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(54) Title: NOVEL LACTAME DERIVATIVES AS RENIN INHIBITORS

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



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NOVEL LACTAME DERIVATIVES AS RENIN INHIBITORS

- 5 The invention relates to novel five-membered heteroaryl derivatives of the general 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.
- 10 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 AT₁ and AT₂. Whereas
- 15 AT₁ seems to transmit most of the known functions of Ang II, the role of AT₂ is still unknown.

Modulation of the RAS represents a major advance in the treatment of cardiovascular diseases. ACE inhibitors and AT₁ blockers have been accepted to treat hypertension (Waeber B. *et al.*, "The renin-angiotensin system: role in

20 experimental and human hypertension", in Berkenhager W. H., Reid J. L. (eds): *Hypertension*, Amsterdam, Elsevier Science Publishing Co, 1996, 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

25 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 AT₁ receptor (e.g. by losartan) on the other hand overexposes other AT-receptor subtypes (e.g. AT₂) to Ang II, whose concentration is significantly increased by the blockade of AT₁ receptors. In summary, renin inhibitors are expected to demonstrate a different pharmaceutical profile than ACE inhibitors and AT₁ blockers with regard to efficacy in blocking the RAS and in safety aspects.

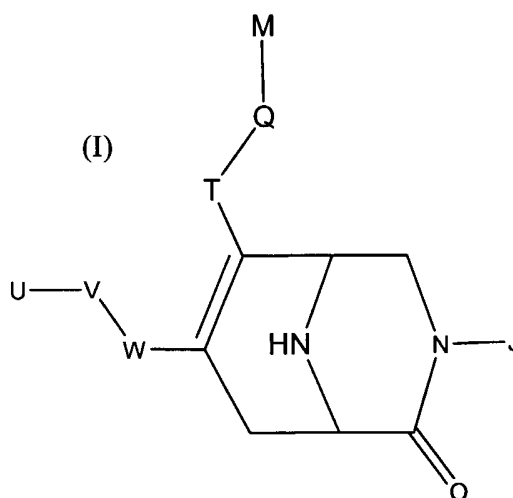
Only limited clinical experience (Azizi M. *et al.*, *J. Hypertens.*, **1994**, *12*, 419; Neutel J. M. *et al.*, *Am. Heart*, **1991**, *122*, 1094) has been created with renin inhibitors because of their insufficient oral activity due to their peptidomimetic character (Kleinert H. D., *Cardiovasc. Drugs*, **1995**, *9*, 645). The clinical development of several compounds has been stopped because of this problem together with the high cost of goods. Only one compound containing four chiral centers has entered clinical trials (Rahuel J. *et al.*, *Chem. Biol.*, **2000**, *7*, 493; Mealy N. E., *Drugs of the Future*, **2001**, *26*, 1139). Thus, renin inhibitors with good oral bioavailability and long duration of action are required. Recently, the first non-peptide renin inhibitors were described which show high *in vitro* activity (Oefner C. *et al.*, *Chem. Biol.*, **1999**, *6*, 127; Patent Application WO97/09311; Märki H. P. *et al.*, *Il Farmaco*, **2001**, *56*, 21). However, the development status of these compounds is not known.

The present invention relates to the identification of renin inhibitors of a non-peptidic nature and of low molecular weight. Described are orally active renin inhibitors of long duration of action which are active in indications beyond blood pressure regulation where the tissular renin-chymase system may be activated

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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.

- 5 The present invention relates to novel bicyclic derivatives of the general formula (I),



wherein

10

W represents a 1,4-disubstituted phenyl, substituted by V in *para* position;

V represents oxy-lower alkyl; lower alkyloxy or oxy-lower alkyloxy;

15 U represents aryl or mono-, di-, tri- or tetra- substituted aryl, whereby the substituents are halogen, -CF₃, -OCF₃, -CH₂OH or lower alkyl;

T represents -CO-N(R¹)-;

Q represents lower alkylene;

20

M represents phenyl, mono- or di-substituted phenyl, substituted by lower alkyl, lower alkyloxy, -OCF₃, -CF₃, hydroxy-lower alkyl, halogen;

R¹ represents lower alkyl; or cycloalkyl ;

J represents hydrogen or lower alkyl;

5

In a preferred embodiment also the following forms are encompassed: optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts,
10 solvent complexes and morphological forms.

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

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

The term **oxy-lower alkyl** refers to a –O-R group, wherein R is lower alkyl. Examples are oxymethyl, oxyethyl, oxypropyl, oxy-iso-propyl, oxy- tert.-butyl etc.

