with EtOAc, and the combined org. layers were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (1% MeOH in CH_2Cl_2) resulted in 17.00 g of an orange oil as the title compound (93%). LC-MS: t_R = 1.11 min, ES+ = 374.35.

(*rac.*)-(*1R, *5S**)-3-Oxo-8-azabicyclo[3.2.1]oct-2-ane-2,8-dicarboxylic acid 2-benzyl ester 8-*tert*-butyl ester (B2)**

BuLi (1.6 M in hexane, 183 mL, 293 mmol) was added dropwise to a sol. of DIPEA (50.1 mL, 293 mmol) in THF (200 mL) at 0 °C. The sol. was cooled to –78 °C, and a sol. of compound **A2** (60.0 g, 266 mmol) in THF (200 mL) was added dropwise over 1 h. The mixture was stirred for 1 h at –78 °C, and benzylcyanoformate (45.7 mL, 320 mmol) was added dropwise over 30 min. The dry ice bath was removed, and the mixture was stirred overnight while warming up to rt. The mixture was cooled to 0 °C, and AcOH (60 mL) was added dropwise. EtOAc (100 mL) was added, and the mixture

was washed with brine (2x). The combined aq. phases were extracted with EtOAc. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:9) yielded the title compound (45.1 g, 47%).

(*rac.*)-(*1R, *5S**)-3-Trifluoromethanesulfonyloxy-9-azabicyclo[3.3.1]non-2-ene-2,9-dicarboxylic acid 2-benzylester 9-*tert*-butyl ester (C1)**

KHMDS (1.5M in toluene, 11.3 mL, 15.6 mmol) was added dropwise to a cooled sol. (-78°C) of compound **B1** (2.00 g, 15.4 mmol) in THF (24 mL). The reaction mixture was stirred at –78 °C for 20 min, HMPA (1.50 mL, 8.57 mmol) was added, and the mixture was stirred for 10 min at –78 °C, allowed to reach –20 °C and stirred at –20 °C for 15 min, then cooled back to –78 °C. A sol. of *N*-(5-chloro-2-pyridyl)-bis(trifluoromethanesulfonimide) (2.50 g, 6.43 mmol) in THF (12 mL) was added dropwise and the mixture stirred for 1 h at –78 °C, then allowed to warm to rt overnight. The reaction mixture was quenched with MeOH, the solvents were removed *in vacuo*, and the residue was purified by FC (heptane/EtOAc 1:1) to yield 2.57 g of a yellow oil as the title compound (95%). LC-MS: t_R = 1.15 min, ES+ =506.3.

(*rac.*)-(*1R, *5S**)-3-Trifluoromethanesulfonyloxy-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 2-benzyl ester 8-*tert*-butyl ester (C2)**

A sol. of compound **B2** (20.0 g, 55.6 mmol) in THF (200 mL) was added dropwise to a suspension of NaH (60%-suspension in oil, 2.43 g, 56 mmol) in THF (200 mL) at 0 °C. The mixture was stirred for 10 min, and Tf_2NPh (22.3 g, 61.2 mmol) was added. The mixture was stirred overnight while warming up to rt. Brine was added carefully, and EtOAc was added. The phases were separated, and the org. phase was washed with brine. The combined aq. phases were extracted with EtOAc. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (EtOAc/heptane 1:5 → EtOAc) yielded the title compound (22.4 g, 82%).

(*rac.*)-(*1R, *5S**)-3-{2-[3(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2,9-dicarboxylic acid 2-benzylester 9-*tert*-butyl ester (D1)**

BuLi (1.6M in hexane, 2.50 mL, 3.76 mmol) was added dropwise to a cooled (-78 °C) sol. of 2-[3-(*tert*-butyldimethylsilanyloxy)propyl]thiazole (0.92 g, 3.76 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for 1 h, and $ZnCl_2$ (1M in THF, 5 mL, 4.75 mmol) was added dropwise at –78 °C. The cooling bath was then removed and the reaction stirred for 1 h at rt. A sol. of compound **C1** (1.0 g, 1.978 mmol) in THF (5 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (0.07 g, 0.057 mmol). The reaction mixture was stirred at rt for 1 h, then partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane/EtOAc 7:3) yielded the title compound (0.68 g, 56%). LC-MS: t_R = 1.25 min, ES+ = 613.27.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 2-benzyl ester 8-*tert*-butyl ester (D2)**

BuLi (1.6M in hexane, 3.25 mL, 5.29 mmol) was added dropwise to a cooled (-78 °C) sol. of 2-[2-(*tert*-butyldimethylsilanyloxy)ethoxy]thiazole (1.27 g, 4.88 mmol) in THF (10 mL). The reaction mixture was stirred at –78 °C for 1 h, and $ZnCl_2$ (1M in THF, 6.1 mL, 6.1 mmol) was added dropwise at –78 °C. The cooling bath was then removed and the reaction stirred for 1 h at rt. A sol. of compound **C2** (2.00 g, 4.07 mmol) in THF (10 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (120 mg, 0.114 mmol). The reaction mixture was stirred at rt overnight, then partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane/EtOAc 7:3) yielded the title compound (2.29 g, 94%).

