

- 1 -

NEW NON-PEPTIDE DERIVATIVES AS BRADYKININ B1 ANTAGONISTS**FIELD OF THE INVENTION**

5 The present invention relates to new non-peptide derivatives represented by formula (I) and optical antipodes or racemates and/or salts and/or hydrates and/or solvates thereof which are useful in the treatment or prevention of painful and inflammatory processes. The present invention also relates to the processes for producing compounds of formula (I) and to pharmacological compositions containing
10 the same.

BACKGROUND OF THE INVENTION

 Kinins are endogenous peptides formed in plasma and peripheral tissues in
15 response to tissue injury or infection following catalytic cleavage of kininogens by kallikrein enzymes. Kinins play an important role in the pathophysiological processes accompanying pain and inflammation. Their biological actions are mediated by two G-protein coupled membrane receptors, denoted B1 and B2. Both B1 and B2 receptors have been cloned [*Biochem. Biophys. Res. Commun.*, **184** (1992) 260-268 and
20 *J.Biol.Chem.*, **269** (1994) 21583-21586] and the mechanisms regulating their expression, self-maintenance and signalling function is under intensive investigations [*Mol. Pharmacol.*, **56** (1999) 325-333 and *J. Cell. Physiol.* **193** (2002) 275-286].

 The first set of kinins, bradykinin (BK) and kallidin (LysBK) preferentially act through stimulation of constitutively expressed and rapidly desensitising B2 receptors,
25 which are widely distributed in many tissues. On the other hand, their active carboxypeptidase metabolites, the second set of kinins, desArg⁹BK (DABK) and LysdesArg⁹BK (LysDABK) activate inducible and non-desensitising B1 receptors, which are rarely expressed under non-pathological conditions. Generally B1 receptors rapidly appear after injuries of various natures (tissue trauma, infections, *etc.*). Thus the
30 B1 receptor up-regulation appears to be part of a generalized response that includes the

-2 -

local co-expression (eventually up-regulation) of enzymes, receptors, autacoids, cytokines and chemokines that notoriously play key roles in the early and late responses of tissues to various types of injury.

In animal models it has been demonstrated that there is a switch in dominance of function from B2 to B1 in chronic inflammatory states. While the B2 receptor is implicated in the acute phase of the inflammatory and pain response, the B1 receptor is involved in the chronic phase of this response. The involvement of kinin receptors in inflammation and pain transduction has been supported by the results of studies on mice lacking bradykinin B1 receptors. B1 receptor deficient mice are different from wild-type mice in sensory functions, exhibiting increased analgesic thresholds to noxious chemical and heat stimuli, and drastic reduction in the accumulation of polymorphonuclear leukocytes at sites of inflammation [*PNAS*, **97** (2000) 8140-8145 and *Neuropharmacology* **41** (2001) 1006-1012]. Furthermore the most original finding in B1 receptor deficient mice was the direct evidence for a role of central kinin receptors in nociception suggesting that the hypoalgesia seen in B1-receptor knockout mice is partly due to reduced central sensitisation in the spinal cord. However, apart from the above changes B1 knockout mice were apparently normal without any apparent pathological changes.

Apart from the evidence of basal expression of B1 receptors on the periphery recently more and more evidence shows that B1 receptors are constitutively expressed 'centrally' in some neuronal elements, including the spinal cord and some higher structures as well. The function of these receptors is unclear but they have been implicated in pain transmission and hyperalgesia. Therefore, B1 receptor antagonists are believed to be useful in alleviating pain not only via peripheral sites but also to have possibly broader spectrum of analgesic effects if they block central B1 receptors as well [*NeuroReport* **11** (2000) 4003-4005; *NeuroReport*, **12** (2001) 2311-2313; *Neuroscience* **107** (2001) 665-673 and *Neuroscience Letters* **294** (2000) 175-178].

On the basis of scientific data bradykinin receptors are involved in mediation of pain and hyperalgesia in several ways. B1 receptor antagonists may have diverse modes of action. They have (1) indirect ('peripheral') effects on the nociceptors via inhibition of release of other algogenic mediators. N.B. B1 receptors appear upon inflammatory induction on cells adjacent to sensory neurones (macrophages, fibroblasts or endothelial

-3 -

cells) are involved in releasing mediators (prostaglandins, cytokines and nitric oxide) that sensitize or activate the nociceptors. (2) direct ('peripheral') effects on nociceptors expressing B1 receptors (constitutively) or upon induction and (3) 'central' effects on pain processing in the superficial dorsal horn of spinal cord.

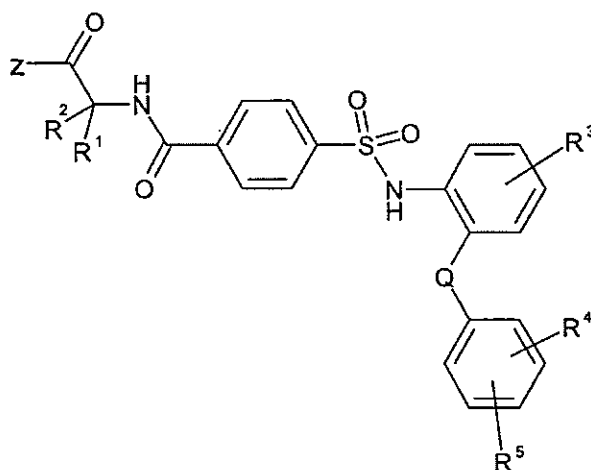
5 Therefore, an orally active non-peptide bradykinin B1 receptor antagonist could be a potential therapeutic agent in the treatment of chronic inflammatory pain.

Several patents and patent applications describe bradykinin B1 receptor antagonists which have different chemical structures. Such documents are for instance the following international patent applications: WO200075107, WO02076964,
10 WO04054584, WO02099388, WO05004810.

SUMMARY OF THE INVENTION

15 We have found a class of non-peptide derivatives which have high affinity for bradykinin B1 receptors and selectivity over bradykinin B2 receptors. The selectivity is particularly important as the undesired side effects of the compounds are much less pronounced.

The present invention relates to new non-peptide derivatives of formula (I)



(I)

wherein

R¹ is hydrogen atom or C₁-C₄ alkyl group;

-4-

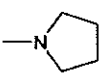
R^2 is selected from (1) hydrogen atom; (2) C_1 - C_6 straight or branched alkyl group; (3) $-(CH_2)_n-NH_2$; (4) $-(CH_2)_n-OH$; (5) $-(CH_2)_n-CO-NH_2$; (6) $-(CH_2)_n-COOR^c$; (7) benzyl optionally substituted with one or more hydroxy group or halogen atom; or

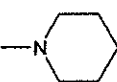
5 R^1 , R^2 and the carbon atom to which they are both attached together form a 3-7 membered cycloalkyl ring;

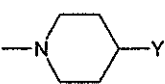
R^3 , R^4 and R^5 are independently of each other hydrogen atom; halogen atom; cyano; nitro; amino; or amino substituted with one or more C_1 - C_4 alkyl group; trifluoromethyl; C_1 - C_4 alkyl; C_1 - C_4 alkoxy; trifluoromethoxy; C_1 - C_4 alkoxy carbonyl; $-C(=O)-NH_2$ or hydroxy group;

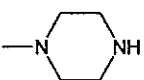
10 Q is selected from (1) oxygen atom; (2) sulfur atom;

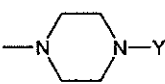
Z is selected from

(1) , optionally substituted with $-(CH_2)_m-OH$ group, or $-(CH_2)_n-X-P$ group;

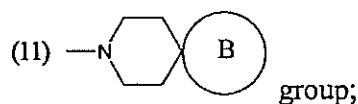
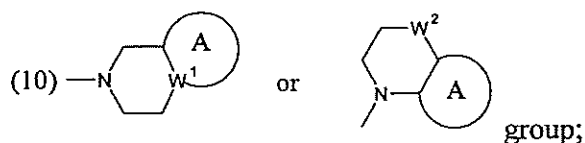
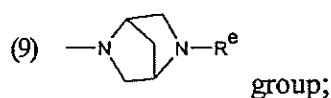
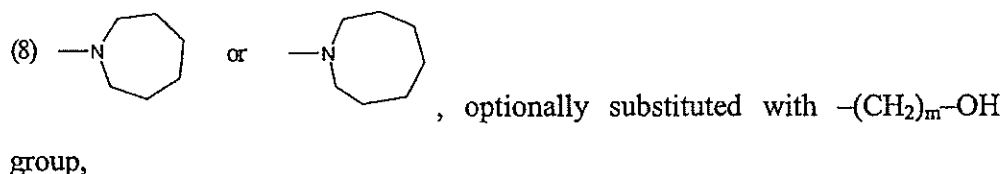
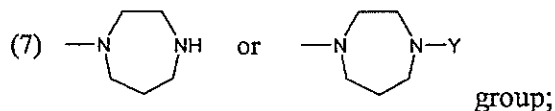
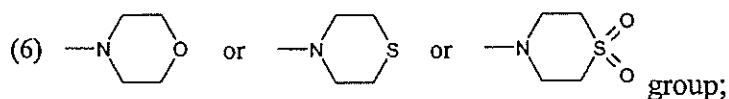
15 (2) , optionally substituted with one or more C_1 - C_4 alkyl group, one or more halogen atom, $-(CH_2)_m-OH$ group, $-(CH_2)_m-NH_2$ group, $-(CH_2)_m-CO-NH_2$ group, trifluoromethyl group, oxo group, $-(CH_2)_m-CN$ group; $-NH-CO-(C_1-C_4 \text{ alkyl})$ group, $-NH-SO_2-(C_1-C_4 \text{ alkyl})$ group, $-(CH_2)_m-COOR^c$ group, $-CO-NR^cR^d$ group, $-(C_1-C_4 \text{ alkoxy})$ group, $-NH-CO-(CH_2)_m-CF_3$ group, $-NH-SO_2-CH_2-CF_3$ group;

(3)  group;

(4) , optionally substituted with oxo group, $-SO_2-(C_1-C_4 \text{ alkyl})$ group, C_1 - C_4 alkyl group, $-CO-(C_1-C_4 \text{ alkyl})$ group, $-(CH_2)_m-O-(CH_2)_m-OH$ group, $-(CH_2)_m-OH$ group, $-SO_2-NR^cR^d$ group, $-CO-NR^cR^d$ group;

25 (5)  group;

-5 -



(12) $-NH-(CH_2)_n-P$ group;

(13) $-NH-(CH_2)_q-NR^aR^b$ group;