The Term **oxy-lower alkyloxy** refers to a -O-R-O- group, wherein R is lower
25 alkylen. Examples are oxymethylenoxy, oxyethylenoxy, oxypropylenoxy, oxy-iso-propylenoxy, oxy-tert.-butylenoxy etc.

The term **lower alkylene**, alone or in combination with other groups, means straight and branched divalent chain groups with one to seven carbon atoms, preferably one to four carbon atoms. Examples of lower alkylene are methylene,
30 ethylene, propylene or butylene.

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

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

The expression **pharmaceutically acceptable** salts encompasses either salts with inorganic acids or organic acids like hydrochloric or hydrobromic acid, sulfuric acid, phosphoric acid, citric acid, formic acid, acetic acid, maleic acid, tartaric acid, benzoic acid, methanesulfonic acid, p-toluenesulfonic 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.

15

The compounds of the general 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, and the meso-form and pharmaceutically acceptable salts thereof.

The present invention encompasses all these forms. Mixtures may be separated in a manner known *per se*, i.e. by column chromatography, thin layer chromatography, HPLC or crystallization Bicyclic derivatives of the general Very Very preferred compounds are compounds of formula (I) wherein W, V, U, J are as defined in general formula (I), T represents -CONR¹-, R¹ represents cycloalkyl; Q represents methylene; M represents phenyl, mono- or di-substituted phenyl substituted with halogen, -CF₃, or -OCF₃,

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

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diastereomeric racemates, and the meso- form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

An especially preferred bicyclic derivative of general formula (I) is:

- 5 (*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.

The invention relates to a method for the treatment and/or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary
10 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
15 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, which method comprises administering a compound as defined above to a human being or animal.

- 20 In another embodiment, the invention relates to a method for the treatment and/or prophylaxis of diseases which are 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, complications resulting from diabetes such as
25 nephropathy, vasculopathy and neuropathy.

In another 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 as well as for the treatment of the above-mentioned diseases.

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

A further aspect of the present invention is related to a pharmaceutical composition containing at least one compound according to general formula (I) and pharmaceutically acceptable carrier materials or adjuvants. This pharmaceutical composition may be used for the treatment or prophylaxis of the above-mentioned disorders; as well as for the preparation of a medicament for the treatment and/or prophylaxis of the above-mentioned diseases.

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

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

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

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

All forms of prodrugs leading to an active component comprised by general formula (I) above are included in the present invention.

Compounds of formula (I) and their pharmaceutically acceptable acid addition salts can be used as medicaments, e. g. in the form of pharmaceutical compositions containing at least one compound of formula (I) and

pharmaceutically acceptable inert carrier material or adjuvants. These 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 pharmaceutical preparations can be effected in a manner which will be familiar to any person skilled in the art by bringing the described compounds of formula (I) and 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.

- 5 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.

