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Y COMPOSICIONES FARMACEUTICAS DE ESTAS

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74. APODERADO DILIA RODRIGUEZ D'ALEMAN

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☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)	Nombre: ISTITUTO LUSO FARMACO D'ITALIA S.P.A.		IDENTIFICACIÓN C.C. ☐ NIT: ☒ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
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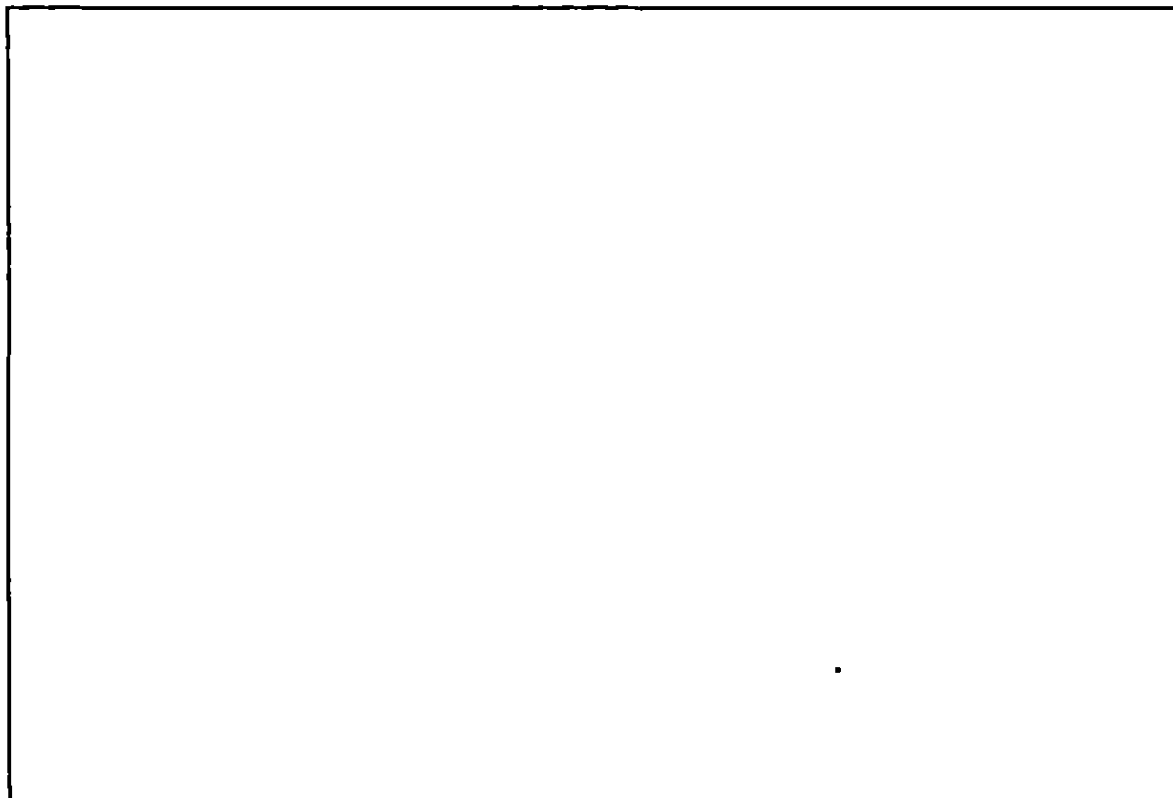
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ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredita la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
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- ☐ Arta final 12 x 12 y 6 x 6 cm
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- ☒ Otros:
 - 1. Reporte Internacional de búsqueda
 - 2. Solicitud PCT

11) FIGURA CARACTERÍSTICA:



12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:

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(54) Title: NON-PEPTIDE BRADYKININ ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREFROM

(57) Abstract: Non-peptide compounds having activity as selective antagonists of bradykinin (BK) B2 receptor. The compounds are chemically characterized by the presence of an amino acid alpha substituted with a cyclic group and by a tetraalkylammonium group.

65

NON-PEPTIDE BRADYKININ ANTAGONISTS AND
PHARMACEUTICAL COMPOSITIONS THEREFROM

FIELD OF THE INVENTION

The present invention relates to non-peptide compounds containing a quaternary ammonium group, having activity as specific antagonists of bradykinin (BK) B2 receptor, pharmaceutical compositions containing them
5 and the use thereof for the treatment of all the conditions in which activation of bradykinin B2 receptors are involved.

PRIOR ART

Bradykinin (BK) belongs to Kinins and forms, together with Kallidin and T-Kinin, the sub-group of Kinins present in mammals. Kinins play an
10 important role as mediators of pain and inflammation, both in the central and peripheral nervous system. Bradykinin is, in particular, a nonapeptide



produced by the body in physiopathological conditions.

Two types of Kinins receptors exist, B1 and B2. The main characteristic
15 of the B1 receptor is that it is more inducible than constitutive. It is expressed in tissues in inflammation or stress conditions. On the other hand, B2 is a constitutive receptor normally present in all tissues and acts a mediator during the inflammatory processes. Bradykinin and Kallidin are released from their protein precursors (known as kininogens), by proteolytic enzymes named
20 kininogenases. Among these, the main role is played by Kallikreins which however, once released by the precursor, can exert their action only for a short time as they are quickly destroyed by a series of circulating enzymes and membranes generically defined as Kininases. One of these Kininases cleaves bradykinin at the C-terminal arginine thus forming a des-Arg-BK which acts
25 as B1 receptor agonist.

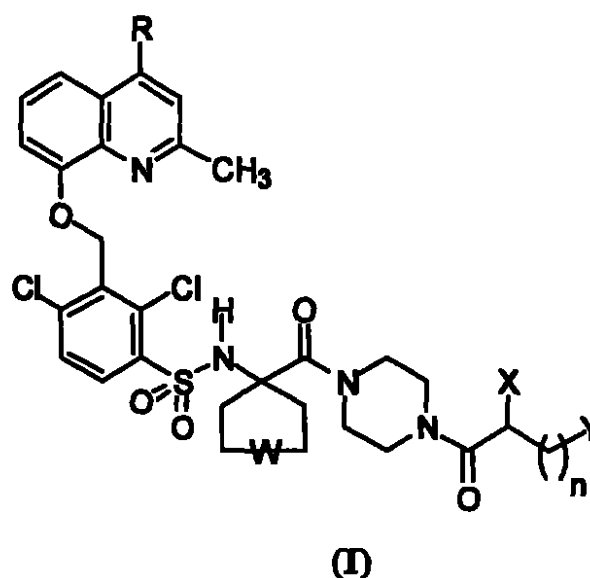
The activation of bradykinin B1 and B2 receptors induces relaxation of
vasal muscles with consequent hypotension, increase in vascular permeability,
contraction of smooth muscles of intestine and respiratory tract, stimulation of
nociceptive neurons, alteration of ionic epithelial secretion, production of
5 nitroxide and release of cytokines by leukocytes and eicosanoids from
different cell types. As a consequence, antagonistic compounds of BK
receptors can be considered a novel class of medicaments supposedly active in
various disorders. Possible therapeutical applications for said antagonists are
inflammatory, allergic and autoimmune disorders, such as asthma and chronic
10 bronchitis (also induced by irritants), allergic, vasomotor and viral rhinitis,
obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic
inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis),
glomerulonephritis, psoriasis, rash, acute and chronic cystitis; degenerative
disorders characterized by fibrosis, such as hepatic cirrhosis, glomerulopathies
15 and pulmonary fibrosis, arteriosclerosis; thanks to their analgesic activity, in
the treatment of both acute and chronic pain, for example in burns, cephealea,
insects bites, chronic pain in cancer patients; in disorders of the cardiovascular
apparatus such as septic, allergic and post-traumatic shocks, and hepatic
cirrhosis by hepatorenal syndrome; as anticancer and antiangiogenetics; in the
20 treatment of hypotension and of alopecia.

Different peptide and non-peptide antagonists of bradykinin B2 receptor
are known in literature. WO03103671 discloses a large family of compounds
with antagonistic activity on bradykinin B2 receptor. The compounds of the
present invention, although being included in the general formula of
25 WO03103671, are not described or characterized in said document.

DETAILED DISCLOSURE

The present invention relates to non-peptide compounds which show
high affinity and antagonistic activity towards B2 receptor, having general

formula (I):



in which:

- 5 - R is hydrogen or methyl;
- W is a single bond or an oxygen atom;
- $n = 3, 4$;
- X is hydrogen or a $-NR_1R_2$ amino group in which R_1 and R_2 can be independently hydrogen or a group selected from methyl, ethyl, n-propyl, isopropyl;
- 10 - Y is a $-NR_3R_4R_5$ quaternary ammonium group in which R_3, R_4, R_5 can be independently a group selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl; and

the salts thereof with pharmaceutically acceptable acids.

- 15 Preferably, compounds (I) are salified with inorganic or organic acids selected from hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, acetic, trifluoroacetic, propionic, oxalic, malic, maleic, succinic, malonic, aspartic, glutamic acids. Moreover, due to the presence of a chiral center, the invention also comprises the two enantiomers or mixtures thereof, in any
- 20 proportion, including racemic mixtures.

The compounds of general formula (I) have both *in vivo* and *in vitro*

antagonistic activity towards B2 receptor higher than the more structurally similar analogues as described in WO03103671.

Preferred are the compounds of general formula (I) in which:

$n = 3$;

5 $X = \text{hydrogen or a } -\text{NH}_2 \text{ group};$

$Y = -\text{N}(\text{CH}_3)_3^+$ quaternary ammonium group;

the other substituents being as defined above.

Particularly preferred are the compounds (I) wherein:

R is hydrogen or methyl;

10 W is an oxygen atom;

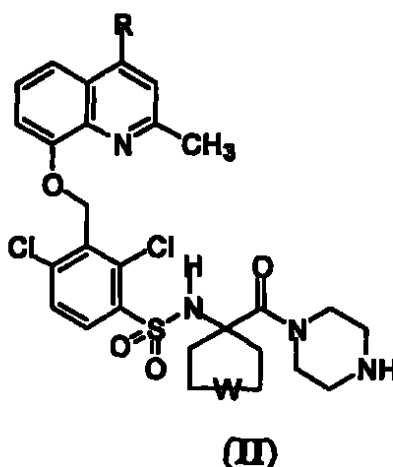
$n = 3$;

X is hydrogen or a group $-\text{NH}_2$;

Y is a $-\text{N}(\text{CH}_3)_3^+$ quaternary ammonium group.

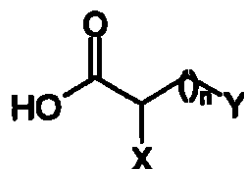
15 The compounds object of the present invention can be prepared according to well known synthetic routes.

Preferably, the compounds of general formula (I) as defined above are prepared by condensation, in the presence of a suitable condensing agent, of the intermediate of general formula (II), obtained as disclosed in WO03103671



20 with the compound of formula (10)

5

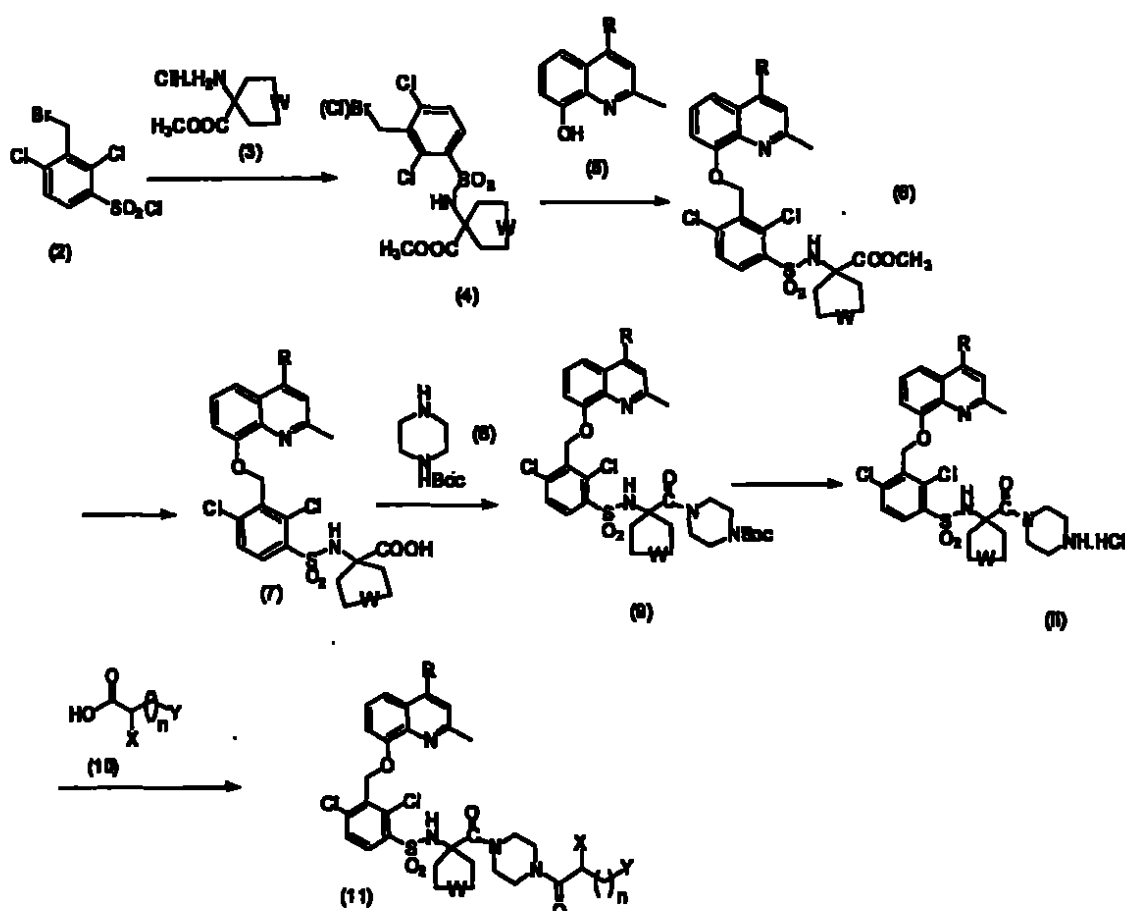


(10)

or a derivative thereof in which the carboxylic group is suitably activated.

5

The synthetic process is illustrated in Scheme 1



Scheme 1

10

The compound of formula (2) is prepared as described in *J. Med. Chem.* 2001, 44, 1674-1689 by bromination of the corresponding toluene derivative, which is in turn obtained as described in *J. Fluorine Chemistry*, 2000, 101:85-89.

The first step concerns the formation of the sulfonamido bond (4)

obtained by condensation of intermediates (2) and (3). This reaction is carried out at room temperature, preferably in acetonitrile/water (2:1), in the presence of sodium hydrogen carbonate (NaHCO_3). Said reaction takes place with exchange of chlorine and bromine at the benzyl position: the resulting
5 products mixture is directly used in the subsequent step. The reaction of the halogen derivatives mixture with a disubstituted hydroxyquinoline (5), in the presence of potassium carbonate (K_2CO_3) and potassium iodide (KI), in acetone under reflux, yields the ester derivative (6).

Compound of formula (5) i.e. 2,4-dimethyl-8-hydroxy quinoline, in
10 which $\text{R}_4=\text{R}_5=\text{CH}_3$, is prepared as disclosed in WO9640639.

The methyl ester of formula (6) is hydrolysed under basic conditions to carboxylic acid (7), which is condensed with Boc-piperazine (8), to yield intermediate (9). Said condensation reaction is carried out according to a known procedure for the peptide synthesis, using hydroxybenzotriazole to
15 activate the carboxylic moiety, a condensing agent such as 1-ethyl-3-(3'-dimethylpropyl) carbodiimide and an amount of tertiary amine, namely diisopropylethylamine, of three equivalents on the basis of the condensing agent. Compound (II) is obtained by cleavage of the Boc group from intermediate (9), by means of a hydrochloric acid solution (4N) in dioxane and
20 isolating the free amine instead of the hydrochloride.

Derivative (11) is obtained by condensation of intermediate (10) with the amino acid (11) according the procedure described for the preparation of (9) from (7). Any Boc group present can be removed from intermediate (11), with a hydrochloric acid solution (4N) in dioxane, thus obtaining the final
25 compound. When case the trialkylammonium group is not present in any commercially available intermediates, it can be synthesized starting from the corresponding amine with known procedures (Rapoport et al, *J. Org. Chem*, 1977, 42:139-141; Chen et al, *J. Biochem.*, 1978, 56:150-152).

The compounds of the invention are used in the treatment of all those disorders in which the activation of bradykinin receptor has to be blocked or reduced. They are particularly suitable for the treatment of inflammatory, allergic and autoimmune disorders, such as asthma and chronic bronchitis, 5 allergic, vasomotor and viral rhinitis, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis), glomerulonephritis, psoriasis, rash, acute and chronic cystitis, hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis, both acute and chronic pain, septic, allergic and post- 10 traumatic shocks, hepatic cirrhosis by hepatorenal syndrome, hypotension, alopecia, or as anticancer and antiangiogenetics.

For use in therapy, the compounds of the invention will be suitably formulated together with pharmaceutically acceptable carriers/excipients. Preferred are pharmaceutical forms suitable for the oral administration, such 15 as tablets, capsules, granules, powders, solutions, suspensions, syrups or the like. These pharmaceutical preparations can be prepared with conventional procedures using ingredients known in technique, such as ligands, disintegrants, lubricants, fillers, stabilizing agents, diluents, dyes, flavours, wetting agents and other excipients known to those skilled in the art. The oral 20 formulations also comprise protracted-release forms, such as enteric-coated tablets or granules. The solid oral compositions can be prepared with conventional mixing, filling or compression methods. The liquid oral preparations can be in the form of, for example, aqueous or oily suspensions or solutions, emulsions, syrups, or can be presented as dry product for 25 reconstitution with water or other suitable carrier before use.

The dosage can range depending on the age and general conditions of the patient, nature and severity of the disease or disorder and route and type of administration. As a rule, in case of oral administration to a human adult

patient, the compounds of the present invention will be generally administered in a total daily dosage ranging from 1 to 1000 mg, preferably from 5 to 300 mg, in a single dose or in subdivided doses.

The following examples illustrate the invention in greater detail.

5 EXAMPLE 1

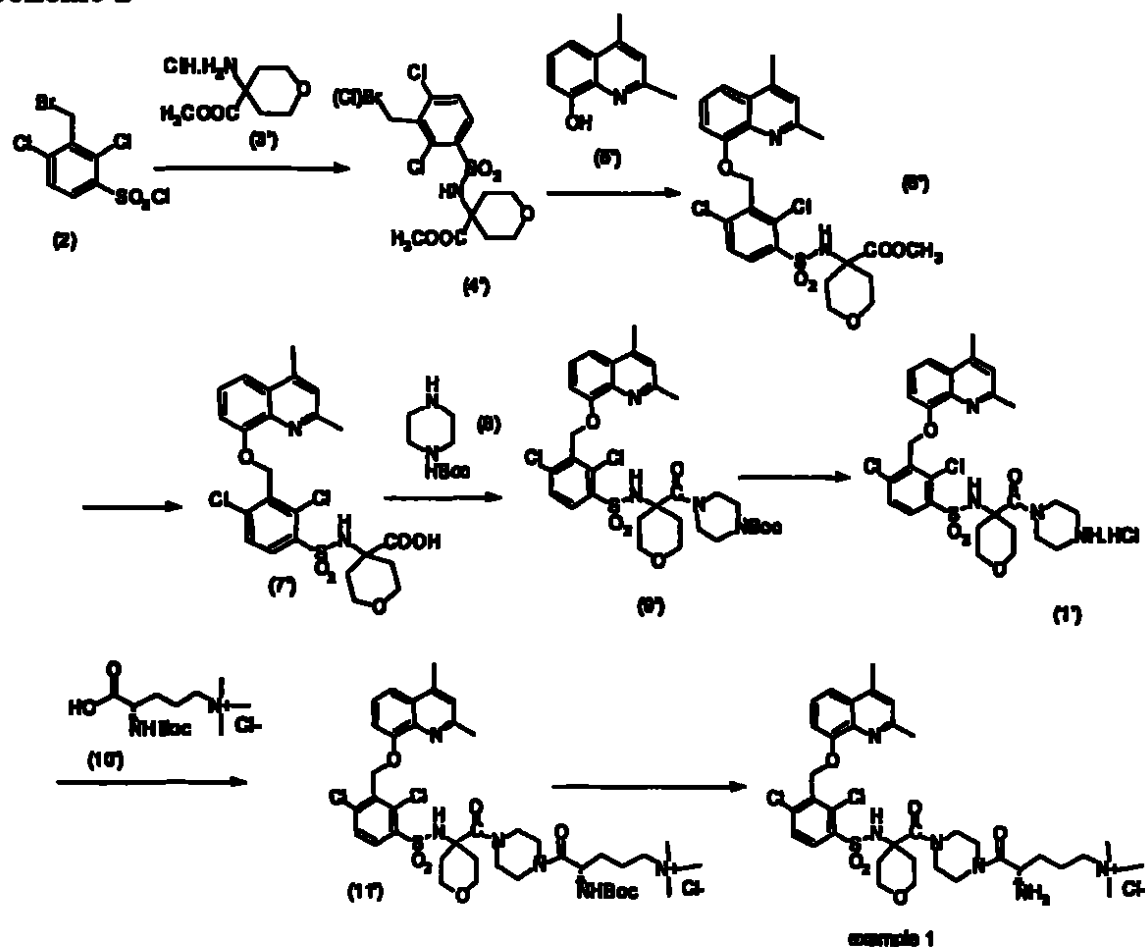
(4-(S)-amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carbonyl}piperazin-1-yl)-5-oxopentyl]trimethyl-ammonium chloride, dihydrochloride

(Compound of general formula I in which R = CH₃, W = -O-, X = NH₂,

10 $n = 3, Y = N(CH_3)_3^+Cl^-$.

The compound is synthesized following the synthetic route illustrated in

Scheme 2



GENERAL METHODS: analytic HPLC: Flow: 1 ml/min; Mobile phase: A-0.1% trifluoroacetic acid in water, B-0.1% trifluoroacetic acid in acetonitrile; Column: Zorbax Eclipse XDB C8, 5 micron, 150 x 4,6 mm.

Intermediate (2) 2,4-Dichloro-3-bromomethyl-benzenesulfonyl chloride

5 10 ml of chlorosulfonic acid are dropwise added with 4.8 ml of 2,6-dichlorotoluene in two hours, under magnetic stirring at room temperature. After completion of the addition, the mixture is heated at 40°C for two hours, thereby obtaining a purple solution, which is cooled and carefully poured into ice-water (0.5 l), stirring vigorously. The separated white solid is filtered,
10 triturated, washed with water, dried over KOH and purified by washing with n-hexane, adding 200 ml of solvent under strong stirring. The mixture is filtered, the solid is discarded and the solvent is evaporated to dryness to obtain 2,4-dichloro-3-methyl-benzenesulfonyl chloride as a crystalline white solid. Yield: 85%.

15 HPLC purity: 86% (30% B, 3%/min, Rt=19.7 min).

¹H-NMR (CDCl₃): δ (ppm) 2.6 (s, 3H), 7.5 (d, 1H), 7.95 (d, 1H);

ESI(+)-MS: m/z 260 [M+H]⁺.

 This intermediate is brominated under the following conditions: 20 mmols of 2,4-dichloro-3-methyl-benzenesulfonyl chloride are dissolved in
20 acetonitrile. 2 eq of NBS are added under stirring at room temperature until completed solubilization of NBS. Finally, 0.1 eq of azo-bisisobutyronitrile (AIBN) is added and the mixture is heated at 70°C for approx. 6 hours. The solution is evaporated, the residue is taken up with ethyl acetate, washed with H₂O and 5% NaHCO₃, dried over dry Na₂SO₄ and filtered. The organic phase
25 is evaporated thereby obtaining a viscous, light colored liquid which is taken up into petroleum ether. The residue is filtered, and the solution yields (2') as a light colored crystalline solid.

HPLC purity: 95% (50% B to 5%/min, Rt=18.72).

¹H-NMR (CDCl₃): δ (ppm) 4.85 (s, 2H), 7.58 (d, 1H), 8.08 (d, 1H);
ESI(+)-MS: m/z 338.1 [M+H]⁺.

Intermediate (3') 4-Amino-tetrahydropyran-4-carboxylic acid methyl ester hydrochloride

5 4-Amino-tetrahydropyran-4-carboxylic acid hydrochloride (0.025 mols) is suspended in 13 ml of CH₃OH, cooled to -60°C and dropwise added with SOCl₂ (3 eq) under stirring. After completion of the addition, the mixture is left to warm to room temperature, then gradually heated to ebullition to obtain a clear solution (approx. 2 hours), which is cooled, the residue is filtered and
10 concentrated under vacuum.