10 Y is selected from (1) $-(CH_2)_n-NR^aR^b$; (2) $-(CH_2)_n-X-P$ group;

n is an integer from 0 to 6;

m is an integer from 0 to 3;

q is an integer from 1 to 6;

X is selected from (1) single bond; (2) oxygen atom; (3) $-CO-NR^c$ group; (4) CO or SO_2 group;

15 P is selected from (1) phenyl group, optionally substituted with one or more halogen atom, hydroxy, cyano, amino, [1,4']bipiperidiny-1'-yl or C_1-C_4 alkyl group; (2) a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO_2 and N; wherein said ring is
20 optionally substituted with one or more halogen atom, oxo, hydroxy, cyano, amino, piperidin-1-yl or C_1-C_4 alkyl group; (3) C_5-C_8 cycloalkyl group, optionally substituted with $-(CH_2)_m-NR^aR^b$ group;

-6 -

- R^a and R^b are (1) hydrogen atom, with the proviso that R^a and R^b can not be simultaneously hydrogen atom; (2) straight or branched C₁-C₆ alkyl group; (3) R^a, R^b and the nitrogen atom to which they are both attached together form a saturated, partially unsaturated or aromatic 4-7 membered ring containing 0-3
5 heteroatom (in addition to the nitrogen atom to which R^a and R^b attached) selected from O, S, SO₂ and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, cyano, hydroxy or C₁-C₄ alkyl group;
- R^c is hydrogen atom or C₁-C₄ alkyl group;
- R^d is hydrogen atom, C₁-C₄ alkyl group, C₁-C₄ hydroxyalkyl group, C₃-C₈
10 cycloalkyl group;
- R^e is hydrogen atom, C₁-C₄ alkyl group, benzyl group;
- A is (1) a C₄-C₇ cycloalkyl ring; (2) a saturated, partially unsaturated or aromatic 5-7 membered ring containing 0-4 heteroatom including W¹ selected from O, S, SO₂ and N; wherein said ring is optionally substituted with one or more halogen
15 atom, oxo, cyano, hydroxy, amino, phenyl or C₁-C₄ alkyl group;
- B is a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO₂ and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, cyano, hydroxy, amino, phenyl or C₁-C₄ alkyl group;
- W¹ is carbon atom, nitrogen atom, or CH group;
- W² is oxygen atom, sulfur atom, NH, CH₂ or SO₂ group;
- and optical antipodes or racemates and/or salts and/or hydrates and/or solvates thereof.

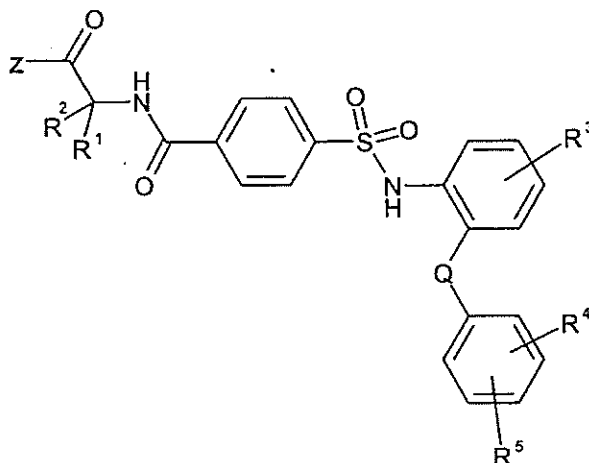
The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) or optical antipodes or racemates or salts or hydrates or
25 solvates thereof as active ingredient.

Furthermore objects of the present invention are the synthesis of compounds of formula (I), and the chemical and pharmaceutical manufacture of medicaments containing these compounds, as well as the methods of treatment with these compounds, which means administering to a mammal to be treated - including human -
30 effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

-7-

DETAILED DESCRIPTION OF THE INVENTION

The present invention relates to new bradykinin B1 receptor antagonist non-peptide derivatives of formula (I)



(I)

wherein

R^1 is hydrogen atom or C_1 - C_4 alkyl group;

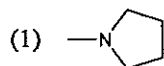
R^2 is selected from (1) hydrogen atom; (2) C_1 - C_6 straight or branched alkyl group; (3) $-(CH_2)_n-NH_2$; (4) $-(CH_2)_n-OH$; (5) $-(CH_2)_n-CO-NH_2$; (6) $-(CH_2)_n-COOR^c$; (7) benzyl optionally substituted with one or more hydroxy group or halogen atom; or

R^1 , R^2 and the carbon atom to which they are both attached together form a 3-7 membered cycloalkyl ring;

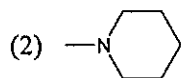
R^3 , R^4 and R^5 are independently of each other hydrogen atom; halogen atom; cyano; nitro; amino; or amino substituted with one or more C_1 - C_4 alkyl group; trifluoromethyl; C_1 - C_4 alkyl; C_1 - C_4 alkoxy; trifluoromethoxy; C_1 - C_4 alkoxycarbonyl; $-C(=O)-NH_2$ or hydroxy group;

Q is selected from (1) oxygen atom; (2) sulfur atom;

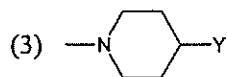
Z is selected from



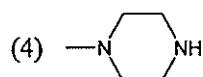
, optionally substituted with $-(CH_2)_m-OH$ group, or $-(CH_2)_n-X-P$ group;



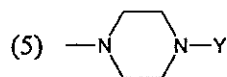
, optionally substituted with one or more C₁-C₄ alkyl group, one or more halogen atom, -(CH₂)_m-OH group, -(CH₂)_m-NH₂ group, -(CH₂)_m-CO-NH₂ group, trifluoromethyl group, oxo group, -(CH₂)_m-CN group; -NH-CO-(C₁-C₄ alkyl) group, -NH-SO₂-(C₁-C₄ alkyl) group, -(CH₂)_m-COOR^c group, -CO-NR^cR^d group, -(C₁-C₄ alkoxy) group, -NH-CO-(CH₂)_m-CF₃ group, -NH-SO₂-CH₂-CF₃ group;



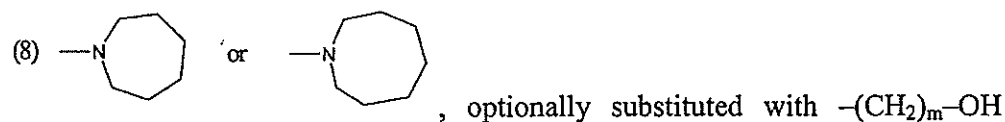
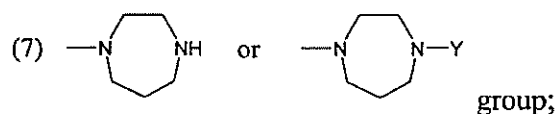
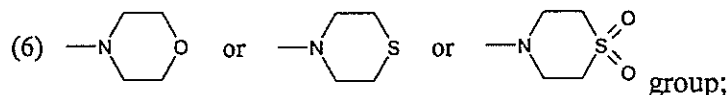
group;



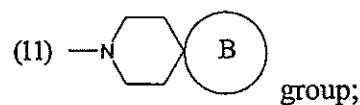
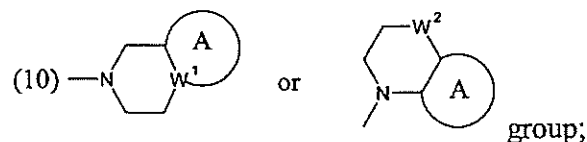
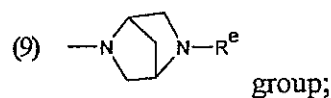
, optionally substituted with oxo group, -SO₂-(C₁-C₄ alkyl) group, C₁-C₄ alkyl group, -CO-(C₁-C₄ alkyl) group, -(CH₂)_m-O-(CH₂)_m-OH group, -(CH₂)_m-OH group, -SO₂-NR^cR^d group, -CO-NR^cR^d group;



group;



group,



- (12) $-\text{NH}-(\text{CH}_2)_n-\text{P}$ group;
(13) $-\text{NH}-(\text{CH}_2)_q-\text{NR}^a\text{R}^b$ group;
- Y is selected from (1) $-(\text{CH}_2)_n-\text{NR}^a\text{R}^b$; (2) $-(\text{CH}_2)_n-\text{X}-\text{P}$ group;
- n is an integer from 0 to 6;
- 5 m is an integer from 0 to 3;
- q is an integer from 1 to 6;
- X is selected from (1) single bond; (2) oxygen atom; (3) $-\text{CO}-\text{NR}^c$ group; (4) CO or SO_2 group;
- P is selected from (1) phenyl group, optionally substituted with one or more
10 halogen atom, hydroxy, cyano, amino, [1,4']bipiperidinyl-1'-yl or C_1 - C_4 alkyl group; (2) a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, hydroxy, cyano, amino, piperidin-1-yl or C_1 - C_4 alkyl group; (3) C_5 - C_8 cycloalkyl group,
15 optionally substituted with $-(\text{CH}_2)_m-\text{NR}^a\text{R}^b$ group;
- R^a and R^b are (1) hydrogen atom, with the proviso that R^a and R^b can not be simultaneously hydrogen atom; (2) straight or branched C_1 - C_6 alkyl group; (3) R^a , R^b and the nitrogen atom to which they are both attached together form a saturated, partially unsaturated or aromatic 4-7 membered ring containing 0-3
20 heteroatom (in addition to the nitrogen atom to which R^a and R^b attached) selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, cyano, hydroxy or C_1 - C_4 alkyl group;
- R^c is hydrogen atom or C_1 - C_4 alkyl group;
- R^d is hydrogen atom, C_1 - C_4 alkyl group, C_1 - C_4 hydroxyalkyl group, C_3 - C_8
25 cycloalkyl group;
- R^e is hydrogen atom, C_1 - C_4 alkyl group, benzyl group;
- A is (1) a C_4 - C_7 cycloalkyl ring; (2) a saturated, partially unsaturated or aromatic 5-7 membered ring containing 0-4 heteroatom including W^1 selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen
30 atom, oxo, cyano, hydroxy, amino, phenyl or C_1 - C_4 alkyl group;
- B is a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO_2 and N; wherein said ring is optionally

-10 -

substituted with one or more halogen atom, oxo, cyano, hydroxy, amino, phenyl or C₁-C₄ alkyl group;

W¹ is carbon atom, nitrogen atom, or CH group;

W² is oxygen atom, sulfur atom, NH, CH₂ or SO₂ group;

5 and optical antipodes or racemates and/or salts and/or hydrates and/or solvates thereof.