(*rac.*)-(*1R, *5S**)-3-{2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 2-benzyl ester 8-*tert*-butyl ester (D3)**

BuLi (1.6 M in hexane, 17 mL, 27.1 mmol) was added dropwise to a cooled (-78 °C) sol. of 2-[3-(*tert*-butyldimethylsilanyloxy)propyl]thiazole (6.60 g, 25.6 mmol) in THF (65 mL). The reaction mixture was stirred at –78 °C for 1 h, and $ZnCl_2$ (1M in THF, 34

mL, 34 mmol) was added dropwise at –78 °C. The cooling bath was then removed and the reaction stirred for 1 h while warming up to rt. A sol. of compound **C2** (7.00 g, 14.24 mmol) in THF (10 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (477 mg, 0.414 mmol). The reaction mixture was stirred at rt for 1 h, then partitioned between EtOAc and 1N NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane/EtOAc 7:3) yielded the title compound (4.97 g, 58%). LC-MS: t_R = 1.24 min, ES+ = 599.21.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 2-benzyl ester 8-*tert*-butyl ester (D4)**

BuLi (1.6 M in hexane, 26 mL, 42.25 mmol) was added dropwise over 20 min to a cooled (-78 °C) sol. of 2-[2-(*tert*-butyldimethylsilanyloxy)ethoxymethyl]thiazole (10.95 g, 40.03 mmol) in THF (85 mL). The reaction mixture was stirred at –78 °C for 1 h, and $ZnCl_2$ (1M in THF, 53.0 mL, 53.0 mmol) was added dropwise at –78 °C. The cooling bath was removed, and the reaction stirred for 1 h while warming up to rt. A sol. of compound **C2** (10.93 g, 22.24 mmol) in THF (30 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (745 mg, 0.645 mmol). The reaction mixture was stirred at rt for 1 h, partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. phases were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane/EtOAc 7:3) yielded a brown oil as the title compound (7.39 g, 54%). LC-MS: t_R = 1.23 min, ES+ = 615.25.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2,9-dicarboxylic acid 2-benzyl ester 9-*tert*-butyl ester (D5)**

BuLi (1.6 M in hexane, 17 mL, 27.06 mmol) was added dropwise over 20 min to a cooled (-78 °C) sol. of 2-[2-(*tert*-butyldimethylsilanyloxy)ethoxymethyl]thiazole (7.01 g, 25.63 mmol) in THF (65 mL). The reaction mixture was stirred at –78 °C for 1 h,

and $ZnCl_2$ (1M in THF) (34.18 mL, 34.18 mmol) was added dropwise at -78°C. The cooling bath was removed and the reaction was stirred for 1 h at rt. A sol. of compound **C1** (7.20 g, 14.24 mmol) in THF (10 mL) was added dropwise, followed by $Pd(PPh_3)_4$ (477 mg, 0.414 mmol). The reaction mixture was stirred at rt for 1 h, partitioned between EtOAc and aq. 1M NaOH, and the layers were separated. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with brine, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (heptane/EtOAc 7:3) resulted in a brown oil as the title compound (6.04 g, 67%). LC-MS: t_R = 1.24 min, ES+ = 629.25.

(*rac.*)-(*1R, *5S**)-3-{2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2,9-dicarboxylic acid 9-*tert*-butyl ester (E1)**

To a stirred sol. of compound **D1** (3.948 g, 6.442 mmol) in Et_2O (32 mL) at rt was added Me_3SiOK (1.24 g, 9.663 mmol). The reaction mixture was stirred at rt overnight, then partitioned between EtOAc and aq. sat. NH_4Cl. The layers were separated and the aq. phase was extracted with EtOAc. The aq. layer was acidified with aq. 1M HCl to pH 4-5, and extracted again with EtOAc. The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give a brown oil as the title compound, which was not further purified (4.62 g, quantitative yield). LC-MS: t_R = 1.11 min, ES+ =523.24.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (E2)**

To a stirred sol. of compound **D2** (2.25 g, 3.75mmol) in Et_2O (55 mL) at rt was added Me_3SiOK (801 mg, 5.62 mmol). The reaction mixture was stirred at rt for 2 h, and $NaHCO_3$ (0.8 g) was added. The mixture was stirred for 5 min, and aq. sat. NH_4Cl was added. The mixture was extracted with EtOAc (3x). The combined org. extracts were dried over Na_2SO_4, filtered, and the solvents were removed under reduced pressure. The crude material (2.08 g, quantitative yield) was used without further purification.