Yield 80%. Purity (NMR): 85%.

¹H-NMR (DMSO-d₆): δ (ppm) 1.91-2.04 (m, 4H), 3.78 (s, 3H), 3.60-3.85 (m, 4H), 9.00 (s, 3H). ESI(+)-MS: m/z 160.1 [M+H]⁺.

Intermediate (4') 4-(3-Bromomethyl-2,4-dichloro-benzenesulfonylamino)-tetrahydropyran-4-carboxylic acid methyl ester

15 The intermediate (3') (1.1 eq) is dissolved in water together with 4 equivalents of K₂CO₃. This solution is added with a solution of 1 equivalent (10 mmols) of intermediate (2) in acetonitrile and stirred at room temperature until a precipitate forms (4 hours). The solvent is evaporated off and the
20 residue is dissolved in ethyl acetate and 0.1M HCl (1/1). The organic phase is separated and dried over Na₂SO₄. The solvent is evaporated off, the resulting solid is washed with cyclohexane, thereby obtaining a white solid in which chloro/bromo derivatives are present in 10/1 ratio. Yield: 60%.

HPLC purity: 88% (20% B at 3%/min; Rt=14.11 (Br) and 14.47 (Cl)).

25 ¹H-NMR (CDCl₃): δ (ppm) 1.81-1.99 (2H, m), 2.07-2.25 (2H, m), 3.49-3.71 (7H, m), 4.81 (1.5H, s, [Br]), 4.94 (0.3H, s, [Cl]), 5.30 (1H, brs), 7.47-7.53 (1H, m), [7.49 (d, J 8.5Hz, X = Br), 7.51 (d, J 8.5Hz, X = Cl)], 7.91-7.98 (1H, m), [7.94 (d, J 8.5Hz, X = Br), 7.96 (d, J 8.5Hz, X = Cl)].

Intermediate (6') 4-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid methyl ester

Quinoline (5') (0.48 mmols) and LiOH (2.5 eq) are mixed at room temperature under nitrogen in methyl ethyl ketone (MEK). The mixture is kept
5 under stirring and under nitrogen for 90 min. Intermediate (4) is dissolved in MEK/dry DMF (2/1) (42 ml, 12 ml/mmol), and the solution containing the quinoline is dropwise added to the reaction mixture, under stirring. Stirring is kept for 16 hours. The reaction mixture is concentrated under vacuum and the residue dissolved in ethyl acetate (50 ml, 100 ml/mmol). The organic phase is
10 washed (3x50 ml) with a buffer solution pH=4.2, dried over Na₂SO₄, filtered and concentrated under vacuum to obtain a yellow oil. Yield: 33%. HPLC purity: 77% (20% B, 3%/min; Rt=9.54).

¹H-NMR (DMSO-d₆): δ (ppm) 1.80-1.95 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.32-3.40 (m, 2H), 3.42-3.55 (m, 2H), 3.60 (s, 3H), 5.57 (s, 2H),
15 7.30 (s, 1H), 7.39 (d, 1H), 7.50 (dd, 1H), 7.67 (d, 1H), 7.78 (d, 1H), 8.02 (d, 1H), 8.77 (bs, 1H); ESI(+)MS: m/z 553.1 [M+H]⁺.

Intermediate (7') 4-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carboxylic acid

Intermediate of formula (6') is dissolved in THF and the solution is
20 added with 10 eq of 1M LiOH in water. The mixture is stirred for 4 hours at 40°C, then the solvent is evaporated off. The residue is dissolved in water and 0.1M HCl is added to pH=4. The aqueous phase is extracted with dichloromethane and the organic phase is dried over Na₂SO₄. Solvent is evaporated off and to obtain a yellow solid residue. Yield: 90%. HPLC purity:
25 99% (20%B, 3%/min; Rt=7.72).

¹H-NMR (DMSO-d₆): δ (ppm) 1.75-1.90 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.10-3.35 (m, 2H), 3.38-3.50 (m, 2H), 5.58 (s, 2H), 7.30 (s, 1H),

7.37 (d, 1H), 7.46 (t, 1H), 7.67 (d, 1H), 7.75 (d, 1H), 8.03 (d, 1H), 8.64 (bs, 1H). ESI(+)MS: m/z 539.1 [M+H]⁺.

Intermediate (9') 4-tert-butoxycarbonyl-((4-(2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)benzenesulfonylamino)-tetrahydropyran-4-carbonyl)-piperazin-1-yl)

(7') (1.3 mmols) and HOBt (1.1 eq) are suspended in 50 ml of dry DMF in a 100 ml round-bottom flask under nitrogen. The mixture is cooled to +4°C and added with EDCI. HCl (1.1 eq) under stirring. Stirring at +4°C is continued for an hour, then DIPEA (2 eq) and Boc-piperazine (1 eq) are added and the mixture is left to warm to room temperature, under stirring. After 12 h the solvent is evaporated off, the residue is dissolved in 40 ml of DCM and the organic phase is washed with brine (20 ml) and dried over Na₂SO₄. The solvent is evaporated off to obtain an oil which is purified on a Varian Mega Bond (flash master system) 70 g column (ethyl acetate, R_f=0.50), thereby obtaining a yellow solid.

Yield: 96%. HPLC purity: 98% (20% B, 3% B/min, R_t=11.14).

¹H-NMR (CDCl₃): δ (ppm) 1.45 (s, 9H); 1.55-1.80 (m, 2H), 2.05-2.20 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.38-3.90 (m, 10H), 5.58 (s, 2H), 7.10 (s, 1H), 7.30 (s, 1H), 7.37 (d, 1H), 7.46 (t, 1H), 7.67 (d, 1H), 7.75 (d, 1H), 8.03 (d, 1H), 8.64 (bs, 1H). ESI(+)MS: m/z 707.2 [M+H]⁺.

Intermediate (1') (4-(2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino)-tetrahydropyran-4-carbonyl)-piperazin-1-yl

0.62 mmols of (9') are added with 10 ml of HCl/dioxane 4M and the mixture is kept under stirring for 3 hours. The solvent is evaporated off and the residue is freeze-dried, to obtain hydrochloride (1') as yellow solid. Yield: 98%. HPLC purity: 92% (20% B, 3%/min; R_t=5.34).

¹H-NMR (D₂O): δ (ppm) 1.55-2.10 (m, 7H), 2.90-3.10 (m, 9H), 3.20-3.55 (m, 9H), 6.0 (s, 2H), 7.60-8.10 (m, 8H), 8.95 (d, 1H).

ESI(+)-MS: m/z 609.1 $[M+H]^+$.

Intermediate (10') (4-tert-butoxycarbonylamino-4-carboxy-butyl)-trimethylammonium

10 mmols of Boc-Orn-OH are suspended in methanol (20 ml) and the
5 suspension is added with 44 mmols of isourea. The flask is plugged and kept under stirring at room temperature for 2 days. The resulting solution is monitored by TLC (eluent: $CHCl_3/CH_3OH/NH_4OH$ 40/54/6; Boc-Orn-OH $R_f=0.29$; (10') R_f : 0.11, detection $KMnO_4$).

Methanol is evaporated off under vacuum and the residue is digested in
10 150 ml of water and filtered. The round-bottom flask and the solid are washed with water (2x50 ml) and all the washing aqueous fractions are combined, then concentrated under vacuum (40 ml). The resulting solid (4.068 g) is suspended in water (40 ml), filtered (to remove any traces of urea) and purified by FCC on reversed phase LiChroprep RP-18 (40-63 micron). The
15 column (19 x 7 cm) is eluted with 3% CH_3CN in water and the fractions (approx. 100 ml) are analyzed by TLC. The fractions containing the pure product (500 ml) are combined, concentrated under vacuum to remove CH_3CN , freeze-dried, and finally evaporated from 150 ml of absolute ethanol, to give 442 mg of a white, highly hygroscopic solid. Yield: 16%.

20 1H -NMR ($DMSO-d_6$): δ (ppm) 1.38 (s, 9H) 1.58-1.75 (m, 4H), 3.03 (s, 9H), 3.29 (m, 2H), 3.45 (m, 1H), 6.49 (d, d, 1H); ESI(+)-MS: m/z 275.2 $[M+H]^+$.

Intermediate (11') (4-(S)-tert-Butoxycarbonylamino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)benzenesulfonylamino]tetrahydro-pyran-4-carbonyl}piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium chloride

25

Intermediate (10'), 1.2 mmols, is dissolved in DMF and the solution is added with dicyclohexylcarbodiimide (1.2 eq) and HOBt (1.2 eq). The mixture is kept under stirring for 30 min, then added with diisopropylaminomethyl-

polystyrene (1.5 eq) and intermediate (1') (1 eq). The mixture is left under stirring for 24 hours. The resin is filtered, the solvent is evaporated off and the residue is dissolved in water and ethyl acetate. The aqueous phase is separated and freeze-dried. The crude product is purified by preparative HPLC (column
5 Vydac 218TP, C18, 250x50 mm, flow 60 ml/min, gradient 10% to 70% CH₃CN/0.1% TFA in 120 min, detector UV at 240 nm, collection 55 to 75 min) thereby affording intermediate (11') which is freeze-dried as a white solid. Yield: 46%. HPLC purity: 98% (20% B, 3%/min; Rt=7.68).

¹H NMR (DMSO-d₆) δ: 1.4 (s, 9H), 1.8-1.45 (m, 6H), 1.95-1.85 (m,
10 2H), 2.81 (m, 6H), 3.08 (s, 9H), 3.70-3.18 (m, 7H), 4.01-3.56 (5H, m), 4.57-4.45 (m, 1H), 5.59 (s, 2H), 7.25 (d, 1H), 7.90-7.43 (m, 4H), 8.02 (d, 1H), 8.85 (s, 1H). ESI(+)MS: m/z 863.2 [M+H]⁺.

(4-(S)-Amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carbonyl}piperazin-1-yl)-5-oxo-
15 pentyl]trimethyl-ammonium chloride, dihydrochloride

0.45 mmols of (11') are added with 10 ml of HCl/dioxane 4M. The mixture is kept under stirring for 6 hours, the solvent is evaporated off and the residue is freeze-dried, thereby obtaining the final compound as a white solid. Yield: 87%. HPLC purity: 98% (20% B, 3%/min; Rt=5.14).

¹H NMR (DMSO-d₆) δ: 1.95-1.60 (m, 8H), 2.81 (m, 6H), 3.08 (s, 9H),
20 3.70-3.18 (m, 12H), 4.57-4.45 (m, 1H), 5.59 (s, 2H), 7.90-7.60 (m, 4H), 8.02 (d, 1H), 8.5 (s, 3H), 8.85 (s, 1H).

ESI(+)MS: m/z 763.1 [M+H]⁺.

EXAMPLE 2

25 (4-(S)-Amino-5-(4-(4-(2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino)tetrahydropyran-4-carbonyl)-piperazin-1-yl)-5-oxo-pentyl)-trimethylammonium chloride, hydrochloride

¹H NMR (DMSO-d₆) δ: 8.90 (1H, s), 8.47-8.34 (4H, m), 8.02 (1H, d), 7.81 (1H, d), 7.73-7.37 (4H, m), 5.62 (2H, s), 4.57-4.45 (1H, m), 4.01-3.56 (5H, m), 3.43-3.18 (7H, m), 3.06 (9H, s), 2.78-2.61 (4H, m), 2.89 (1H, s), 1.97-1.60 (9H, m). HPLC: t_R = 9.26 min. MS: [M]⁺ 749.

5 EXAMPLE 3

[5-(4-{4-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzene-sulfonylamino]tetrahydropyran-4-carbonyl}piperazin-1-yl)-5-oxo-pentyl]-trimethyl-ammonium trifluoroacetate.

¹H-NMR (DMSO-d₆): δ (ppm) 1.53 (s, 2H, m); 1.69 (m, 4H); 1.90 (m, 2
10 H); 2.45 (t, 2 H); 2.78 (m, 6 H); 3.04 (9 H, s); 3.23 - 3.57 (7 H, m); 5.68 (2H, s); 7.38-8.18 (5 H, m); 8.04 (1H, d, J = 8.42 Hz); 8.82 (1 H, s). HPLC: t_R = 5.65 min. MS: [M]⁺ 748.

EXAMPLE 4

[4-(S)-Amino-5-(4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-
15 benzenesulfonylamino]cyclopentanecarbonyl}piperazin-1-yl)-5-oxo-pentyl]-trimethyl-ammonium chloride, dihydrochloride.

¹H NMR (DMSO-d₆) δ: 8.90 (1H, s), 8.48 (3H, s), 8.02 (1H, d), 7.95-7.63 (3H, m), 5.59 (2H, s), 4.57-4.45 (1H, m), 3.97-3.24 (10H, m), 3.08 (9H, s), 2.95-2.61 (5H, m), 1.97-1.72 (8H, m), 1.42 (4H, s); HPLC: t_R = 5.88 min.
20 MS: [M]⁺ 747.2.

Biological Activity

The evaluation of the B2 receptor affinity of the compounds of the present invention was carried out with studies of binding to the human B2 receptor expressed in CHO cells, following the procedure described by
25 Bellucci et al, *Br. J. Pharmacol.* 2003, 140:500-506; the binding values are reported expressed as pKi.

Antagonistic activity (expressed as pA₂) was evaluated as the inhibition of the bradykinin-induced production of inositols in CHO cells transfected

with B2 human receptor, according to the procedure described in Bellucci et al, *Br. J. Pharmacol.* 2003, 140:500-506.

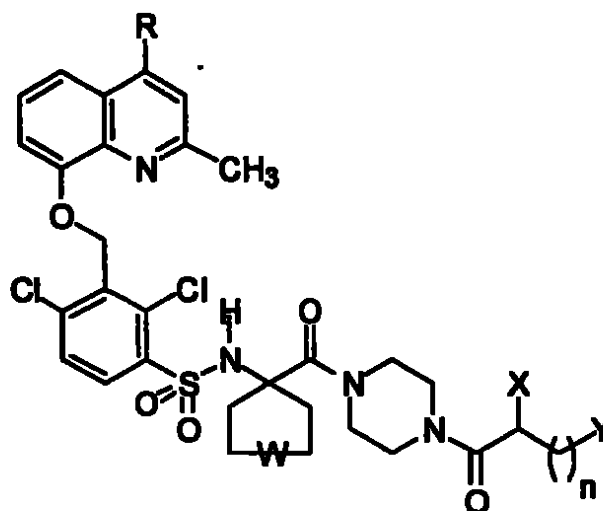
The *in vivo* activity of the compounds of the present invention was evaluated as effectiveness in inhibiting BK-induced bronchospasm in the guinea pig (Tramontana et al., *J. Pharmacol. Exp. Therap.*, 296:1051-1057, 2001), measuring the it dose (it=intratracheal administration) (in nmols/kg) which inhibited by 80% bronchial constriction for at least 210 min.

Example	W	R	X	Y	n	pKi	pA2	it Dose
WO03103671 ex 55	bond	H	NH ₂	NHC(=NH)NH ₂	3	8.7	8.4	300
WO03103671 ex 63	bond	CH ₃	NH ₂	NH ₂	4	9.1	8.9	300
WO03103671 ex 57	bond	H	NH ₂	N(CH ₃) ₂	4	8.8	8.3	300
WO03103671 ex 59	bond	CH ₃	NH ₂	N(CH ₃) ₂	4	8.8	9.0	300
WO03103671 ex 44	bond	CH ₃	NH ₂	NHC(=NEt)NHBt	3	10.1	9.0	300
WO03103671 ex 88	bond	CH ₃	N(CH ₃) ₃	N(CH ₃) ₃	4	9.7	8.2	-
Example 1	O	CH ₃	NH ₂	N(CH ₃) ₃	3	10.3	10.3	30
Example 2	O	H	NH ₂	N(CH ₃) ₃	3	10.2	9.7	100
Example 3	O	CH ₃	H	N(CH ₃) ₃	3	10.1	9.5	100
Example 4	bond	CH ₃	NH ₂	N(CH ₃) ₃	3	10.1	9.4	100

The preferred compounds of the present invention were compared with those more structurally similar disclosed in WO03103671. It has surprisingly been found that the compounds of the invention have *in vivo* and *in vitro* activities higher than the structurally related analogues of WO03103671. Both the antagonistic activity test on cells transfected with the human receptor and the *in vivo* test are highly predictive of the expected dose for therapeutical applications in humans.

ABBREVIATIONS

it = intratracheal administration; iv = intravenous administration; eq = equivalent;
10 DCM = dichloromethane; MeOH = methanol; THF = tetrahydrofuran; DMSO = dimethylsulfoxide; DMF = dimethylformamide; AcOEt = ethyl acetate; AcOH = acetic acid; TFA = trifluoroacetic acid; NBS = N_α-bromosuccinimide; bpo = benzoyl peroxide; Boc = tert-butoxycarbonyl; HOBt = 1-hydroxy-benzotriazole; EDC = 1-ethyl-3-(3'-dimethylpropyl)carbodiimide; DIPEA =
15 diisopropylethylamine; HPLC = high pressure liquid chromatography; TLC = thin-layer chromatography; NMR = nuclear magnetic resonance; ESI = electron spray ionization; MS = mass spectrometry; FCC = Flash Column Chromatography; Rt = retention time.

CLAIMS**1. Compounds of general formula (I)****(I)****in which**

- R is hydrogen or methyl;
- W is a single bond or an oxygen atom;
- n = 3, 4;
- X is hydrogen or a -NR₁R₂ amino group in which R₁ and R₂ can be independently hydrogen or a group selected from methyl, ethyl, n-propyl, isopropyl;
- Y is a -NR₃R₄R₅ quaternary ammonium group in which R₃, R₄, R₅ can be independently a group selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl; and

the pharmaceutically acceptable salts, enantiomers and enantiomeric mixtures thereof.

- 2. Salts of the compounds of general formula (I) with inorganic or organic acids selected from hydrochloric, hydrobromic, hydroiodic, sulfuric,**

phosphoric, acetic, trifluoroacetic, propionic, oxalic, malic, maleic, succinic, malonic, aspartic, glutamic acids.

3. Compounds as claimed in claim 1 or 2, wherein:

W is a single bond;

5 n = 3;

X is selected from hydrogen or a -NH₂ group;

Y is a -N(CH₃)₃⁺ quaternary ammonium group;

the other substituents being as defined in claim 1.

4. Compounds as claimed in claim 1 or 2, in which:

10 R is selected from hydrogen or methyl;

W is an oxygen atom;

n = 3;

X is selected from hydrogen or a -NH₂ group;

Y is a -N(CH₃)₃⁺ quaternary ammonium group;

15 the other substituents being as defined in claim 1.

5. The following compound as claimed in claim 3:

[4-(S)-amino-5-(4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)benzenesulfonylamino]-cyclopentanecarbonyl}piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium chloride, dihydrochloride

20 6. The following compounds as claimed in claim 4:

- (4-(S)-amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy-methyl)benzenesulfonylamino]tetrahydropyran-4-carbonyl}-piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium chloride, dihydrochloride;

- (4-(S)-amino-5-(4-(4-(2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonylamino)-tetrahydropyran-4-carbonyl)-piperazin-1-yl)-5-oxo-pentyl)-trimethyl-ammonium chloride, hydrochloride;

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- [5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carbonyl}piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium trifluoroacetate.

7. Pharmaceutical compositions containing as the active ingredient a
5 compound as claimed in claims 1 to 6 together with pharmaceutically acceptable excipients.

8. The use of a compound as claimed in claims 1 to 6 for the preparation of pharmaceutical compositions for the treatment of all the conditions in which activation of bradykinin B2 receptors is involved.

10 9. The use of a compound as claimed in claim 8 for the preparation of pharmaceutical compositions for the treatment of inflammatory, allergic and autoimmune conditions.

10. The use of a compound as claimed in claim 8 for the preparation of pharmaceutical compositions for the treatment of asthma and chronic
15 bronchitis, allergic, vasomotor and viral rhinitis, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis), glomerulonephritis, psoriasis, rash, acute and chronic cystitis, hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis, both
20 acute and chronic pain, septic, allergic and post-traumatic shocks, hepatorenal syndrome by hepatic cirrhosis, hypotension, alopecia, cancer and antiangiogenetic diseases.

INTERNATIONAL SEARCH REPORT

International application No

PCT/EP2005/010412

A. CLASSIFICATION OF SUBJECT MATTER

A61K31/47 A61P29/00 C07D215/26

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)

A61K A61P 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, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/103671 A (MENARINI RICERCHE S.P.A; CALVANI, FEDERICO; CATRAMBONE, FERNANDO; FEL) 18 December 2003 (2003-12-18) cited in the application page 55; claims; examples 79,83 page 15	1-10
A	HEITSCH H ET AL: "Novel Series of O-Substituted 8-Quinolines and 4-Benzothiazoles as Potent Antagonists of the Bradykinin B2 Receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 3, 8 February 1999 (1999-02-08), pages 327-332, XP004157223 ISSN: 0960-894X table 1; compound 8B	1-10
-/-		



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

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

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

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

A document member of the same patent family

Date of the actual completion of the international search

23 February 2006

Date of mailing of the international search report

13/03/2006

Name and mailing address of the ISA/

European Patent Office, P.O. Box 5818 Patentplan 2
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Härtinger, S

INTERNATIONAL SEARCH REPORT

International application No

PCV7 EP2005/010412

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HEITSCH H: "Non-peptide antagonists and agonists of the bradykinin B(2) receptor." CURRENT MEDICINAL CHEMISTRY. MAY 2002, vol. 9, no. 9, May 2002 (2002-05), pages 913-928, XP002369396 ISSN: 0929-8673 figure 3	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PC77EP2005/010412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WD 03103671 A	18-12-2003	AU 2003242628 A1	22-12-2003
		BR 0311825 A	15-03-2005
		CA 2488565 A1	18-12-2003
		CN 1658877 A	24-08-2005
		EP 1513531 A1	16-03-2005
		IT MI20021247 A1	09-12-2003
		JP 2005532354 T	27-10-2005
		MX PA04012193 A	25-02-2005

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ANTAGONISTAS DE BRADICININA NO PEPTÍDICA Y COMPOSICIONES
FARMACÉUTICAS DE ESTAS

CAMPO DE LA INVENCION

La presente invención se relaciona con compuestos no peptídicos que contienen un grupo amonio cuaternario, que tiene actividad como antagonistas específicos del receptor B2 de bradicinina (BK), composiciones farmacéuticas que los contienen y el uso de estos para el tratamiento de todas las condiciones en las que la activación de los receptores de bradicinina B2 se involucran.

TÉCNICA ANTERIOR

La bradicinina (BK) pertenece a cininas y formas, junto con calidina y T-Cinina, el subgrupo de Cininas presentes en mamíferos. Las Cininas juegan un importante papel como mediadoras de dolor e inflamación, ambos en el sistema nervioso central y periférico. La bradicinina es, en particular, un nonapéptido.

(H-Arg¹Pro²Pro³Gly⁴Phe⁵Ser⁶Pro⁷Phe⁸-Arg⁹-OH) producidas por el cuerpo en condiciones fisiopatológicas.

Existen dos tipos de receptores Cinina, B1 y B2. La característica principal del receptor B1 es que es más inducible que constitutivo. Se expresa en tejidos en

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condiciones de inflamación y estrés. Por otra parte, B2 es un receptor constitutivo normalmente presente en todos los tejidos y actúa como mediador durante el proceso inflamatorio. La Bradicinina y Calidina se liberan de sus precursores de proteína (conocidos como cininógenos), mediante enzimas proteolíticas llamadas cininogenasas. Entre estas, la calicreína juega el papel principal la cual sin embargo, una vez liberada por el precursor, puede ejercer su acción solo en un corto tiempo ya que ellas son destruidas rápidamente por una serie de enzimas circulantes y membranas genéricamente definidas como Cininasas. Una de estas Cininasas cliva la bradisinina en el terminal C de arginina que forma así una des-Arg-BK que actúa como agonista del receptor B1.