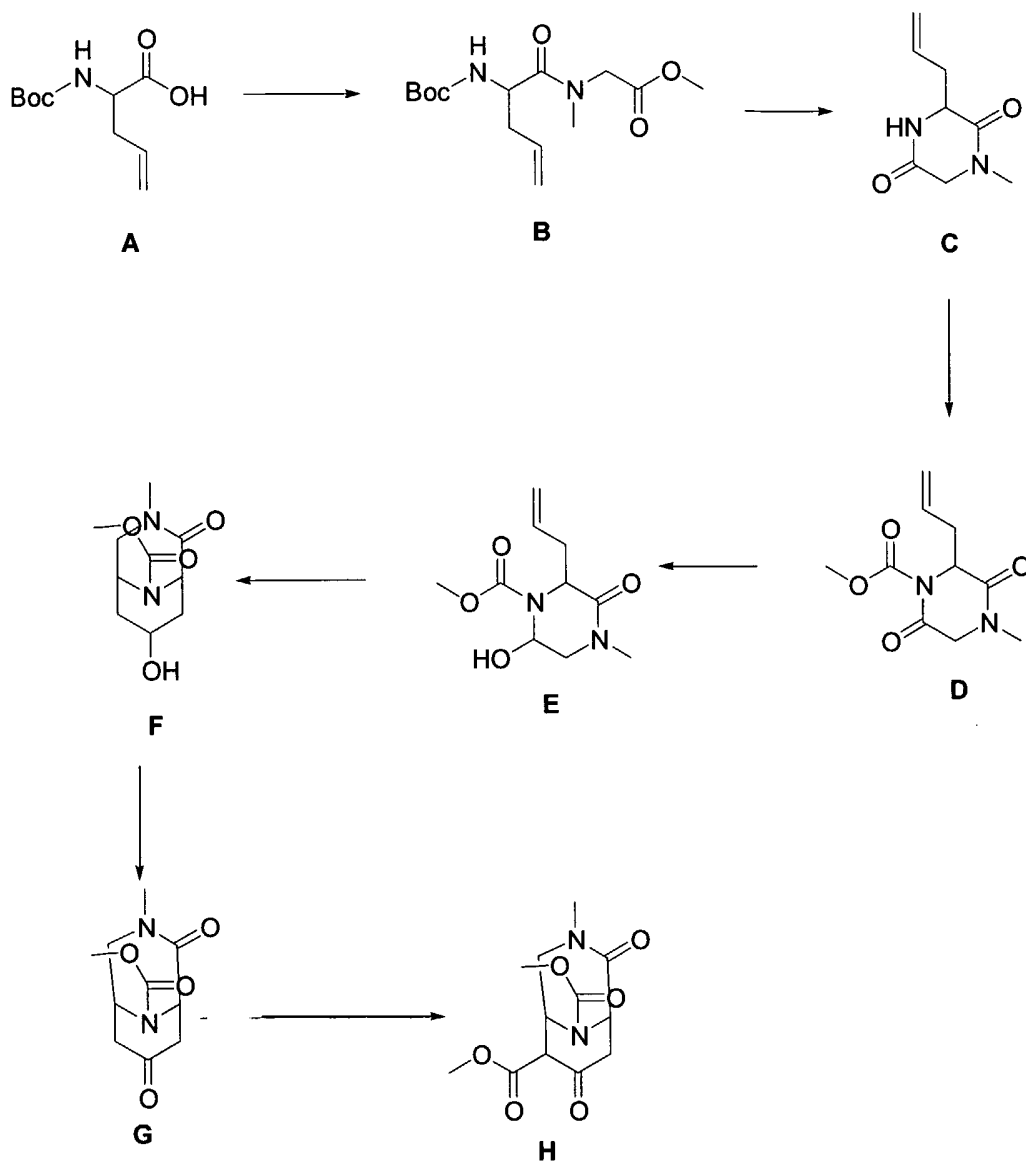
Another aspect of the invention is related to a process for the preparation of a
10 pharmaceutical composition comprising a derivative of the general formula (I). According to said process, one or more active ingredients of the general formula (I) are mixing with inert excipients in a manner known *per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