(*rac.*)-(*1R, *5S**)-3-{2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (E3)**

To a stirred sol. of compound **D3** (53 mg, 0.89 mmol) in Et_2O (0.5 mL) at rt was added Me_3SiOK (17 mg, 1.33 mmol). The reaction mixture was stirred at rt overnight, then partitioned between EtOAc and aq. sat. NH_4Cl. The layers were separated, and the aq. phase was extracted with EtOAc. The aq. layer was acidified with aq. 1M HCl to pH 4-5, and extracted again with EtOAc. The combined org. layers were washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give a brown oil as the title compound, which was not further purified (35 mg, 78%). LC-MS: t_R = 1.10 min, ES+ =509.22.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2,8-dicarboxylic acid 8-*tert*-butyl ester (E4)**

A stirred sol. of compound **D4** (7.390 g, 12.02 mmol) in Et_2O (60 mL) at rt was treated with Me_3SiOK (2.312 g, 18.03 mmol). The reaction mixture was stirred at rt for 2 h, and partitioned between EtOAc and aq. sat. NH_4Cl. The layers were separated and the aq. phase was extracted with EtOAc. The aq. layer was acidified with aq. 1M HCl to pH 4-5, and extracted again with EtOAc (3x). The combined org. extracts were washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure to give an orange oil as the title compound (6.3 g, >99 %) that was not further purified. LC-MS: t_R = 1.09 min, ES+ = 525.21.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2,9-dicarboxylic acid 9-*tert*-butyl ester (E5)**

A stirred sol. of compound **D5** (5.84 g, 9.28 mmol) in Et_2O (46 mL) at rt was treated with Me_3SiOK (1.785 g, 13.92 mmol). The reaction mixture was stirred at rt overnight, and partitioned between EtOAc and aq. sat. NH_4Cl. The layers were separated, and the aq. phase was extracted with EtOAc. The aq. layer was acidified with aq. 1M HCl to pH 4-5, and extracted again with EtOAc (3x). The combined org. extracts were dried over $MgSO_4$, filtered, and the solvents removed under reduced pressure to give an orange oil as the title compound (4.11 g, 82 %) that was not further purified. LC-MS: t_R = 1.11 min, ES+ = 539.37.

(*rac.*)-(*1R, *5S**)-3-{2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-2-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F1)**

To a stirred solution of the compound **E1** (4.619 g, 8.84 mmol) in CH_2Cl_2 (45 mL) were added EDC•HCl (4.235 g, 22.093 mmol), HOBt (1.623 g, 10.61 mmol), DMAP (0.027 g, 0.221 mmol), and DIPEA (6.945 mL, 39.77 mmol). After 15 min cyclopropyl-(2,3-dichlorobenzyl)amine (7.64 g, 35.35 mmol) was added, and stirring was continued over 3 days. Twice were added cyclopropyl-(2,3-dichlorobenzyl)amine (2.55 g, 8.84 mmol) and HOBt (0.676 g, 4.42 mmol). The reaction mixture was partitioned between aq. 1M HCl and CH_2Cl_2 and the phases were separated. The org. layer was washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (heptane/EtOAc 9:1 → 7:3) yielded the title product (1.21g, 20%). LC-MS: t_R = 1.29 min, ES+ =720.42.

(*rac.*)-(*1R, *5S**)-2-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3-[2-(3-hydroxy-propyl)thiazol-5-yl]-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F2)**

To a sol. compound **F1** (1.21 g, 1.679 mmol) in MeOH (17 mL) was added *p*-toluenesulfonic acid (0.351 g, 1.847 mmol), and the mixture was stirred at rt for 30 min. The reaction mixture was quenched with aq. 10% Na_2CO_3, and the solvents were removed under pressure. The aq. layer was extracted with EtOAc. The combined org. extracts were washed with $NaHCO_3$, brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo* to yield 0.97 g of a pale yellow foam as the title compound, which was not further purified (95 %). LC-MS: t_R = 1.07 min, ES+ = 606.43.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxy]thiazol-5-yl}-2-[cyclo-propyl-(3-methoxy-2-methylbenzyl)carbamoyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F3)**

A mixture of compound **E2** (2.02 g, 3.96 mmol), cyclopropyl-(3-methoxy-2-methylbenzyl)amine (prepared by reductive amination from 3-methoxy-2-methylbenzaldehyde, Comins, D. L.; Brown, J. D., *J. Org. Chem.*, 1989, *54*, 3730, and

cyclopropylamine, 1.39 g, 7.28 mmol), *N*-methylmorpholine (0.603 mL, 5.48 mmol), HOBt (567 mg, 4.20 mmol) and EDC•HCl (835 mg, 4.36 mmol) in DMF (23 mL) was stirred at rt for 22 h. The mixture was diluted with CH_2Cl_2, and washed with water (4x), aq. 2.5% citric acid (1x), water (1x), and brine (1x). The org. phase was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification of the crude by FC (CH_2Cl_2 → MeOH/CH_2Cl_2 1:49) yielded the title compound (1.85 g, 69%).