La activación de los receptores de bradisinina B1 y B2 inducen relajación de los músculos vasculares con consecuencia de hipotensión arterial, incremento en la permeabilidad vascular, contracción del músculo liso del tracto intestinal y respiratorio, estimulación de neuronas nociceptivas, alteración de secreción epitelial iónica, producción de nitróxido y liberación de citocinas por leucocitos y eicosanoides de diferentes tipos de células. Como una consecuencia, compuestos antagonistas de los receptores BK se pueden considerar como una clase novedosa de medicamentos según cabe suponer activos en varios trastornos. Aplicaciones terapéuticas posibles para dichos antagonistas son trastornos inflamatorios, alérgicos y autoinmunes, tales

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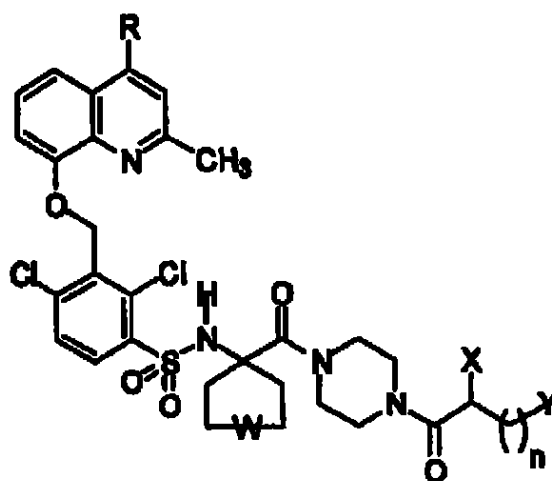
como asma y bronquitis crónica (también inducida por irritantes), rinitis alérgica, vasomotora y vírica, enfermedades obstructivas pulmonares crónicas (EPOD), artritis reumatoide, enfermedades inflamatorias crónicas del intestino (enfermedad de Crohn y colitis ulcerosa), glomerulonefritis, soriasis, erupción cutánea, cistitis aguda y crónica; enfermedades degenerativas caracterizadas por fibrosis, tales como cirrosis hepática, glomerulopatías y fibrosis pulmonar, arteriosclerosis; gracias a su actividad analgésica, en el tratamiento del dolor tanto agudo como crónico, por ejemplo en quemaduras, cefalea, mordedura de insectos, dolor crónico en pacientes con cáncer; en trastornos del aparato cardiovascular tales como choque séptico, alérgico y post-traumático, y cirrosis hepática por síndrome hepatorrenal; como anticáncer y antiangiogénéticos; en el tratamiento de hipotensión y de alopecia.

Péptidos diferentes y antagonistas de no péptidos del receptor de bradicinina B2 son conocidos en la literatura. La WO03103671 describe una gran familia de compuestos con actividad antagónica en el receptor de bradicinina B2. Los compuestos de la presente invención, aunque se incluyen en la fórmula general de la WO03103671, no se describen o caracterizan en dicho documento.

DESCRIPCIÓN DETALLADA

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La presente invención se relaciona con compuestos no peptídicos que muestran alta afinidad y actividad antagónica hacia el receptor B2, que tiene la fórmula general (I):



(I)

en la que:

- R es hidrógeno o metilo;
- W es un enlace sencillo o un átomo de oxígeno;
- n = 3, 4;
- X es hidrógeno o un grupo amino NR₁R₂ en el que R₁ y R₂ pueden ser independientemente hidrógeno o un grupo seleccionado de metilo, etilo, n-propilo, isopropilo;
- Y es un grupo -NR₃R₄R₅ de amonio cuaternario en el que R₃, R₄, R₅ pueden ser independientemente un grupo seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, n-pentilo; y

las sales de estos con ácidos farmacéuticamente aceptables.

Preferiblemente, los compuestos (I) se salifican con ácidos orgánicos e inorgánicos seleccionados de ácido

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clorhídrico, bromhídrico, yodhídrico, sulfúrico, fosfórico, acético, trifluoroacético, propiónico, oxálico, málico, maleico, succínico, malónico, aspártico, glutámico. Más aún, debido a la presencia de un centro quiral, la invención también comprende los dos enantiómeros o mezclas de estos, en cualquier proporción, que incluye mezclas racémicas.

Los compuestos de fórmula general (I) tienen ambas actividades antagonistas *in vivo* e *in vitro* hacia el receptor B2 mayores que los análogos más similares estructuralmente descritos en la WO03103671.

Se prefieren los compuestos de fórmula general (I) en los que:

- $n = 3$;
- $X =$ hidrógeno o un grupo $-NH_2$;
- $Y =$ grupo amonio cuaternario $-N(CH_3)_3^+$; los otros sustituyentes son como se definió anteriormente.

Particularmente se prefieren los compuestos (I) en donde:

R es hidrógeno o metilo;

W es un átomo de oxígeno;

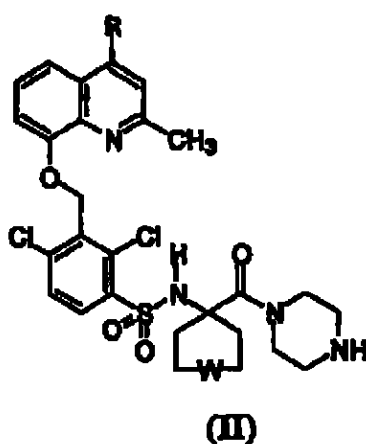
$n = 3$; X es hidrógeno o un grupo $-NH_2$;

Y es un grupo amonio cuaternario $-N(CH_3)_3^+$.

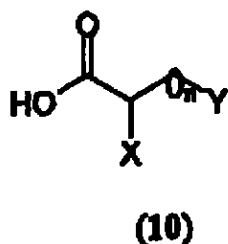
Los compuestos objeto de la presente invención se pueden preparar de acuerdo con rutas sintéticas bien conocidas.

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Preferiblemente, los compuestos de fórmula general (I) como se definió anteriormente se preparan por condensación, en la presencia de un agente de condensación adecuado, del intermediario de la fórmula general (II), obtenido como se describe en la WO03103671.



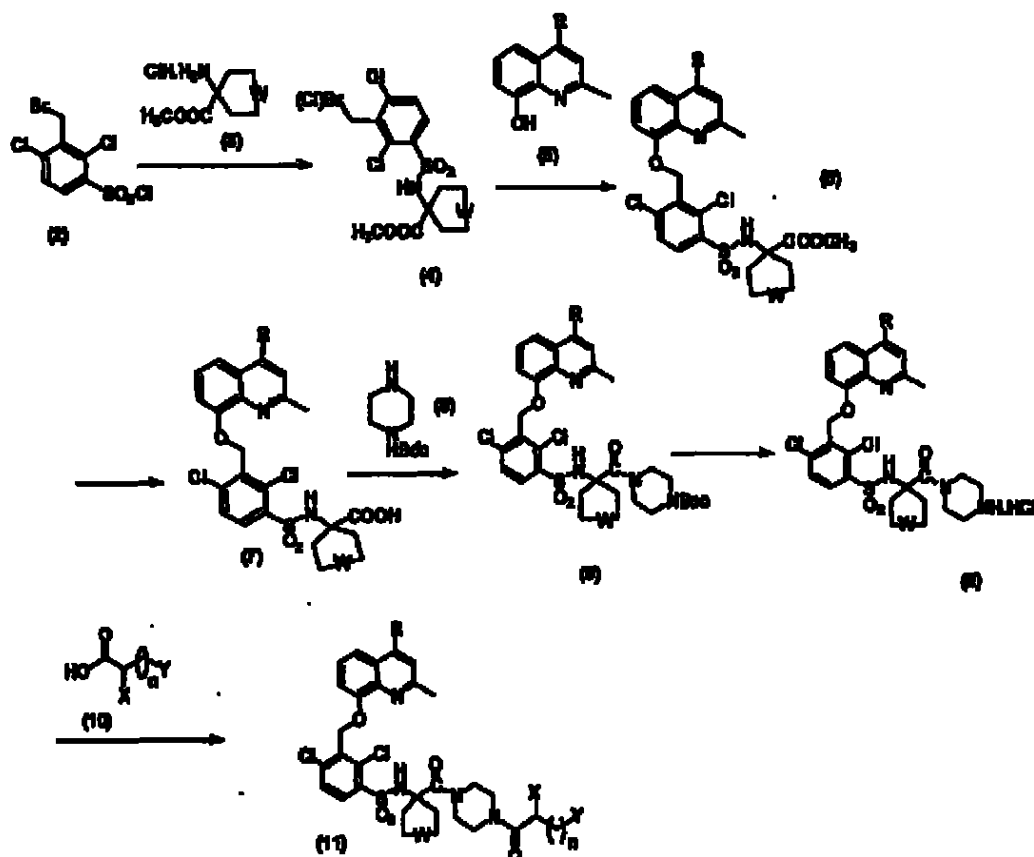
con el compuesto de fórmula (10)



o un derivado de este en la que el grupo carboxílico se activa adecuadamente.

El proceso sintético se ilustra en el Esquema 1

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Esquema 1

El compuesto de fórmula (2) se prepara como se describe en *J. Med. Chem.* 2001, 44, 1674-1689 por brominación del derivado de tolueno correspondiente, que se obtiene en cambio como se describe en *J. Fluorine Chemistry*, 2000. 101:85- 89.

La primera etapa tiene que ver con la formación del enlace sulfonamido (4) que se obtiene por la condensación de intermediarios (2) y (3). Se lleva a cabo esta reacción a temperatura ambiente, preferiblemente en acetonitrilo/agua (2:1), en la presencia de hidrógeno carbonato de sodio (NaHCO_3). Dicha reacción ocurre con el intercambio de cloro y bromo en la posición bencilo: se utiliza directamente la mezcla de productos resultantes en la siguiente etapa. La

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reacción de la mezcla de los derivados de halógeno con una hidroxiquinolina disustituida (5), en la presencia de carbonato de potasio (K_2CO_3) y yoduro de potasio (KI), en acetona bajo reflujo, produce el derivado de éster (6).

El compuesto de fórmula (5) es decir 2,4-dimetil-8-hidroxi quinolina, en la que $R_4=R_5=CH_3$, se prepara como se describe en la WO9640639.

El éster de metilo de fórmula (6) se hidroliza bajo condiciones básicas con ácido carboxílico (7), el cual se condensa con Boc-piperazina (8), para producir el intermediario (9). Se lleva a cabo dicha reacción de condensación de acuerdo con un procedimiento conocido para la síntesis de péptido, utilizando hidroxibenzotriazol para activar la porción carboxílica, un agente de condensación tal como 1-etil-3-(3'-dimetilpropil) carbodiimida y una cantidad de amina terciaria, a saber diisopropiletilamina, de tres equivalentes en la base del agente condensante. El compuesto (II) se obtiene por clivaje del grupo Boc del intermediario (9), por medio de una solución de ácido clorhídrico (4N) en dioxano y se aísla la amina libre en lugar del clorhidrato.

Se obtiene el derivado (11) por condensación del intermediario (10) con el aminoácido (11) de acuerdo con el procedimiento descrito para la preparación de (9) a partir de (7). Cualquier grupo Boc presente se puede remover del intermediario (11), con una solución de ácido clorhídrico

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(4N) en dioxano, así se obtiene el compuesto final. En el caso cuando el grupo trialkilamonio no está presente en cualquier intermediario disponible comercialmente, este se puede sintetizar partiendo de la correspondiente amina con procedimientos conocidos (Rapoport et al, *J. Org. Chem*, 1977, 42:139-141; Chen et al, *J. Biochem.*, 1978, 56:150-152).

Se utilizan los compuestos de la invención en el tratamiento de todos aquellos trastornos en los que la activación del receptor de bradicinina tiene que ser bloqueado o reducido. Ellos son particularmente adecuados para el tratamiento de trastornos inflamatorios, alérgicos y autoinmunes, tales como asma y bronquitis crónica, rinitis alérgica, vasomotora y vírica, enfermedades pulmonares obstructivas crónicas (EPOC), artritis reumatoide, enfermedades inflamatorias crónicas del intestino (Enfermedad de Crohn y colitis ulcerosa), glomerulonefritis, soriasis, erupción cutánea, cistitis crónica y aguda, cirrosis hepática, glomerulopatías y fibrosis pulmonar, arteriosclerosis, dolor tanto agudo como crónico, choques sépticos, alérgicos y post-traumáticos, cirrosis hepática por síndrome hepatorrenal, hipotensión, alopecia, o como anticáncer y antiangiogénicos.

Para uso en terapia, los compuestos de la invención serán formulados adecuadamente junto con portadores farmacéuticamente aceptables/excipientes. Se prefieren las formas farmacéuticas adecuadas para la administración oral,

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tales como tabletas, cápsulas, gránulos, polvos, soluciones, suspensiones, jarabes o similares. estas preparaciones farmacéuticas se pueden preparar con procedimientos convencionales utilizando ingredientes conocidos en la técnica, tales como ligandos, desintegrantes, lubricantes, llenadores, agentes estabilizantes, diluyentes, colorantes, saborizantes, agentes humectantes y otros excipientes conocidos por aquellos expertos en la técnica. Las formulaciones orales también comprenden formas de liberación prolongada, tales como comprimido gastrorresistente o gránulos. Las composiciones orales sólidas se pueden preparar por métodos de mezclado, llenado o compresión convencionales. Las preparaciones orales líquidas pueden estar en la forma de, por ejemplo, soluciones o suspensiones acuosas o en aceite, emulsiones, jarabes, o se pueden presentar como para reconstitución con agua u otro portador adecuado antes de uso.

La dosificación puede variar dependiendo de la edad y condiciones generales del paciente, naturaleza y severidad de la enfermedad o trastorno y la ruta y tipo de administración. Según una regla, en caso de administración oral a un paciente humano adulto, los compuestos de la presente invención serán generalmente administrados en un total de dosis diarias que varían de 1 a 1000 mg, preferiblemente de 5 a 300 mg, en una dosis única o en dosis subdivididas.

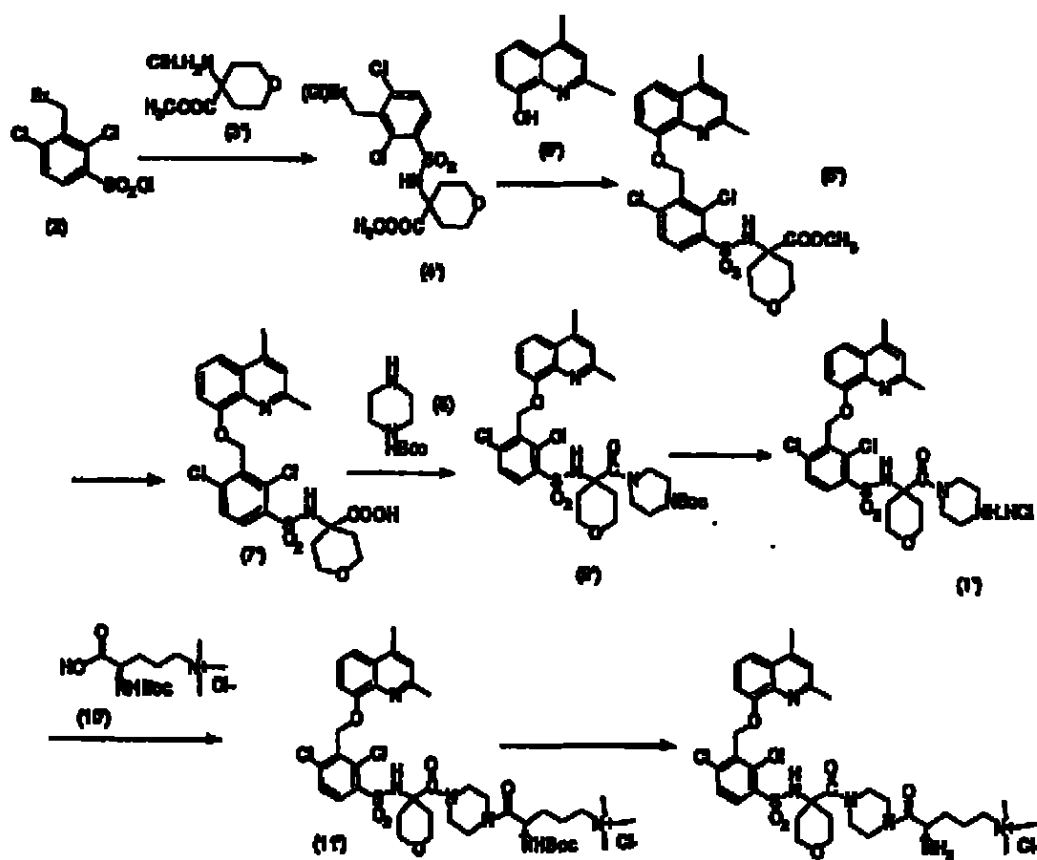
Los siguientes ejemplos ilustran la invención en gran detalle.

EJEMPLO 1

Diclorhidrato, cloruro de (4-(S)-amino-5-(4-{4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio

(Compuesto de fórmula general I en el que $R = \text{CH}_3$, $W = -\text{O}-$, $X = \text{NH}_2$, $n = 3$, $Y = \text{N}(\text{CH}_3)_3^+\text{Cl}^-$).

El compuesto se sintetiza siguiendo la ruta sintética que se ilustra en el Esquema 2



ejemplo 1

Esquema 2

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MÉTODOS GENERALES: HPLC analítico: Flujo: 1 ml/min; Fase móvil: A-0.1% de ácido trifluoroacético en agua, B-0.1% de ácido trifluoroacético en acetonitrilo; Columna: Zorbax Eclipse XDB C8, 5 micron, 150 x 4,6 mm.

Intermediario (2) cloruro de 2,4-Dicloro-3-bromometil-bencenosulfonilo

Se agrega en forma gota 10 ml de ácido clorosulfónico con 4.8 ml de 2,6-diclorotolueno en dos horas, bajo agitación magnética a temperatura ambiente. Después que se completa la adición, se calienta la mezcla a 40° C durante dos horas, por lo cual se obtiene una solución púrpura, que se enfría y se vierte cuidadosamente en agua helada (0.5 l), con agitación vigorosa. Se filtra el sólido blanco separado, se tritura, se lava con agua, se seca sobre KOH y se purifica por lavado con n-hexano, se adiciona 200 ml de solvente bajo fuerte agitación. Se filtra la mezcla, se descarga el sólido y se evapora el solvente hasta secado para obtener cloruro de 2,4-dicloro-3-metil-bencenosulfonilo como un sólido blanco cristalino. Rendimiento: 85%.

Pureza HPLC: 86% (30% B, 3%/min, Rt=19.7 min).

RMN ¹H (CDCl₃): δ (ppm) 2.6 (s, 3H), 7.5 (d, 1H), 7.95 (d, 1H);

ESI(+)-MS: m/z 260 [M+H]⁺.

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Se bromina este intermediario bajo las siguientes condiciones: Se disuelven 20 mmols de cloruro de 2,4-dicloro-3-metil-bencenosulfonilo en acetonitrilo. Se agregan 2 eq de NBS bajo agitación a temperatura ambiente hasta completar la solubilización de NBS. Finalmente, se agrega 0.1 eq de azobisisobutironitrilo (AIBN) y se calienta la mezcla a 70° C durante aproximadamente 6 horas. Se evapora la solución, se toma el residuo con acetato de etilo, se lava con H₂O y 5% de NaHCO₃, se seca sobre Na₂SO₄ seco y se filtra. Se evapora la fase orgánica por lo cual se obtiene un líquido coloreado claro, viscoso que se pone en éter de petróleo. Se filtra el residuo, y la solución produce (2') como un sólido cristalino coloreado claro.

Pureza HPLC: 95% (50% B a 5%/min, Rt=18.72).

RMN ¹H (CDCl₃): δ (ppm) 4.85 (s, 2H), 7.58 (d, 1H), 8.08 (d, 1H);

ESI(+)MS: m/z 338.1 [M+H]⁺.

Intermediario (3') clorhidrato de éster de metilo de ácido 4-Amino-tetrahidropiran-4-carboxílico

Clorhidrato de ácido 4-Amino-tetrahidropiran-4-carboxílico (0.025 mols) se suspende en 13 ml de CH₃OH, se enfría a -60° C y se agrega en forma de gota con SOCl₂ (3 eq) bajo agitación. Después que se completa la adición, se deja calentar la mezcla a temperatura ambiente, luego se calienta gradualmente hasta ebullición para obtener una solución clara

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(aproximadamente 2 horas), la cual se enfría, se filtra el residuo y se concentra bajo vacío.

Rendimiento 80%. Pureza (RMN): 85%.

RMN ^1H (DMSO- d_6): δ (ppm) 1.91-2.04 (m, 4H), 3.78 (s, 3H), 3.60-3.85 (m, 4H), 9.00 (s, 3H). ESI(+)MS: m/z 160.1 $[\text{M}+\text{H}]^+$.

Intermediario (4') éster de metilo de ácido 4-(3-Bromometil-2,4-dicloro-bencenosulfonilamino)-tetrahidropiran-4-carboxílico

El intermediario (3') (1.1 eq) se disuelve en agua junto con 4 equivalentes de K_2CO_3 . Esta solución se agrega con una solución de 1 equivalente (10 mmols) de intermediario (2) en acetonitrilo y se agita a temperatura ambiente hasta que se forma un precipitado (4 horas). Se evapora el solvente y se disuelve el residuo en acetato de etilo y 0.1M de HCl (1/1). Se separa la fase orgánica y se seca sobre Na_2SO_4 . Se evapora el solvente, se lava el residuo resultante con ciclohexano, por lo cual se obtiene un sólido blanco en el que los derivados de cloro/bromo se presentan en una proporción de 10/1. Rendimiento: 60%.

Pureza HPLC: 88% (20% B a 3%/min; R_t =H.11 (Br) y 14.47 (Cl)). RMN ^1H (CDCl_3): δ (ppm) 1.81-1.99 (2H, m), 2.07-2.25 (2H, m), 3.49-3.71 (7H, m), 4.81 (1.5H, s, [Br]), 4.94 (0.3H, s, [Cl]), 5.30 (1H, brs), 7.47-7.53 (1H, m),

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[7.49 (d, J 8.5Hz, X = Br), 7.51 (d, J 8.5Hz, X = Cl), 7.91-7.98 (1H, m), [7.94 (d, J 8.5Hz, X = Br), 7.96 (d, J 8.5Hz, X = Cl)].

Intermediario (6') éster de metilo de ácido 4-[2.4-Dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carboxílico

Se mezclan quinolina (5') (0.48 mmols) y LiOH (2.5 eq) a temperatura ambiente bajo nitrógeno en cetona etil metilo (MEK). Se mantiene la mezcla bajo agitación y bajo nitrógeno durante 90 min. Se disuelve el intermediario (4) en MEK/DMF seco (2/1) (42 ml, 12 ml/mmol), y se agrega en forma de gota la solución que contiene la quinolina a la mezcla de reacción, bajo agitación. La agitación se mantiene durante 16 horas. Se concentra la mezcla de reacción bajo vacío y se disuelve el residuo en acetato de etilo (50 ml, 100 ml/mmol). Se lava la fase orgánica (3x50 ml) con una solución de amortiguador con pH=4.2, se seca sobre Na₂SO₄, se filtra y se concentra bajo vacío para obtener un aceite amarillo. Rendimiento: 33%. Pureza HPLC: 77% (20% B, 3%/min; Rt=9.54).

RMN ¹H (DMSO-d₆): δ (ppm) 1.80-1.95 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.32-3.40 (m, 2H), 3.42-3.55 (m, 2H), 3.60 (s, 3H), 5.57 (s, 2H), 7.30 (s, 1H), 7.39 (d, 1H), 7.50 (dd, 1H), 7.67 (d, 1H), 7.78 (d, 1H), 8.02 (d, 1H), 8.77 (bs, 1H); ESI(+)-MS: m/z 553.1 [M+H]⁺.

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Intermediario (7') ácido 4-[2,4-Dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carboxílico

Se disuelve el intermediario de fórmula (6') en THF y se agrega la solución con 10 eq de LiOH 1M en agua. Se agita la mezcla durante 4 horas a 40° C, luego se evapora el solvente. Se disuelve el residuo en agua y se agrega 0.1M HCl a pH=4. Se extrae la fase acuosa con diclorometano y se seca la fase orgánica sobre Na₂SO₄. Se evapora el solvente y para obtener un residuo sólido amarillo. Rendimiento: 90%. Pureza HPLC: 99% (20%B, 3%/min; Rt=7.72).

RMN ¹H (DMSO-d₆): δ (ppm) 1.75-1.90 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.10-3.35 (m, 2H), 3.38-3.50 (m, 2H), 5.58 (s, 2H), 7.30 (s, 1H), 7.37 (d, 1H), 7.46 (t, 1H), 7.67 (d, 1H), 7.75 (d, 1H), 8.03 (d, 1H), 8.64 (bs, 1H). ESI(+)MS: m/z 539.1 [M+H]⁺.

Intermediario (9') 4-terc-butoxicarbonil-((4-(2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino)-tetrahidropiran-4-carbonil-piperazin-1-il)

Se suspenden (7') (1.3 mmols) y HOBt (1.1 eq) en 50 ml de DMF seco en un matraz de fondo redondo de 100 ml bajo nitrógeno. Se enfría la mezcla a +4° C y se agrega con EDCI. HCl (1.1 eq) bajo agitación. La agitación a +4° C se continúa durante una hora, luego se agregan DIPEA (2 eq) y Boc-

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piperazina (1 eq) y se deja calentar la mezcla a temperatura ambiente, bajo agitación. Después de 12 h se evapora el solvente, se disuelve el residuo en 40 ml de DCM y se lava la fase orgánica con salina (20 ml) y se seca sobre Na₂SO₄. Se evapora el solvente para obtener un aceite que se purifica en una columna Varian Mega Bond (flash master system) 70 g (acetato de etilo, R_f=0.50), por lo cual se obtiene un sólido amarillo.