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

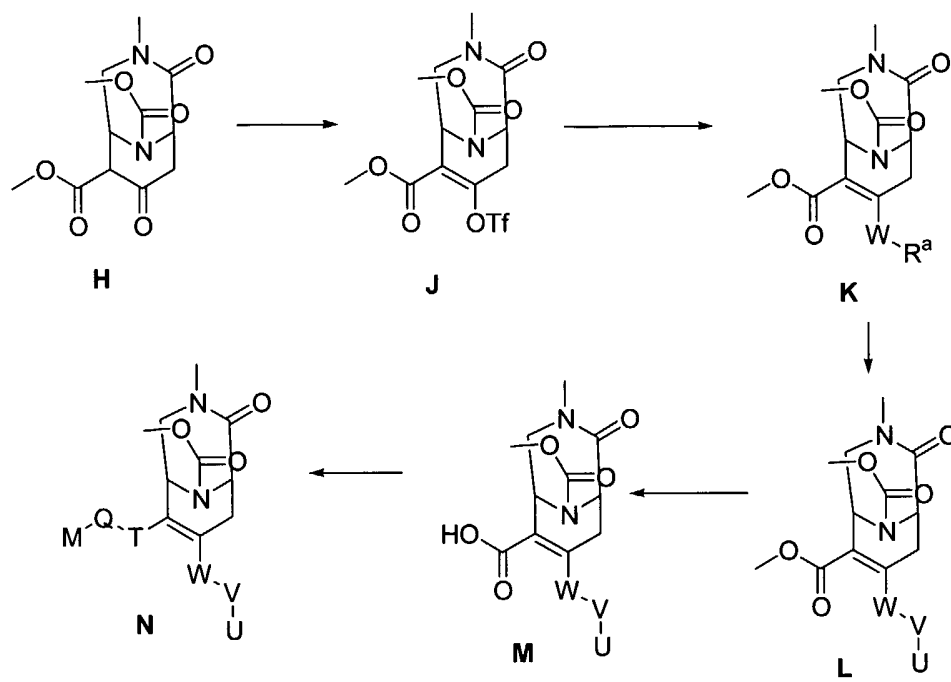
Chemistry

- 20 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 is then reprotected to compound **D**. Partial reduction to compound **E** allows the second cyclization to take place and leads to compound **F**. Compound
25 **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**, whereas the substituent R^a stands for a precursor for the group U-V as defined in general formula I. After manipulations this compound is transformed into a compound of type **L**. Hydrolysis of the ester leads to compound of type **M**, and
- 10 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 general formula (I), by simple cleavage of the methoxycarbonyl protecting group.

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

ExamplesAbbreviations

15

ACE	Angiotensin Converting Enzyme
AcOH	acetic acid
Ang	Angiotensin
aq.	aqueous
20 Bn	Benzyl

	Boc	<i>tert</i> -Butyloxycarbonyl
	BSA	Bovine serum albumine
	BuLi	<i>n</i> -Butyllithium
	conc.	concentrated
5	DIPEA	Diisopropylethylamine
	DMAP	4- <i>N,N</i> -Dimethylaminopyridine
	DMSO	Dimethylsulfoxide
	EDC·HCl	Ethyl- <i>N,N</i> -dimethylaminopropylcarbodiimide hydrochloride
	EIA	Enzyme immunoassay
10	eq.	equivalent
	Et	Ethyl
	EtOAc	Ethyl acetate
	FC	Flash Chromatography
	HOBt	Hydroxybenzotriazol
15	KHMDS	Potassium hexamethyldisilazide
	MeOH	Methanol
	NMO	<i>N</i> -Methylmorpholine <i>N</i> -oxide
	org.	organic
	PG	protecting group
20	Ph	Phenyl
	RAS	<u>Renin Angiotensin System</u>
	rt	room temperature
	sol.	Solution
	TBAF	Tetra- <i>n</i> -butylammonium fluoride
25	TBDMS	<i>tert</i> -Butyldimethylsilyl
	<i>t</i> BuOH	<i>tert</i> -Butanol
	<i>t</i> BuOK	Potassium <i>tert</i> -butylate
	Tf	Trifluoromethylsulfonyl
	THF	Tetrahydrofuran
30	TLC	Thin Layer Chromatography

The compounds are characterized at least by LC-MS and $^1\text{H-NMR}$. Only the LC-MS data are given here (Zorbax SB-AQ column, 5 μm , 4.6x50 mm; eluent A: 0.04% trifluoroacetic acid in water; eluent B: acetonitrile; gradient 5% $\rightarrow$ 100% eluent B over 1.5 min, flow 1 mL/min)

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Example

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

- 10 A solution of DL-allylglycine (20.2 g; 175mmol) in THF/H₂O (670/670 ml) was cooled to 0 °C. NaHCO₃ (44.11g; 525mmol) was added portionwise and Boc₂O (68.8g; 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 carefully addition of saturated citric acid at 0°C, and the mixture
- 15 was extracted with 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 ester (B)

20

- PyBop (24.06g; 46.3 mmol) was added to a sol. of compound B (9.00 g; 42.04mmol) in DMF (200 mL) under N₂ at rt. The sol. was stirred for 10 min at rt, and sarcosine methylester hydrochloride (6.46g; 46.3 mmol) and DIPEA (23.8
- 25 mL; 139 mmol) were added dropwise. The mixture was stirred at rt for 3 hours. EtOAc (400 mL) was added and the resulting organic 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 with water (2x). The
- 30 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)

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 (172/172 mL), and K₂CO₃ (244 g; 33.81 mmol) was added. The mixture was stirred 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 (17.22 g; 141 mmol) and 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 organic 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 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)

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 as 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. 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 MgSO₄, filtered, and the solvents were removed under reduced pressure. The title compound was obtained as a yellow oil (4.70 g, quantitative).

5 **(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 1h. The solvents were removed under reduced
10 pressure, and the residue was evaporated azeotropically twice with toluene. The residue was diluted in NH₃ (7 M in MeOH) (44,6mL), and the mixture was stirred at rt for 1h15. The solvents were removed under reduced pressure. Purification by FC (CH₂Cl₂/MeOH 20:1) yielded the title compound as a pale yellow solid (5.06 g, 51%).

15

(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*-methylmorpholine (3.95 g; 33.7 mmol) was added
20 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 (CH₂Cl₂/MeOH 20:1) yielded the title compound (4.55 g 75%).