(*rac.*)-(*1R, *5S**)-2-[Cyclopropyl-(3-methoxy-2-methylbenzyl)carbamoyl]-3-[2-(2-hydroxyethoxy)thiazol-5-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F4)**

TBAF (829 mg, 2.68 mmol) was added to a sol. of compound **F3** (1.85 g, 2.44 mmol) in THF (50 mL). The mixture was stirred for 6 h, and the solvents were removed under reduced pressure. The residue was diluted with EtOAc, and the mixture was washed with water (4x). The org. phase was dried over $MgSO_4$, filtered, and the solvents were removed under reduced pressure. Purification by FC (MeOH/CH_2Cl_2 3:97) yielded the title compound (1.48 g, quantitative).

(*rac.*)-(*1R, *5S**)-3-{2-[3-(*tert*-Butyldimethylsilanyloxy)propyl]thiazol-5-yl}-2-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F5)**

To a stirred sol. of the compound **E3** (4.199 g, 8.255 mmol) in CH_2Cl_2 (41 mL) were added EDC•HCl (3.956 g, 20.63 mmol), HOBt (1.516 g, 9.91 mmol), DMAP (25 mg, 0.207 mmol), and DIPEA (6.488 mL, 37.15 mmol). After 15 min cyclopropyl-(2,3-dichlorobenzyl)amine (5.35 g, 24.77 mmol) was added, and stirring was continued over 5 days. The reaction mixture was partitioned between aq. 1M HCl and CH_2Cl_2, and the phases were separated. The org. layer was washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (heptane/EtOAc 8:2 to → 7:3) yielded the title product (3.54 g, 61%). LC-MS: t_R = 1.28 min, ES+ =706.33.

(*rac.*)-(*1R, *5S**)-2-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3-[2-(3-hydroxy-propyl)thiazol-5-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F6)**

To a sol. of compound **F5** (3.54 g, 5.008 mmol) in MeOH (50 mL) was added *p*-toluenesulfonic acid (1.05 g, 5.51 mmol), and the mixture was stirred at rt for 30 min. The reaction mixture was quenched with aq. sat. Na_2CO_3, and the solvents were removed under reduced pressure. The aq. layer was extracted with EtOAc, and the org. phase was washed with aq. 10% Na_2CO_3, aq. sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (EtOAc) yielded the title product as a light yellow oil (2.21 g, 74%). LC-MS: t_R = 1.05 min, ES+ = 592.31.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-2-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F7)**

To a stirred sol. of compound **E4** (6.30 g, 12.0 mmol) in CH_2Cl_2 (60 mL) were added EDC•HCl (5.753 g, 30.02 mmol), HOBt (2.21 g, 14.41 mmol), DMAP (36 mg, 0.301 mmol), and DIPEA (9.436 mL, 54.03 mmol). After 15 min cyclopropyl-(2,3-dichloro-benzyl)amine (10.38 g, 48.0 mmol) was added, and stirring was continued over 5 days. The reaction mixture was partitioned between aq. 1M HCl and CH_2Cl_2 and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (2x). The combined org. extracts were washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (heptane/EtOAc 8:2 → 7:3) yielded the title product (3.45 g, 40%) as a pale orange foam. LC-MS: t_R = 1.27 min, ES+ = 722.33.

(*rac.*)-(*1R, *5S**)-2-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3-[2-(2-hydroxy-ethoxymethyl)thiazol-5-yl]-8-azabicyclo[3.2.1]oct-2-ene-8-carboxylic acid *tert*-butyl ester (F8)**

To a sol. of compound **F7** (3.45 g, 4.78 mmol) in MeOH (48 mL) was added *p*-toluenesulfonic acid (1.00 g, 5.26 mmol), and the mixture was stirred at rt over 30 min. The reaction mixture was quenched with aq. 10% Na_2CO_3, and the solvents were

removed under reduced pressure. The aq. layer was extracted with EtOAc. The org. phase was washed with aq. 10% Na_2CO_3, aq. sat. $NaHCO_3$, and brine, dried over $MgSO_4$, filtered and the solvent removed *in vacuo* to yield a white foam as the title compound (2.91 g, >99 %) that was not further purified. LC-MS: t_R = 1.03 min, ES+ = 608.30.

(*rac.*)-(*1R, *5S**)-3-{2-[2-(*tert*-Butyldimethylsilanyloxy)ethoxymethyl]thiazol-5-yl}-2-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F9)**

To a stirred sol. of the compound **E5** (4.109 g, 7.63 mmol) in CH_2Cl_2 (40 mL) were added EDC•HCl (3.66 g, 19.07 mmol), HOBt (1.40 g, 9.15 mmol), DMAP (23.3 mg, 0.191 mmol), and DIPEA (5.995 mL, 34.32 mmol). After 15 min cyclopropyl-(2,3-dichloro-benzyl)amine (6.594 g, 30.51 mmol) was added, and stirring was continued over 3 days. Twice were added cyclopropyl-(2,3-dichlorobenzyl)amine (1.65 g, 7.63 mmol) and HOBt (515 mg, 3.82 mmol). The reaction mixture was partitioned between aq. 1M HCl and CH_2Cl_2, and the phases were separated. The aq. layer was extracted with CH_2Cl_2 (2x). The combined org. extracts were washed with aq. sat. $NaHCO_3$, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the crude by FC (heptane/EtOAc 9:1 → 8:2) yielded the title product (2.12 g, 38%) as a yellow oil. LC-MS: t_R = 1.29 min, ES+ = 736.42.