Rendimiento: 96%. Pureza HPLC: 98% (20% B, 3% B/min, R_t=11.14).

RMN ¹H (CDCl₃): δ (ppm) 1.45 (s, 9H); 1.55-1.80 (m, 2H), 2.05-2.20 (m, 4H), 2.56 (s, 3H), 2.64 (s, 3H), 3.38-3.90 (m, 10H), 5.58 (s, 2H), 7.10 (s, 1H), 7.30 (s, 1H), 7.37 (d, 1H), 7.46 (t, 1H), 7.67 (d, 1H), 7.75 (d, 1H), 8.03 (d, 1H), 8.64 (bs, 1H). ESI(+)MS: m/z 707.2 [M+H]⁺.

Intermediario (1') (4-(2,4-Dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino)-tetrahidropiran-4-carbonil)-piperazin-1-il

Se agregan 0.62 mmols de (9') con 10 ml de HCl/dioxano 4M y se mantiene la mezcla bajo agitación durante 3 horas. Se evapora el solvente y el residuo se seca en frío, para obtener clorhidrato (1') como sólido amarillo. Rendimiento: 98%. Pureza HPLC: 92% (20% B, 3% B/min; R_t=5.34).

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RMN ^1H (D_2O): δ (ppm) 1.55-2.10 (m, 7H), 2.90-3.10 (m, 9H), 3.20-3.55 (m, 9H), 6.0 (s, 2H), 7.60-8.10 (m, 8H), 8.95 (d, 1H).

ESI(+)MS: m/z 609.1 $[\text{M}+\text{H}]^+$.

Intermediario (10') (4-terc-butoxicarbonilamino-4-carboxi-butyl)-trimetilamonio

Se suspenden 10 mmols de Boc-Orn-OH en metanol (20 ml) y se agrega la suspensión con 44 mmols de isourea. Se tapa el frasco y se mantiene bajo agitación a temperatura ambiente durante 2 días. Se monitorea la solución por TLC (eluyente: $\text{CHCl}_3/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$ 40/54/6; Boc-Orn-OH $R_f=0.29$; (10') R_f : 0.11, detección KMnO_4).

Se evapora metanol bajo vacío y se digiere el residuo en 150 ml de agua y se filtra. El matraz de fondo redondo y el sólido se lavan con agua (2x50 ml) y se combinan todas las fracciones acuosas lavadas, luego se concentra bajo vacío (40 ml). El sólido resultante (4.068 g) se suspende en agua (40 ml), se filtra (para remover cualquier traza de urea) y se purifica por FCC en fase reversa LiChroprep RP-18 (40-63 micrones). La columna (19 x 7 cm) se eluye con 3% de CH_3CN en agua y se combinan las fracciones (aproximadamente 100 ml) se analizan por TLC. Las fracciones que contienen el producto crudo (500 ml), se concentra bajo vacío para remover CH_3CN , se seca en frío, y finalmente se evapora de 150 ml de etanol

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absoluto, para dar 442 mg de un sólido altamente higroscópico blanco. Rendimiento: 16%.

RMN ^1H (DMSO- d_6): δ (ppm) 1.38 (s, 9H) 1.58-1.75 (m, 4H), 3.03 (s, 9H), 3.29 (m, 2H), 3.45 (m, 1H), 6.49 (d, d, 1H); ESI(+)MS: m/z 275.2 [M+H] $^+$.

Intermediario (11') cloruro de (4-(S)-terc-Butoxicarbonilamino-5-(4-(4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino $^+$ tetrahidro-piran-4-carbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio

Se disuelve el intermediario (10'), 1.2 mmols, en DMF y se agrega la solución con diciclohexilcarbodiimida (1.2 eq) y HOBt (1.2 eq). Se mantiene la mezcla bajo agitación durante 30 min, luego se agrega con diisopropilaminometil-poliestireno (1.5 eq) e intermediario (1') (1 eq). Se deja la mezcla bajo agitación durante 24 horas. Se filtra la resina, se evapora el solvente y se disuelve el residuo en agua y acetato de etilo. Se separa la fase acuosa y se seca en frío. Se purifica el producto crudo por HPLC preparativo (Columna Vydac 218TP, C 18, 250x50 mm, Flujo 60 ml/min, gradiente 10% a 70% de CH_3CN /0.1% de TFA En 120 min, detector UV a 240 nm, colección 55 a 75 min) con lo cual se proporciona el intermediario (11') que se seca en frío como un sólido blanco. Rendimiento: 46%. Pureza HPLC: 98% (20% B, 3%/min; $R_t=7.68$).

^1H RMN (DMSO- d_6) δ : 1.4 (s, 9H), 1.8-1.45 (m, 6H), 1.95-1.85 (m, 2H), 2.81 (m, 6H), 3.08 (s, 9H), 3.70-3.18 (m,

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9b

7H), 4.01-3.56 (5H, m), 4.57-4,45 (m, 1H), 5.59 (s, 2H), 7.25 (d, 1H), 7.90-7.43 (m, 4H), 8.02 (d, 1H), 8.85 (s, 1H). ESI(+)-MS: m/z 863.2 [M+H]⁺.

Diclorhidrato, cloruro de (4-(S)-Amino-5-(4-(4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carbonil)piperazin-1-il)-5-oxo-pentil]trimetil-amonio

Se agregan 0.45 mmols de (11') con 10 ml de HCl/dioxano 4M. Se mantiene la mezcla bajo agitación durante 6 horas, se evapora el solvente y el residuo se seca en frío, por lo cual se obtiene el compuesto final como un sólido blanco. Rendimiento: 87%. Pureza HPLC: 98% (20% B, 3%/min; Rt=5.14).

RMN ¹H (DMSO-d₆) δ: 1.95-1.60 (m, 8H), 2.81 (m, 6H), 3.08 (s, 9H), 3.70-3.18 (m, 12H), 4.57-4,45 (m, 1H), 5.59 (s, 2H), 7.90-7.60 (m, 4H), 8.02 (d, 1H), 8.5 (s, 3H), 8.85 (s, 1H).

ESI(+)-MS: m/z 763.1 [M+H]⁺.

EJEMPLO 2

Clorhidrato, cloruro de (4-(S)-Amino-5-(4-(4-(2,4-dicloro-3-(2-metil-quinolin-8-iloximetil)-bencenosulfonilamino)tetrahidropiran-4-carbonil)-piperazin-1-il)-5-oxo-pentil)-trimetilamonio

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^1H RMN (DMSO- d_6) δ : 8.90 (1H, s), 8.47-8.34 (4H, m), 8.02 (1H, d), 7.81 (1H, d), 7.73-7.37 (4H, m), 5.62 (2H, s), 4.57-4.45 (1H, m), 4.01-3.56 (5H, m), 3.43-3.18 (7H, m), 3.06 (9H, s), 2.78-2.61 (4H, m), 2.89 (1H, s), 1.97-1.60 (9H, m). HPLC: t_R = 9.26 min. MS: $[M]^+$ 749.

EJEMPLO 3

Trifluoroacetato de [5-(4-{4-[2,4-Dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-benceno-sulfonilamino]tetrahidropiran-4-carbonil}piperazin-1-il)-5-oxo-pentil]-trimetil-amonio.

RMN ^1H (DMSO- d_6): δ (ppm) 1.53 (s, 2H₅ m); 1.69 (m, 4H); 1.90 (m, 2 H); 2.45 (t, 2 H); 2.78 (m, 6 H); 3.04 (9 H, s); 3.23-3.57 (7 H₅ m); 5.68 (2H, s); 7.38-8.18 (5 H, m); 8.04 (1H, d, J = 8.42 Hz); 8.82 (1 H, s). HPLC: t_R - 5.65 min. MS: $[M]^+$ 748.

EJEMPLO 4

Diclorhidrato, cloruro de [4-(S)-Amino-5-(4-{1-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]ciclopentanocarbonil}piperazin-1-il)-5-oxo-pentil]-trimetil-amonio.

^1H RMN (DMSO- d_6) δ : 8.90 (1H, s), 8.48 (3H, s), 8.02 (1H, d), 7.95- 7.63 (3H, m), 5.59 (2H, s), 4.57-4.45 (1H, m), 3.97-3.24 (10H, m), 3.08 (9H, s), 2.95-2.61 (5H, m), 1.97-

37

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1.72 (8H, m), 1.42 (4H, s); HPLC: t_R = 5.88 min. MS: $[M]^+$ 747.2.

Actividad Biológica

La evaluación de la afinidad del receptor B2 de los compuestos de la presente invención se lleva a cabo con estudios de unión del receptor B2 humano expresado en células CHO, siguiendo el procedimiento descrito por Bellucci et al, *Br. J. Pharmacol.* 2003, 140:500-506; los valores de unión reportados se expresan como pKi.

La actividad antagonista (expresada como pA2) se evalúa como la inhibición de producción inducida de bradicinina de inositoles en células CHO transfectadas con receptor humano B2, de acuerdo con el procedimiento descrito en Bellucci et al, *Br. J. Pharmacol.* 2003, 140:500-506.

La actividad *in vivo* de los compuestos de la presente invención se evalúa como la efectividad en la inhibición de broncoespasmos inducidos por BK en los conejillos de indias (Tramontana et al., *J. Pharmacol. Exp. Therap.*, 296: 1051-1057, 2001), que lo mide en dosis (it=administración intratraqueal) (en nmoles/kg) que se inhibe por 80% de constricción bronquial durante al menos 210 min.

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Ejemplo	W	R	X	Y	n	pK _i	pA ₂	Dosis
W003103671 ej 55	enlace	H	NH ₂	NHC(=NH)NH ₂	3	8.7	8.4	300
W003103671 ej 63	enlace	CH ₃	NH ₂	NH ₂	4	9.1	8.9	300
W003103671 ej 57	enlace	H	NH ₂	N(CH ₃) ₂	4	8.8	8.3	300
W003103671 ej 59	enlace	CH ₃	NH ₂	N(CH ₃) ₂	4	8.8	9.0	300
W003103671 ej 44	enlace	CH ₃	NH ₂	NHC(=NH)NHR _t	3	10.1	9.0	300
W003103671 ej 88	enlace	CH ₃	N(CH ₃) ₃	N(CH ₃) ₃	4	9.7	8.2	-
Ejemplo 1	O	CH ₃	NH ₂	N(CH ₃) ₃	3	10.3	10.3	30
Ejemplo 2	O	H	NH ₂	N(CH ₃) ₃	3	10.2	9.7	100
Ejemplo 3	O	CH ₃	H	N(CH ₃) ₃	3	10.1	9.5	100
Ejemplo 4	enlace	CH ₃	NH ₂	N(CH ₃) ₃	3	10.1	9.4	100

Los compuestos preferidos de la presente invención se comparan con aquellos más estructuralmente similares descritos en la W003103671. Sorprendentemente se ha encontrado que los compuestos de la invención tienen actividad *in vivo* y *in vitro* mayores que los análogos relacionados estructuralmente de la W003103671. Ambos ensayos de actividad antagonista en células transfectadas con el receptor humano y el ensayo *in vivo* altamente predictivo de la dosis esperada para aplicaciones terapéuticas en humanos.

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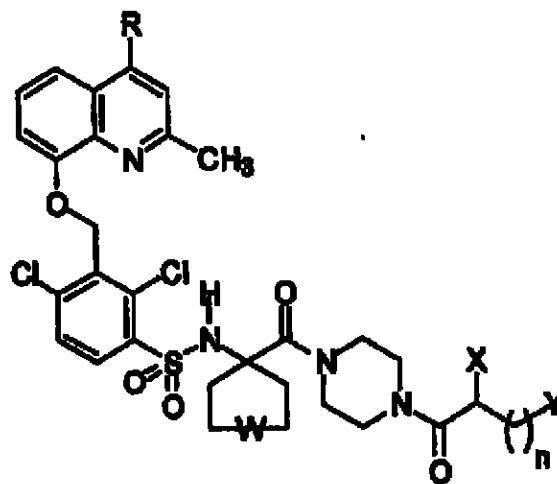
ABREVIATURAS it = administración intratraqueal; iv = administración intravenosa; eq = equivalente; DCM = diclorometano; MeOH = metanol; THF = tetrahidrofurano; DMSO = dimetilsulfóxido; DMF = dimetilformamida; AcOEt = acetato de etilo; AcOH = ácido acético; TFA = ácido trifluoroacético; NBS = N_α-bromosuccinimida; bpo = peróxido de benzoilo; Boc = terc-butoxicarbonil; HOBT = 1-hidroxi-benzotriazol; EDC = 1-etil-3-(3'-dimetilpropil)carbodiimida; DIPEA diisopropiletilamina; HPLC = cromatografía líquida de alta presión; TLC = cromatografía de capa fina; RMN = resonancia magnética nuclear; ESI= ionización por rociado de electrón; MS = espectrometría de masa; FCC = Cromatografía de columna Flash; Rt = tiempo de retención.

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REIVINDICACIONES

1. Los compuestos de fórmula (I)



(I)

en la que

- R es hidrógeno o metilo;
- W es un enlace sencillo o un átomo de oxígeno;
- n = 3, 4;
- X es hidrógeno o un grupo amino -NR₁R₂ en el que R₁ y R₂ pueden ser independientemente hidrógeno o un grupo seleccionado de metilo, etilo, n-propilo, isopropilo;
- Y es un grupo amonio cuaternario -NR₃R₄R₅ en el que R₃, R₄, R₅ pueden ser independientemente un grupo seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, n-pentilo; y
las sales farmacéuticamente aceptables, enantiómeros y mezclas enantioméricas de estos.

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2. Las sales de los compuestos de fórmula general (I) con ácidos orgánicos e inorgánicos seleccionados de ácidos clorhídrico, bromhídrico, yodhídrico, sulfúrico, fosfórico, acético, trifluoroacético, propiónico, oxálico, málico, maleico, succínico, malónico, aspártico, glutámico.
3. Los compuestos como se reivindica en la reivindicación 1 o 2, en donde:
W es un enlace sencillo;
 $n = 3$;
X se selecciona de hidrógeno o un grupo $-NH_2$;
Y es un grupo amonio cuaternario $-N(CH_3)_3^+$;
los otros sustituyentes son como se define en la reivindicación 1.
4. Los compuestos como se reivindica en la reivindicación 1 o 2, en la que:
R se selecciona de hidrógeno o metilo;
W es un átomo de oxígeno;
 $n = 3$;
X se selecciona de hidrógeno o un grupo $-NH_2$;
Y es un grupo amonio cuaternario $-N(CH_3)_3^+$;
los otros sustituyentes son como se define en la reivindicación 1.
5. Los siguientes compuestos son como se reivindica en la reivindicación 3:

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Diclorhidrato, cloruro de [4-(S)-amino-5-(4-{1-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino]-ciclopentanocarbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio.

6. Los siguientes compuestos son como se reivindica en la reivindicación 4:

- Diclorhidrato, cloruro de (4-(S)-amino-5-(4-{4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino]tetrahidropiran-4-carbonil}-piperazin-1-il)-5-oxo-pentil]trimetil-amonio;
- Clorhidrato, cloruro de (4-(S)-amino-5-(4-(4-(2,4-dicloro-3-(2-metil-quinolin-8-iloximetil)-bencenosulfonilamino)-tetrahidropiran-4-carbonil)-piperazin-1-il)-5-oxo-pentil)-trimetil-amonio;
- Trifluoroacetato de [5-(4-{4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio.

7. Composiciones farmacéuticas que contienen como el ingrediente activo un compuesto como se reivindica en

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las reivindicaciones 1 a 6 junto con excipientes farmacéuticamente aceptables.

8. El uso de un compuesto como se reivindica en las reivindicaciones 1 a 6 para la preparación de composiciones farmacéuticas para el tratamiento de todas las condiciones en la que se involucra la activación de receptores B2 de bradicinina.
9. El uso de un compuesto como se reivindica en la reivindicación 8 para la preparación de composiciones farmacéuticas para el tratamiento de condiciones inflamatorias alérgicas y autoinmunes.
10. El uso de un compuesto como se reivindica en la reivindicación 8 para la preparación de composiciones farmacéuticas para el tratamiento de asma y bronquitis crónica, rinitis alérgica, vasomotora y vírica, enfermedades pulmonares obstructivas crónicas (COPD), artritis reumatoide, enfermedades inflamatorias crónicas del intestino (Enfermedad de Crohn y colitis ulcerosa), glomerulonefritis, soriasis, erupción cutánea, cistitis crónica y aguda, cirrosis hepática, glomerulopatías y fibrosis pulmonar, arteriosclerosis, dolor tanto agudo como crónico, choques sépticos, alérgicos y post-traumáticos, cirrosis hepática por síndrome hepatorrenal, hipotensión, alopecia, o como enfermedades de cáncer y antiangiogénicas.

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ANTAGONISTAS DE BRADICININA NO PEPTÍDICA Y COMPOSICIONES
FARMACÉUTICAS DE ESTAS

RESUMEN

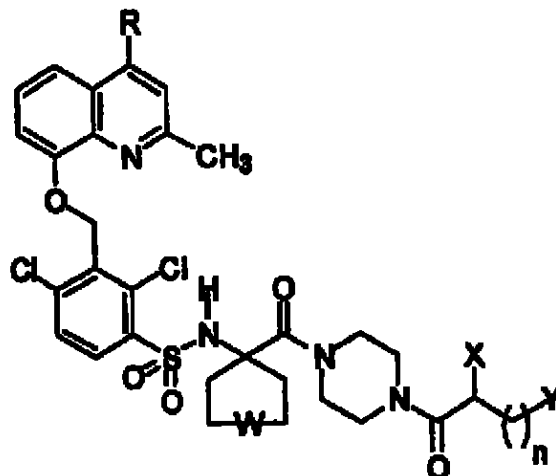
Los compuestos no peptídicos que tienen actividad como antagonistas selectivos del receptor B2 de bradicinina (BK). Los compuestos se caracterizan químicamente por la presencia de un aminoácido alfa sustituido con un grupo cíclico y por un grupo tetraalquilamonio.

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REIVINDICACIONES

1. Los compuestos de fórmula (I)



(I)

en la que

- R es hidrógeno o metilo;
- W es un enlace sencillo o un átomo de oxígeno;
- n = 3;
- X es hidrógeno o un grupo amino -NR₁R₂ en el que R₁ y R₂ pueden ser independientemente hidrógeno o un grupo seleccionado de metilo, etilo, n-propilo, isopropilo;
- Y es un grupo amonio cuaternario -NR₃R₄R₅ en el que R₃, R₄, R₅ pueden ser independientemente un grupo seleccionado de metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, n-pentilo; y
las sales farmacéuticamente aceptables, enantiómeros y mezclas enantioméricas de estos.

HOJA CORREGIDA

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2. Las sales de los compuestos de fórmula general (I) con ácidos orgánicos e inorgánicos seleccionados de ácidos clorhídrico, bromhídrico, yodhídrico, sulfúrico, fosfórico, acético, trifluoroacético, propiónico, oxálico, málico, maleico, succínico, malónico, aspártico, glutámico.
3. Los compuestos como se reivindica en la reivindicación 1 o 2, en donde:
- W es un enlace sencillo;
- n = 3;
- X se selecciona de hidrógeno o un grupo -NH₂;
- Y es un grupo amonio cuaternario -N(CH₃)₃⁺;
- los otros sustituyentes son como se define en la reivindicación 1.
4. Los compuestos como se reivindica en la reivindicación 1 o 2, en la que:
- R se selecciona de hidrógeno o metilo;
- W es un átomo de oxígeno;
- n = 3;
- X se selecciona de hidrógeno o un grupo -NH₂;
- Y es un grupo amonio cuaternario -N(CH₃)₃⁺;
- los otros sustituyentes son como se define en la reivindicación 1.
5. Los siguientes compuestos son como se reivindica en la reivindicación 3:

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Diclorhidrato, cloruro de [4-(S)-amino-5-(4-{1-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino]-ciclopentanocarbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio.

6. Los siguientes compuestos son como se reivindica en la reivindicación 4:

- Diclorhidrato, cloruro de (4-(S)-amino-5-(4-{4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)bencenosulfonilamino]tetrahidropiran-4-carbonil}-piperazin-1-il)-5-oxo-pentil]trimetil-amonio;
- Clorhidrato, cloruro de (4-(S)-amino-5-(4-(4-(2,4-dicloro-3-(2-metil-quinolin-8-iloximetil)-bencenosulfonilamino)-tetrahidropiran-4-carbonil)-piperazin-1-il)-5-oxo-pentil)-trimetil-amonio;
- Trifluoroacetato de [5-(4-{4-[2,4-dicloro-3-(2,4-dimetil-quinolin-8-iloximetil)-bencenosulfonilamino]tetrahidropiran-4-carbonil}piperazin-1-il)-5-oxo-pentil]trimetil-amonio.

7. Composiciones farmacéuticas que contienen como el ingrediente activo un compuesto como se reivindica en

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las reivindicaciones 1 a 6 junto con excipientes farmacéuticamente aceptables.

8. El uso de un compuesto como se reivindica en las reivindicaciones 1 a 6 para la preparación de composiciones farmacéuticas para el tratamiento de todas las condiciones en la que se involucra la activación de receptores B2 de bradicinina.
9. El uso de un compuesto como se reivindica en la reivindicación 8 para la preparación de composiciones farmacéuticas para el tratamiento de condiciones inflamatorias alérgicas y autoinmunes.
10. El uso de un compuesto como se reivindica en la reivindicación 8 para la preparación de composiciones farmacéuticas para el tratamiento de asma y bronquitis crónica, rinitis alérgica, vasomotora y vírica, enfermedades pulmonares obstructivas crónicas (COPD), artritis reumatoide, enfermedades inflamatorias crónicas del intestino (Enfermedad de Crohn y colitis ulcerosa), glomerulonefritis, soriasis, erupción cutánea, cistitis crónica y aguda, cirrosis hepática, glomerulopatías y fibrosis pulmonar, arteriosclerosis, dolor tanto agudo como crónico, choques sépticos, alérgicos y post-traumáticos, cirrosis hepática por síndrome hepatorrenal, hipotensión, alopecia, o como anticáncer y enfermedades antiangiogénicas.

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PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

BANFI, Paolo
Bianchetti Bracco Minoja S.r.l.
Via Plinio, 63
I-20129 Milano
ITALIE

**RICEVUTO IL
RECEIVED ON**

15 GEN. 2007

BIANCHETTI-BRACCO-MINOJA S.r.l.

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY

(PCT Rule 71.1)

Date of mailing
(day/month/year)

12.01.2007

Applicant's or agent's file reference
SCB 969 PCT

IMPORTANT NOTIFICATION

International application No.
PCT/EP2005/010412

International filing date (day/month/year)
27.09.2005

Priority date (day/month/year)
15.10.2004

Applicant

ISTITUTO LUSO FARMACO D'ITALIA S.P.A.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary report on patentability and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary report on patentability. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international
preliminary examining authority:



European Patent Office
D-80288 Munich
Tel. +49 89 2399 - 0 Tlx: 523656 epmu d
Fax: +49 89 2399 - 4485

Authorized Officer

Stark, Saskia

Tel. +49 89 2399-4764



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference SCB 969 PCT	FOR FURTHER ACTION		See Form PCT/PEAA16
International application No. PCT/EP2005/010412	International filing date (day/month/year) 27.08.2005	Priority date (day/month/year) 15.10.2004	
International Patent Classification (IPC) or national classification and IPC INV. A61K31/47 A61P29/00 C07D215/26			
Applicant ISTITUTO LUSO FARMACO D'ITALIA S.P.A.			
1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 5 sheets, including this cover sheet. 3. This report is also accompanied by ANNEXES, comprising: a. ☒ sent to the applicant and to the International Bureau) a total of 4 sheets, as follows: ☒ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions). ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box. b. ☐ (sent to the International Bureau only) a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in electronic form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).			
4. This report contains indications relating to the following items: ☒ Box No. I Basis of the report ☐ Box No. II Priority ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability ☐ Box No. IV Lack of unity of invention ☒ Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement ☐ Box No. VI Certain documents cited ☐ Box No. VII Certain defects in the international application ☐ Box No. VIII Certain observations on the international application			
Date of submission of the demand 08.08.2006		Date of completion of this report 12.01.2007	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized officer Härtinger, Stefan Telephone No. +49 89 2399-8289 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/010412

Box No. I Basis of the report

1. With regard to the language, this report is based on

- ☒ the international application in the language in which it was filed
- ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3(a) and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4(a))
 - ☐ international preliminary examination (under Rules 55.2(a) and/or 55.3(a))

2. With regard to the elements* of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report):*

Description, Pages

1-17 as originally filed

Claims, Numbers

6(part), 7-10 received on 09.08.2006 with letter of 08.08.2006

1-5, 6(part) received on 02.11.2006 with letter of 31.10.2006

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages
- ☐ the claims, Nos.
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

4. ☒ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

- ☐ the description, pages
- ☒ the claims, Nos. 1
- ☐ the drawings, sheets/figs
- ☐ the sequence listing *(specify):*
- ☐ any table(s) related to sequence listing *(specify):*

* If item 4 applies, some or all of these sheets may be marked "superseded."

