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(54) Title: NOVEL BICYCLIC DERIVATIVES

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



WO 2006/059304 A2

Novel Bicyclic Derivatives

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

In the renin-angiotensin system (RAS) the biologically active angiotensin II
10 (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 AT₁ and AT₂. Whereas AT₁ seems to transmit most of the known functions of Ang II, the role of AT₂ is still unknown.

15 Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT₁ blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in experimental and human hypertension", in Birkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, 1986, 489-519; Weber M. A., *Am. J. Hypertens.*, 1992,
20 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,
25 669).

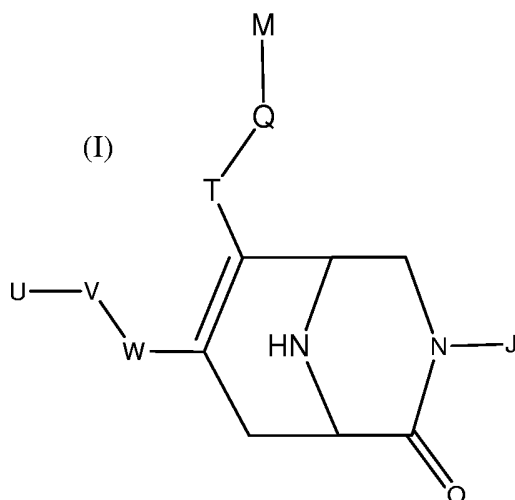
The rationale to develop renin inhibitors is the specificity of renin (Kleinert H. D., *Cardiovasc. Drugs*, 1995, 9, 645). The only substrate known for renin is angiotensinogen, which can only be processed (under physiological conditions) by renin. In contrast, ACE can also cleave bradykinin besides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

inhibition of ACE thus leads to bradykinin accumulation causing cough (5-20%) and potentially life-threatening angioneurotic edema (0.1-0.2%) (Israili Z. H. *et al.*, *Annals of Internal Medicine*, 1992, 117, 234). Chymase is not inhibited by ACE inhibitors. Therefore, the formation of Ang II is still possible in patients treated with ACE inhibitors. Blockade of the AT₁ receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT₂) to Ang II, whose concentration is significantly increased by the blockade of AT₁ receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT₁ blockers with regard to efficacy in blocking the RAS and in safety aspects.

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

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

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



wherein

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

V represents alkylenoxy or alkylendioxy, wherein alkylenoxy can be oriented in both possible ways;

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

T represents -CO-N(R¹)-;

Q represents alkylene;

M represents phenyl or pyridinyl, wherein these two radicals can be mono- or di-substituted, wherein the substituents are independently selected from alkyl; alkoxy; -OCF₃; -CF₃; hydroxy-alkyl; halogen; alkyl-O-(CH₂)₀₋₄-CH₂-; alkyl-O-(CH₂)₂₋₄-O-; and R'₂N-(CH₂)₀₋₄-CH₂-, wherein R' is independently selected from the group consisting of hydrogen, alkyl, cyclopropyl, and -C(=O)-R'' wherein R'' is C₁-C₄-alkyl, -CF₃, -CH₂-CF₃ or cyclopropyl;

R¹ represents alkyl or cycloalkyl, especially cyclopropyl; and

J represents hydrogen or alkyl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of
5 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:

10

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
15 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.

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

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

The term alkylenoxy refers to an -L-O- group, wherein L is an alkylene. Examples of
30 alkylenoxy groups are methylenoxy, ethylenoxy, propylenoxy, iso-propylenoxy, iso-butylenoxy, sec-butylenoxy and tert-butylenoxy.

The term alkylenedioxy refers to an -O-L-O- group, wherein L is an alkylene. Examples are oxymethylenoxy, oxyethylenoxy, oxypropylenoxy, oxy-iso-propylenoxy, oxy-tert-butylenoxy, etc.

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

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

The term cycloalkyl, alone or in combination, means a saturated cyclic hydrocarbon
10 ring system with 3 to 7, preferably 3 to 6 carbon atoms, i.e. cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl.

The expression pharmaceutically acceptable salts encompasses either salts with
15 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,
20 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.

25

The compounds of the formula (I) can 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
30 encompasses all these forms. Mixtures may be separated in a manner known *per se*, e.g. by column chromatography, thin layer chromatography, HPLC or crystallization.

Very preferred compounds are compounds of formula (I) wherein T represents -CONR¹-; R¹ represents cycloalkyl, especially cyclopropyl; Q represents methylene; and M represents phenyl, or mono- or di-substituted phenyl, wherein the substituents
5 are independently selected from CH₃O(CH₂)₂₋₃-, halogen, and -CF₃.