(*rac.*)-(*1R, *5S**)-2-[Cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3-[2-(2-hydroxy-ethoxymethyl)thiazol-5-yl]-9-azabicyclo[3.3.1]non-2-ene-9-carboxylic acid *tert*-butyl ester (F10)**

To a sol. of compound **F9** (2.12 g, 2.88 mmol) in MeOH (29 mL) was added *p*-toluenesulfonic acid (602 mg, 3.165 mmol), and the mixture was stirred at rt over 30 min. The reaction mixture was quenched with aq. 10% Na_2CO_3, and the solvents were removed under pressure. The aq. layer was extracted with EtOAc, and the combined org. extracts were washed with $NaHCO_3$, and brine, dried over $MgSO_4$, filtered, and the solvents were removed *in vacuo*. Purification of the residue by FC (EtOAc) yielded the title product (1.27 g, 71%) as a white foam. LC-MS: t_R = 1.05 min, ES+ = 622.13.

EXAMPLES

Example 1

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2-Chloro-3,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.93 min; ES+: 670.24.

Example 2

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichlorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 2,6-dichlorophenol. LC-MS: t_R = 0.93 min; ES+: 668.26.

Example 3

(*rac.*)-(*1R, *5S**)-3-{2-[2-(3-Chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.93 min; ES+: 670.23.

Example 4

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.96 min; ES+: 682.28.

Example 5

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2-Chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.94 min; ES+: 666.27.

Example 6

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2-Chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.96 min; ES+: 652.24.

Example 7

(*rac.*)-(*1R, *5S**)-3-{2-[3-(4,5-Dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 4,5-dimethyl-isoxazol-3-ol (Katritzky, A. R.; Oeksne, S., *Proc. Chem. Soc.*, **1961**, 387). LC-MS: t_R = 0.88 min; ES+: 601.33.

Example 8

(*rac.*)-(*1R, *5S**)-3-{2-[3-(5-Ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 5-ethyl-4-fluoroisoxazol-3-ol. LC-MS: t_R = 0.91 min; ES+: 619.34.

Example 9

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichlorophenoxy)propyl]thiazol-5-yl}-9-azabicyclo-[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 2,6-dichlorophenol. LC-MS: t_R = 0.95 min; ES+: 652.25.

Example 10

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.97 min; ES+: 666.27.

Example 11

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2-Chloro-6-fluoro-3-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.96 min; ES+: 648.29.

Example 12

Mixture of (*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

This mixture is prepared from compound **F2**, according to the general procedures A and B, and with (*rac.*)-4-[1-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.89 min; ES+: 682.23.

Example 13

Mixture of (*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-ethoxymethyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-ethoxymethyl}thiazol-5-yl)-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide

This mixture is prepared from compound **F8**, according to the general procedures A and B, and with (*rac.*)-4-[1-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.88 min; ES+: 698.23.

Example 14

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2-Chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.93 min; ES+: 638.24.

Example 15

(*rac.*)-(*1R, *5S**)-3-{2-[3-(4,5-Dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 4,5-dimethyl-isoxazol-3-ol (Katritzky, A. R.; Oeksne, S., *Proc. Chem. Soc.*, **1961**, 387). LC-MS: t_R = 0.93 min; ES+: 589.30.

Example 16

(*rac.*)-(*1R, *5S**)-3-{2-[3-(5-Ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 5-ethyl-4-fluoroisoxazol-3-ol. LC-MS: t_R = 0.90 min; ES+: 605.23.

Example 17

(*rac.*)-(*1R, *5S**)-3-{2-[3-(4-Chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-propyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-ol (EP 304409 A1). LC-MS: t_R = 0.93 min; ES+: 674.25.

Example 18

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichlorophenoxy)propyl]thiazol-5-yl}-8-azabicyclo-[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 2,6-dichlorophenol. LC-MS: t_R = 0.94 min; ES+: 638.22.

Example 19

(*rac.*)-(*1R, *5S**)-3-{2-[3-(3-Chloro-2,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.93 min; ES+: 640.25.

Example 20

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.96 min; ES+: 652.24.

Example 21

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2-Chloro-6-fluoro-3-methylphenoxy)propyl]-thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.95 min; ES+: 636.24.

Example 22

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2-Chloro-3,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2-chloro-3,6-difluorophenol. LC-MS: t_R = 0.91 min; ES+: 656.22.

Example 23

(*rac.*)-(*1R, *5S**)-3-{2-[2-(4-Chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclo-propyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-ol (EP 304409 A1). LC-MS: t_R = 0.92 min; ES+: 690.25.

Example 24

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichlorophenoxy)ethoxymethyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2,6-dichlorophenol. LC-MS: t_R = 0.92 min; ES+: 654.20.