The invention also relates to the pharmaceutical compositions containing the compounds of formula (I) or optical antipodes or racemates or salts or hydrates or solvates thereof as active ingredient.

Furthermore objects of the present invention are the synthesis of compounds of
10 formula (I), and the chemical and pharmaceutical manufacture of medicaments containing these compounds, as well as the methods of treatment with these compounds, which means administering to a mammal to be treated - including human - effective amount/amounts of compounds of formula (I) of the present invention as such or as medicament.

15 The term "halogen" substituent denotes fluorine, chlorine, bromine or iodine atoms. The term C₁-C₄ alkyl group used in the present description denotes methyl, ethyl, normal- and isopropyl and different butyl groups. These C₁-C₄ alkyl groups can be in the C₁-C₄ alkoxy groups and C₁-C₄ hydroxyalkyl groups.

The 4-7 membered heterocyclic ring in the meaning of R^a and R^b can be *e.g.*
20 piperidine, pyrrolidine, piperazine, homopiperazine, morpholine, thiomorpholine and the like.

The 4-7 membered heterocyclic ring in the meaning of P and B can be *e.g.* imidazole, triazole, oxazol, tiazole, tetrazole, furan, tetrahydrofuran, pyrimidine, pyridine, piperidine, pyrrolidine, pyrazine, piperazine, homopiperazine, morpholine,
25 thiomorpholine and the like.

The saturated, partially unsaturated or aromatic 5-7 membered ring in the meaning of A can be *e.g.* imidazole, triazole, oxazol, tiazole, tetrazole, pyrimidine, pyridine, piperidine, pyrrolidine, pyrazine, piperazine, homopiperazine, morpholine, thiomorpholine and the like.

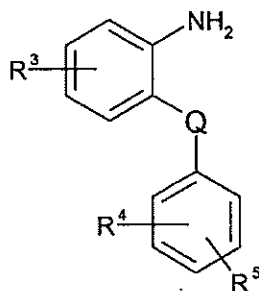
30 The invention relates also to the salts of compounds of formula (I) formed with acids or bases.

-11 -

Both organic and inorganic acids can be used for the formation of acid addition salts. Suitable inorganic acids can be *e.g.* hydrochloric acid, sulfuric acid and phosphoric acid. Representatives of monovalent organic acids can be *e.g.* formic acid, acetic acid, trifluoroacetic acid, propionic acid, and different butyric acids, valeric acids and capric acids. Representatives of bivalent organic acids can be *e.g.* oxalic acid, malonic acid, maleic acid, fumaric acid and succinic acid. Other organic acids can also be used, such as hydroxy acids *e.g.* citric acid, tartaric acid, or aromatic carboxylic acids *e.g.* benzoic acid or salicylic acid, as well as aliphatic and aromatic sulfonic acids *e.g.* methanesulfonic acid and p-toluenesulfonic acid. Especially valuable group of the acid addition salts is in which the acid component itself does not have therapeutical effect in the applied dose or it does not have unfavorable influence on the effect of the active ingredient. These acid addition salts are pharmaceutically acceptable acid addition salts. The reason why acid addition salts, which do not belong to the pharmaceutically acceptable acid addition salts belong to the present invention is, that in given case they can be advantageous in the purification and isolation of the desired compounds.

Among the salts formed with bases especially important are the salts formed with alkali metals, *e.g.* sodium, potassium, alkaline-earth metals, *e.g.* calcium and magnesium, as well as with ammonia or organic amines. The latter bases can have further substituents, *e.g.* hydroxy or amino groups, which can influence *e.g.* the solubility and the handling of the product. The salts formed with bases are pharmaceutically acceptable base addition salts.

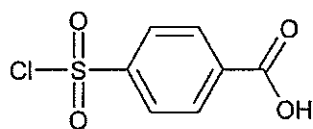
According to the invention the compounds of formula (I) can be synthesized by reacting an amine derivative of formula (II)



(II)

wherein the meaning of R³, R⁴, R⁵ and Q is as described above for the formula (I) – with sulfonyl chloride of formula (III)

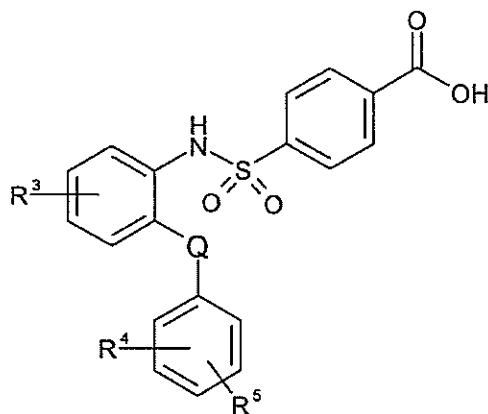
-12 -



(III)

then the so obtained phenylsulfamoyl benzoic acid derivative of formula (IV)

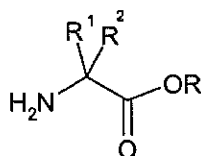
5



(IV)

- wherein the meaning of R^3 , R^4 , R^5 and Q is as described above for the formula (I) – is reacted with an amino acid of formula (V)

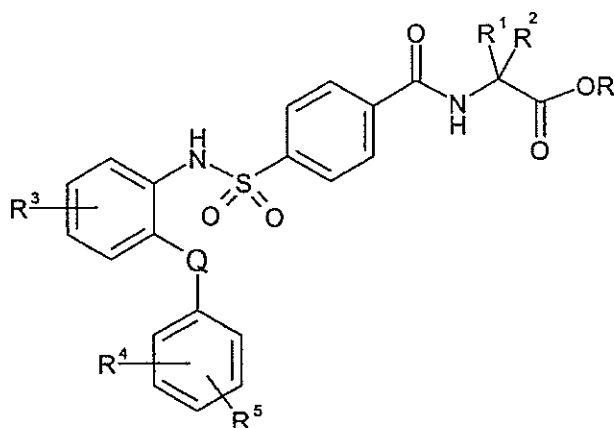
10



(V)

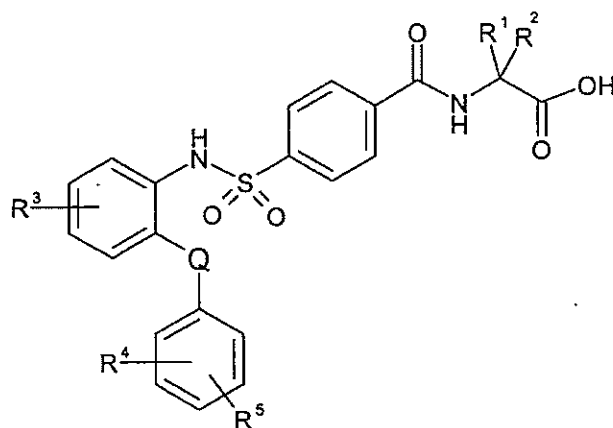
- wherein the meaning of R^1 and R^2 is as described above for the formula (I) and R is C_1 - C_4 alkyl – and the so obtained compound of formula (VI)

-13 -



(VI)

- wherein the meaning of R^1 , R^2 , R^3 , R^4 , R^5 , R and Q is as defined above – is
 5 hydrolyzed to furnish a carboxylic acid derivative of formula (VII)



(VII)

- wherein the meaning of R^1 , R^2 , R^3 , R^4 , R^5 and Q is as defined above – finally the latter
 10 is reacted with an amine derivative Z and the obtained non-peptide derivative of
 formula (I) in given case can be transformed into an other compound of formula (I) by
 introducing new substituents and/or modifying or removing the existing ones, and/or
 salt formation and/or liberating the compound from salts.

The sulfonylation reaction is preferably carried out in a proper solvent,
 15 preferably in the presence of a base. The reactions are followed by thin layer
 chromatography. The necessary reaction time is 6-20 h. The work-up of the reaction
 mixture can be carried out by different methods.

a) The reaction mixture is concentrated and the product is isolated by crystallization or extraction. If the crude product is not pure enough, then column chromatography can be used for the purification of it. The column chromatography is carried out either on normal phase using Kieselgel 60 as adsorbent and different solvent systems, *e.g.* n-hexane/ethyl acetate, chloroform/methanol, dichloromethane/ethyl acetate or chloroform/acetone as eluents, or on reversed phase using YMC-Pack ODS-AQ type packings (produced by YMC) and acetonitrile/water/trifluoroacetic acid or acetonitrile/water/acetic acid as eluent.

b) The reaction mixture is poured into ice-water and the product is isolated by filtration or extraction. The crude product is crystallized or purified by column chromatography as described above. The structures of the products are determined by IR, NMR and mass spectrometry.

Hydrolysis of a compound of formula (VI) can be carried out with a base, *e.g.* alkali metal hydroxide, preferably sodium or lithium hydroxide, or with an acid, *e.g.* organic acid, preferably trifluoroacetic acid.

The amide bond formations are preferably carried out by preparing an active derivative from a carboxylic acid of formula (IV) or (VII) which is reacted with an amino acid of formula (V) or an amine Z, respectively, preferably in the presence of a base.

The transformation of a carboxylic acid into an active derivative can be carried out *in situ* during the amide bond formation in a proper solvent (*e.g.* dimethylformamide, acetonitrile, chlorinated hydrocarbons or hydrocarbons or the mixture thereof). The active derivatives can be acid chlorides (*e.g.* prepared from carboxylic acid with thionyl chloride), mixed anhydrides (*e.g.* prepared from carboxylic acid with isobutyl chloroformate in the presence of a base, *e.g.* triethylamine), active esters (*e.g.* prepared from carboxylic acid with hydroxybenzotriazol (HOBt) and dicyclohexyl-carbodiimide (DCC) or O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (HBTU) in the presence of a base *e.g.* triethylamine). The active derivatives can be prepared at a temperature in the range of 0 °C to room temperature. A proper amino acid of formula (V) or an amine Z is added as a base or as a salt formed with inorganic acid to the so obtained solution or suspension in the presence of a base, *e.g.* triethylamine, needed for the liberation of the amine. The

condensation reactions are followed by thin layer chromatography. The necessary reaction time is 6-20 h. The work-up of the reaction mixture can be carried out by different methods.

a) The reaction mixture is concentrated, and the residue is crystallized or
5 extracted with a proper organic solvent and in given case purified by column chromatography. The column chromatography is carried out on normal phase using Kieselgel 60 as adsorbent and different solvent systems, *e.g.* toluene/methanol, chloroform/methanol or toluene/acetone, as eluents or on reversed phase using YMC-Pack ODS-AQ type packings (produced by YMC) and acetonitrile/water/trifluoroacetic
10 acid or acetonitrile/water/acetic acid as eluent.

b) The reaction mixture is directly purified by column chromatography as described above to yield the pure product.