25 **(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
30 (1.09 g; 4.82 mmol) in THF (8.19 mL) was added dropwise at such a rate as the interne temperature did not exceed -70°C. The resulting yellow mixture was stirred at -78 °C for 3 h. Methylcyanoformate (0.497 mL, 6.26 mmol) was added

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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/H₂O 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. NH₃ (15.32 mL) was added. The mixture was extracted with CH₂Cl₂ (9x). The combined org. extracts were dried over MgSO₄, filtered, and the solvents were removed under reduced pressure. Purification by FC (CH₂Cl₂/MeOH 40:1) the title compound as a pale Yellow oil (0.81 g, 60%).

10 **(rac.)-(1R*, 5S*)-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 solution 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 this solution 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 min. An orange homogeneous solution 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 1h, 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 dryness under reduced pressure. Purification of the residue by FC (CH₂Cl₂/CH₃OH, 25:1) yielded the title compound (735 mg, 62 %). LC-MS: t_{R} = 0.87 min; ES+: 458.25.

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

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.

5 ZnCl₂ (1.0 M in THF, 5.13 mL 5.13 mmol) was added. The colorless reaction mixture was allowed to warm-up to rt, and a brown homogeneous solution of triflate J (735 mg, 1.765 mmol) and Pd(PPh₃)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° for 1h15. The reaction mixture was cooled to 0°C ,

10 and aq. sat. NaHCO₃ (15 mL) was added to this reaction mixture, followed by EtOAc (70 mL) and water (10 mL). The phases were separated and the organic 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. Purification by FC

15 (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.)-(1R*, 5S*)-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)

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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 4.5h. EtOAc (100 mL), and water (20 mL) were added. The phases were shaken

25 and separated. The slightly yellow org. phase was washed with water (20 mL). The combined org. extracts were 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.

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

To a slightly yellow homogeneous solution of compound **K2** (500 mg, 1.13 mmol) 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. 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.

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

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.)-(1R*, 5S*)-7-{4-[3-(2-Chloro-3,6-difluorophenoxy)propyl]phenyl}-6-[cyclopropyl-(2,3-dichlorobenzyl)carbamoyl]-3-methyl-2-oxo-3,9-diazabicyclo[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 concentrated 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

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(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 33h. 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**Inhibition of human recombinant renin by the compounds of the invention**

5 The enzymatic in vitro assay was performed in 384-well polypropylene plates (Nunc). The assay buffer consisted of 10 mM PBS (Gibco BRL) including 1 mM EDTA and 0.1% BSA. The incubates were composed of 50 μ L per well of an enzyme mix and 2.5 μ L of renin inhibitors in DMSO. The enzyme mix was premixed at 4°C and consists of the following components:

- 10 • human recombinant renin (0.16 ng/mL) • synthetic human angiotensin(1-14) (0.5 μ M)
• hydroxyquinoline sulfate (1 mM)

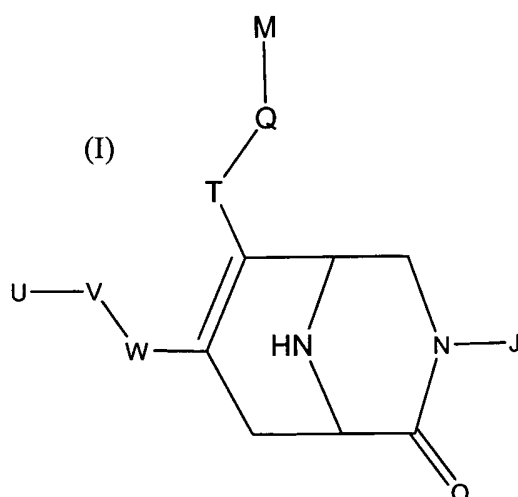
The mixtures were then incubated at 37°C for 3 h.