Especially preferred compounds are further compounds of formula (I) wherein V is propylenoxy; U represents phenyl which is tri-substituted with halogen; T represents -CONR¹-, wherein R¹ is cyclopropyl; Q represents methylene; M represents
10 phenyl which is di-substituted with halogen; and J represents alkyl, especially methyl.

An especially preferred compound of formula (I) is:
(1*R**, 5*S**)-7-[4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl]-3-methyl-2-oxo-
3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-
15 dichlorobenzyl)amide.

The compounds of formula (I) are useful for the treatment and/or prophylaxis of diseases such as or related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac
20 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,
25 anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases related to the renin-angiotensin system.

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

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

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

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

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

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

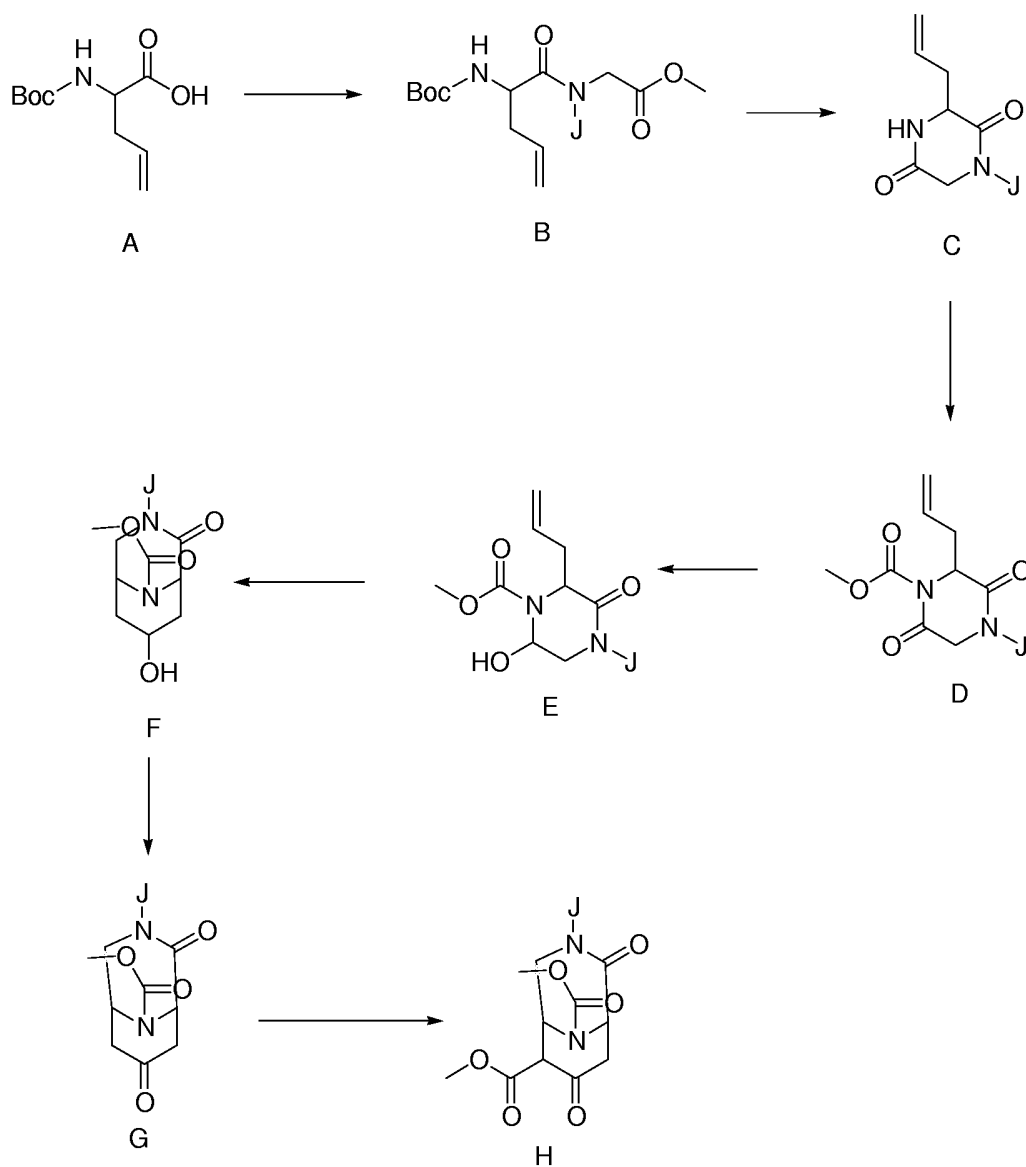
The present invention also relates to pro-drugs of a compound of formula (I) that convert *in vivo* to the compound of formula (I) as such. Any reference to a compound of formula (I) is therefore to be understood as referring also to the corresponding pro-
10 drugs of the compound of formula (I), as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