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

International application No.
PCT/EP2005/010412

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-10
	No: Claims	
Inventive step (IS)	Yes: Claims	1-10
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-10
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

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Re Item V.

1 The application relates to antagonists of bradykinin B2 receptor with the general formula (I) which have been restricted according to the applicant's submissions of 31.10.2006 to variants with $n = 3$, i.e. piperazine compounds with ammonium group substituted oxypentyl side-chains. The relevant prior art is the following documents: D1 = WO 03/103671 A; D2 = HEITSCH H ET AL, BIOORG. MED. CHEM. LETT., OXFORD, 1999, 327-332, XP004157223; D3= HEITSCH H, CURRENT MED. CHEM., 2002, 913-928, XP002369396.

2 The claimed compounds represent a novel selection from the class of bradykinin receptor active products disclosed on page 15 in document D1. While the prior art teaches that variables required to form the present class of compounds are among preferred possibilities, D1 does not make available to the public the selected combination of 4-acyl-piperazine derivatives with a quaternary ammonium group bonded to a 5-oxopentyl linker.

With regard to D2 and D3, novelty resides from the sulfonamide containing substituent of the dichlorophenyl residue.

The claimed subject-matter which always refers to the novel class of oxopentyl compounds appears therefore to meet the requirements of Art. 33(2) PCT.

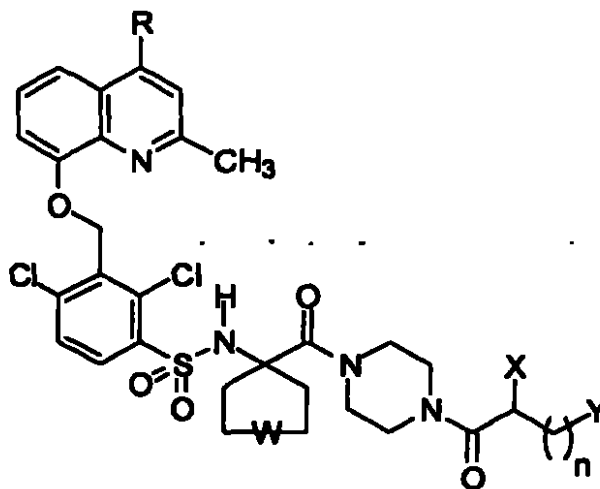
3 With the letter dated 08.08.2006 bradykinin binding data have been filed where the present examples 1-4 have been compared with the compounds of examples 79 and 83 of D1. The comparison between the present example 4 and example 79 of D1, both compounds are within the definition of general formula (I) in present claim 1, reveals that the length of the alkylene spacer has a significant influence on the quantitative ability to interact with the bradykinin receptor. It would appear that compounds with $n=3$ are superior to compounds with $n=4$. Likewise, the comparison of example 83 of D1 with present examples 3 and 4 shows that compounds with $n=3$ are also superior to compounds with $n=2$. The comparative test data appear therefor to support the view that the present oxypentyl compounds ($n=3$) are more active.

Starting from D1 as the closest prior art, the selected oxypentyl compounds solve the problem of providing improved bradykinin antagonists. The solution appears to have involved an inventive step, because the closest prior art does not point to the quantitative improvement which is achievable by selecting the class of oxypentyl derivatives. Accordingly, the claimed subject-matter also meets the requirements of Art. 33(3) PCT.

B

CLAIMS

1. Compounds of general formula (I)



(I)

in which

- R is hydrogen or methyl;
- W is a single bond or an oxygen atom;
- $n = 3$;
- X is hydrogen or a $-NR_1R_2$ amino group in which R_1 and R_2 can be independently hydrogen or a group selected from methyl, ethyl, n-propyl, isopropyl;
- Y is a $-NR_3R_4R_5$ quaternary ammonium group in which R_3 , R_4 , R_5 can be independently a group selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, n-pentyl; and

the pharmaceutically acceptable salts, enantiomers and enantiomeric mixtures thereof,

~~with the exclusion of the compound N-[1-[4-(2-(S)-amino-6-trimethylammonium-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-~~

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~~dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide~~ ~~tris~~
~~trifluoroacetate~~

2. Salts of the compounds of general formula (I) with inorganic or organic
5 acids selected from hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric,
acetic, trifluoroacetic, propionic, oxalic, malic, maleic, succinic, malonic,
aspartic, glutamic acids.

3. Compounds as claimed in claim 1 or 2, wherein:

W is a single bond;

10 n = 3;

X is selected from hydrogen or a -NH₂ group;

Y is a -N(CH₃)₃⁺ quaternary ammonium group;

the other substituents being as defined in claim 1.

4. Compounds as claimed in claim 1 or 2, in which:

15 R is selected from hydrogen or methyl;

W is an oxygen atom;

n = 3;

X is selected from hydrogen or a -NH₂ group;

Y is a -N(CH₃)₃⁺ quaternary ammonium group;

20 the other substituents being as defined in claim 1.

5. The following compound as claimed in claim 3:

[4-(S)-amino-5-(4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-
yloxymethyl)benzenesulfonylamino]-cyclopentanecarbonyl}piperazin-1-
yl)-5-oxo-pentyl]trimethyl-ammonium chloride, dihydrochloride

25 6. The following compounds as claimed in claim 4:

- (4-(S)-amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy-methyl)benzenesulfonylamino]tetrahydropyran-4-carbonyl}-piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium chloride, dihydrochloride;
- (4-(S)-amino-5-(4-(4-(2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonylamino)-tetrahydropyran-4-carbonyl)-piperazin-1-yl)-5-oxo-pentyl)-trimethyl-ammonium chloride, hydrochloride;
- [5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]tetrahydropyran-4-carbonyl}piperazin-1-yl)-5-oxo-pentyl]trimethyl-ammonium trifluoroacetate.

7. Pharmaceutical compositions containing as the active ingredient a compound as claimed in claims 1 to 6 together with pharmaceutically acceptable excipients.

8. The use of a compound as claimed in claims 1 to 6 for the preparation of pharmaceutical compositions for the treatment of all the conditions in which activation of bradykinin B2 receptors is involved.

9. The use of a compound as claimed in claim 8 for the preparation of pharmaceutical compositions for the treatment of inflammatory, allergic and autoimmune conditions.

10. The use of a compound as claimed in claim 8 for the preparation of pharmaceutical compositions for the treatment of asthma and chronic bronchitis, allergic, vasomotor and viral rhinitis, chronic obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis), glomerulonephritis, psoriasis, rash, acute and chronic cystitis, hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis, both acute and chronic pain, septic, allergic and post-traumatic shocks, hepatorenal

h

syndrome by hepatic cirrhosis, hypotension, alopecia, cancer and antiangiogenic diseases.

5

10

h

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

BIANCHETTI BRACCO MINOJA S.R.L.
Attn. Banfi, Paolo
Via Plinio 63
I-20129 Milano
ITALY

**RICEVUTO IL
RECEIVED ON**

13 MAR. 2006

BIANCHETTI-BRACCO-MINOJA S.R.L.

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT AND
THE WRITTEN OPINION OF THE INTERNATIONAL
SEARCHING AUTHORITY, OR THE DECLARATION

(PCT Rule 44.1)

 Date of mailing
(day/month/year)

13/03/2006

Applicant's or agent's file reference

SCB 969 PCT

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/EP2005/010412

 International filing date
(day/month/year)

27/09/2005

Applicant

ISTITUTO LUSO FARMACO D'ITALIA S.P.A.

1. ☒ The applicant is hereby notified that the International search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

- ☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Office.
☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Reminders

Shortly after the expiration of 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an International preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within 19 months from the priority date, but only in respect of some designated Offices, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later); otherwise, the applicant must, within 20 months from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of 30 months (or later) will apply even if no demand is filed within 19 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the International Searching Authority

 European Patent Office, P.B. 5818 Patentlaan 2
NL-2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax: (+31-70) 340-3018

Authorized officer

Josef Ullrich

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These Notes are intended to give the basic instructions concerning the filing of amendments under article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the letter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed where the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume IA, paragraph 286).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 48.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Administrative Instructions, Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

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PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference SCB 969 PCT	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2005/010412	International filing date (day/month/year) 27/09/2005	(Earliest) Priority Date (day/month/year) 15/10/2004
Applicant ISTITUTO LUSO FARMACO D'ITALIA S.P.A.		

This international search report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This international search report consists of a total of 4 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of:

- ☒ the international application in the language in which it was filed
☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b))

b. ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2. ☐ Certain claims were found unsearchable (See Box No. II)

3. ☐ Unity of invention is lacking (see Box No. III)

4. With regard to the title,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established by this Authority to read as follows:

5. With regard to the abstract,

- ☒ the text is approved as submitted by the applicant
☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority

6. With regard to the drawings,

- a. the figure of the drawings to be published with the abstract is Figure No. _____
☐ as suggested by the applicant
☐ as selected by this Authority, because the applicant failed to suggest a figure
☐ as selected by this Authority, because this figure better characterizes the invention
- b. ☐ none of the figures is to be published with the abstract

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/010412A. CLASSIFICATION OF SUBJECT MATTER
A61K31/47 A61P29/00 C07D215/26

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)

A61K A61P 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, BIOSIS, EMBASE, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 03/103671 A (MENARINI RICERCHE S.P.A; CALVANI, FEDERICO; CATRAMBONE, FERNANDO; FEL) 18 December 2003 (2003-12-18) cited in the application page 55; claims; examples 79,83 page 15	1-10
A	HEITSCH H ET AL: "Novel Series of O-Substituted 8-Quinolines and 4-Benzothiazoles as Potent Antagonists of the Bradykinin B2 Receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 3, 8 February 1999 (1999-02-08), pages 327-332, XP004157223 ISSN: 0960-894X table 1; compound 88	1-10
-/-		

☒ Further documents are listed in the continuation of Box C.☒ See patent family annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

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

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

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

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

"B" document member of the same patent family

Date of the actual completion of the international search

23 February 2006

Date of mailing of the international search report

13/03/2006

Name and mailing address of the ISA/

European Patent Office, P.B. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 851 epo nl,
Fax (+31-70) 340-3018

Authorized officer

Härtinger, S

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2005/010412

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	HEITSCH H: "Non-peptide antagonists and agonists of the bradykinin B(2) receptor." CURRENT MEDICINAL CHEMISTRY. MAY 2002, vol. 9, no. 9, May 2002 (2002-05), pages 913-928, XP002369396 ISSN: 0929-8673 figure 3 -----	1-10

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2005/010412

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 03103671	A	18-12-2003	
		AU 2003242628 A1	22-12-2003
		BR 0311825 A	15-03-2005
		CA 2488565 A1	18-12-2003
		CN 1658877 A	24-08-2005
		EP 1513531 A1	16-03-2005
		IT MI20021247 A1	09-12-2003
		JP 2005532354 T	27-10-2005
		MX PA04012193 A	25-02-2005

PATENT COOPERATION TREATY

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From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY (PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2005/010412

International filing date (day/month/year)
27.09.2005

Priority date (day/month/year)
15.10.2004

International Patent Classification (IPC) or both national classification and IPC
A81K31/47, A81P29/00, C07D215/26

Applicant
ISTITUTO LUSO FARMACO D'ITALIA S.P.A.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☐ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. FURTHER ACTION

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



European Patent Office
D-80296 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Härtinger, S

Telephone No. +49 89 2399-8289



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**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2005/010412

Box No. 1 Basis of the opinion

1. With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Re Item V.

1 Reference is made to the following documents:

- D1: WO 03/103671 A (MENARINI RICERCHE S.P.A; CALVANI, FREDERICO; CATRAMBONE, FERNANDO; FEL) 18 December 2003 (2003-12-18)
D2: HEITSCH H ET AL: "Novel Series of O-Substituted 8-Quinolines and 4-Benzothiazoles as Potent Antagonists of the Bradykinin B2 Receptors" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 3, 8 February 1999 (1999-02-08), pages 327-332, XP004157223 ISSN: 0960-894X
D3: HEITSCH H: "Non-peptide antagonists and agonists of the bradykinin B(2) receptor." CURRENT MEDICINAL CHEMISTRY. MAY 2002, vol. 9, no. 9, May 2002 (2002-05), pages 913-928, XP002369396 ISSN: 0929-8673

2 The present application does not meet the criteria of Art. 33(1) PCT, because the claimed subject-matter is not new in the sense of Art. 33(2) PCT and does not involve an inventive step (Art. 33(3) PCT).

Document D1 discloses in the examples 79 and 83 products which fall under the scope of claims 1 and 2. In the light of the test results for these compounds on page 55 of D1, these compounds share the utility with the present products as bradykinin receptor antagonists. By consequence, the subject-matter of claims 7-10 lack also novelty.

As to the present claims 3-6, a selection has been made from the preferred 4-acyl-piperazine derivatives disclosed on page 15 of D1. The selection is regarded as novel since it would appear that the combination of a quaternary ammonium group with a 5-oxopentyl linker has not been disclosed.

3 The present comparative test data on page 16 are not meaningful since compounds of D1 have been selected which are more remote than the structurally closest products of examples 79 and 83. As such, the allegation made in the present application that the claimed ammonium products were more active than the products

of D1 cannot be taken in support of inventive step. Since the common core of the present compounds is the same as in D1, and this prior art already suggests to use a quaternary ammonium group in place of an amino group (see for instance, page 61, line 13), the structural modifications done starting from the mentioned examples and claim 2 of D1 are obvious. The present compounds solve therefore in an obvious manner the problem of providing further bradykinin receptor antagonists. As no meaningful data are available which would make credible non-predictable properties for essentially all variants covered by the present claims, the present claims do not meet the requirements of Art. 33(3) PCT.

Novel Series of O-Substituted 8-Quinolines and 4-Benzothiazoles as Potent Antagonists of the Bradykinin B₂ Receptors

Holger Heitsch^{a,b}, Adalbert Wagner, Bernhard A. Schölkens, Klaus Wirth

Hoechst Marion Roussel GmbH, D-65926 Frankfurt/Main, Germany

Received 16 October 1998; accepted 9 December 1998

Abstract: The synthesis and the SAR study of novel O-substituted 8-quinolines and 4-benzothiazoles as highly potent non-peptide bradykinin B₂ receptor antagonists are described. Several members of this series of antagonists efficiently inhibited the BK-induced vasoconstriction on different isolated organ preparations. © 1999 Elsevier Science Ltd. All rights reserved.

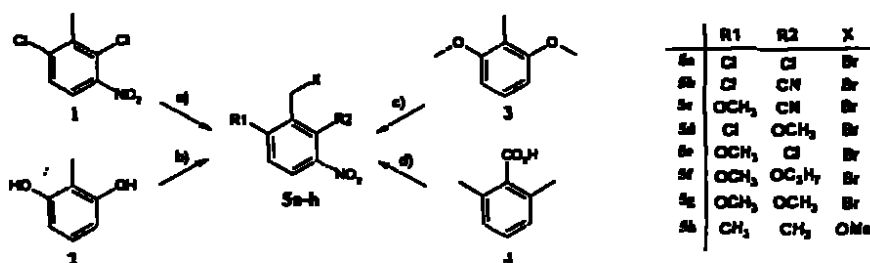
It is now well established that bradykinin (BK) participates in the pathophysiology of various diseases like inflammation, pain, asthma, allergic rhinitis, arthritis, shock, and acute pancreatitis.^{1–4} Its involvement in the avid sodium retention of liver cirrhosis has also been demonstrated recently.⁵

The major part of the acute pathophysiological actions of BK is mediated by the B₂ receptor.⁴ In the past decade, antagonism of this receptor was restricted to BK-derived peptides like the “second generation” antagonists icatibant (HOE 140)⁷ and bradycor (CP0127).⁸ Recently, researchers from Fujisawa delineated the first “third generation” of B₂ receptor antagonists, which were orally active non-peptide antagonists of this BK receptor subtype.⁹ Prototypes of this new class of antagonists are FR 167 344 and FR 173 657.^{9,10,11}

Herein we report the synthesis and SAR study of novel series of O-substituted quinolin-8-ols and benzothiazol-4-ols with particular emphasis on the influence of the 2,6-substituents of their central 3-*N*-methylamidobenzyl moiety on the affinity towards the BK B₂ receptor. Most of these compounds exhibit high affinity to the BK B₂ receptor on guinea pig ileum membranes and have a pronounced inhibitory action on the BK-induced vasoconstriction in different isolated organ preparations.

The BK receptor antagonists 8a–o and 13a–h of the quinoline and the benzothiazole series described here are shown in Table 1 and 2 and their synthetic access is outlined in the Schemes 1–3.

Scheme 1:



I. X=H: a) 1. CuCN, DMF, 150 °C, 10 h; 2. MeOH, Na, reflux, 2 h or MeOH, NaH, DMF, rt, 2h, separation; b) 1. NaNO₂, H₂SO₄, H₂O, 0 °C, 30 min.; 2. HNO₃, 5 °C, 30 min.; 3. (CH₃O)₂SO₂, K₂CO₃, acetone, rt, 15 h; 4. C₂H₅Br, NaH, DMF, 70 °C, 7 h; c) HNO₃, 0 °C, 15 min.; II. X=Ar: 1,3-dibromo-5,5-dimethylhydantoin, (PhCO)₂O, PhCl, reflux, 12 h; d) 1. HNO₃, H₂SO₄, 0 °C, 1 h; 2. (CH₃)₂SiCl₂, BzNEt₃BH₄, CH₂Cl₂, 0 °C, 2 h; 3. NaCl, NEt₃, CH₂Cl₂, rt, 30 min.

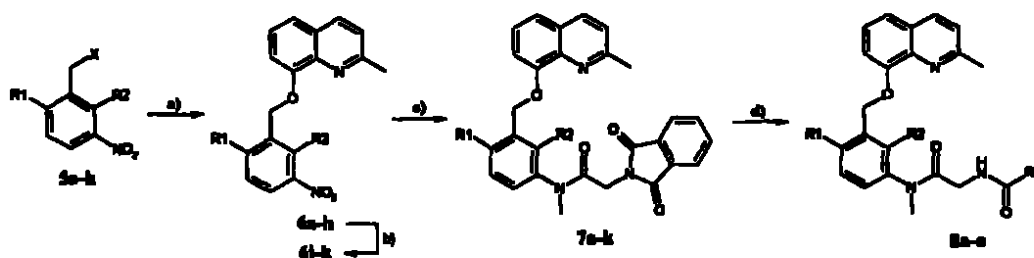
^a e-mail: holger.heitsch@hmrug.com; fax: +49 69 305 80226
0960-894X/99/\$ - see front matter © 1999 Elsevier Science Ltd. All rights reserved.
PII: S0960-894X(98)00736-7

The first step in the synthesis of these B_2 receptor antagonists is the preparation of the 2,6-disubstituted nitrobenzylbromides **5a–f** and nitrobenzylmesylate **5g** as outlined in Scheme 1.

The benzylbromides **5a–e** are prepared by bromination of their appropriate toluene precursors along with selective nucleophilic substitution of chloride in **1** by copper(I) cyanide¹² and sodium methoxide. The 2,6-dialkoxy substituted benzylbromide **5f** is obtained by nitrosation of 2,6-dihydroxytoluene **2**, oxidation of the nitroso intermediate, regioselective alkylation of the 6-hydroxy group with dimethoxysulfate¹³, alkylation of the hydroxyl in position 2 by treatment with propylbromide followed by benzylic bromination. The dimethoxy derivative **5g** results from 2,6-dimethoxytoluene **3** by nitration¹⁴ and successive bromination. The benzylmesylate **5h** derives from 2,6-dimethylbenzoic acid **4** by nitration, selective reduction of the carboxyl group with benzyltriethylammonium borohydride-chlorotrimethyl-silane¹⁵ and subsequent treatment of the benzylalcohol intermediate with methanesulphonyl chloride.

As shown in Scheme 2 the synthesis proceeds⁹ with the alkylation of 8-hydroxyquinoline with benzylbromides **5a–g** and benzylmesylate **5h** to afford benzyloxy-substituted quinolines **6a–h**. The methylthio-ethers **6i–k** derived from successive selective displacement of the appropriate chloro substituents by treatment with sodium methanethiolate. Subsequent reduction of the nitro group of **6a–k** with SnCl_2 dihydrate gives the intermediate amines, which are coupled with the acid chloride of phthaloylglycine. Subsequent N-alkylation of the amide nitrogen with methyl iodide affords the corresponding N-methylacetamides **7a–k**. Deprotection of **7a–k** with hydrazine monohydrate and acylation with appropriate acylating agents provides the desired quinolines **8a–o** listed in Table 2.

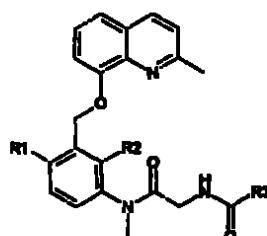
Scheme 2:



a) 8-hydroxyquinoline, K_2CO_3 , DMF, rt, 2 h; b) MeSNa , DMF, rt, 12 h; c) 1. $\text{SnCl}_2 \times 2\text{H}_2\text{O}$, EtH, reflux, 1 h; 2. $\text{PhthCH}_2\text{COCl}$, DMAP, pyridine, 50 °C, 2 h; 3. CH_3I , NaH, DMF, 50 °C, 4 h; d) 1. $\text{H}_2\text{NNH}_2 \times \text{H}_2\text{O}$, CH_2Cl_2 , EtOH, reflux, 2 h; 2. R_3COCl , NEt_3 , CH_2Cl_2 , reflux, 1 h or R_3NCO , DMF, rt, 2 h or R_3NH_2 , $(\text{ImCO})_2\text{O}$, $\text{EtN}(\text{Pr})_2$, DMF, rt, 4 h.

As revealed in Table 2, the synthesized antagonists **8a–o** in the quinoline series exhibited nanomolar or better affinity towards the BK B_2 receptors on guinea pig ileum membranes. The antagonistic properties of **8a–o** could also be confirmed functionally by their high efficacy in the inhibition of the BK-induced contraction of isolated organ preparations from the guinea pig ileum and the rabbit jugular vein. From the

modifications of R1, R2 and R3 described here, those of R1 and R2 were more important for the potency of the antagonists than changes in R3. The best antagonists 8b, 8d and 8e had two electron-withdrawing substituents R1 and R2 in the 2,6-position of the benzyloxy moiety of the quinolines, and had IC_{50} -values of 0.9, 0.7 and 1.2 nM, respectively. The exchange of one of these two R1/R2 substituents by an electron-donating group like methoxy, thiomethoxy or methyl^a in 8f–s is associated with a significant loss in activity of one to two orders of magnitude. The least potent B_2 antagonist in the quinoline series is 8m, having a methoxy group in position 2 and a thiomethoxy group in position 6. The affinity of 8l, with a 2-propoxy group, is only slightly lower in comparison to 8e or 8g which suggests that in contrast to this electrostatic interaction, steric features seems to be of minor importance. Nevertheless, the only moderate B_2 receptor binding affinity of 8m indicates that steric requirements for position 6 are more influential than those for position 2.