The structures of the products are determined by IR, NMR and mass spectrometry.

15 The obtained non-peptide derivatives of formula (I) – independently from the method of preparation – in given case can be transformed into another compound of formula (I) by introducing further substituents and/or modifying and/or removing the existing ones, and/or formation of salts with acids and/or liberating the non-peptide derivative of formula (I) from the obtained acid addition salts by treatment with a base
20 and/or the free sulfonamide derivative of formula (I) can be transformed into a salt by treatment with a base.

For instance cleaving the benzyl group from N-benzyl group, which stands for R^e , can be carried out *e.g.* with catalytic hydrogenation or with chloroethyl chloroformate in a proper solvent. The compounds of formula (I) containing free
25 hydroxy group can be transformed into acyloxy or sulfoxy derivatives with different acylating or sulfonylating agents. The reactions can be carried out for example in chlorinated hydrocarbons using acid chloride or acid anhydride as acylating agent in the presence of a base (*e.g.* triethylamine or sodium carbonate). The sulfonamide derivatives of formula (I) containing a nitro group can be transformed into amines by
30 reduction and the amines can be further reacted to give acid amides as described for the acylation of hydroxy groups or carbamate derivatives can be synthesized. Ester groups can be hydrolyzed and the obtained free carboxylic acids can be transformed into

amides by reacting with proper amine derivatives. N-(*tert*-Butoxycarbonyl) group can be cleaved by organic or inorganic acids (e.g. trifluoroacetic acid or hydrogen chloride). Cyano groups can be transformed into amide, N-hydroxy-amidine or different N-containing heterocyclic groups.

5 Most of the amino acids of formula (V) and amines Z are either commercially available or can be synthesized by different known methods. The syntheses of some new amines Z are described in the Examples. Following these procedures the other amines Z can also be prepared.

10 The compounds of the present invention as well as their pharmaceutically acceptable salts or hydrates or solvates can be used as such or suitably in the form of pharmaceutical compositions. These compositions (drugs) can be in solid, liquid or semiliquid form and pharmaceutical adjuvant and auxiliary materials can be added, which are commonly used in practice, such as carriers, excipients, diluents, stabilizers,
15 wetting or emulsifying agents, pH- and osmotic pressure-influencing, flavoring or aromatizing, as well as formulation-promoting or formulation-providing additives.

The dosage required to exert the therapeutical effect can vary within wide limits and will be fitted to the individual requirements in each of the particular case, depending on the stage of the disease, the condition and the bodyweight of the patient to
20 be treated, as well as the sensitivity of the patient against the active ingredient, route of administration and number of daily treatments. The actual dose of the active ingredient to be used can safely be determined by the attending physician skilled in the art in the knowledge of the patient to be treated.

The pharmaceutical compositions containing the active ingredient according to
25 the present invention usually contain 0.01 to 100 mg of active ingredient in a single dosage unit. It is, of course possible that the amount of the active ingredient in some compositions exceeds the upper or lower limits defined above.

The solid forms of the pharmaceutical compositions can be e.g. tablets, dragées, capsules, pills or lyophilized powder ampoules useful for the preparation of injections.
30 Liquid compositions are the injectable and infusable compositions, fluid medicines, packing fluids and drops. Semiliquid compositions can be ointments, balsams, creams, shaking mixtures and suppositories.

For the sake of a simple administration it is suitable if the pharmaceutical compositions comprise dosage units containing the amount of the active ingredient to be administered once, or a few multiples or a half, third or fourth part thereof. Such dosage units are *e.g.* tablets, which can be powdered with grooves promoting the halving or quartering of the tablet in order to exactly administer the required amount of the active ingredient.

Tablets can be coated with an acid-soluble layer in order to assure the release of the active ingredient content after leaving the stomach. Such tablets are enteric-coated. A similar effect can be achieved also by encapsulating the active ingredient.

The pharmaceutical compositions for oral administration can contain *e.g.* lactose or starch as excipients, sodium carboxymethylcellulose, methylcellulose, polyvinyl pyrrolidone or starch paste as binders or granulating agents. Potato starch or microcrystalline cellulose is added as disintegration agents, but ultraamylopectin or formaldehyde casein can also be used. Talcum, colloidal silicic acid, stearin, calcium or magnesium stearate can be used as antiadhesive and lubricants.

The tablets can be manufactured *e.g.* by wet granulation, followed by pressing. The mixed active ingredients and excipients, as well as in given case part of the disintegrants are granulated with an aqueous, alcoholic or aqueous alcoholic solution of the binders in an appropriate equipment, then the granulate is dried. The other disintegrants, lubricants and antiadhesive agents are added to the dried granulate, and the mixture is pressed to a tablet. In given case the tablets are made with halving groove to ease the administration.

The tablets can be made directly from the mixture of the active ingredient and the proper auxiliaries by pressing. In given case, the tablets can be coated by using additives commonly used in the pharmaceutical practice, *e.g.* stabilizers, flavoring, coloring agents, such as sugar, cellulose derivatives (methyl- or ethylcellulose, sodium carboxymethylcellulose, etc), polyvinyl pyrrolidone, calcium phosphate, calcium carbonate, food coloring agents, food laces, aroma agents, iron oxide pigments, etc. In the case of capsules the mixture of the active ingredient and the auxiliaries is filled into capsules.

Liquid oral compositions, *e.g.* suspensions, syrups, elixirs can be made by using water, glycols, oils, alcohols, coloring and flavoring agents.

-18 -

For rectal administration the composition is formulated in suppositories or clysters. The suppository can contain beside the active ingredient a carrier, so called adeps pro suppository. Carriers can be vegetable oils, such as hydrogenated vegetable oils, triglycerides of C₁₂-C₁₈ fatty acids (preferably the carriers under the trade name Witepsol). The active ingredient is homogeneously mixed with the melted adeps pro
5 suppository and the suppositories are moulded.

For parenteral administration the composition is formulated as injection solution. For manufacturing the injection solution the active ingredients are dissolved in distilled water and/or in different organic solvents, such as glycolethers, in given case in the
10 presence of solubilizers, *e.g.* polioxyethylensorbitane-monolaurate, -monooleate, or monostearate (Tween 20, Tween 60, Tween 80). The injection solution can also contain different auxiliaries, such as conserving agents, *e.g.* ethylenediamine tetraacetate, as well as pH adjusting agents and buffers and in given case local anaesthetic, *e.g.* lidocain. The injection solution containing the active ingredient of the invention is filtered before it is
15 filled into ampoules, and it is sterilized after filling.

If the active ingredient is hygroscopic, then it can be stabilized by liophylization.

Utilities

20 The compounds of the present invention are bradykinin receptor antagonists, in particular selective bradykinin B1 receptor antagonists, consequently are useful in the treatment or prevention of painful and inflammatory processes. The compounds would be effective in the treatment of pain including, *e.g.*, chronic pain, particularly inflammatory pain, hyperalgesia, bone and joint pain (osteoarthritis), repetitive motion
25 pain, myofascial pain (muscular injury, fibromyalgia), visceral pain (ulcerative colitis, pancreatitis, cystitis, uveitis), perioperative pain (general surgery, gynecological), postoperative pain (postsurgical pain syndrome), posttraumatic pain (*e.g.* sprains or fracture), neuropathic pain (postherpetic neuralgia, nerve injury, phantom limb pain, mononeuropathy, polyneuropathy) dental pain, and cancer pain. Furthermore for the
30 treatment of pain associated with angina, menstruation, diabetic vasculopathy, post capillary resistance or diabetic symptoms associated with insulinitis (*e.g.* hyperglycemia, diuresis, proteinurea and increased nitrite and kallikrein urinary excretion), diabethic

hyperalgeisa. Moreover the compounds may be used for the treatment angioedema, atherosclerosis, septic shock *e.g.* as anti-hypovolemic and/or anti-hypotensive agents, and sepsis. They may be used as smooth muscle relaxants for the treatment of spasm of the gastrointestinal tract or uterus. Further, the compounds of this invention can additionally be used to treat inflammatory skin disorders, such as psoriasis and eczema, and skin injuries including burning and sunburning (UV-erythema and pain). The compounds may be used to treat inflammatory pain of varied origins (*e.g.* rheumatoid arthritis, rheumatic disease, tenosynovitis, liver disease, irritable bowel syndrome, inflammatory bowel disease, Crohn's disease, nephritis, allergic rhinitis, vasomotor rhinitis, uveitis, gingivitis), allergies. Such compounds may be used therapeutically to treat inflammatory airways disease *e.g.* chronic obstructive pulmonary disease, adult respiratory distress syndrome, bronchitis, pneumonia, asthma. They may be used to control, restrict or reverse airways hyperreactivity in asthma, to treat intrinsic and extrinsic asthma including allergic asthma (atopic or non-atopic), occupational asthma, viral or bacterial exacerbated asthma, other non-allergic asthmas, "wheezy-infant syndrome", as well as exercise-induced bronchoconstriction. They may be effective against pneumoconiosis, including aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tabacosis and byssinosis. Additionally, they may be effective in some neurological disorders, *e.g.* against multiple sclerosis, Alzheimer's disease, epilepsy, cerebral edema, headache including cluster headache, migraine including prophylactic and acute use, as well as closed head trauma.

-20 -

Biological evaluationFunctional assay:

Assessment of antagonist potency at B1 and B2 receptors *in vitro* by measurement of cytosolic calcium ion concentration with a plate reader fluorimeter in cells expressing recombinant human B1 or B2 receptors

Cell culture

Chinese hamster ovary (CHO) cells stably expressing recombinant human B1 (CHO-B1, Euroscreen) or B2 (CHO-B2, Perkin-Elmer) receptors were cultured in Dulbecco's Modified Eagle's Medium (DMEM) containing 10% Fetal Calf Serum (FCS), 100 U/ml penicillin, 0.1 mg/ml streptomycin, 0.25 µg/ml amphotericin B, 1% Minimum Essential Medium Eagle (MEM), non essential amino acid solution, 600 µg/ml G418, 1% pyruvate (for the B2 cell line). Cells were kept at 37°C in a humidified incubator in an atmosphere of 5% CO₂/95% air and were passaged 1:4 three times a week. Cells were plated at 1.5-2.5×10⁴ cell/well on standard 96-well microplates, measurements of cytosolic calcium ion concentration ([Ca²⁺]_i) were carried out 1-2 days after cell plating.