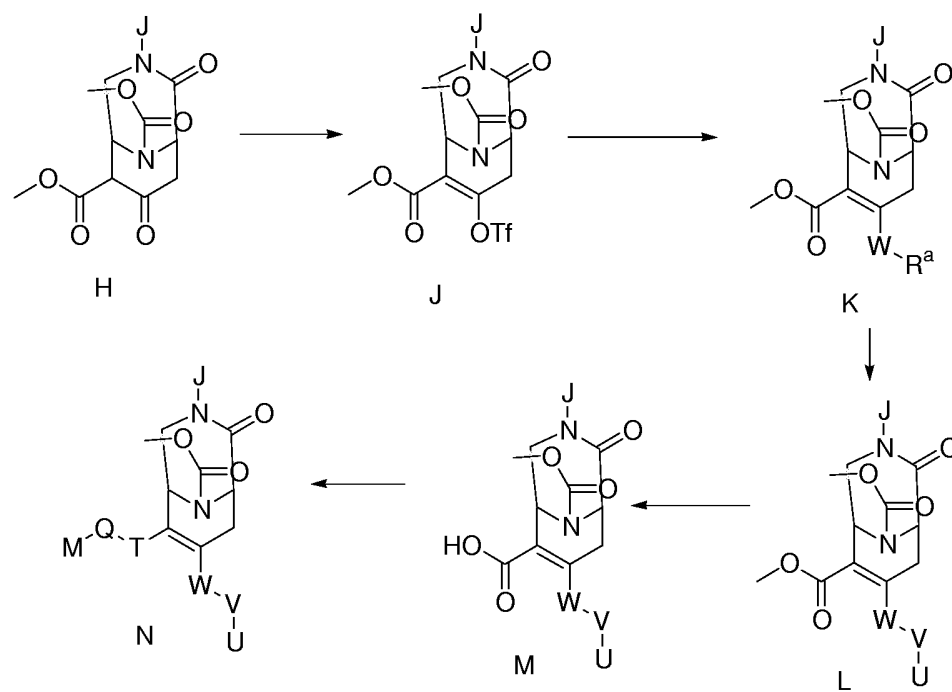
15 Chemistry

From Boc-protected allylglycine A the dipeptide B is prepared (Scheme 1) using known chemistry (H. Hiemstra *et al.*, *J. Org. Chem.*, 2003, 68, 4486). Removal of the Boc-protecting group and simultaneous cyclization leads to diketopiperazine C, which
20 is then reprotected to compound D. Partial reduction to compound E allows the second cyclization to take place and leads to compound F. Compound F is then oxidized to compound G, which is then acylated to compound H (Majewski, M; *et al.*; *J. Org. Chem.*, 1995, 60, 5825).

Scheme 1



- 5 The vinylic triflate of compound H can be prepared using standard conditions and leads to compound J (Scheme 2). A carbon-carbon coupling catalysed by a transition metal, typically a Pd- or a Co-complex, leads to a compound of type K, wherein the substituent R^a stands for a precursor for the group U-V as defined in formula I. After manipulations this compound is transformed into a compound of type L. Hydrolysis of
- 10 the ester leads to compound of type M, and for instance amide coupling leads then to a compound of type N.

Scheme 2

5 Preparation of final compounds

A compound of type N can be deprotected to a final compound as described in formula (I), by simple cleavage of the methoxycarbonyl protecting group.

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)

ACE	Angiotensin Converting Enzyme
15 AcOH	acetic acid
Ang	Angiotensin
aq.	aqueous
Boc	<i>tert</i> -Butyloxycarbonyl
BSA	Bovine serum albumine
20 BuLi	<i>n</i> -Butyllithium