Example 25

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-4-fluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2,6-dichloro-4-fluorophenol. LC-MS: t_R = 0.93 min; ES+: 672.20.

Example 26

(*rac.*)-(*1R, *5S**)-3-{2-[2-(3-Chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 3-chloro-2,6-difluorophenol. LC-MS: t_R = 0.92 min; ES+: 656.26.

Example 27

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2,6-dichloro-*p*-cresol. LC-MS: t_R = 0.95 min; ES+: 668.24.

Example 28

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2-Chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2-chloro-6-fluoro-3-methylphenol. LC-MS: t_R = 0.93 min; ES+: 652.28.

Example 29

Mixture of (*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-ethoxymethyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid

cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

This mixture is prepared from compound **F10**, according to the general procedures A and B, and with (*rac.*)-4-[1-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.89 min; ES+: 712.26.

Example 30

(*rac.*)-(*1R, *5S**)-3-(2-{2-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.89 min; ES+: 712.28.

Example 31

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

This compound is prepared from compound **F10**, according to the general procedures A and B, and with 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 0.89 min; ES+: 696.26.

Example 32

Mixture of (*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, (*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxy-ethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid

cyclopropyl-(2,3-dichlorobenzyl)amide, (*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide, and (*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxy-ethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide

This mixture is prepared from compound **F2**, according to the general procedures A and B, and with (*rac.*)-4-[1-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.90 min; ES+: 696.27.

Example 33

(*rac.*)-(*1R, *5S**)-3-(2-{3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.90 min; ES+: 696.23.

Example 34

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F2**, according to the general procedures A and B, and with 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 1.00 min; ES+: 680.29.

Example 35

(*rac.*)-(*1R, *5S**)-3-(2-{3-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.89 min; ES+: 682.23.

Example 36

(*rac.*)-(*1R, *5S**)-3-{2-[3-(2,6-Dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide**

This compound is prepared from compound **F6**, according to the general procedures A and B, and with 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 0.89 min; ES+: 666.26.

Example 37

(*rac.*)-(*1R, *5S**)-3-(2-{2-[2,6-Dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 4-[2-(*tert*-butyldimethylsilanyloxy)ethyl]-2,6-dichlorophenol. LC-MS: t_R = 0.87 min; ES+: 598.31.

Example 38

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide**

This compound is prepared from compound **F8**, according to the general procedures A and B, and with 2,6-dichloro-3,4-dimethylphenol. LC-MS: t_R = 0.97 min; ES+: 682.26.

Example 39

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2-Chloro-3,6-difluorophenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)-amide**

To a sol. of compound **F4** (200 mg, 0.352 mmol) and 2-chloro-3,6-difluorophenol (75 mg, 0.46 mmol) in toluene (5.00 mL) were sequentially added azodicarboxylic dipiperidide (115 mg, 0.457 mmol) and PBu_3 (0.199 mL, 0.808 mmol). The resulting mixture was heated to 110°C for 90 min. The mixture was allowed to cool to rt, and was diluted with hexane/EtOAc 2:1. The mixture was filtered off, and the filtrate was

evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH 19/1). The obtained product was dissolved in CH_2Cl_2 (1.00 mL) and treated with TFA (0.162 mL) for 24 h. NH_3 (7M in MeOH) was added, and the solvents were removed under reduced pressure. Purification by preparative TLC (CH_2Cl_2/MeOH 9/1) yielded the title compound (66.3 mg, 31%).

Example 40

(*rac.*)-(*1R, *5S**)-3-{2-[2-(2,6-Dichloro-4-methylphenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide**

To a sol. of compound **F4** (200 mg, 0.352 mmol) and 2,6-dichloro-*p*-cresol (81 mg, 0.46 mmol) in toluene (5.00 mL) were sequentially added azodicarboxylic dipiperidide (115 mg, 0.457 mmol) and PBu_3 (0.199 mL, 0.808 mmol). The resulting mixture was heated to 110°C for 90 min. The mixture was allowed to cool to rt, and was diluted with hexane/EtOAc 2:1. The mixture was filtered off, and the filtrate was evaporated under reduced pressure. The residue was purified by preparative TLC (CH_2Cl_2/MeOH 19/1). The obtained product was dissolved in CH_2Cl_2 (1.00 mL) and treated with TFA (0.162 mL) for 24 h. NH_3 (7M in MeOH) was added, and the solvents were removed under reduced pressure. Purification by preparative TLC (CH_2Cl_2/MeOH 9/1) yielded the title compound (72.6 mg, 33%).

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 μmol) of AngI [1-10 (Bachem, H-1680)] and 17 mg (0.26 μmol) of BSA (Fluka, 05475) were dissolved in 4 mL of 0.1M phosphate buffer, pH 7.4, after which 2 mL of a 1:100 dilution of glutaraldehyde in H_2O (Sigma G-5882) was added dropwise. The mixture was incubated overnight at 4 °C, then dialyzed against 2 liters of 0.9% NaCl, twice for 4 h at rt, followed by dialysis against 2 liters of PBS 1X overnight at rt.