Fluorimetric measurement of cytosolic calcium concentration

Measurements of [Ca²⁺]_i were carried out on CHO-B1 and CHO-B2 cells stably expressing human B1 and B2 receptors, respectively. Cells were grown in standard 96-well microplates and before the measurement were loaded with a fluorescent Ca²⁺-sensitive dye, fluo-4/AM (2 µM): after removing the culture medium the dye was added to the cells (dissolved in assay buffer: 145 mM NaCl, 5 mM KCl, 2 mM MgCl₂, 2 mM CaCl₂, 10 mM HEPES, 20 mM D-glucose, 2 mM probenecid, 100 µl/well) and cells were incubated at 37°C in a humidified incubator in an atmosphere of 5% CO₂/95% air for 40-120 min. To stop dye loading cells were washed twice with assay buffer. After washing, various concentrations of the test compounds (diluted in extracellular medium

-21 -

from a DMSO stock solution, final DMSO concentration was <0.1%) or buffer were added to each well depending on the experimental setup. After incubation at 37°C for 20-25 min. baseline and agonist-evoked changes of $[Ca^{2+}]_i$ were measured column by column with a plate reader fluorimeter (Fluoroskan Ascent, Labsystems). Excitation and detection of emission was carried out from the bottom of the plate. Filters used for Fluo-4: excitation filter – 485 nm, emission filter – 538 nm. The whole measurement process was performed at 37°C and was controlled by custom software. Inhibitory potency of the test compounds was assessed by measuring the reduction in the agonist-evoked $[Ca^{2+}]_i$ -elevation in the presence of different concentrations of the compounds. The agonists were LysDABK for CHO-B1, and bradykinin for CHO-B2 cells. Agonists were applied at an EC_{80} concentration, the EC_{80} -values were derived from daily determined dose-response curves. Fluorescence data were expressed as $\Delta F/F$ (fluorescence change normalized to baseline). All treatments on a single plate were measured in multiple wells. Data from all wells with the same treatment were averaged and the average values were used for analysis. Inhibitory potency of a compound at a single concentration point was expressed as percent inhibition of the control agonist response. Sigmoidal concentration-inhibition curves were fitted to the data (derived from at least three independent experiments) and IC_{50} -values were determined as the concentration that produces half of the maximal inhibition caused by the compound.

The examined reference compounds measured in functional and binding tests are the following:

- 1) 4-{2-[(2,2-diphenyl-ethyl)-amino]-5-{4-[4-[(4-methyl-1-piperazinyl)-carbonyl]-1-piperidinyl]-sulfonyl}-benzoyl}-morpholine (NVP-SAA164, Br. J. Pharmacol.144 (2005) 889-899); K_i 8 nM; IC_{50} : 33 nM;
- 2) (R)-N-[2,3-dihydro-2-oxo-5-(2-phenyl-ethyl)-1-propyl-1H-1,4-benzodiazepin-3-yl]-N'-{4-[4-(4-pyridinyl)-1-piperazinyl]-phenyl}-urea (J. Med. Chem. 46 (2003) 1803-1806); K_i 0.59 nM; IC_{50} 1.9 nM;
- 3) N-[4-(4'-bipiperidin)-1'-ylphenyl]-N'-[(3R)-2,3-dihydro-5-(4-methyl-phenyl)-2-oxo-1-propyl-1H-1,4-benzodiazepin-3-yl]-urea (J. Med. Chem. 46 (2003) 1803-1806); K_i 13.4 nM; IC_{50} 64.5 nM

-22 -

The K_i and IC_{50} data measured by us for the reference compounds are in good agreement with the data given in the literature.

In Table I the most effective compounds of this invention measured in functional assay are listed.

5

Table I

Number of example	B1 func.	Number of example	B1 func.
1	++++	27	++++
2	++++	29	++++
3	++++	30	++++
4	+++	31	++++
5	+++	32	++++
6	+++	33	++++
7	+++	34	++++
8	+++	35	++++
9	+++	37	++++
26	++++	39	++++

+ $IC_{50} > 0.5 \mu M$

+++ IC_{50} is between 20 and 100 nM

++ IC_{50} is between 0.1 and 0.5 μM

++++ $IC_{50} < 20$ nM

10

Receptor binding assays

1. Human recombinant bradykinin B1 receptor binding

15

Binding assays were carried out on human recombinant bradykinin₁ receptors (expressed in CHO cells) according to the Euroscreen Technical Data Sheet (Cat.No.:ES-091). 20 μ g protein/tube was incubated with [3,4-prolyl-3,4-³H(N)]-[Des-Arg¹⁰] Kallidin as radioligand. Non specific binding was determined in the presence of 10 μ M Lys-des-Arg⁹-Bradykinin. The final incubation volume was 250 μ l. Samples were incubated for 15 min. at 25 °C then were rapidly vacuum filtered through GF/B

20

filters presoaked for at least 1 h in 0.5 % PEI. Radioactivity was determined by liquid scintillation spectroscopy.

In Table II the most effective compounds of this invention measured in binding assay are listed.

5

Table II

Number of example	B1 binding	Number of example	B1 binding
1	++++	27	++++
2	++++	29	++++
3	++++	30	++++
4	+++	31	++++
5	+++	32	++++
6	+++	33	++++
7	+++	34	++++
8	+++	35	++++
9	+++	37	++++
26	++++	39	++++

+ $K_i > 0.5 \mu\text{M}$

+++ K_i is between 20 and 100 nM

++ K_i is between 0.1 and 0.5 μM

++++ $K_i < 20 \text{ nM}$

10

2. Human recombinant bradykinin B2 receptor binding

Binding assays were carried out on human recombinant bradykinin2 receptors (expressed in CHO cells) according to the Receptor Biology Technical Data Sheet (Cat.No.:RBHB2M) with minor modifications. 8.4 μg protein/tube was incubated with [2,3,-prolyl-3,4- $^3\text{H}(\text{N})$]-Bradykinin as radioligand. Non specific binding was determined in the presence of 5 μM bradykinin. The final incubation volume was 200 μl . Samples were incubated for 90 min. at +4 °C then were rapidly vacuum filtered through GF/B

15

-24 -

filters presoaked for at least 1 h in 0.5 % PEI. Radioactivity was determined by liquid scintillation spectroscopy.

The compounds exhibited high affinity and selectivity (>50 fold) for the human B1 receptor over the human B2 receptor according to both functional and binding
5 assays.

The synthesis of compounds and pharmaceutical compositions according to the invention is illustrated by the following not limiting Examples.

Reference Example 1**Trans-4-(2-pyrrolidin-1-yl-ethyl)-cyclohexylamine dihydrochloride****a) Trans-2-{1-[4-(*N*-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethanol**

A solution of trans-2-{1-[4-(*N*-tert-butoxycarbonyl)-amino]-cyclohexyl}-acetic acid methyl ester [*J. Med. Chem.* **43** (2000) 1878-1885] (28.5 g, 105.2 mmol) in dry tetrahydrofuran (500 mL) was cooled to -2 °C, lithium aluminum hydride (5.4 g, 142 mmol) was added portionwise and the mixture was stirred at -2 °C for 60 minutes. The reaction mixture was cooled to -10 °C and quenched with ethyl acetate (15 mL), then brine (43 ml) was slowly added to the mixture at 0 °C. The precipitated salts were filtered, and washed with ethyl acetate. The filtrate was concentrated *in vacuo*. The residue was recrystallized from diisopropyl ether (100 ml) to yield 23.7 g (93 %) of the title compound as a white powder.

b) Methanesulfonic acid trans-2-(4-tert-butoxycarbonylamino-cyclohexyl)-ethyl ester

To a stirred solution of trans-2-{1-[4-(*N*-tert-butoxycarbonyl)-amino]-cyclohexyl}-ethanol (15 g, 62 mmol), and triethylamine (10.5 mL, 75 mmol) in dry dichloromethane (150 mL) methanesulfonyl chloride (5.7 mL, 73.4 mmol) in dichloromethane (25 mL) was added dropwise at 0 °C. After stirring 30 minutes at 0 °C, the solution was extracted three times with water. The organic solution was dried over sodium sulfate and concentrated *in vacuo* to yield 13.0 g (65 %) of the title compound.

c) Trans-[4-(2-pyrrolidin-1-yl-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester

A mixture of methanesulfonic acid trans-2-(4-tert-butoxycarbonylamino-cyclohexyl)-ethyl ester (3.2 g, 10 mmol), potassium carbonate (1.4 g, 10 mmol) and pyrrolidine (1.25 mL, 15 mmol) in acetonitrile (40 mL) was stirred at 60 °C for 2 hours. The mixture was cooled to room temperature and poured into water (200 mL). The precipitated white crystals were filtered off and washed with water to yield 1.9 g (64 %) of the title compound.

d) Trans-4-(2-pyrrolidin-1-yl-ethyl)-cyclohexylamine dihydrochloride

A mixture of trans-[4-(2-pyrrolidin-1-yl-ethyl)-cyclohexyl]-carbamic acid *tert*-butyl ester (2.5 g, 8.46 mmol), dry dioxane (20 mL) and 6.5 N hydrogen chloride in

dioxane (40 mL) was stirred at room temperature overnight, then diluted with diethyl ether and stirred at 0 °C for 1 h. The precipitated crystals were filtered off, washed with diethyl ether and dried to yield 2.25 g (99 %) of the title compound as an off-white solid.

5

Reference Example 2

(3-[1,4']Bipiperidinyl-1'-yl)-propylamine trihydrochloride

a) (3-[1,4']Bipiperidinyl-1'-yl-propyl)-carbamic acid tert-butyl ester

A mixture of 4-piperidinopiperidine (Aldrich) (2.0 g, 11.88 mmol), (3-bromo-propyl)-carbamic acid *tert*-butyl ester [*Eur. J. Med. Chem. Chim. Ther.* 37 (2002) 573-584] (3.96 g, 16.63 mmol), dimethylformamide (130 mL) and potassium carbonate (1.64 g, 11.88 mmol) was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was dissolved in water (150 mL), extracted with dichloromethane (3x150 mL), the combined organic layers were washed with brine (150 mL), dried over sodium sulfate, filtered and concentrated. The crude product was submitted to column chromatography using Kieselgel 60 (0.040-0.063 mm) (Merck) as adsorbent, and chloroform:methanol:ammonium hydroxide = 10:1:0.1 as eluent to yield 2.27 g (59 %) of the title compound as an oil.

b) 3-[1,4']Bipiperidinyl-1'-yl-propylamine trihydrochloride

A mixture of (3-[1,4']bipiperidinyl-1'-yl-propyl)-carbamic acid *tert*-butyl ester (2.15 g, 6.6 mmol), dry dioxane (40 mL) and 6.5 N hydrogen chloride in dioxane (22 mL) was stirred at room temperature overnight, then diluted with diethyl ether and stirred at 0 °C for 1 h. The precipitated crystals were filtered off, washed with diethyl ether and dried to yield 2.03 g (92 %) of the title compound as a beige solid.