	conc.	concentrated
	DIPEA	Diisopropylethylamine
	DMAP	4- <i>N,N</i> -Dimethylaminopyridine
	DMF	<i>N,N</i> -dimethylformamide
5	DMSO	Dimethylsulfoxide
	EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	Enzyme immunoassay
	ELSD	Evaporative light-scattering detection
	ES+	Electro spray positive ionization
10	Et	Ethyl
	EtOAc	Ethyl acetate
	EtOH	Ethanol
	FC	Flash Chromatography
	h	hour(s)
15	HMPA	hexamethylphosphoramide
	HOBt	Hydroxybenzotriazol
	KHMDS	Potassium hexamethyldisilazide
	LC-MS	Liquid chromatography – mass spectroscopy
	MeOH	Methanol
20	min	minute(s)
	MS	mass spectroscopy
	MTP	Microtiter plates
	org.	organic
	Ph	Phenyl
25	PyBop	(Benzotriazol-1-yloxy)tripyrrolidinophosphonium hexafluorophosphate
	rt	room temperature
	sat.	saturated
	sol.	Solution
	Tf	Trifluoromethylsulfonyl
30	THF	Tetrahydrofuran
	TFA	trifluoroacetic acid
	TPAP	tetrapropylammonium perruthenate
	t _R	retention time

UV ultra violet
vis visible

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

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

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

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

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

All t_R are given in min.

(*rac.*)-2-*tert*-Butoxycarbonylamino-pent-4-enoic acid (A)

20 A solution of (*rac.*)-allylglycine (20.2 g; 175 mmol) in THF/H₂O (670/670 mL) was
cooled to 0 °C. NaHCO₃ (44.11g; 525 mmol) was added portionwise and Boc₂O (68.8
g; 315mmol) was added also portionwise. The reaction mixture was stirred at 0 °C
under N₂ for 5 min, then at rt overnight. The pH of the milky mixture was adjusted to 4
by careful addition of saturated citric acid at 0 °C, and the mixture was extracted with
25 EtOAc. The combined org. layers were washed with brine, dried over MgSO₄, filtered,
and concentrated under reduced pressure. The title compound was isolated as a white
solid (35.1 g, 93%).

(*rac.*)-[(2-*tert*-Butoxycarbonylamino-pent-4-enoyl)methylamino]acetic acid methyl
30 ester (B)

PyBop (24.06g; 46.3 mmol) was added to a sol. of compound B (9.00 g; 42.04 mmol)
in DMF (200 mL) under N₂ at rt. The sol. was stirred for 10 min at rt, and sarcosine
methylester hydrochloride (6.46 g; 46.3 mmol) and DIPEA (23.8 mL; 139 mmol) were

added dropwise. The mixture was stirred at rt for 3 h. EtOAc (400 mL) was added and the resulting org. phase was washed with brine (3x). The combined org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. The crude product was diluted again in EtOAc (150 mL) and the mixture was washed
5 with water (2x). The combined org. layers were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification of the residue by FC (CH₂Cl₂/MeOH 50:1) yielded the title compound (8.82 g, 70%)

(*rac.*)-3-Allyl-1-methylpiperazine-2,5-dione (C)

10 TFA (80 mL) was added dropwise at rt to a sol. of compound B (10.36 g; 34.5 mmol) in CH₂Cl₂ (160 mL) under N₂. The mixture was stirred at rt for 1 h. The solvents were removed under reduced pressure, and were evaporated azeotropically twice with toluene. The crude brown product was diluted in a mixture of H₂O / EtOAc (172 mL / 172 mL), and K₂CO₃ (244 g; 33.81 mmol) was added. The mixture was stirred
15 overnight at rt. The solvents were removed under reduced pressure. Purification of the residue by FC (CH₂Cl₂/MeOH 20:1) yielded the title compound (9.68 g, 79%).

(*rac.*) 2-Allyl-4-methyl-3,6-dioxopiperazine-1-carboxylic acid methyl ester (D)

A mixture of compound C (11.85 g; 70.46 mmol), DMAP (17.22g; 141 mmol) and
20 Et₃N (19.61 mL; 141 mmol) in CH₂Cl₂ (250 mL) was cooled to 0 °C. Methylchloroformate (21.77 mL; 282 mmol) was added dropwise over 90 min and with gas evolution. The reaction mixture was allowed to warm up to rt and stirred overnight. The org. layer was washed with aq. 1M HCl (2x), then with brine (2x). The org. layer was dried over MgSO₄, filtered, and the solvents were removed under
25 reduced pressure. Purification of the residue by FC (CH₂Cl₂/MeOH 20:1) yielded the title compound as a yellow oil (13.37 g, 84%).

(*rac.*)-2-Allyl-6-hydroxy-4-methyl-3-oxo-piperazine-1-carboxylic acid methyl ester (E)

30 A sol. of compound D (4.70 g; 20.8 mmol) in THF (49 mL) was cooled at -78 °C and LiBHEt₃ (1M in THF, 20.8 mL, 20.8 mmol) was added dropwise at such a rate that the internal temperature did not exceed -70 °C (over 1 h 20 min). The reaction mixture was stirred at -78 °C for 25 min. The mixture was quenched with aq. sat. NaHCO₃ (33

mL) at -78°C , and was allowed to warm up to rt. EtOAc (75 mL) was added and the phases were separated. The aq. phase was extracted with EtOAc (2x). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. The title compound was obtained as a yellow oil (4.70 g, quantitative).