To determine the enzymatic activity and its inhibition, the accumulated Ang I was
15 detected by an enzyme immunoassay (EIA) in 384-well plates (Nunc). 5 μ L of the incubates or standards were transferred to immuno plates which were previously coated with a covalent complex of Ang I and bovine serum albumin (Ang I – BSA). 75 μ L of Ang I-antibodies in assaybuffer above including 0.01% Tween 20 were added and a primary incubation made at 4 °C overnight. The plates were
20 washed 3 times with PBS including 0.01% Tween 20, and then incubated for 2 h at rt with an antirabbit-peroxidase coupled antibody (WA 934, Amersham). After washing the plates 3 times, the *peroxidase substrate* ABTS (2,2'-azino-di-(3-ethyl-benzthiazolinsulfonate), was added and the plates incubated for 60 min at room temperature. After stopping the reaction with 0.1 M citric acid pH 4.3 the plate
25 was evaluated in a microplate reader at 405 nm. The percentage of inhibition was calculated of each concentration point and the concentration of renin inhibition was determined that inhibited the enzyme activity by 50% (IC₅₀). The IC₅₀-values of all compounds tested are below 100 nM. However selected compounds exhibit a very good bioavailability and are metabolically more stable than prior art
30 compounds.

The exemplified compound displayed an IC₅₀-value of 2.1 nM.

Claims

1. Novel bicyclic derivatives of the general formula (I),



wherein

W represents a 1,4-disubstituted phenyl, substituted by V in *para* position;

V represents oxy-lower alkyl; lower alkyloxy or oxy-lower alkyloxy;

U represents aryl or mono-, di-, tri- or tetra- substituted aryl, whereby the substituents are halogen, -CF₃, -OCF₃, -CH₂OH or lower alkyl;

T represents -CO-N(R¹)-;

Q represents lower alkylene;

M represents phenyl, mono- or di-substituted phenyl, substituted by lower alkyl, lower alkyloxy, -OCF₃, -CF₃, hydroxy-lower alkyl, halogen;

R¹ represents lower alkyl; or cycloalkyl ;

J represents hydrogen or lower alkyl;

and optically pure enantiomers, mixtures of enantiomers such as racemates, diastereomers, mixtures of diastereomers, diastereomeric racemates, mixtures of diastereomeric racemates, and the meso-form; as well as pharmaceutically acceptable salts, solvent complexes and morphological forms.

2. Bicyclic derivatives of the general formula (I) according to claim 1 wherein W, V, U, J are as defined in general formula (I), T represents -CONR¹-, R¹ represents cycloalkyl; Q represents methylene; M represents phenyl, mono- or di-substituted phenyl substituted with halogen, -CF₃, or -OCF₃.

3. A bicyclic derivative according to any of claims 1 to 2 selected from the group consisting of:

(*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.

4. A pharmaceutical composition containing at least one bicyclic derivative according to any of claims 1 to 3 and pharmaceutically acceptable carrier materials or adjuvants.

5. A compound according to any of claims 1 to 3, or composition according to claim 4, for use as medicament.

6. Use of a compound according to any of claims 1 to 3, or a composition according to claim 4, for the manufacture of a medicament for the treatment or prophylaxis of diseases which are 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
5 diseases known to be related to the renin-angiotensin system.

7. A method for the treatment or prophylaxis of diseases which are related to hypertension, congestive heart failure, pulmonary hypertension, renal insufficiency, renal ischemia, renal failure, renal fibrosis, cardiac insufficiency,
10 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
15 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, comprising the administration to a patient of a pharmaceutically active amount of a five-membered heteroaryl derivative according to any of claims 1 to 3, or composition according to claim 4.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013610

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07D471/08 A61K31/4995 A61P13/12

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)

IPC 7 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, BEILSTEIN Data, CHEM ABS Data, EMBASE, BIOSIS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2004/096116 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; BUR, DANIEL; FISCHLI,) 11 November 2004 (2004-11-11) claim 1	1-7
Y	WO 2004/096803 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; BUR, DANIEL; FISCHLI,) 11 November 2004 (2004-11-11) claim 1	1-7
Y	WO 2004/096366 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVER; BUR, DANIEL; FISCHLI,) 11 November 2004 (2004-11-11) claim 1	1-7
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☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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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

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Date of the actual completion of the international search

15 September 2005

Date of mailing of the international search report

05/10/2005

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP2004/013610

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
T	WO 2005/040173 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; SIFFERLEN, THIERRY; B) 6 May 2005 (2005-05-06) claim 1 -----	1-7
T	WO 2005/054244 A (ACTELION PHARMACEUTICALS LTD; BEZENCON, OLIVIER; SIFFERLEN, THIERRY; B) 16 June 2005 (2005-06-16) claim 1 -----	1-7

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2004/013610

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004096116 A	11-11-2004	NONE	
WO 2004096803 A	11-11-2004	NONE	
WO 2004096366 A	11-11-2004	NONE	
WO 2005040173 A	06-05-2005	NONE	
WO 2005054244 A	16-06-2005	NONE	