Table 1: *Quinolines*

	R1	R2	R3	B_2 ^a		EC ₅₀ or % inhibition ^b	
				IC ₅₀ [nM]	K _i [nM]	GPI [M]	RJV [M]
8a	-Cl	-CN	-NH-CH ₂ -CH ₃	64.8	8.3	2.9×10^{-7}	10^{-5} : 66 %
8b	-Cl	-CN	-NH-(CH ₂) ₄ -NH ₂	0.9	0.1	3.5×10^{-7}	10^{-5} : 72 %
8c	-Cl	-CN	-NH-(CH ₂) ₃ -CO ₂ H	25.7	2.9	4.0×10^{-7}	10^{-5} : 80 %
8d	-Cl	-CN	-CH=CH-C ₆ H ₅ -(<i>m</i> -OCH ₃)	0.7	0.1	4.1×10^{-9}	10^{-5} : 78 %
8e	-Cl	-CN	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	1.2	0.3	5.6×10^{-8}	10^{-5} : 82 %
8f	-OCH ₃	-CN	-NH-CH ₂ -CH ₃	53.8	6.0	4.5×10^{-7}	10^{-5} : 59 %
8g	-Cl	-OCH ₃	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	21.9	2.5	5.5×10^{-8}	2.8×10^{-8}
8h	-OCH ₃	-Cl	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	11.5	1.3	1.3×10^{-7}	2.6×10^{-7}
8i	-OCH ₃	-OC ₃ H ₇	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	32.9	3.9	2.2×10^{-7}	10^{-5} : 82 %
8j	-OCH ₃	-OCH ₃	-CH=CH-C ₆ H ₅ -(<i>m</i> -CH ₃)	81.3	9.2	n.d. ^c	10^{-5} : 68 %
8k	-OCH ₃	-SCH ₃	-CH=CH-3-Pyridyl-(6-NHAc)	5.2	0.6	5.9×10^{-8}	10^{-5} : 95 %
8l	-OCH ₃	-SCH ₃	-(CH ₂) ₄ -CO ₂ CH ₃	47.2	5.4	4.8×10^{-7}	10^{-5} : 55 %
8m	-SCH ₃	-OCH ₃	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	393.0	45.4	1.1×10^{-6}	10^{-6} : 41 %
8n	-SCH ₃	-SCH ₃	-CH=CH-C ₆ H ₅ -(<i>p</i> -OCH ₃)	56.9	6.3	6.6×10^{-7}	8.7×10^{-6}
8o	-CH ₃	-CH ₃	-CH=CH-C ₆ H ₅ -(<i>p</i> -CF ₃)	11.8	1.3	n.d. ^c	10^{-5} : 81 %

a) IC₅₀ and K_i for inhibition of specific binding of [³H]-BK to guinea pig ileum (GPI) membrane preparations; n = 3–8

b) EC₅₀ for inhibition of BK-induced (4×10^{-8} M) contraction of isolated GPI and rabbit jugular vein (RJV); n = 6

c) Not determined

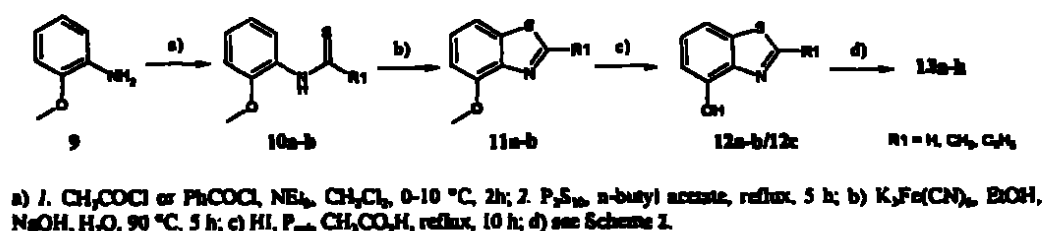
For the terminal group R3 a great variety of acyl substituents are tolerated indicating that this residue interferes with an receptor binding site less important for the affinity of the antagonists. However, the weaker binding affinity of 8a and 8f suggests that an ethylamino residue is obviously too small for an optimal interaction of the antagonists with the B₂ receptor. All other terminal residues (i.e. cinnamoyls as in 8d, 8e, 8g–j and 8m–o, amidobutylamine as in 8b, and amidobutanoic acid as in 8c) are well tolerated, indicating that modifications in this position could be used to adjust the physicochemical properties of the antagonists in this series towards the desired route of application without concomitant loss in binding affinity.

Accordingly to the recently published SAR studies of closely related series of antagonist on human B₂ receptors expressed in CHO cells by Fujisawa¹⁶, this high tolerance in the N-substituents of the glycine moiety seems to be restricted only to the guinea pig ileum B₂ receptor. They discovered that in this series of antagonists only compounds with an extended basic framework incorporating an N-terminal cinnamamide residue on the glycine moiety overcome the species differences in affinity between BK B₂ receptors in guinea pig ileums and humans resulting in highly potent antagonist of the human B₂ receptor.

Various attempts to modify the 3-N-methylamidobenzoyloxy moiety⁹ failed to produce antagonists of the BK B₂ receptor with an binding affinity comparable to this of the reported quinolines or the benzothiazoles listed in Table 2. This basic skeleton seems to be an essential structural requirement of antagonists to adopt the appropriate bioactive conformation.

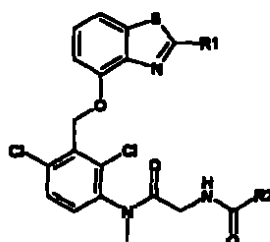
The synthetic route to obtain the antagonists 13a–h of the benzothiazole series is shown in Scheme 3. The 2-methyl- and 2-phenyl-substituted 4-hydroxybenzothiazole moieties 12a–b are synthesized from 2-methoxyanilines 9 in a 5-step procedure.¹⁶ In the first step of this procedure, amine 9 is acylated and the resulting amides are converted to the corresponding thioamides 10a–b. Radical-induced cyclization of 10a–b with potassium hexacyanoferrate(III) gave the 4-methoxy-substituted benzothiazoles 11a–b. Ether cleavage of intermediates 11a–b gave the desired 4-hydroxybenzothiazoles 12a–b suitable for further modifications. The 4-hydroxybenzothiazole 12c without a substituent in position 2 was synthesized according to a procedure known from the literature.¹⁷ These three 4-hydroxybenzothiazoles are then used for further conversions towards the antagonists 13a–h listed in Table 2 analogously to the procedures described for the antagonists of the quinoline series (Scheme 2).

Scheme 3:



As shown in Table 2, very potent BK B₂ receptor antagonists derived also in the benzothiazole series. In comparison to the quinoline series, both the binding affinity towards the B₂ receptor as well as the functional response for the 2-methyl benzothiazoles 13b-g, are only slightly decreased. Like for the quinoline antagonists a large variety of terminal R₃-substituents are tolerated in the benzothiazole series, too. However, a dramatic drop in binding affinity and in the functional response is observed for 13a in which the 2-methyl benzothiazole moiety of 13b-g is replaced by a benzothiazole unsubstituted in position 2. The replacement of the 2-methyl substituted benzothiazole moiety of 13b-g by a 2-phenyl substituted benzothiazole as in 13h results in a total loss in binding affinity. These findings substantiate that a 2-methyl group is an essential requirement for highly efficient antagonism of the BK B₂ receptor in the benzothiazole series.

Table 2: Benzothiazoles:



	R1	R2	B ₂ ^a		EC ₅₀ or % inhibition ^a	
			IC ₅₀ [nM]	K _i [nM]	GPI [M]	RJV [M]
13a	-H	-CH=CH-C ₆ H ₅ -(p-CH ₃)	1350	160	1.3 x 10 ⁻⁶	10 ⁻⁵ : 17 %
13b	-CH ₃	-CH=CH-C ₆ H ₅ -(p-CH ₃)	14.2	1.8	2.3 x 10 ⁻⁸	6.6 x 10 ⁻⁸
13c	-CH ₃	-CH=CH-C ₆ H ₅ -(p-CF ₃)	23.0	2.8	1.0 x 10 ⁻⁷	7.6 x 10 ⁻⁸
13d	-CH ₃	-CH=CH-C ₆ H ₅ -(m-OCH ₃)	10.3	1.3	5.4 x 10 ⁻⁸	1.8 x 10 ⁻⁷
13e	-CH ₃	-CH=CH-(2-furyl)	29.8	3.4	n.d. ^a	7.8 x 10 ⁻⁷
13f	-CH ₃	-CH=CH-CH=CH ₂	26.2	3.1	2.6 x 10 ⁻⁷	5.2 x 10 ⁻⁶
13g	-CH ₃	-O-CH ₂ -C ₆ H ₅	77.8	9.1	n.d. ^a	10 ⁻⁵ : 73 %
13h	-C ₆ H ₅	-CH=CH-C ₆ H ₅ -(p-CH ₃)	11000	1300	2.0 x 10 ⁻⁵	10 ⁻⁵ : 15 %

a) - c): see legend of table 1

In summary, novel series of O-substituted 8-quinolines and 4-benzothiazoles as potent non-peptide antagonists of the BK B₂ receptor based on lead structures delineated by Fujisawa were discovered. The potency of the quinolines were found to be slightly superior to those found for the corresponding benzothiazoles. The most potent antagonist 8d is derived from the quinoline series and exhibits an IC₅₀-value of 0.7 nM and an EC₅₀-value of 4.1 nM. The described compounds may serve as valuable tools to further aid in the understanding of the BK B₂ receptor.

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Non-peptide Antagonists and Agonists of the Bradykinin B₂ Receptor

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Abstract: Stimulation of the bradykinin (BK) B₂ receptor by kinins is associated with pathophysiological as well as pronounced beneficial effects. Consequently, interference with BK B₂ receptors by either antagonism or agonism offers promising therapeutic approaches for the development of drugs for the treatment of various human diseases. BK B₂ receptor antagonists may prove useful for the treatment of pathological situations caused by excessively increased local kinin concentrations, such as inflammation, tissue injury and pain. Beneficial effects of peptide BK B₂ receptor antagonists in perennial rhinitis, asthma and brain edema have already been demonstrated in clinical trials. On the other hand, kinins have also been identified as potent vasodilatory and organ-protective peptides. Therefore, BK B₂ receptor agonists may have the potential to become valuable therapeutics in the treatment of cardiovascular diseases such as hypertension, myocardial hypertrophy, myocardial infarction and arrhythmias as well as diabetic disorders. For both approaches, potent, selective and even orally active non-peptide compounds have been discovered recently. Prototypes of these novel 'third generation' classes of compounds are the alkylphosphonium salt WIN-64338, the pseudopeptide NPC-18884, the thiosemicarbazide bradyzide and especially the imidazo[1,2-*a*]pyridine FR-167344 and the quinolines FR-173657 and LF-16.0687 as non-peptide BK B₂ receptor antagonists, whereas the 4-(2-pyridylmethoxy)-substituted quinoline FR-190997 and the 3-(2-pyridylmethyl)-substituted benzimidazole FR-191413 emerged as non-peptide BK B₂ receptor agonists. These antagonists and agonists of the BK B₂ receptor have already demonstrated efficacy a various animal models of human diseases, which offers promising therapeutic approaches for the development of drugs for the treatment or even prevention of a variety of severe human diseases either via stimulation or via blockade of BK B₂ receptors.

INTRODUCTION

Human kinins consists of two endogenous peptide hormones, the nonapeptide bradykinin (BK, Arg¹-Pro²-Pro³-Gly⁴-Phe⁵-Ser⁶-Pro⁷-Phe⁸-Arg⁹) and the related decapeptide kallidin (Lys⁰-BK), which are formed as components of the kallikrein-kinin system (KKS) [1,2]. They are thought to act as local (paracrine) hormones, acting near the site at which they are generated. In mammals, the biological effects of kinins are mediated through the activation of two distinct BK receptor subtypes, B₁ and B₂ [3-6]. These kinin receptors are G-protein coupled, seven transmembrane receptors and are distributed in a wide variety of cells and tissues. BK B₂ receptors have high affinity for BK and kallidin and are constitutively expressed ready to respond to newly formed kinins. In contrast, BK B₁ receptors, which have high affinity for des-Arg⁹-BK and des-Arg⁹-kallidin, are inducible, which means that their expression is markedly up-regulated in response to inflammation/tissue injury, whereas they are poorly expressed or absent under normal ('resting') physiological conditions [7].

The majority of the prominent physiological actions of kinins seems to be mediated by the stimulation of the

constitutive BK B₂ receptor. The data collected with potent and metabolically stable BK B₂ receptor antagonists support the assumption that kinins are involved in several important physiological functions, such as regulation of local and systemic haemodynamics, vascular permeability, inflammatory response, neuronal activation, cell proliferation, and passage of water and electrolytes across epithelia [2]. Their physiological role becomes more apparent when local concentrations are enhanced by blocking their degradation.

In a variety of studies in animals and in human it has been demonstrated over the recent years that stimulation of BK B₂ receptors by kinins is associated with severe pathophysiological as well as pronounced beneficial physiological effects [8-10]. Consequently, interaction with the BK B₂ receptor by either its blockade or its stimulation offers promising therapeutic approaches for drug developments.

THERAPEUTIC POTENTIAL OF BK B₂ RECEPTOR ANTAGONISM AND AGONISM

By stimulation of BK B₂ receptors, kinins exert a wide variety of diverse biological actions. In various animal models and humans it has been demonstrated that the stimulation of BK B₂ receptors is not only implicated in the pathogenesis of inflammation, pain and tissue injury, but also in powerful organ- and cardioprotective mechanisms. The kinin-mediated effects, their pathophysiological or

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beneficial consequences and the associated scope of possible target indications for either antagonists or agonists of the BK B₂ receptor are summarized in Fig. 1.

Pathophysiological Effects of Kinins

There is compelling evidence that exogenously applied or endogenously generated kinins, via stimulation of BK B₂ receptors, activate sensory nerve terminals, producing pain and hyperalgesia, and induce the release of proinflammatory and hyperalgesic mediators such as neuropeptides and metabolites derived from arachidonic acid pathways like leukotrienes and cytokines, which also largely contribute to their proinflammatory and nociceptive properties [1,3,11-14]. Kinins also cause the formation of edema by increasing vascular permeability, plasma extravasation and contraction of smooth muscle cells, promote the migration of cells from blood to tissues and activate various tissue components such as mast cells, fibroblasts, macrophages and cells of the immune system [1,3,15-18]. These BK B₂ receptor-mediated pharmacological effects are the underlying cause of the strong proinflammatory properties of kinins, and it is believed that excessively increased local kinin concentrations contribute significantly to diseases like septic shock, pancreatitis, edema, rhinitis, asthma, colitis, arthritis and pain [8,9]. These diseases might be promising target

indications for the development of BK B₂ receptor antagonists.

As well as these long-proposed 'classical' indications for BK B₂ receptor antagonists, recently reported investigations suggest possible novel attractive indications for their use, such as hepatorenal syndrome, small cell lung cancer, bacterial and viral infections, ulcerative colitis and Alzheimer's disease [9].

Beneficial Physiological Effects of Kinins

Accumulating evidence suggests that kinins act as mediators of endogenous cardioprotective mechanisms: (1) kinin-generating pathways are present in the heart, (2) kinins are released under conditions of ischemia, (3) local administration or inhibition of the breakdown of kinins exerts beneficial cardiac effects, (4) antagonism of BK B₂ receptors worsens ischemia-induced effects, and (5) kinins contribute to the cardioprotective effects associated with ischemic preconditioning [8-10,19].

The observed vasodilatory, antihypertrophic, antiproliferative and antiatherosclerotic efficacy of kinins results from stimulation of BK B₂ receptors located on the surface of endothelial cells, which causes the synthesis and

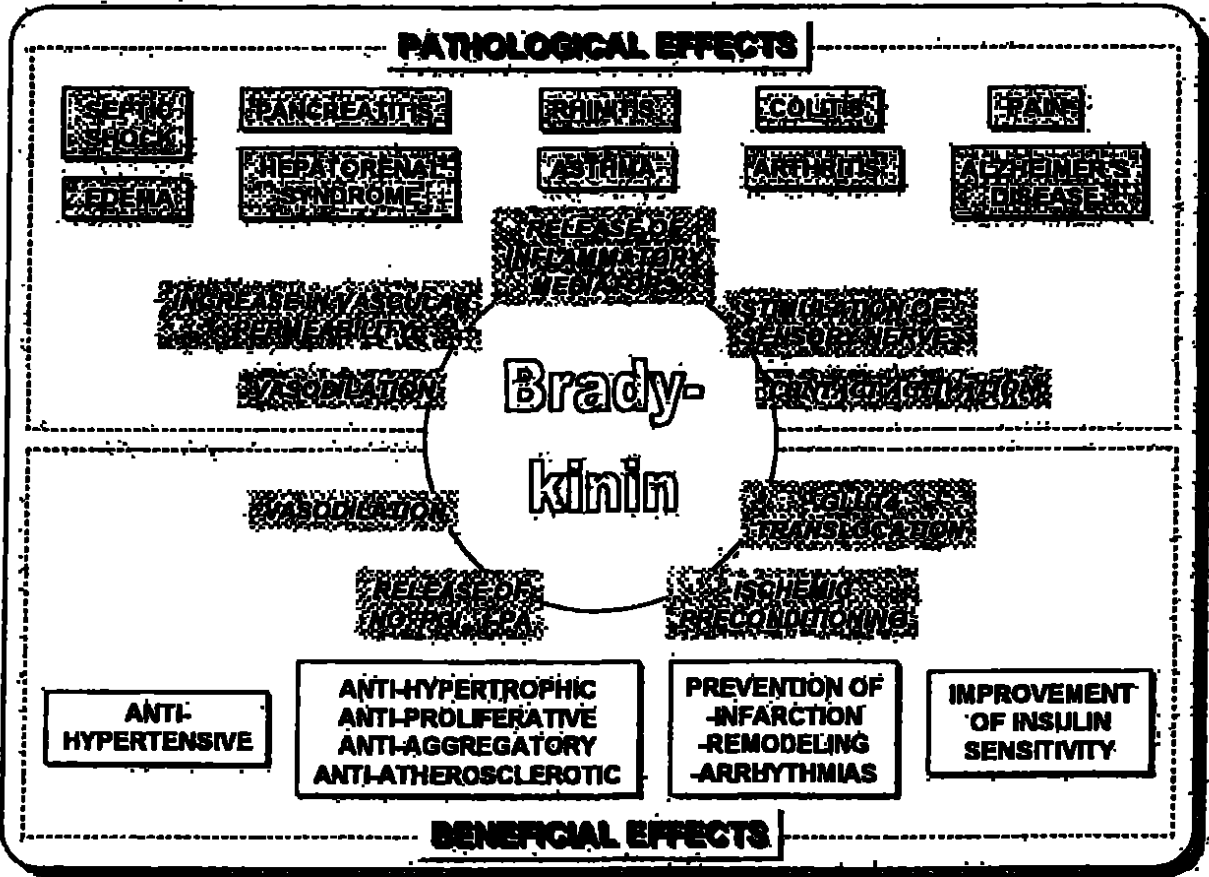


Fig. (1). BK-mediated pharmacological responses (gray), their associated pathophysiological (red) or beneficial (yellow) consequences.

release of the endothelial mediators nitric oxide (NO), prostaglandins (PGI₂) and tissue plasminogen activator (t-PA) and triggers ischemic preconditioning and an increase in insulin sensitivity [7,19-30]. Through these mechanisms, kinins reduce vascular peripheral resistance and, most importantly, maintain the protective function of the endothelium [10,19].

The involvement of kinins in cardiovascular functions has been confirmed in transgenic and knockout mice models [31]. In a transgenic mouse model, over-expression of human BK B₂ receptor lead to the development of sustained lifetime hypotension and the enhancement of renal function, demonstrating the protective effect of the KKS in the pathogenesis of hypertension [32,33]. Complementary to this result, in BK B₂ receptor knockout mice, disruption of the BK B₂ receptors lead to hypertension, left ventricular remodeling and functional impairment [34,35].

The described pronounced beneficial cardiovascular and metabolic effects associated with the stimulation of BK B₂ receptors by kinins was mainly evidenced by the comparable effects of exogenously added BK or ACE inhibitors in a variety of physiological and pathophysiological conditions. In different *in vitro* and *in vivo* experimental models, it was observed that BK B₂ receptor antagonists attenuated or even completely abolished most of the cardiovascular effects of ACE inhibitors as well as of BK [10,19,20]. It is assumed that locally increased kinin concentrations as a consequence of the blockade of ACE, the major kinin-degrading enzyme, significantly contributes to the apparent beneficial effects of ACE inhibitors, including their antihypertensive and renal effects, their inhibitory effect on myocardial hypertrophy and fibrosis, their antiarrhythmic and infarct-size reducing effects and their improvement of insulin sensitivity [19,30,36-41]. Therefore, cardiovascular diseases such as hypertension, myocardial hypertrophy, myocardial infarction, post-PTCA ventricular remodeling, arrhythmias or diabetic disorders such as diabetic nephropathy might be promising target indications for the development of BK B₂ receptor agonists.

For both approaches, selective, potent and also orally available non-peptide compounds, which allow even chronic administration, have been identified in recent years. However, further studies are required to demonstrate that there is a sufficient therapeutic window between the pathophysiological and beneficial BK B₂ receptor-mediated effects, which would allow the treatment of inflammatory disorders and chronic pain with BK B₂ receptor antagonists without diminution of the beneficial systemic and cardiovascular effects of endogenous kinins and, vice versa, the treatment of cardiovascular and metabolic diseases with BK B₂ receptor agonists without concomitant proinflammatory side effects, especially upon chronic administration.

BK B₂ RECEPTOR ANTAGONISTS

Because of the important role kinins might play in various diseases, the search for antagonists for the BK B₂ receptor to inhibit kinin-mediated pathological actions has been pursued for many years [42,43]. Since the discovery of

the first BK B₂ receptor antagonists like NPC-567 [D-Arg-Arg-Pro-Hyp-Gly-Phe-Ser-D-Phe-Phe-Arg] by Vavrek and Stewart in 1985 starting with replacement of L-Pro⁷ in the native hormone by D-Phe as the key sequence alteration to produce antagonists, several linear, BK sequence-related peptide BK B₂ receptor antagonists differing in potency, tissue selectivity and stability against enzymatic degradation have been synthesized and characterized in the last two decades [44]. The most promising, best characterized and metabolically reasonably stable 'second generation' peptide BK B₂ receptor antagonists are icatibant (HOE-140, [D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg]) from the former Hoechst AG and the dimer of two single-chain decapeptide bradykinin (delibant, CP-0127, [D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Phe-Leu-Arg]₂BSH) from Cortech Inc. [45-47]. Both antagonists have demonstrated inhibitory efficacy in various animal models of inflammation, asthma, pain, tissue injury, sepsis and endotoxic and traumatic shock [8,46,48,49]. Icatibant and bradykinin have even been evaluated in clinical trials on asthma, postoperative pain, systemic inflammatory response syndrome, sepsis and head injury [8,9]. In phase II studies HOE-140 was found to be effective in patients with perennial rhinitis challenged with house dust mite antigen and in patients with chronic bronchial asthma [50,51], whereas Bradykinin demonstrated efficacy in patients with Gram-negative infections and closed head injury [52,53]. Although the overall outcome of these clinical trials was less convincing than expected, the trials support the assumption that BK B₂ receptors play an important role in the human diseases studied.

For many years antagonism of the BK B₂ receptor was restricted to these peptide antagonists. Despite the relative stability of the 'second generation' peptide BK B₂ receptor antagonists, their therapeutic potential is limited since peptides do not possess all the favorable pharmacokinetic properties that are required for widespread therapeutic use in humans. These limitations should be overcome by non-peptide antagonists which could be suitable for long term oral administration to treat chronic human diseases. In the previous seven years several series of these long-sought potent, selective and orally active non-peptide 'third generation' antagonists of the BK B₂ receptor have been identified. The best characterized representative examples of the different series of BK B₂ receptor antagonists with proven *in vivo* efficacy in specific animal disease models, WIN-64338, NPC-18884, FR-167344, FR-173657, LF-16.0687 and bradykinin, are shown in Fig. 2. Their synthesis and pharmacological properties will be presented in the subsequent paragraphs.