25

Example 1

(R)-N-{1-Methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

a) 4-(2-Phenoxy-phenylsulfamoyl)-benzoic acid

Under an atmosphere of argon to an ice cooled solution of 2-phenoxy-phenylamine (Aldrich) (49.76 g, 268.65 mmol) in dry pyridine (290 mL) 4-

30

-27 -

chlorosulfonyl benzoic acid (59.42 g, 269.32 mmol) was added portion-wise. The reaction mixture was stirred at room temperature overnight. The mixture was evaporated *in vacuo*, the residue was treated with 1N hydrochloric acid (300 mL), and extracted with ethyl acetate (3x300 mL). The combined organic layers were washed
5 with 1N hydrochloric acid, water and brine, dried over sodium sulfate, filtered and concentrated in *vacuo*. The residue was treated with toluene, the obtained crystalline product was filtered and washed with toluene to yield 84.86 g (85.5 %) of the title compound as a light pink solid. MS (EI) 370.2 (MH⁺).

10 b) (R)-2-[4-(2-Phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester

The solution of 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (2.5 g, 6.76 mmol), triethylamine (1.5 mL, 10.8 mmol) and HBTU [O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium hexafluorophosphate (Advanced Chem. Tech.)) (2.9 g, 7.64 mmol) in dry dimethyl formamide (50 mL) was stirred at room temperature for five minutes
15 before (R)-2-amino-propionic acid methyl ester (0.95 g, 6.8 mmol) was added. The pH of the reaction mixture was adjusted to 8 by the addition of triethylamine, the so obtained mixture was stirred at room temperature overnight, then concentrated *in vacuo*. The residue was treated with saturated sodium hydrogencarbonate solution (50 mL), extracted with ethyl acetate (3x50 mL), the combined organic layers were washed with
20 saturated sodium hydrogencarbonate solution, water and brine, dried over sodium sulfate, filtered and concentrated. The residue was purified by column chromatography using Kieselgel 60 (0.040-0.063 mm) as adsorbent (Merck) and toluene:acetone = 6:1 as eluent to yield 2.4 g (78 %) of the title compound as light yellowish amorphous solid. MS (EI) 455.3 (MH⁺).

25

c) (R)-2-[4-(2-Phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

To a stirred solution of (R)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester (0.2 g, 0.44 mmol) in a mixture of tetrahydrofuran (1.0 mL), water (0.5 mL) and methanol (0.5 mL) lithium hydroxide monohydrate (0.093 g, 2.2
30 mmol) was added and the reaction mixture was stirred at room temperature for 2 h. The mixture was concentrated, the residue was dissolved in water, acidified with 1M hydrochloric acid, the precipitated solid was filtered off, washed with water and dried to

-28 -

yield 0.158 g (81.5 %) of the title compound as an off-white solid. MS (EI) 441.3 (MH⁺).

d) (R)-N-{1-Methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

To a stirred solution of (R)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid (37 mg, 0.085 mmol) in a mixture of dichloromethane (2 mL) and dimethylformamide (0.2 mL) 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) (18 mg, 0.1 mmol), HBTU (46 mg, 0.12 mmol) and triethylamine (60 µL, 0.4 mmol) were added. The mixture was stirred at room temperature for 24 h, then purified by column chromatography using Kieselgel 60 (0.015-0.040 mm) as adsorbent (Merck) and gradient elution starting with 100% A eluent and processing to a mixture of 70% A and 30% B eluent over a period of 15 minutes (eluent A: chloroform; eluent B: methanol containing 5% of ammonium hydroxide) to yield 38.5 mg (75 %) of the title compound. MS (EI) 605.6 (MH⁺).

Example 2

N-{2-Oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide

a) 4-(2-Phenylsulfanyl-phenylsulfamoyl)-benzoic acid

The title compound was prepared from 2-phenylsulfanyl-phenylamine [*J. Med. Chem.*; **18** (1975) 386-391] according to the method described in Example 1/a. MS (EI) 386.2 (MH⁺).

b) [4-(2-Phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid ethyl ester

The title compound was prepared from 4-(2-phenylsulfanyl-phenylsulfamoyl)-benzoic acid and glycine ethyl ester hydrochloride according to the method described in Example 1/b.

c) [4-(2-Phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid

The title compound was prepared from [4-(2-phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid ethyl ester according to the method described in Example 1/c. MS (EI) 443.2 (MH⁺).

5 d) *N*-{2-Oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide

The title compound was prepared from [4-(2-phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS (EI) 607.5 (MH⁺).

10

Compounds of Table 1 were prepared from [4-(2-phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid (Example 2/c) according to the method described in Example 1/d.

15 **Table 1**

Example	Name	MS (EI) (MH ⁺)
3	<i>N</i> -[2-Oxo-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	579.4
4	<i>N</i> -{2-[4-(2-Dimethylamino-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	582.2
5	<i>N</i> -{2-Oxo-2-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	622.2
6	<i>N</i> -{2-[4-(3-Dimethylamino-propyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	596.2
7	<i>N</i> -{2-Oxo-2-[4-(3-pyrrolidin-1-yl-propyl)-[1,4]diazepan-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	636.2
8	<i>N</i> -{2-[4-(1-Methyl-piperidin-3-ylmethyl)-piperazin-1-yl]-2-	622.2

	oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	
9	<i>N</i> -{2-[4-(2-Morpholin-4-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	624.2
10	<i>N</i> -{2-[4-(2-Morpholin-4-yl-2-oxo-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	638.1
11	<i>N</i> -[(4-[1,4']Bipiperidiny-1'-yl-phenylcarbamoyl)-methyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	684.2
12	4-(2-Phenylsulfanyl-phenylsulfamoyl)- <i>N</i> -{[4-(2-pyrrolidin-1-yl-ethyl)-cyclohexylcarbamoyl]-methyl}-benzamide	621.2
13	<i>N</i> -[(3-Dimethylamino-propylcarbamoyl)-methyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	527.1
14	<i>N</i> -[2-(4-Hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	526.1
15	<i>N</i> -(2-{4-[2-(2-Hydroxy-ethoxy)-ethyl]-piperazin-1-yl}-2-oxo-ethyl)-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	599.1
16	1-{2-[4-(2-Phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetyl}-piperidine-4-carboxylic acid amide	553.1
17	<i>N</i> -[2-Oxo-2-(4-oxo-piperidin-1-yl)-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	524.1
18	<i>N</i> -[2-Oxo-2-(3-oxo-piperazin-1-yl)-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	525.0
19	<i>N</i> -[2-(4-Hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	540.1
20	<i>N</i> -[2-(3-Hydroxy-pyrrolidin-1-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	512.1
21	<i>N</i> -(2-Morpholin-4-yl-2-oxo-ethyl)-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	512.1

22	<i>N</i> -[2-(4-Acetyl-piperazin-1-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	553.1
23	<i>N</i> -[2-(1,1-Dioxo-1 λ^6 -thiomorpholin-4-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	560.1
24	<i>N</i> -[2-(4-Methyl-piperazin-1-yl)-2-oxo-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	525.1
25	<i>N</i> -[(3-[1,4']Bipiperidiny1-1'-yl-propylcarbamoyl)-methyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide	650.2

Example 26**(S)-N-{1-Methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide**5 **a) (S)-2-[4-(2-Phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid benzyl ester**

The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and (S)-2-amino-propionic acid benzyl ester hydrochloride according to the method described in Example 1/b. MS (EI) 531.6 (MH⁺).

10 **b) (S)-2-[4-(2-Phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid**

The title compound was prepared from (S)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid benzyl ester according to the method described in Example 1/c. MS (EI) 441.3 (MH⁺).

15 **c) (S)-N-{1-Methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide**

The title compound was prepared from (S)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS (EI) 605.5 (MH⁺).

20

Example 27

(R)-N-{1-Hydroxymethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

a) (R)-3-Hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester

5 The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and (R)-2-amino-3-hydroxy-propionic acid methyl ester according to the method described in Example 1/b. MS (EI) 471.3 (MH⁺).

b) (R)-3-Hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

10 The title compound was prepared from (R)-3-hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester according to the method described in Example 1/c. MS (EI) 457.3 (MH⁺).

c) (R)-N-{1-Hydroxymethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

15 The title compound was prepared from (R)-3-hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS (EI) 621.5 (MH⁺).

20 **Example 28**

(S)-N-{1-Hydroxymethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

a) (S)-3-Hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester

25 The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and (S)-2-amino-3-hydroxy-propionic acid methyl ester according to the method described in Example 1/b. MS (EI) 471.3 (MH⁺).

30 b) (S)-3-Hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

The title compound was prepared from (*S*)-3-hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester according to the method described in Example 1/c. MS (EI) 457.3 (MH^+).

- 5 c) (*S*)-*N*-{1-Hydroxymethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

The title compound was prepared from (*S*)-3-hydroxy-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS
10 (EI) 621.5 (MH^+).

Example 29

(*R*)-*N*-[1-(4-Hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide

- 15 a) (*R*)-3-(4-Hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester

The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and (*R*)-2-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester according to the method described in Example 1/b. MS (EI) 547.4 (MH^+).

20

- b) (*R*)-3-(4-Hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

The title compound was prepared from (*R*)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester according to the
25 method described in Example 1/c. MS (EI) 533.3 (MH^+).

- c) (*R*)-*N*-[1-(4-Hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide

The title compound was prepared from (*R*)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 4-hydroxypiperidine according to the method described in Example 1/d. MS (EI) 616.5 (MH^+).

30

Example 30**(R)-N-[1-(4-Hydroxy-benzyl)-2-(4-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide**

The title compound was prepared from (R)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid (Example 30/b) and piperidin-4-yl-methanol according to the method described in Example 1/d. MS (EI) 630.6 (MH⁺).

Example 31**(R)-N-[1-(4-Hydroxy-benzyl)-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide**

The title compound was prepared from (R)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid (Example 30/b) and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS (EI) 697.5 (MH⁺).

Example 32**(S)-N-[1-(4-Hydroxy-benzyl)-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide****a) (S)-3-(4-Hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester**

The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and (S)-2-amino-3-(4-hydroxy-phenyl)-propionic acid methyl ester according to the method described in Example 1/b. MS (EI) 547.4 (MH⁺).