(*rac.*)-(1*R**, 5*S**)-7-Hydroxy-3-methyl-2-oxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylic acid methyl ester (F)

Compound E (4.74 g, 20.8 mmol) was diluted in formic acid (418 mL) at rt, and the sol. was stirred at rt for 1 h. The solvents were removed under reduced pressure, and the residue was evaporated azeotropically twice with toluene. The residue was diluted in NH_3 (7 M in MeOH) (44.6 mL), and the mixture was stirred at rt for 75 min. The solvents were removed under reduced pressure. Purification by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) yielded the title compound as a pale yellow solid (5.06 g, 51%).

(*rac.*)-(1*R**, 5*S**)-3-Methyl-2,7-dioxo-3,9-diazabicyclo[3.3.1]nonane-9-carboxylic acid methyl ester (G)

TPAP (0.74 g) and *N*-methyldmorpholine (3.95 g; 33.7 mmol) was added successively to a sol. of compound F (6.15 g; 27.0 mmol) in acetone (328 mL). The black mixture was stirred at rt for 1 h, and the solvents were removed under reduced pressure. Purification of the residue by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 20:1) yielded the title compound (4.55 g 75%).

(*rac.*)-(1*R**, 5*S**)-3-Methyl-2,7-dioxo-3,9-diazabicyclo[3.3.1]nonane-6,9-dicarboxylic acid dimethyl ester (H)

A sol. of diisopropylamine (0.742 mL; 5.29mmmol) in THF (13 mL) was cooled to -78°C . BuLi (1.6 M in hexane, 3.37 mL; 5.39 mmol) was added dropwise over 15 min. The mixture was stirred at -78°C for 15 min, and a sol. of compound G (1.09 g; 4.82 mmol) in THF (8.19 mL) was added dropwise at such a rate that the internal temperature did not exceed -70°C . The resulting yellow mixture was stirred at -78°C for 3 h. Methyl cyanoformate (0.497 mL, 6.26 mmol) was added at -78°C , and the mixture was stirred at -78°C for 1 h. A silver nitrate sol. (1.17 g; 22.1 mmol) in THF/ H_2O 1/1 (4.8 / 4.8 mL) was added at -78°C . After 10 min, water (3.37 mL) and AcOH (3.37 mL) were added at -78°C . The mixture was allowed to warm up to rt,

and aq. conc. NH_3 (15.32 mL) was added. The mixture was extracted with CH_2Cl_2 (9x). The combined org. extracts were dried over MgSO_4 , filtered, and the solvents were removed under reduced pressure. Purification by FC ($\text{CH}_2\text{Cl}_2/\text{MeOH}$ 40:1) yielded the title compound as a pale, yellow oil (0.81 g, 60%).

5

(*rac.*)-(1*R**, 5*S**)-3-Methyl-2-oxo-7-trifluoromethanesulfonyloxy-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid dimethyl ester (J)

A homogeneous sol. of compound H (806 mg, 2.83 mmol) in THF (16 mL) was cooled to -78°C . KHMDS in toluene (0.5 M, 5.95 mL, 2.98 mmol) was added dropwise to
10 this sol. while keeping the temperature below -70°C . The resulting mixture was further stirred at -78°C for 20 min, and then HMPA (0.788 mL, 4.53 mmol) was added in one portion. Stirring at -78°C was continued for 10 min and the reaction mixture was allowed to warm up to -20°C . The mixture was stirred further at this temperature for 15 min. The reaction mixture was cooled again to -78°C , and stirred during 10
15 min. An orange homogeneous sol. of *N*-(5-chloro-2-pyridyl)bis(trifluoromethanesulfonimide) (1.34 g, 3.40 mmol) in anhydrous THF (8 mL) was added dropwise at -78°C . The mixture was stirred further at -78°C for 1 h, and the resulting yellow reaction mixture was allowed to warm up slowly to rt overnight. Methanol (4 mL) was added. The reaction mixture was concentrated to
20 dryness under reduced pressure. Purification of the residue by FC ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$, 25:1) yielded the title compound (735 mg, 62 %). LC-MS: $t_R = 0.87$ min; ES+: 458.25.