The solution was then filtered with a Syringe filter, 0.45 µm (Nalgene, Cat. No. 194-2545). The conjugate can be stored in polypropylene tubes in 0.05% sodium azide at 4 °C for at least 12 months.

1.2 Preparation of BSA-AngI coated MTP

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

1.3 AngI-EIA in 384 well MTP

The AngI (1-10)/BSA coated MTP were washed 3 times with wash buffer (PBS 1X, 0.01% Tween 20) and filled with 75 µl of primary antibody solution (anti-AngI antiserum, pre-diluted 1:10 in horse serum), diluted to a final concentration of 1:100'000 in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4). 5 µl of the renin reaction (or standards in assay buffer) (see below) were added to the primary antibody solution and the plates were incubated overnight at 4 °C. After the incubation the plates were washed 3 times with wash buffer and incubated with secondary antibody [anti-rabbit IgG, linked to horseradish peroxidase (Amersham Bioscience, NA 934V), diluted 1:2'000 in wash buffer] for 2 h at rt. The plates were washed 3 times with wash buffer and then incubated for 1 h at rt with substrate solution [1.89mM ABTS (2.2'-azino-di-(3-ethyl-benzthiazolinsulfonate)] (Roche Diagnostics, 102 946) and 2.36mM H_2O_2 [30%, (Fluka, 95300] in substrate buffer (0.1M sodium acetate, 0.05M sodium dihydrogen phosphate, pH 4.2). The OD of the plate was read at 405 nm in a microplate reader (FLUOStar Optima from BMG). The production of AngI during the renin reaction was quantified by comparing the OD of the sample with the OD of a standard curve of AngI(1-10), measured in parallel.

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

The renin assay was adapted from an assay described before (Fischli W. *et al., Hypertension,* **1991**, 18:22-31) and consists of two steps: in the first step, recombinant human renin is incubated with its substrate (commercial human tetradecapeptide renin substrate) to create the product Angiotensin I (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 this primary assay down to low pM concentration.

2.1 Methodology

Recombinant human renin (3 pg/µl) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5µM in 10mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30mM in H_2O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 µl per well of this premix was transferred into polypropylene plates (MTP384, Nunc). Test compounds were dissolved and diluted in 100% DMSO and 2.5 µl added to the premix, then incubated at 37 °C for 3 h. At the end of the incubation period, 5 µl of the renin reaction (or standards in assay buffer) were transferred into EIA assays (as described above) and 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% (IC_{50}). The compounds of formula (I) exhibit IC_{50} values between 0.1 nM to 300 nM, especially between 1 nM to 30 nM.

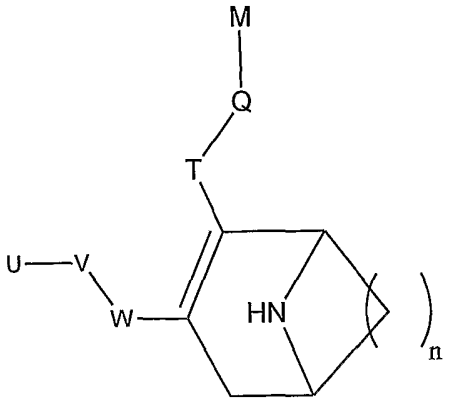
Examples of inhibition:

Compound of Example No.	**IC_{50} [nM]**
2	11

4	3.7
10	1.5
12	4.3
20	3.3
29	8.3
36	16

Claims

1. A compound selected from the group consisting of five-membered heteroaryl compounds of the formula (**I**)



(**I**)

wherein

W represents a five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, said heteroaryl being optionally substituted by alkyl;

V represents $-CH_2CH_2-O-$, $-CH_2CH_2CH_2-O-$, $-O-CH_2CH_2-O-$, $-O-CH_2CH_2CH_2-O-$, $-CH_2-O-CH_2CH_2-O-$, $-O-CH_2CH_2-O-CH_2-$, or $-O-CH_2CH_2CH_2-O-CH_2-$;

U represents unsubstituted aryl; mono-, di-, tri or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-CF_3$, $-OCF_3$, halogen and hydroxy-alkyl; unsubstituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S; or mono-, di- or tri-substituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-CF_3$, $-OCF_3$ and halogen;

T represents $-CONR^1-$ or $-CH_2CONR^1-$;

Q represents methylene;

M represents unsubstituted aryl; or mono- or di-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, alkoxy, $-OCF_3$, $-CF_3$, hydroxy-alkyl and halogen;

R^1 represents alkyl or cycloalkyl; and

n is the integer 2 or 3;

and optically pure enantiomers, mixtures of enantiomers such as a racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixture 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 W represents a thiazolyl ring substituted by V at position 2 and attached in position 5 to the bicyclic template of formula (I).

3. A compound according to claim 1 or 2, wherein T represents $-CONR^1-$.

4. A compound according to any one of claims 1-3, wherein R^1 represents a cyclopropyl group.

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

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

7. A compound according to any one of claims 1-6, wherein V represents $-CH_2CH_2CH_2-O-$, $-O-CH_2CH_2-O-$ or $-CH_2-O-CH_2CH_2-O-$.