25

b) (S)-3-(4-Hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

The title compound was prepared from (S)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester according to the method described in Example 1/c. MS (EI) 533.3 (MH⁺).

30

c) (S)-N-[1-(4-Hydroxy-benzyl)-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide

The title compound was prepared from (S)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d.
 5 MS (EI) 697.6 (MH⁺).

Compounds of Table 2 were prepared from (S)-3-(4-hydroxy-phenyl)-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid (Example 33/b) according to the
 10 method described in Example 1/d.

Table 2

Example	Name	MS (EI) (MH ⁺)
33	(S)-N-[1-(4-Hydroxy-benzyl)-2-oxo-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide	669.5
34	(S)-N-[1-(4-Hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide	616.4
35	(S)-N-{1-(4-Hydroxy-benzyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide	644.5
36	(S)-N-[2-Azepan-1-yl-1-(4-hydroxy-benzyl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide	614.5
37	(S)-N-{1-(4-Hydroxy-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide	698.5

Example 38**N-{1,1-Dimethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide****a) 2-Methyl-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester**

The title compound was prepared from 4-(2-phenoxy-phenylsulfamoyl)-benzoic acid (Example 1/a) and α -amino-isobutyric acid methyl ester hydrochloride [*Collect. Czech. Chem. Commun.*; **63** (1998) 85-93] according to the method described in Example 1/b. MS (EI) 469.1 (MH^+).

b) 2-Methyl-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid

The title compound was prepared from 2-methyl-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid methyl ester according to the method described in Example 1/c. MS (EI) 455.1 (MH^+).

c) N-{1,1-Dimethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide

The title compound was prepared from 2-methyl-2-[4-(2-phenoxy-phenylsulfamoyl)-benzoylamino]-propionic acid and 1-(2-pyrrolidin-1-yl-ethyl)-piperazine (EMKA-Chemie) according to the method described in Example 1/d. MS (EI) 588.3 (MH^+).

Example 39**4-(2-Phenylsulfanyl-phenylsulfamoyl)-N-[(piperidin-4-ylmethyl)-carbamoyl]-methyl}-benzamide hydrochloride**

To a stirred solution of [4-(2-phenylsulfanyl-phenylsulfamoyl)-benzoylamino]-acetic acid (Example 2/c) (37.6 mg, 0.085 mmol) in a mixture of dichloromethane (2 mL) and dimethylformamide (0.2 mL) and 4-aminomethyl-piperidine-1-carboxylic acid *tert*-butyl ester (21.4 mg, 0.1 mmol), HBTU (46 mg, 0.12 mmol) and triethylamine (30 μ L, 0.2 mmol) were added. The mixture was stirred at room temperature for 24 h, then purified by column chromatography using Kieselgel 60 (0.015-0.040 mm) as adsorbent (Merck) and gradient elution starting with 100% A eluent and processing to 100% B

-37 -

eluent over a period of 20 minutes (eluent A: n-hexane; eluent B: ethyl acetate). The purified compound was dissolved in ethyl acetate (0.5 mL) 2.5 M hydrogen chloride in ethyl acetate (2.0 mL) was added and the mixture was stirred at room temperature for 24 h. The precipitated product was filtered, washed with diethyl ether and dried in vacuum to yield 30 mg (62 %) of the title compound. MS (EI) 539.4 (MH⁺).

Example 40**Preparation of pharmaceutical compositions:****a) Tablets:**

0.01-50 % of active ingredient of formula (I), 15-50 % of lactose, 15-50 % of potato starch, 5-15 % of polyvinyl pyrrolidone, 1-5 % of talc, 0.01-3 % of magnesium stearate, 1-3 % of colloid silicon dioxide and 2-7 % of ultraamylopectin were mixed, then granulated by wet granulation and pressed to tablets.

b) Dragées, filmcoated tablets:

The tablets made according to the method described above were coated by a layer consisting of entero- or gastrosolvent film, or of sugar and talc. The dragées were polished by a mixture of beeswax and carnuba wax.

c) Capsules:

0.01-50 % of active ingredient of formula (I), 1-5 % of sodium lauryl sulfate, 15-50 % of starch, 15-50 % of lactose, 1-3 % of colloid silicon dioxide and 0.01-3 % of magnesium stearate were thoroughly mixed, the mixture was passed through a sieve and filled in hard gelatin capsules.

d) Suspensions:

Ingredients: 0.01-15 % of active ingredient of formula (I), 0.1-2 % of sodium hydroxide, 0.1-3 % of citric acid, 0.05-0.2 % of nipagin (sodium methyl 4-hydroxybenzoate), 0.005-0.02 % of nipasol, 0.01-0.5 % of carbopol (polyacrylic acid), 0.1-5 % of 96 % ethanol, 0.1-1 % of flavoring agent, 20-70 % of sorbitol (70 % aqueous solution) and 30-50 % of distilled water.

To solution of nipagin and citric acid in 20 ml of distilled water, carbopol was added in small portions under vigorous stirring, and the solution was left to stand for 10-12 h. Then the sodium hydroxide in 1 ml of distilled water, the aqueous solution of sorbitol and finally the ethanolic raspberry flavor were added with stirring. To this

carrier the active ingredient was added in small portions and suspended with an immersing homogenizator. Finally the suspension was filled up to the desired final volume with distilled water and the suspension syrup was passed through a colloid milling equipment.

5 **e) Suppositories:**

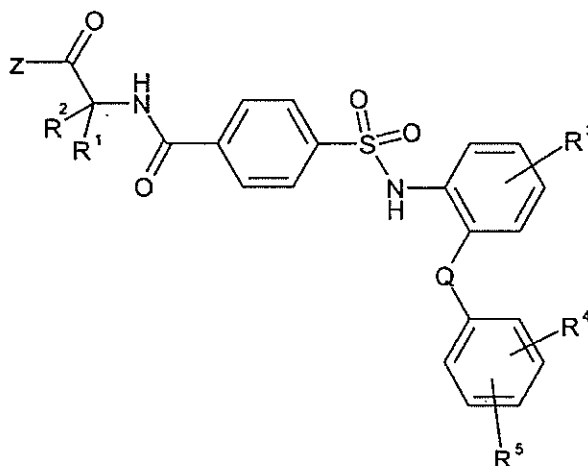
For each suppository 0.01-15% of active ingredient of formula (I) and 1-20% of lactose were thoroughly mixed, then 50-95% of adeps pro suppository (for example Witepsol 4) was melted, cooled to 35 °C and the mixture of active ingredient and lactose was mixed in it with homogenizator. The obtained mixture was mould in cooled
10 forms.

f) Lyophilized powder ampoule compositions:

A 5 % solution of mannitol or lactose was made with bidistilled water for injection use, and the solution was filtered so as to have sterile solution. A 0.01-5 % solution of the active ingredient of formula (I) was also made with bidistilled water for
15 injection use, and this solution was filtered so as to have sterile solution. These two solutions were mixed under aseptic conditions, filled in 1 ml portions into ampoules, the content of the ampoules was lyophilized, and the ampoules were sealed under nitrogen. The contents of the ampoules were dissolved in sterile water or 0.9 % (physiological) sterile aqueous sodium chloride solution before administration.

Claims

1. Bradykinin B1 receptor antagonist non-peptide derivatives of formula (I)



(I)

wherein

R^1 is hydrogen atom or C_1 - C_4 alkyl group;

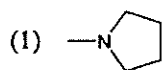
R^2 is selected from (1) hydrogen atom; (2) C_1 - C_6 straight or branched alkyl group; (3) $-(CH_2)_n-NH_2$; (4) $-(CH_2)_n-OH$; (5) $-(CH_2)_n-CO-NH_2$; (6) $-(CH_2)_n-COOR^e$; (7) benzyl optionally substituted with one or more hydroxy group or halogen atom; or

R^1 , R^2 and the carbon atom to which they are both attached together form a 3-7 membered cycloalkyl ring;

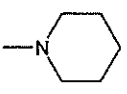
R^3 , R^4 and R^5 are independently of each other hydrogen atom; halogen atom; cyano; nitro; amino; or amino substituted with one or more C_1 - C_4 alkyl group; trifluoromethyl; C_1 - C_4 alkyl; C_1 - C_4 alkoxy; trifluoromethoxy; C_1 - C_4 alkoxycarbonyl; $-C(=O)-NH_2$ or hydroxy group;

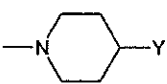
Q is selected from (1) oxygen atom; (2) sulfur atom;

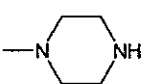
Z is selected from

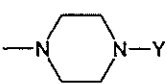


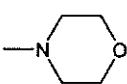
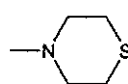
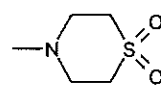
, optionally substituted with $-(CH_2)_m-OH$ group, or $-(CH_2)_n-X-P$ group;

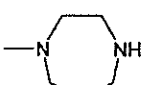
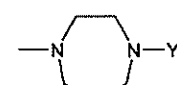
(2) , optionally substituted with one or more C₁-C₄ alkyl group, one or more halogen atom, -(CH₂)_m-OH group, -(CH₂)_m-NH₂ group, -(CH₂)_m-CO-NH₂ group, trifluoromethyl group, oxo group, -(CH₂)_m-CN group; -NH-CO-(C₁-C₄ alkyl) group, -NH-SO₂-(C₁-C₄ alkyl) group, -(CH₂)_m-COOR^c group, -CO-NR^cR^d group, -(C₁-C₄ alkoxy) group, -NH-CO-(CH₂)_m-CF₃ group, -NH-SO₂-CH₂-CF₃ group;

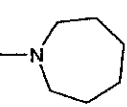
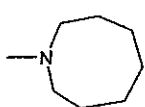
(3)  group;

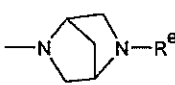
(4) , optionally substituted with oxo group, -SO₂-(C₁-C₄ alkyl) group, C₁-C₄ alkyl group, -CO-(C₁-C₄ alkyl) group, -(CH₂)_m-O-(CH₂)_m-OH group, -(CH₂)_m-OH group, -SO₂-NR^cR^d group, -CO-NR^cR^d group;

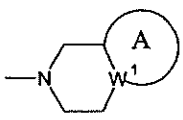
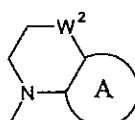
(5)  group;

(6)  or  or  group;

(7)  or  group;

(8)  or , optionally substituted with -(CH₂)_m-OH group,

(9)  group;