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(*tert*-Butyldimethylsilyloxy)propyl]phenyl}-3-methyl-2-oxo-3,9-diaza-bicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid dimethyl ester (K1)

25 A sol. of [3-(4-bromophenyl)propoxy]-*tert*-butyldimethylsilane (Kiesewetter D. O., *Tetrahedron Asymmetry*, 1993, 4, 2183, 1.53 g; 4.65 mmol) in THF (16 mL) was cooled at -78°C . BuLi (3.00 mL; 4.80 mmol) was added. After completion of the addition, the resulting sol. was stirred at -78°C for 30 min. ZnCl_2 (1.0 M in THF, 5.13 mL 5.13 mmol) was added. The colorless reaction mixture was allowed to warm up to
30 rt, and a brown homogeneous solution of triflate J (735 mg, 1.765 mmol) and $\text{Pd}(\text{PPh}_3)_4$ (102 mg, 0.088 mmol) in THF (3 mL) were added. The resulting homogeneous yellow sol. was stirred further at rt for 5 min, and then at 45°C for 75 min. The reaction mixture was cooled to 0°C , and aq. sat. NaHCO_3 (15 mL) was

added to this reaction mixture, followed by EtOAc (70 mL) and water (10 mL). The phases were separated and the org. phase was further washed with brine (2x). The combined aq. phases were further extracted with EtOAc (25 mL). The combined org. extracts were dried over MgSO₄, filtered, and concentrated under reduced pressure.

- 5 Purification by FC (CH₂Cl₂/CH₃OH, 30:1) yielded the title compound as a yellow oil (848 mg, 93%). LC-MS: t_R = 1.15 min; ES+: 558.49.

(*rac.*)-(1*R**, 5*S**)-7-[4-(3-Hydroxypropyl)phenyl]-3-methyl-2-oxo-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid dimethyl ester (K2)

- 10 To a yellow, homogeneous sol. of compound K1 (804 mg, 1.44 mmol) in anhydrous MeOH (16 mL) was added in one fraction and at rt pyridinium toluene-4-sulfonate (509 mg, 1.87 mmol). The resulting sol. was further stirred at rt for 4.5 h. EtOAc (100 mL), and water (20 mL) were added. The phases were shaken and separated. The slightly yellow org. phase was washed with water (20 mL). The combined org. extracts were
15 dried over MgSO₄, filtered, and concentrated under reduced pressure. Purification by FC (CH₂Cl₂/CH₃OH, 20:1) yielded the title compound (509 mg, 81%). LC-MS: t_R = 0.77 min; ES+: 444.40.

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3-methyl-2-oxo-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid dimethyl ester (L)

- 20 To a slightly yellow homogeneous solution of compound K2 (500 mg, 1.13 mmol) in toluene (15 mL) were added successively at rt 2-chloro-3,6-difluorophenol (409 mg, 2.25 mmol), azodicarboxylic dipiperidide (627 mg, 2.25 mmol), and tributylphosphine (0.93 mL, 3.38 mmol). The mixture was stirred at rt for 2.5 h, and at 50 °C for 18 h.
25 The mixture was allowed to cool to rt. The solvents were removed under reduced pressure. Purification of the residue by FC (EtOAc/hexane, 1:1→ 9/1) yielded the title compound (668 mg, 98%). LC-MS: t_R = 1.08 min; ES+: 549.19.

(*rac.*)-(1*R**, 5*S**)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-3-methyl-2-oxo-3,9-diazabicyclo[3.3.1]non-6-ene-6,9-dicarboxylic acid 9-methyl ester (M)

- 30 To a cooled (0 °C; ice-water bath) homogeneous sol. of compound L (614 mg, 1.12 mmol) in anhydrous EtOH (12 mL) was added dropwise aq. 1M NaOH (1.22 mL, 1.22 mmol). The resulting homogeneous, slightly yellow reaction mixture was further

stirred at 0 °C for 5 min and then at rt for 32 h, while adding 2 mL-portions of aq. 1M NaOH when the reaction did not proceed further. The reaction mixture was cooled to 0°C. Aq. 1M HCl (3.40 mL, 3.40 mmol) was then added dropwise to pH 4. The solvents were partially removed under reduced pressure. Water (15 mL) was added as well as a few drops of aq. 1M HCl in order to reach pH 1-2. EtOAc (40 mL) was then added and the 2 phases were shaken and separated. The aq. phase was further extracted with EtOAc (2x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Drying the residue under high vacuum yielded the crude title compound (500.4 mg, 83.7%), which was used without further purification. LC-MS: t_R = 0.99 min.