WIN-64338

In 1993, Sterling Winthrop researchers started to reported the design, synthesis and pharmacological characterization of WIN-64338 as the first potent non-peptide antagonist of the BK B₂ receptor, which displayed competitive antagonism in several *in vitro* functional assays [54-58]. Key structural features of this antagonist is the presence of two terminal positively charged moieties attached to a rigid and hydrophobic central scaffold at a distance which is in agreement with that postulated between the two charged

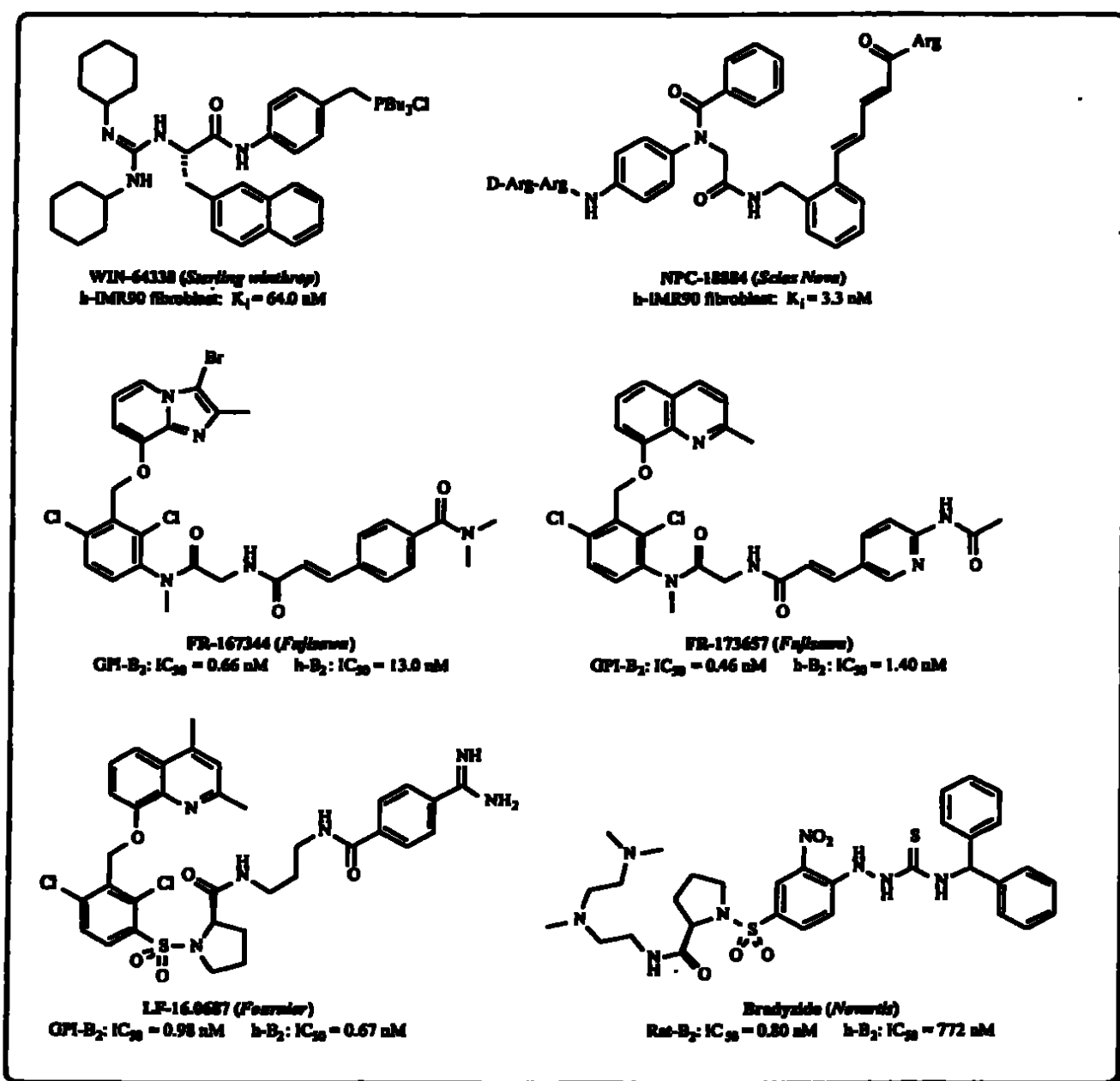


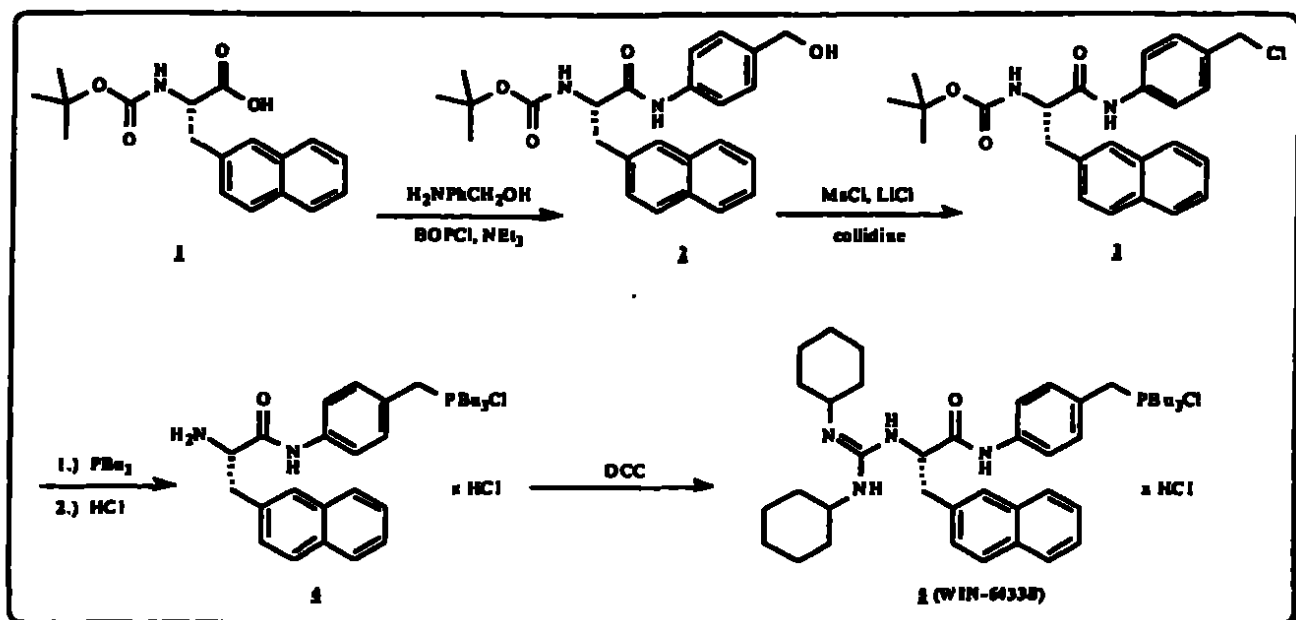
Fig. (2). Non-peptide antagonists of the BK B₂ receptor.

Arg¹ and Arg⁹ side chains in an assumed bioactive conformation of BK [56].

The synthetic route to WIN-64338 is shown in Scheme 1. WIN-64338 (5) was synthesized using a linear five step procedure starting from *N*-BOC protected L-8-(2-naphthyl)alanine 1. This amino acid derivative was coupled to 4-aminobenzyl alcohol using BOP-Cl in acetonitrile. Conversion of the obtained benzylic alcohol 2 to the corresponding benzylic chloride 3 was accomplished by treatment of 2 with methane sulphonyl chloride in the presence of collidine followed by the addition of excess lithium chloride. The resulting benzylic chloride 3 was then reacted with tributyl phosphine in refluxing toluene to

produce after subsequent cleavage of *N*-BOC protecting group the ammonium salt 4. Finally, 4 was treated with *N,N'*-dicyclohexyl carbodiimide in acetonitrile to furnish WIN-64338 (5) [57].

WIN-64338 exhibits a K_i value of 64 nM in a radioligand binding assay on human IMR-90 fetal lung fibroblasts and demonstrated a competitive inhibition of BK-stimulated $^{45}\text{Ca}^{2+}$ efflux in the same cells. WIN-64338 also moderately inhibited BK-induced contraction of the GPI. However, besides its particular structure WIN-64338 has several drawbacks. It exhibits significantly lower specificity than the known peptide antagonists with a high affinity for muscarinic receptors and species-dependent



Scheme 1. Synthesis of the BK B₂ receptor antagonist WIN-64338 (5) from Sterling Winthrop.

variable affinity for BK B₂ receptors with a much reduced binding affinity for human and rabbit B₂ receptors as compared to the guinea pig BK B₂ receptor [58].

NPC-18884

Following the strategy to systematically reduce the number of peptide bonds and size of the known peptide leads to identify antagonists with superior profile to the prior-art 'second generation' peptide BK B₂ receptor antagonists led to the identification of NPC-18884 by researches from Scios Nova [59-62]. This compound was derived by rational design from a structurally directed library approach based on a library of the type D-Arg-X₁-X₂-X₃-X₄-Arg [60]. Although the pharmacological properties of this novel BK B₂ receptor antagonist seem to vary according to the animal species used, it was demonstrated that NPC-18884 caused a dose- and time-dependent inhibition of BK- and carrageenin-induced acute inflammatory response in a mouse model of pleurisy upon intraperitoneal and oral administration [61]. NPC-18884, given either intraperitoneally or orally, also exhibited a dose-dependent inhibition of plasma exudation and cell content caused by intrapleural injection of carrageenin. It was demonstrated recently that orally dosed NPC-18884 produced potent and relatively long-lasting paw edema inhibition and antihyperalgesic effects in rat and mice [62].

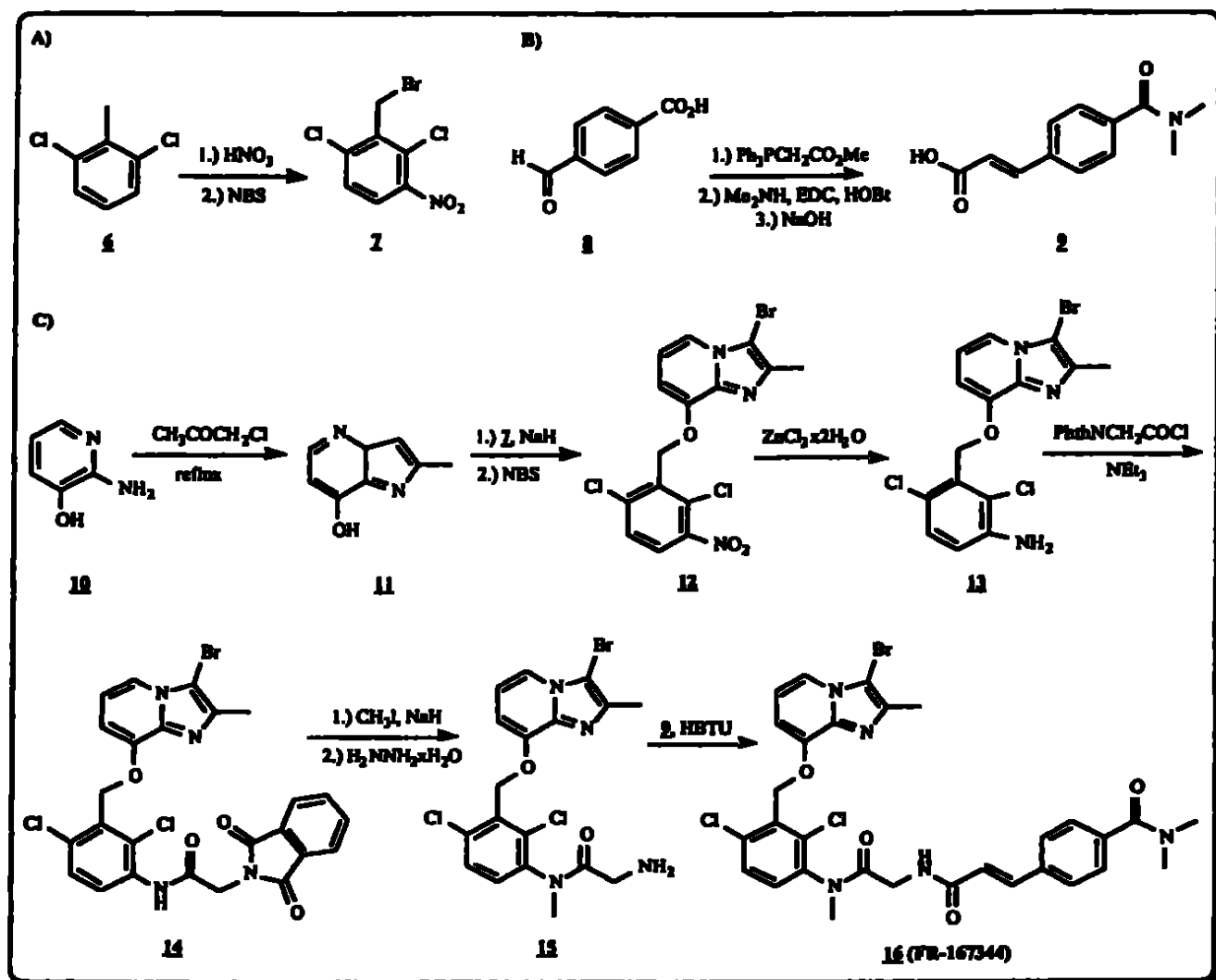
FR-167344 and FR-173657

A significant breakthrough in the search for compounds that block BK B₂ receptors was the identification of different series of potent non-peptide and orally active 'third generation' BK B₂ receptor antagonists by researchers from Fujisawa [63-79]. They discovered a number of imidazo[1,2-*a*]-pyridine, benzimidazole, quinoxaline and quinoline

derivatives with high binding affinity and selectivity for BK B₂ receptors [69-73]. These antagonists were derived from extensive medicinal chemistry modifications of a unique non-peptide lead discovered by a directed random screening in a series of angiotensin II subtype AT₁ receptor antagonists. This lead discovery strategy made use of the relationship between BK and angiotensin II (ANGII) based on the very high homology (29%) of the ANGII AT₁ receptor to the BK B₂ receptor, which is surpassed among G-protein coupled receptors only by the BK B₁ receptors, which has a 35% homology [69,73].

Representative and pharmacologically intensively characterized members of this series are the imidazo[1,2-*a*]pyridine derivative FR-167344 and the quinoline derivative FR-173657. The synthetic paths to these two BK B₂ antagonists are outlined in Scheme 2 and Scheme 3, respectively.

As shown in Scheme 2, FR-167344 (16) can be prepared in a 13-step procedure via O-alkylation of 8-hydroxy-imidazo[1,2-*a*]pyridine 11 with the benzylbromide 7 (C). 11 was obtained by treatment of 2-amino-3-hydroxy-pyridine 10 with chloroacetone, whereas 7 derived from nitration of 2,6-dichlorotoluene 6 followed by bromination of the intermediate nitrotoluene derivative with *N*-bromosuccinimide (NBS) (A). Selective halogenation in position 3 of the imidazo[1,2-*a*]pyridine moiety with NBS gave 12. Subsequent reduction of the nitro group of 11 produced the corresponding aniline derivative 13, which was then coupled with the acid chloride of *N*-phthaloylglycine to yield the *N*-phthaloylglycineamide 14. Alkylation of 14 with methyl iodide followed by deprotection of the amino group with hydrazine monohydrate provided 15, which was finally acylated with *trans*-4-(dimethyl-carbamoyl)-cinnamic acid 9 to afford FR-167344 (16). The cinnamic acid 9 resulted from 4-formyl benzoic acid 8 by Horner-Emmons-type Wittig reaction with methyl(triphenyl-



Scheme 2. Synthesis of the imidazo[1,2-*a*]pyridine BK B₂ receptor antagonist FR-167344 (16) from Fujisawa.

phosphoranylidene)-acetate, coupling with dimethylamine and hydrolysis of the ester group (C) [63-65].

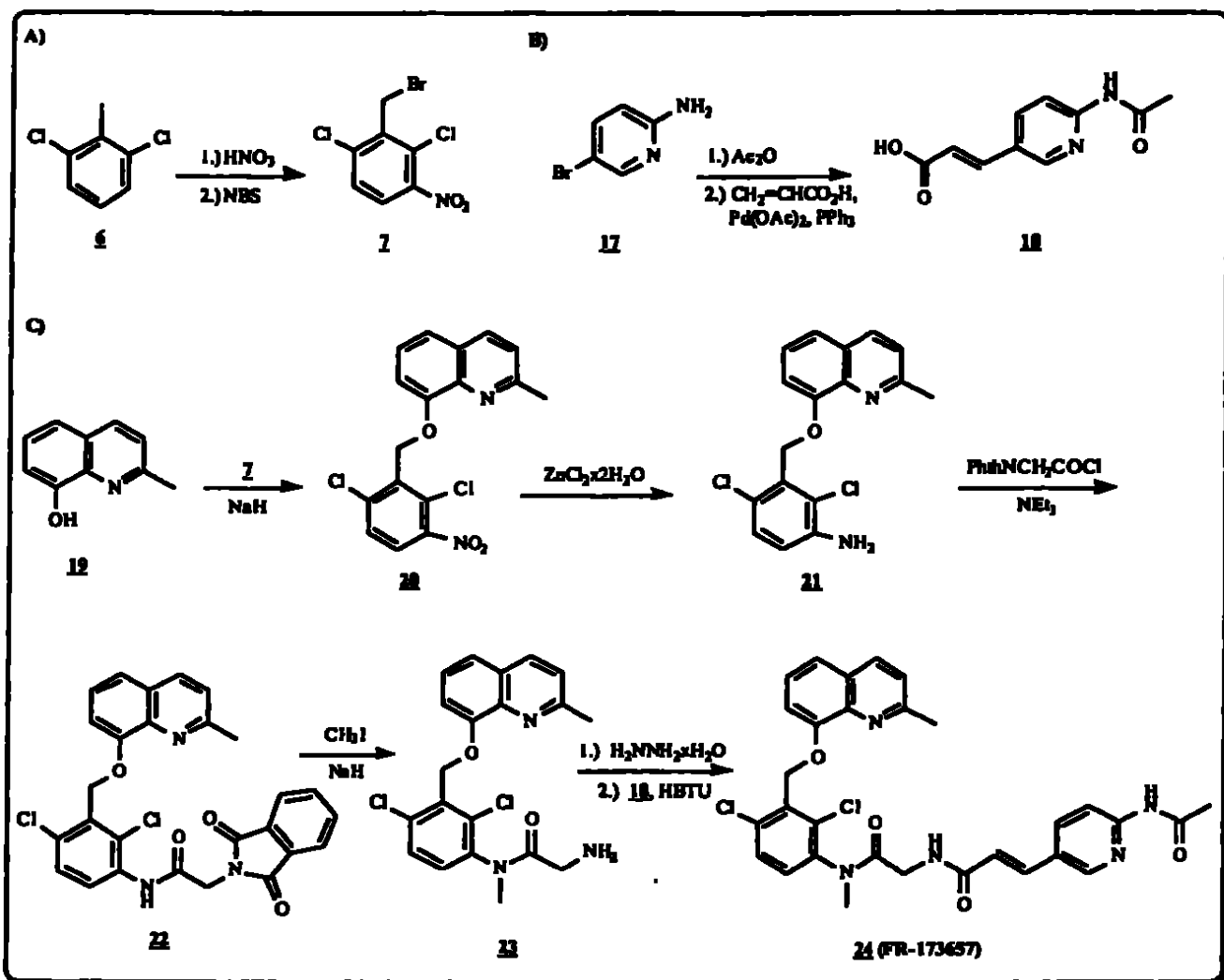
The synthesis of the quinoline derivative FR-173657 (24) is shown in Scheme 3. *O*-Alkylation of 8-hydroxyquinoline 19 with the benzylbromide 7 (A) afforded the nitro derivative 20, which was reduced to the corresponding aniline 21 by treatment with zinc chloride bishydrate in ethyl acetate (C). Subsequent application of preparative procedures similar to those already described above finally provided FR-173657 [67,68,71].

With the introduction of a terminal *trans*-cinnamamide or *trans*-3-(3-pyridyl)acrylamide substituted with an amide or carbamoyl group like in FR-167344 or FR173657 the species differences between human and guinea pigs could be overcome [70]. Obviously a planar substituent in this position is favorable for interaction with both guinea-pig and human BK B₂ receptors. Further modification of the basic framework by replacement of the imidazo[1,2-*a*]pyridine moiety in FR-167344 or the quinoline moiety in FR-

173657 provided further bioisosteric heterocycles such as benzimidazole and quinoxaline [71].

In-depth investigations of the steric requirements for BK B₂ binding affinity as a result of chemical modifications and conformational analysis by Fujisawa led to the discovery of the key role of the *N*-methylanilide moiety attached to the dichlorobenzene ring and a marked preference of the *N*-methylanilide bond to adopt a *cis*-conformation, with the amide and the phenyl plane almost perpendicular to each other. These data might suggest that this class of B₂ ligands binds to the receptor as the *cis*-amide conformer and the 2,6-dichloro-3-*N*-methylanilide moiety plays a key role in stabilizing the active conformation [69,72,73]. The pharmacophore model including all putative hydrophobic, electrostatic, hydrogen donor and acceptor interactions between the antagonists and the BK B₂ receptor proposed by Fujisawa's researchers is depicted in Fig. 3.

FR-167344 and FR-173657 both exhibited high affinity for BK B₂ receptors. In competition binding experiments on



Scheme 3. Synthesis of the quinoline BK B₂ receptor antagonist FR-173657 (24) from Fujisawa.

membranes from GPI and CHO cells expressing the recombinant human BK B₂ receptor FR-167344 displaced binding of [³H]-BK with IC₅₀ values of 0.66 nM and 13.0 nM and FR-173657 with IC₅₀ values of 0.46 nM and 1.4 nM, respectively. They also inhibited BK-induced IP formation in CHO cells expressing the human BK B₂ receptor with a pA₂ values of 8.0 and 9.0, respectively [73,74]. In isolated organs experiments both antagonists acted as competitive antagonists in the human umbilical vein and in the rabbit jugular vein and as non-competitive antagonists in the pig coronary artery with pA₂ values comparable to those of HOE-140. However, in contrast to FR-173657, FR-167344 did not show full specificity as a BK B₂ receptor antagonist since it interacts moderately with the NK₁ receptor system [79]. FR-167344 as well as FR-173657 displayed excellent *in vivo* functional antagonistic activity against BK-induced hypotension and bronchoconstriction in guinea pigs and plasma protein extravasation, as well as high oral efficacy in different animal models of inflammation such as carrageenin-induced paw edema in rats and cerulein-induced pancreatitis in rats [73-75,77,78]. For example, they were orally active against

BK-induced bronchoconstriction in guinea pigs with ED₅₀ values of 0.17 mg/kg for FR-167344 and 0.075 mg/kg for FR-173657 [74].

LF-16.0687

Very potent BK B₂ receptor antagonists structurally related to Fujisawa's quinoline series have also been reported from Fournier [80-86]. Their antagonists differ structurally from those of Fujisawa by the presence of a central sulfonamide linker replacing the *N*-methylamide moiety present in Fujisawa's antagonists. As in FR-173657, one terminus of the molecule consists of a dichlorobenzene-substituted terminal quinoline, linked to a basic terminus containing either a piperidine, a pyrrolidine or an amidinobenzene. Representative and best characterized examples of this class of BK B₂ receptor antagonists are LF-16.0335 and LF-16.0687 [84-86]. Both compounds have quite similar structures, only differing in the presence of piperazine ring in LF-16.0335 replacing the propylendiamine chain in LF-16.0687. However, LF-16.0687 seems to be the

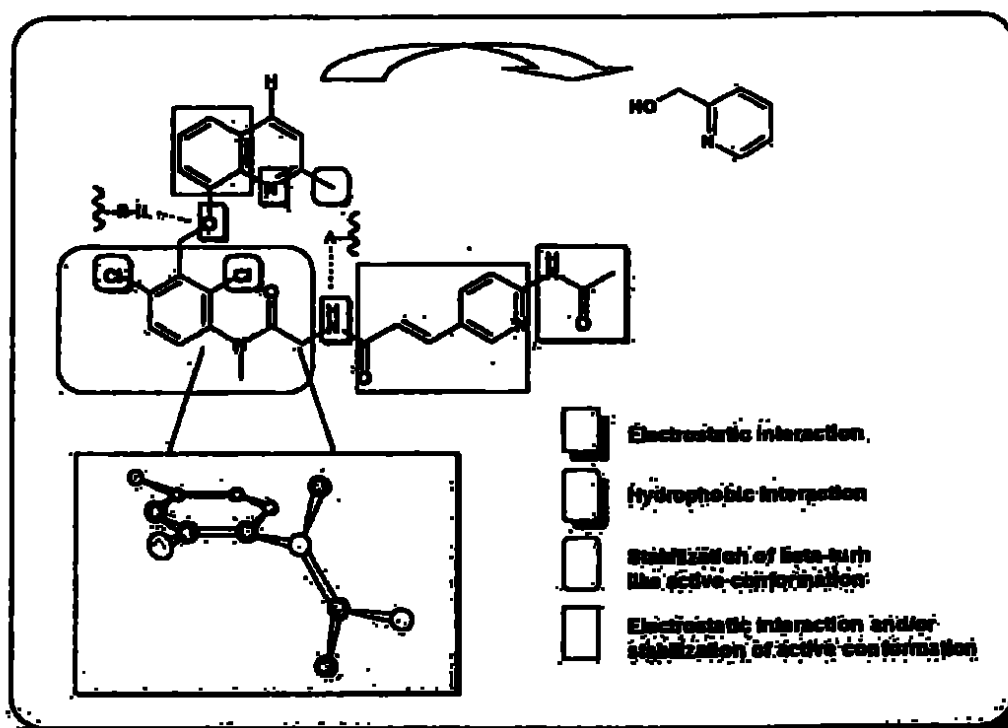


Fig. (3). Pharmacophore model from Fujisawa with putative interactions between FR-173657 and human BK B₂ receptor.

more promising candidate for development due to its higher selectivity towards other receptors in comparison to LF-16.0335, which possesses some weak activity for the human muscarinic M₁ and M₂ receptors [84,85].