(10)  or  group;

(11)  group;

(12) $-\text{NH}-(\text{CH}_2)_n-\text{P}$ group;

(13) $-\text{NH}-(\text{CH}_2)_q-\text{NR}^a\text{R}^b$ group;

Y is selected from (1) $-(\text{CH}_2)_n-\text{NR}^a\text{R}^b$; (2) $-(\text{CH}_2)_n-\text{X}-\text{P}$ group;

n is an integer from 0 to 6;

5 m is an integer from 0 to 3;

q is an integer from 1 to 6;

X is selected from (1) single bond; (2) oxygen atom; (3) $-\text{CO}-\text{NR}^c$ group; (4) CO or SO_2 group;

P is selected from (1) phenyl group, optionally substituted with one or more
10 halogen atom, hydroxy, cyano, amino, [1,4']bipiperidinyl-1'-yl or C_1 - C_4 alkyl group; (2) a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, hydroxy, cyano, amino, piperidin-1-yl or C_1 - C_4 alkyl group; (3) C_5 - C_8 cycloalkyl group,
15 optionally substituted with $-(\text{CH}_2)_m-\text{NR}^a\text{R}^b$ group;

R^a and R^b are (1) hydrogen atom, with the proviso that R^a and R^b can not be simultaneously hydrogen atom; (2) straight or branched C_1 - C_6 alkyl group; (3) R^a , R^b and the nitrogen atom to which they are both attached together form a saturated, partially unsaturated or aromatic 4-7 membered ring containing 0-3
20 heteroatom (in addition to the nitrogen atom to which R^a and R^b attached) selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, cyano, hydroxy or C_1 - C_4 alkyl group;

R^c is hydrogen atom or C_1 - C_4 alkyl group;

R^d is hydrogen atom, C_1 - C_4 alkyl group, C_1 - C_4 hydroxyalkyl group, C_3 - C_8
25 cycloalkyl group;

R^e is hydrogen atom, C_1 - C_4 alkyl group, benzyl group;

A is (1) a C_4 - C_7 cycloalkyl ring; (2) a saturated, partially unsaturated or aromatic 5-7 membered ring containing 0-4 heteroatom including W^1 selected from O, S, SO_2 and N; wherein said ring is optionally substituted with one or more halogen atom, oxo, cyano, hydroxy, amino, phenyl or C_1 - C_4 alkyl group;
30

B is a saturated, partially unsaturated or aromatic 4-7 membered ring containing 1-3 heteroatom selected from O, S, SO_2 and N; wherein said ring is optionally

substituted with one or more halogen atom, oxo, cyano, hydroxy, amino, phenyl or C₁-C₄ alkyl group;

W¹ is carbon atom, nitrogen atom, or CH group;

W² is oxygen atom, sulfur atom, NH, CH₂ or SO₂ group;

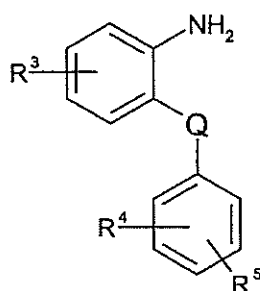
5 and optical antipodes or racemates and/or salts and/or hydrates and/or solvates thereof.

2. A compound of Claim 1 selected from the group of (*R*)-*N*-{1-methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; *N*-{2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-[2-oxo-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-ethyl]-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-[4-(2-dimethylamino-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-oxo-2-[4-(3-pyrrolidin-1-yl-propyl)-piperazin-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-[4-(3-dimethylamino-propyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-oxo-2-[4-(3-pyrrolidin-1-yl-propyl)-[1,4]diazepan-1-yl]-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-[4-(1-methyl-piperidin-3-ylmethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; *N*-{2-[4-(2-morpholin-4-yl-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenylsulfanyl-phenylsulfamoyl)-benzamide; (*S*)-*N*-{1-methyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*R*)-*N*-{1-hydroxymethyl-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*R*)-*N*-[1-(4-hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*R*)-*N*-[1-(4-hydroxy-benzyl)-2-(4-hydroxymethyl-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*R*)-*N*-{1-(4-hydroxy-benzyl)-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*S*)-*N*-{1-(4-hydroxy-benzyl)-2-oxo-2-[4-(2-pyrrolidin-1-yl-ethyl)-piperidin-1-yl]-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*S*)-*N*-[1-(4-hydroxy-benzyl)-2-oxo-2-(4-pyrrolidin-1-yl-piperidin-1-yl)-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*S*)-*N*-[1-(4-hydroxy-benzyl)-2-(4-hydroxy-piperidin-1-yl)-2-oxo-ethyl]-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (*S*)-*N*-

-43 -

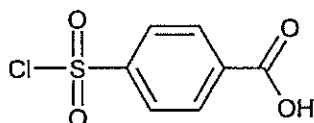
{1-(4-hydroxy-benzyl)-2-[4-(2-hydroxy-ethyl)-piperidin-1-yl]-2-oxo-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; (S)-N-{1-(4-hydroxy-benzyl)-2-[4-(1-methyl-piperidin-4-yl)-piperazin-1-yl]-2-oxo-ethyl}-4-(2-phenoxy-phenylsulfamoyl)-benzamide; 4-(2-phenylsulfanyl-phenylsulfamoyl)-N-
 5 {[(piperidin-4-ylmethyl)-carbamoyl]-methyl}-benzamide hydrochloride.

3. A process for preparing the compounds of formula (I) as claimed in Claim 1 which comprises reacting an amine derivative of formula (II)



(II)

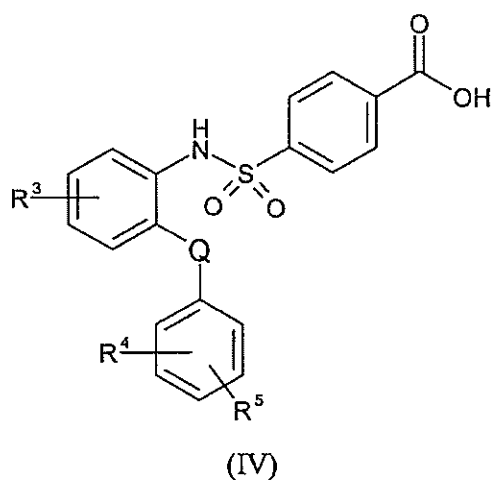
- wherein the meaning of R^3 , R^4 , R^5 and Q is as described above for the formula (I) – with the sulfonyl chloride of formula (III)



(III)

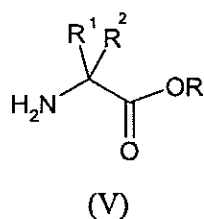
then reacting the so obtained phenylsulfamoyl benzoic acid derivative of formula (IV)

-44 -

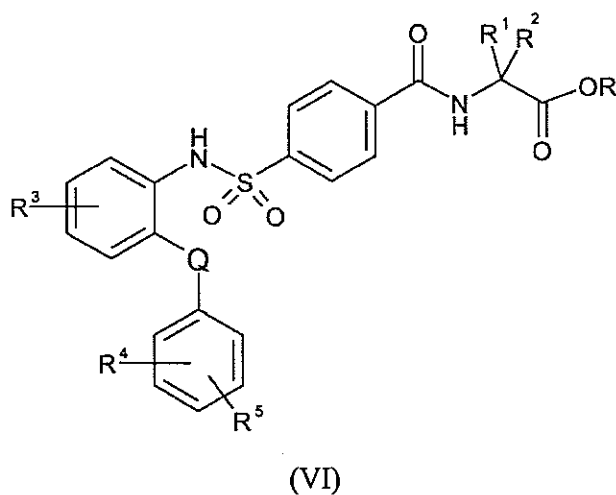


- wherein the meaning of R^3 , R^4 , R^5 and Q is as described above for the formula (I) –
with an amino acid of formula (V)

5



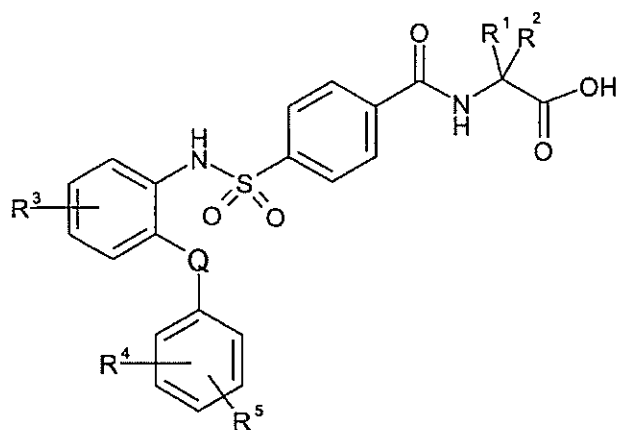
- wherein the meaning of R^1 and R^2 is as described above for the formula (I) and R is
 C_1 - C_4 alkyl group – and hydrolyzing the so obtained compound of formula (VI)



10

- wherein the meaning of R^1 , R^2 , R^3 , R^4 , R^5 , R and Q is as defined above –to furnish an
acid derivative of formula (VII)

-45 -



(VII)

- wherein the meaning of R¹, R², R³, R⁴, R⁵ and Q is as defined above – finally reacting the acid derivative of formula (VII) with an amine derivative Z to obtain a non-peptide derivative of formula (I) or optical antipodes or racemates and/or pharmaceutically acceptable salts and/or hydrates and/or solvates thereof.
4. A process for preparing the compounds of formula (I) as claimed in Claim 1 which comprises transforming a compound of formula (I) into an other compound of formula (I) by introducing new substituents and/or modifying or removing the existing ones, and/or salt formation and/or liberating the compound from salts.
 5. A pharmaceutical composition comprising a therapeutically effective amount of a compound of formula (I) as claimed in Claim 1 or optical antipodes or racemates or pharmaceutically acceptable salt or hydrate or solvate thereof and one or more pharmaceutically acceptable excipients.
 6. Use of a compound of formula (I) as claimed in Claim 1 or optical antipodes or racemates or a pharmaceutically acceptable salt or hydrate or solvate thereof for the manufacture of a medicament for prevention and/or treatment of a condition which requires inhibition of a bradykinin receptor.
 7. Use according to Claim 6 wherein the bradykinin receptor is bradykinin B1 receptor.

8. A compound of formula (I) as claimed in Claim 1 or optical antipodes or racemates or a pharmaceutically acceptable salt or hydrate or solvate thereof for use in the prevention and/or treatment of a condition which requires inhibition of a bradykinin receptor.
9. Use according to Claim 8 wherein the bradykinin receptor is bradykinin B1 receptor.