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

To a homogeneous sol. of the compound M (500 mg; 0.935 mmol) in anhydrous CH₂Cl₂ (10.5 mL) were added successively at rt 2,3-dichlorobenzylcyclopropylamine (607 mg, 2.81 mmol), DIPEA (0.65 mL, 3.80 mmol.), DMAP (29 mg, 0.71 mmol), HOBt (190 mg 1.41 mmol), and EDC·HCl (718 mg, 3.75 mmol). The resulting mixture was stirred at rt for 67 h. CH₂Cl₂ (50 mL) was added to the reaction mixture, and the resulting sol. was washed with aq. 1M HCl (3x). The combined aq. layers were extracted with CH₂Cl₂ (2x), and the combined org. layers were finally washed with aq. sat. NaHCO₃, and the solvents were removed under reduced pressure. Purification of the residue by FC (CH₂Cl₂/CH₃OH, 40/1) yielded the title compound as a colorless solid (421 mg, 61%). LC-MS after FC: t_R = 1.20 min.

Example

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

5.7M HBr in AcOH (11 mL) was added at once at rt in a 25 mL-flask containing the solid colorless compound M (240 mg, 0.327 mmol). The resulting homogeneous yellow sol. was stirred at rt for 33 h. The reaction mixture was cooled to 0°C, and

water (20 mL) was added carefully (dropwise). 2.5M aq. NaOH (80 mL) was added dropwise to this cooled reaction mixture till pH 6. CH₂Cl₂ (100 mL) was added and the phases were shaken and separated. 2.5M aq. NaOH (15 mL) was added to the aq. phase at rt till pH 13. The resulting aq. phase was extracted with CH₂Cl₂. The combined org. extracts were dried over MgSO₄, filtered and the solvents were removed under reduced pressure. Purification of the residue by FC (CH₂Cl₂/CH₃OH, 20/1) yielded the title compound. LC-MS: t_R = 0.95 min.

Biological Assays

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

1.1 Preparation of Ang I-BSA conjugate

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

1.2 Preparation of BSA-Ang I coated MTP

Microtiter plates (MPT384, MaxiSorp™, Nunc) were incubated overnight at 4 °C with 80 µl of Ang I (1-10)/BSA conjugate, diluted 1:100'000 in PBS 1X in a teflon beaker (exact dilution dependent on batch of conjugate), emptied, filled with 90 µl of blocking solution [0.5% BSA (Sigma A-2153) in PBS 1X, 0.02% NaN₃], and incubated for at least 2 h at rt, or overnight at 4 °C. 96 well MTP (MaxiSorp™, Nunc) were coated with 200 µl conjugate and blocked with 250 µl blocking solution as above, except that the blocking solution contained 3% BSA. The plates can be stored in blocking solution at 4 °C for 1 month.

1.3 Ang I-EIA in 384 well MTP

The Ang I (1-10)/BSA coated MTP were washed 3 times with wash buffer (PBS 1X, 0.01% Tween 20) and filled with 75 μ l of primary antibody solution (anti-Ang I antiserum, pre-diluted 1:10 in horse serum), diluted to a final concentration of 1:100'000 in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4). 5 μ l 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 H₂O₂ [30%, (Fluka, 95300)] in substrate buffer (0.1M sodium acetate, 0.05M sodium dihydrogen phosphate, pH 4.2). The OD of the plate was read at 405 nm in a microplate reader (FLUOStar Optima from BMG). The production of Ang I during the renin reaction was quantified by comparing the OD of the sample with the OD of a standard curve of Ang I(1-10), measured in parallel.

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

The renin assay was adapted from an assay described before (Fischli W. *et al.*, *Hypertension*, 1991, 18:22-31) and consists of two steps: in the first step, recombinant human renin is incubated with its substrate (commercial human tetradecapeptide renin substrate) to create the product Angiotensin I (Ang I). In the second step, the accumulated Ang I is measured by an immunological assay (enzyme immuno assay, EIA). The detailed description of this assay is found below. The EIA is very sensitive and well suited for renin activity measurements in buffer or in plasma. Due to the low concentration of renin used in this assay (2 fmol per assay tube or 10 pM) it is possible to measure inhibitor affinities in this primary assay down to low pM concentration.