8. A compound according to any one of claims 1-7, wherein U represents unsubstituted aryl; mono-, di-, tri- or tetra-substituted aryl, wherein the substituents are independently selected from the group consisting of alkyl, halogen and hydroxy-alkyl; unsubstituted five-membered heteroaryl containing two heteroatoms independently selected from O, N and S; or mono-, di- or tri-substituted five-membered heteroaryl containing two heteroatoms independently selected from O, N

and S, wherein the substituents are independently selected from the group consisting of alkyl, $-CF_3$ and halogen.

9. A compound according to claim 1, wherein

W represents a thiazolyl ring, preferably substituted by V at position 2 and attached in position 5 to the bicyclic template of formula (I);

V represents $-CH_2CH_2CH_2-O-$, $-O-CH_2CH_2-O-$, or $-CH_2-O-CH_2CH_2-O-$;

U represents di-, tri or tetra-substituted phenyl, wherein the substituents are independently selected from the group consisting of alkyl, halogen and hydroxy-alkyl; or isoxazol-3-yl or 1H-pyrazol-3-yl, wherein these two heteroaryl radicals are di- or tri-substituted with substituents independently selected from the group consisting of alkyl, $-CF_3$, and halogen;

T represents $-CONR^1-$;

Q represents methylene;

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

R^1 represents cyclopropyl; and

n is the integer 2 or 3.

10. A compound according to claim 1 selected from

(*1R**, *5S**)-3-{2-[2-(2-chloro-3,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichlorophenoxy)ethoxymethyl]-thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(3-chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2-chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(4,5-dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(5-ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichlorophenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-6-fluoro-3-methylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)-phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)-phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R, 5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R, 5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]-oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2-chloro-3,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(4,5-dimethylisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(5-ethyl-4-fluoroisoxazol-3-yloxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-propyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichlorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(3-chloro-2,6-difluorophenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2,6-dichloro-4-methylphenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[3-(2-chloro-6-fluoro-3-methylphenoxy)propyl]-thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2-chloro-3,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(4-chloro-1-methyl-5-trifluoromethyl-1H-pyrazol-3-yloxy)-ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichlorophenoxy)ethoxymethyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-fluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(3-chloro-2,6-difluorophenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2-chloro-6-fluoro-3-methylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)-amide,

(*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]-non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{2-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R**, *5S**)-3-(2-{2-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R**, *5S**)-3-{2-[2-(2,6-dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]-propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, *5S*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxy-ethyl)phenoxy]-propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S*, *5R*)-3-(2-{3-[2,6-dichloro-4-((*R*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1S, 5R*)-3-(2-{3-[2,6-dichloro-4-((*S*)-1-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-9-azabicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-9-aza-bicyclo[3.3.1]non-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{3-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]propyl}thiazol-5-yl)-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[3-(2,6-dichloro-3,4-dimethylphenoxy)propyl]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-(2-{2-[2,6-dichloro-4-(2-hydroxyethyl)phenoxy]ethoxymethyl}-thiazol-5-yl)-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichloro-benzyl)amide,

(*1R*, 5S**)-3-{2-[2-(2,6-dichloro-3,4-dimethylphenoxy)ethoxymethyl]thiazol-5-yl}-8-azabicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(2,3-dichlorobenzyl)amide,

(*1R*, 5S**)-3-{2-[2-(2-chloro-3,6-difluorophenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide, and

(*1R*, 5S**)-3-{2-[2-(2,6-dichloro-4-methylphenoxy)ethoxy]thiazol-5-yl}-8-aza-bicyclo[3.2.1]oct-2-ene-2-carboxylic acid cyclopropyl-(3-methoxy-2-methylbenzyl)amide.

11. A pharmaceutical composition comprising at least one compound according to any one of claims 1-10 and a pharmaceutically acceptable carrier material.

12. A compound according to any one of claims 1-10, or composition according to claim 11, for use as a medicament.

13. Use of a compound according to any one of claims 1-10 for the preparation of a pharmaceutical composition for the treatment 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.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/001827

A. CLASSIFICATION OF SUBJECT MATTER
INV. C07D451/14 C07D451/02 A61K31/46 A61K31/439

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

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, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/096803 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; BUR, DANIEL; FISCHLI,) 11 November 2004 (2004-11-11) paragraph [0001] claim 1	1,12
A	WO 2004/096799 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; BUR, DANIEL; FISCHLI,) 11 November 2004 (2004-11-11) paragraph [0001] claim 1	1,12

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

☒ See patent family annex.

* Special categories of cited documents :

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 June 2006	06/07/2006

Name and mailing address of the ISA/	Authorized officer
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INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/001827

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004096803 A	11-11-2004	AU 2004234038 A1	11-11-2004
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WO 2004096799 A	11-11-2004	AU 2004234042 A1	11-11-2004
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