2.1 Methodology

Recombinant human renin (3 pg/ μ l) in assay buffer (PBS 1X, 1mM EDTA, 0.1% BSA, pH 7.4), human tetradecapeptide (1-14) substrate (Bachem, M-1120) [5 μ M in 10 mM HCl], hydroxyquinoline sulfate (Fluka, 55100) [30 mM in H₂O] and assay buffer were premixed at 4 °C at a ratio of 100:30:10:145. 47.5 μ l per well of this premix was

transferred into polypropylene plates (MTP384, Nunc). Test compounds were dissolved and diluted in 100% DMSO and 2.5 μ l added to the premix, then incubated at 37 °C for 3 h. At the end of the incubation period, 5 μ l of the renin reaction (or standards in assay buffer) were transferred into EIA assays (as described above) and Ang I produced by renin was quantified. The percentage of renin inhibition (Ang I decrease) was calculated for each concentration of compound and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC_{50}). The IC_{50} -values of all compounds tested are below 100 nM. However, selected compounds exhibit a very good bioavailability and are metabolically more stable than prior art compounds.

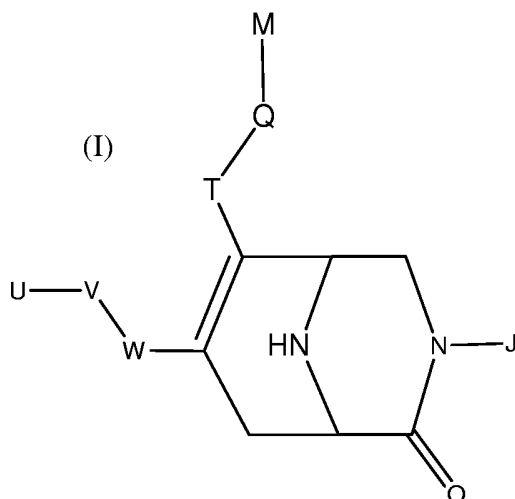
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The exemplified compound displays an IC_{50} -value below 10 nM.

Claims

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

5



wherein

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

10

V represents alkyleneoxy or alkylendioxy, wherein alkyleneoxy can be oriented in both possible ways;

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

15

T represents -CO-N(R¹)-;

Q represents alkylene;

20

M represents phenyl or pyridinyl, wherein these two radicals can be mono- or di-substituted, wherein the substituents are independently selected from alkyl; alkoxy; -OCF₃; -CF₃; hydroxy-alkyl; halogen; alkyl-O-(CH₂)₀₋₄-CH₂-; alkyl-O-(CH₂)₂₋₄-O-; and R'₂N-(CH₂)₀₋₄-CH₂-, wherein R' is independently selected from the group consisting of

hydrogen, alkyl, cyclopropyl, and $-C(=O)-R''$ wherein R'' is C_1-C_4 -alkyl, $-CF_3$, $-CH_2-$
 CF_3 or cyclopropyl;

R^1 represents alkyl or cycloalkyl; and

5

J represents hydrogen or alkyl;

and optically pure enantiomers, mixtures of enantiomers such as racemates,
diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of
10 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 T represents $-\text{CONR}^1-$; R^1 represents
cycloalkyl; Q represents methylene; and M represents phenyl, or mono- or di-
15 substituted phenyl, wherein the substituents are independently selected from
 $\text{CH}_3\text{O}(\text{CH}_2)_{2-3}$ -, halogen, and $-CF_3$.

3. A compound according to claim 1, wherein
V is propylenoxy; U represents phenyl which is tri-substituted with halogen; T
20 represents $-\text{CONR}^1-$, wherein R^1 is cyclopropyl; Q represents methylene; M represents
phenyl which is di-substituted with halogen; and J represents alkyl.

4. A compound according to claim 1 which is:
(*IR**, *5S**)-7-{4-[3-(2-chloro-3,6-difluorophenoxy)propyl]phenyl}-3-methyl-2-oxo-
25 3,9-diazabicyclo[3.3.1]non-6-ene-6-carboxylic acid cyclopropyl-(2,3-
dichlorobenzyl)amide.

5. A pharmaceutical composition comprising a compound according to any one of
claims 1 to 4 and a pharmaceutically acceptable carrier material.

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6. A compound according to any one of claims 1 to 4, or composition according to
claim 5, for use as a medicament.

7. Use of a compound according to any one of claims 1 to 4 for the preparation of a pharmaceutical composition for the treatment and/or prophylaxis of diseases selected from hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency, cardiac hypertrophy, cardiac fibrosis, myocardial ischemia, cardiomyopathy, glomerulonephritis, renal colic, complications resulting from diabetes such as nephropathy, vasculopathy and neuropathy, glaucoma, elevated intra-ocular pressure, atherosclerosis, restenosis post angioplasty, complications following vascular or cardiac surgery, erectile dysfunction, hyperaldosteronism, lung fibrosis, scleroderma, anxiety, cognitive disorders, complications of treatments with immunosuppressive agents, and other diseases related to the renin-angiotensin system.