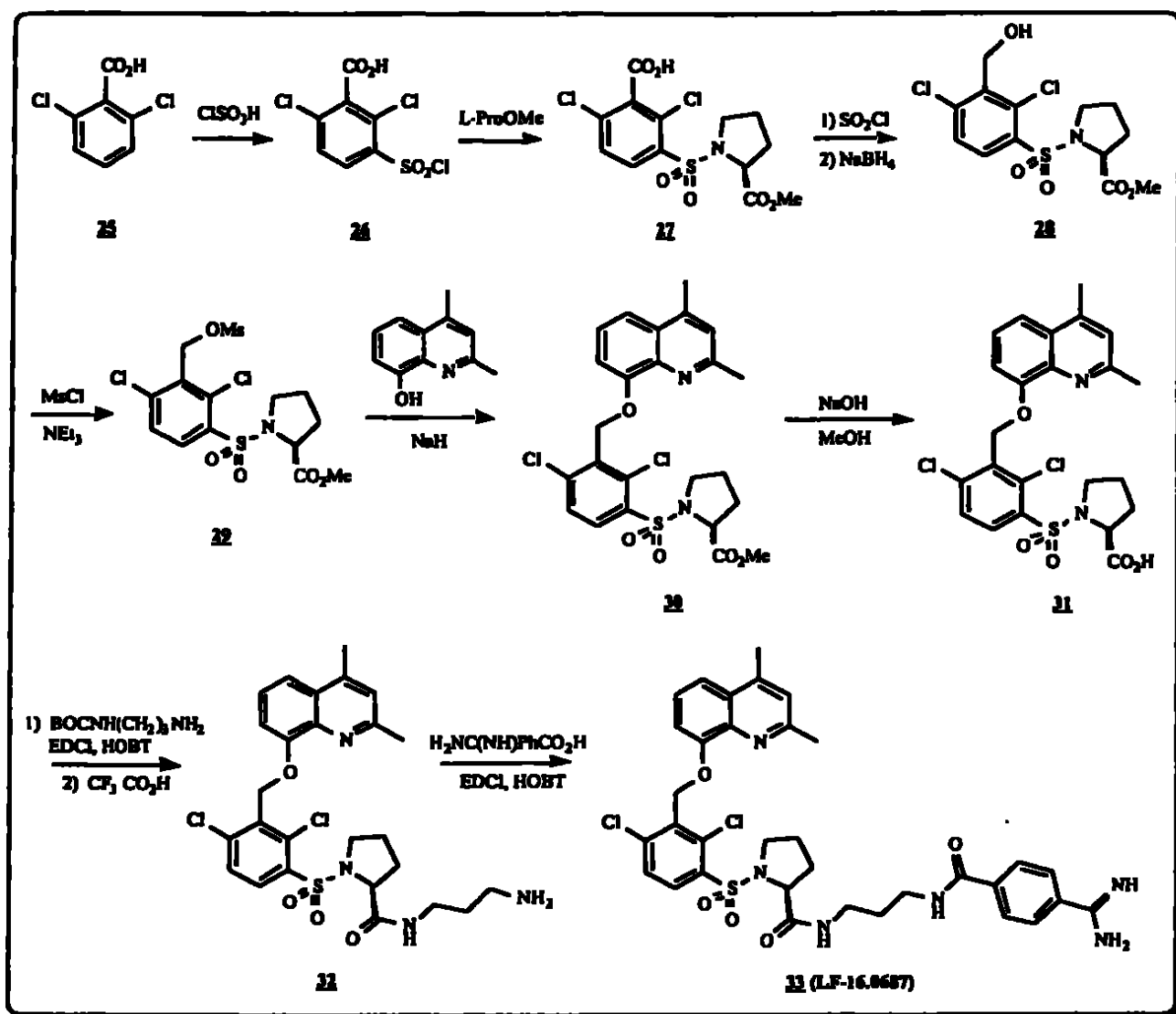
One synthetic path to LF-16.0687 (33) is given in Scheme 4. The linear 10-step synthesis of this antagonist started from 2,6-dichlorobenzoic acid 25, which was converted into the 3-sulfochloride derivative 26 by the treatment with chlorosulfonic acid. Coupling of 26 with L-proline methylester afforded the pyrrolidine sulfonamide 27. Treatment of 27 with SO₂Cl and subsequent reduction with sodium borohydride yielded the benzylic alcohol 28, which was then coupled to 2,4-dimethyl-8-hydroxyquinoline via its mesylate 29. Hydrolysis of the ester group at the pyrrolidine moiety in the resulting quinoline derivative 30 followed by coupling of the resulting carboxylate 31 with mono-*N*-BOC-protected propanediamine and cleavage of the BOC group yielded the amine derivative 32, which finally was acylated with 4-amidino benzoic acid to provide LF-16.0687 (33) [80-83].

Both compounds proved to be very potent, competitive and selective antagonists of human BK B₂ receptors [84-86]. LF-16.0335 displaced [³H]-BK binding in membrane preparations from CHO cells expressing the cloned human BK B₂ receptor and human umbilical vein with K_i values of 0.84 nM and 2.34 nM, respectively. The antagonistic efficacy at BK B₂ receptors was also confirmed by showing that LF-16.0335 blocked BK-stimulated IP production in INT 407 cells and inhibited the BK-induced contraction of

the human umbilical vein [84]. In competition binding studies using [³H]-BK, LF-16.0687 bound to the human, rat and guinea-pig recombinant BK B₂ receptors expressed in CHO cells giving K_i values of 0.67 nM, 1.74 nM and 1.37 nM, respectively. It also bound to the native BK B₂ receptor from human umbilical vein, rat uterus and GPI yielding K_i values of 0.89 nM, 0.28 nM and 0.98 nM, respectively. LF-16.0687 inhibited BK-induced IP₃ formation in INT 407 cells with a pK_B value of 8.7. In isolated organs experiments, LF-16.0687 behaved as a competitive antagonist of BK-mediated contractions giving a pA₂ value of 9.1 in GPI. Binding and functional studies performed on more than 40 different receptors revealed that it was selective for the BK B₂ receptor. A continuous intravenous infusion of LF-16.0687 antagonized in a dose-dependent manner and with a rapid onset of action a BK-induced hypotensive response in rats. Subcutaneous administration of the antagonist at 1.1 μmol/kg to rats also markedly reduced BK-induced edema of the stomach, duodenum and pancreas [85]. In addition, in a rat model of closed head trauma, LF-16.0687 significantly reduced cerebral brain edema of the injured left hemisphere upon continuous infusion of 100 μg/kg/min. over 23 h [86].

Bradyzide

A structurally distinct class of non-peptide BK B₂ receptor antagonists based on a 1-(2-nitrophenyl)-4-benzyl thiosemicarbazide core developed from a high-throughput screening lead was discovered by researchers at Novartis. The



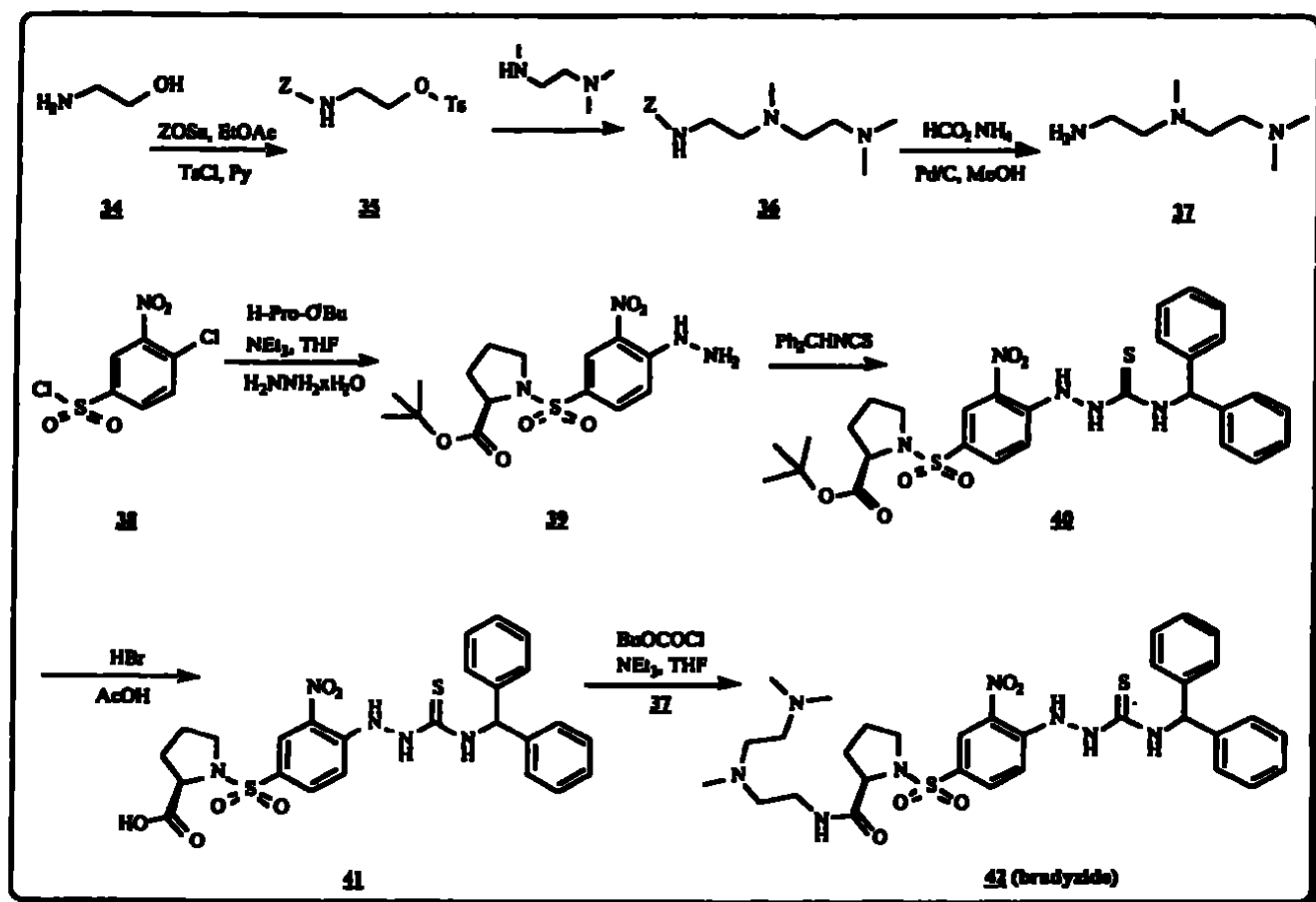
Scheme 4. Synthesis of the sulfonylpyrrolidine BK B₂ receptor antagonist LF-16.0687 (33) from Fournier.

key feature of these antagonists is their high selectivity for the rodent over the human BK B₂ receptors [87,88].

The best characterized BK B₂ antagonist from this series is bradyzide (42), whose synthesis is outlined in Scheme 5 and is illustrative of the approach adopted for the whole class of these type of antagonists. The synthesis of bradyzide 42 started with the preparation of the *N,N,N'*-trimethylethylenediamine spacer 37, which derived from 2-aminoethanol 34 following Z-protection of the amino group and conversion into the tosylate 35, subsequent treatment of 35 with *N,N,N'*-trimethylethylenediamine and deprotection of the resulting intermediate 36. The spacer 37 is then coupled in last step of the synthesis of bradyzide to the carboxyl group of the proline moiety of the nitrophenylthiosemicarbazide 41, which was obtained from 4-chloro-3-nitro-phenylsulfochloride 38 by a 3-step procedure consisting of coupling with L-proline *tert*-butylester and treatment with hydrazine monohydrate to

produce the hydrazide intermediate 39, reaction with diphenylmethylisothiocyanate and hydrolysis of the *tert*-butylester group of the thiosemicarbazide intermediate 40 to yield 41 [87].

Unlike WIN-64338, which is charged at both its terminals and FR-173657, which is largely hydrophobic in nature, bradyzide is amphiphilic, with a diamine terminal and a hydrophobic diphenyl methyl moiety at the opposite terminal. *In vitro*, bradyzide exhibited all the characteristics of a competitive BK B₂ receptor antagonist. It displaced [³H]-BK binding in NG108-15 cell membranes expressing the rat BK B₂ receptor with a K_i value of 0.5 nM. However, when the binding activity of bradyzide was evaluated against the human BK B₂ receptor expressed in COS-7 cells, a significant lower K_i value of only 722 nM was obtained, demonstrating the strong species selectivity of this antagonist being 800 times more potent at the rat than at the human BK B₂ receptor. At concentrations up to 10 μM,



Scheme 5. Synthesis of the thiosemicarbazide BK B₂ receptor antagonist bradyzide (42) from Novartis.

bradyzide does not significantly interact with a wide variety of other related receptors. Bradyzide also inhibited the increase in ⁴⁵Ca²⁺ efflux from NG108-15 cells caused by activation of the BK B₂ receptor with a pA₂ of 8.0 and inhibited BK B₂ receptor-mediated contraction of rat uterus smooth muscle with a pA₂ value of 8.6 in a competitive fashion. *In vivo*, bradyzide has been shown to inhibit BK-induced hypotension and plasma extravasation in rats upon intravenous infusion. Bradyzide also exhibited a long-lasting oral activity in rodent models of inflammatory hyperalgesia by reversing Freud's complete adjuvant-induced mechanical hyperalgesia in the rat knee joint. In this model, it was equipotent with morphine and diclofenac, and 1000 times more potent than paracetamol [88]. However, preliminary pharmacokinetic studies after oral administration revealed that bradyzide achieved only very low plasma levels suggesting a rapid blood clearance. The metabolic fate of this compound *in vivo* remains to be ascertained in further experiments.

BK B₂ RECEPTOR AGONISTS

Investigation of the physiological actions of kinins has been greatly hampered due to their rapid proteolytic degradation. Mimicking the kinin-mediated beneficial effects mentioned above without an accompanying rapid reversal

associated with the breakdown of BK by chronic stimulation of BK B₂ receptors with non-peptide agonists may therefore be a promising approach for the prevention and treatment of cardiovascular diseases and diabetic disorders. However, the tolerable extent of such a stimulation has to be explored.

The first potent, selective non-peptide BK B₂ receptor agonists were discovered in 1997, again by researchers at Fujisawa [89-94]. In Fig. 4, FR-190997 and FR-191413 as representative examples of the identified 4-(2-pyridylmethoxy)-quinoline and 3-(2-pyridylmethyl) benzimidazole series are shown.

Interestingly, the structures of both of these BK B₂ receptor agonists is closely related to those of the BK B₂ receptor antagonists like FR-167344 and FR-173657, a phenomenon which is also known for ANG II subtype AT₁ receptor agonists and for cholecystokinin subtype CCK₁ receptor agonists, which emerged from corresponding closely related antagonists by small structural modifications [95]. The key differentiating features between BK B₂ receptor antagonism and agonism in this series of antagonist/agonist pairs is the substitution of the quinoline moiety in position 4 with an additional 2-pyridylmethoxy group in the case of FR-190997 and the substitution of the benzimidazole moiety in position 3 with an additional 2-pyridylmethyl group in the case of FR-191413. It is assumed that the

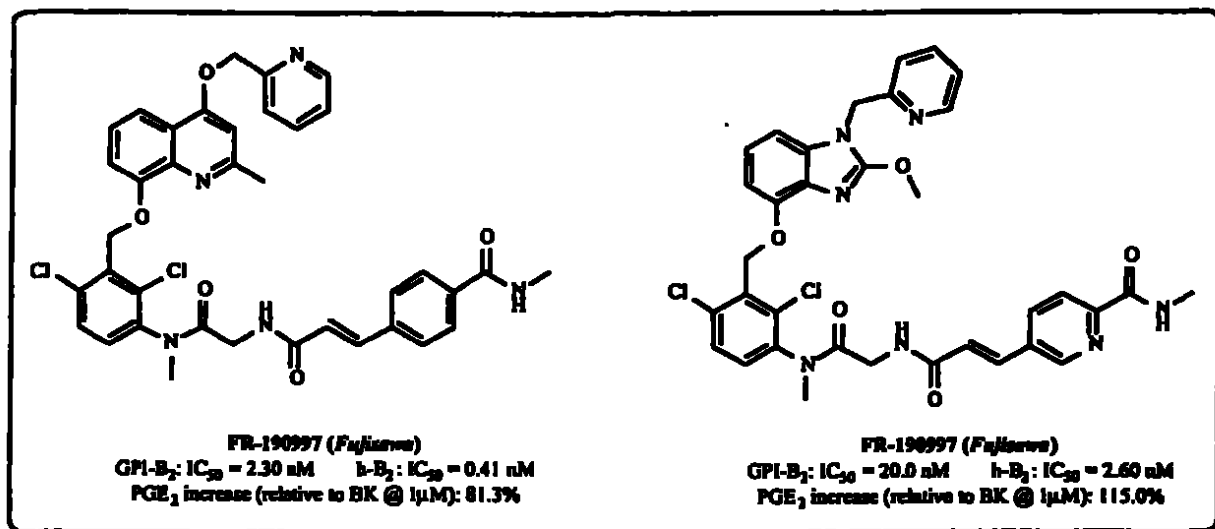


Fig. (4). Non-peptide agonists of the BK B₂ receptor from Fujisawa.

interaction of these residues with the BK B₂ receptor, probably via formation of an additional hydrogen bond between the pyridyl nitrogen atom of the agonist as H-acceptor and a H-donor group in the receptor, might be responsible for stimulating the conversion of the receptor to an active conformation, which results in productive receptor G-protein coupling.

Based on the difference in binding behavior of BK and FR-190997 against peptide and non-peptide antagonists and in their pharmacological profile in guinea-pig ileum preparations it was suggested recently that the native ligand and the non-peptide agonists interact differently at the BK B₂ receptor probably by stabilizing active receptor conformations which are different [96].

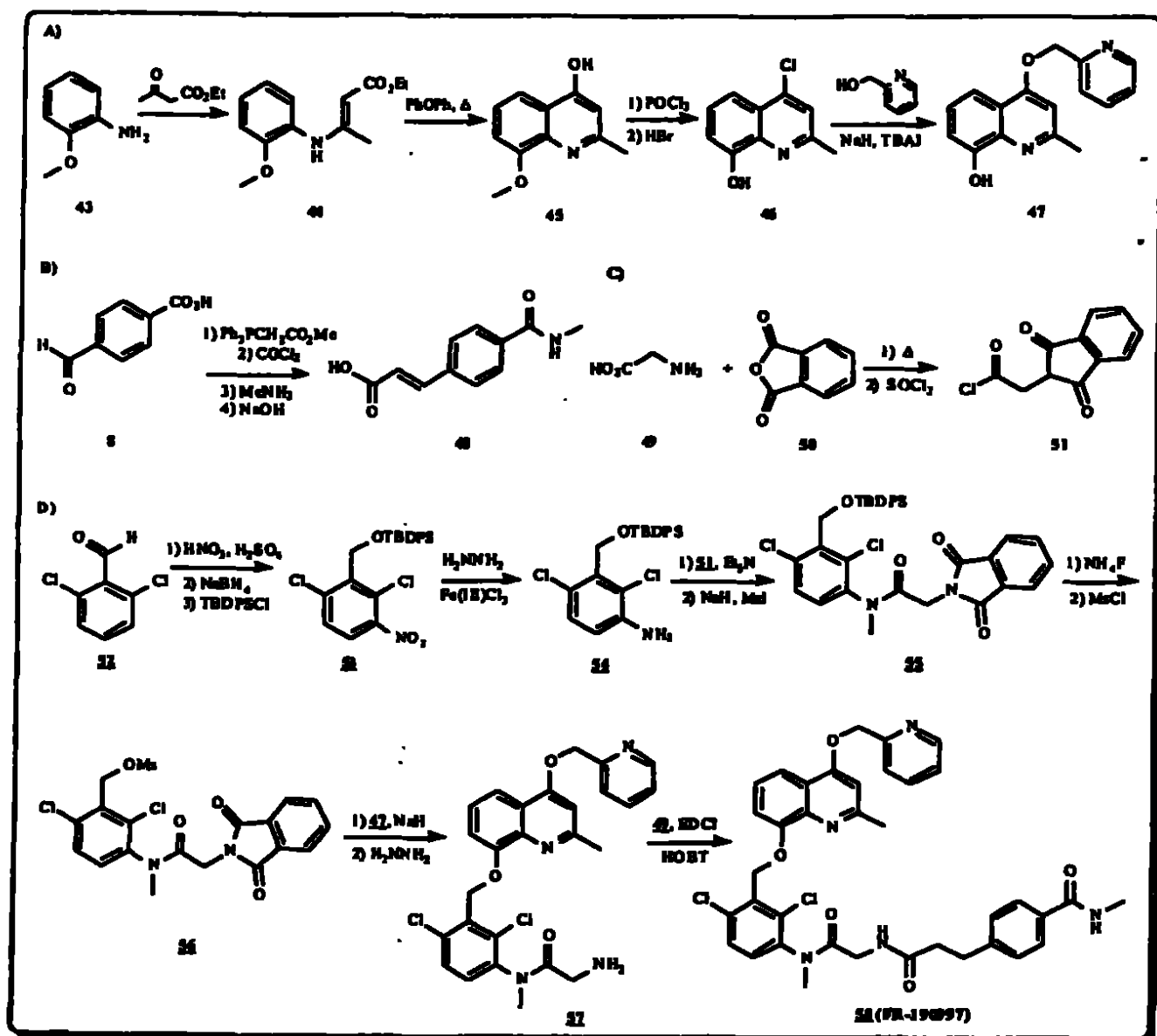
FR-190997

The 4-(2-pyridylmethoxy)-quinoline FR-190997 is the best characterized member of this class of non-peptide BK B₂ receptor agonists [90-94]. The synthesis of FR-190997 following a convergent 14-steps procedure is depicted in Scheme 6.

The synthetic path towards FR-190997 (58) started with the preparation of the 4-(2-pyridylmethoxy)-quinoline moiety 47 in 5-step synthetic procedure (A). Condensation of o-anisidine 43 with ethyl acetoacetate gave the enamine 44, which was converted into the 4-hydroxy quinoline 45 by refluxing in diphenylether. Treatment of 45 with POCl₃ followed by ether cleavage of the methoxy group in concentrated HBr afforded the 4-chloroquinolinol 46. Subsequent addition of 46 to a solution of 2-hydroxymethyl pyridine, NaH and tetrabutylammonium iodide (TBAI) in dimethylimidazolidinone yielded the desired building block 47. The *trans*-4-(methylcarbamoyl)cinnamic acid 49 as terminal building block introduced in the last step of the synthesis of FR-190997 was synthesized in 4 steps (B) from 4-formylbenzoic acid 8 by Horner-Emmons-type Wittig reaction with methyl(triphenyl-phosphoranyl)acetate,

conversion into the intermediate acid chloride using oxalyl chloride, reaction with methylamine, and hydrolysis of the obtained methyl ester with NaOH. The acid chloride of *N*-phthalylglycine 51 needed for the introduction of the central glycine moiety of FR-190997 was prepared by heating a mixture of glycine 49 and phthalic anhydride 50 followed by treatment with thionyl chloride (C). The final reaction sequences towards FR-190997 (D) began with commercially available 2,5-dichlorobenzaldehyde 52, which was converted to the *O*-protected 3-nitrobenzyl alcohol 53 by nitration, reduction of the aldehyde group and subsequent protection of the benzylalcohol intermediate with *tert*-butyldiphenylchlorosilane (TBDPSCI). Reduction of the nitro group of 53 with hydrazine hydrate gave the corresponding amine 54. This amine was then acylated with 51 followed by *N*-methylation of the resulting amide nitrogen after its deprotonation with NaH with methyl iodide to give compound 55. Deprotection of alcohol group of 55 with NH₄F, its conversion into the mesylate 56, coupling of 56 with the quinoline moiety 47 followed by cleavage of the phthalimide group yielded the amine 57, which finally afforded FR-190997 (58) after condensation with the cinnamic acid derivative 49 using 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDCI) and HOBT as coupling agents [89].

FR-190997 is a potent mimetic of the biological actions of BK. FR-190997 was reported to stimulate IP hydrolysis in CHO cells transfected with the human BK B₂ receptor and to increase prostaglandin E₂ production in human fibroblasts. Moreover, FR-190997 induced a concentration-dependent contraction of the isolated GPI. However, detailed *in vitro* evaluations on native human, rabbit and pig vascular BK B₂ receptors revealed that this agonist shows different intrinsic activity depending on the tissue preparations, acting as a partial agonist in the human umbilical vein and especially in the rabbit jugular vein, but as a pure antagonist in the pig coronary artery [92]. From this study it was suggested that the addition of a 2-pyridylmethoxy group to the basic structure of the antagonist FR173657 might not be fully sufficient to change the pharmacological spectrum of a



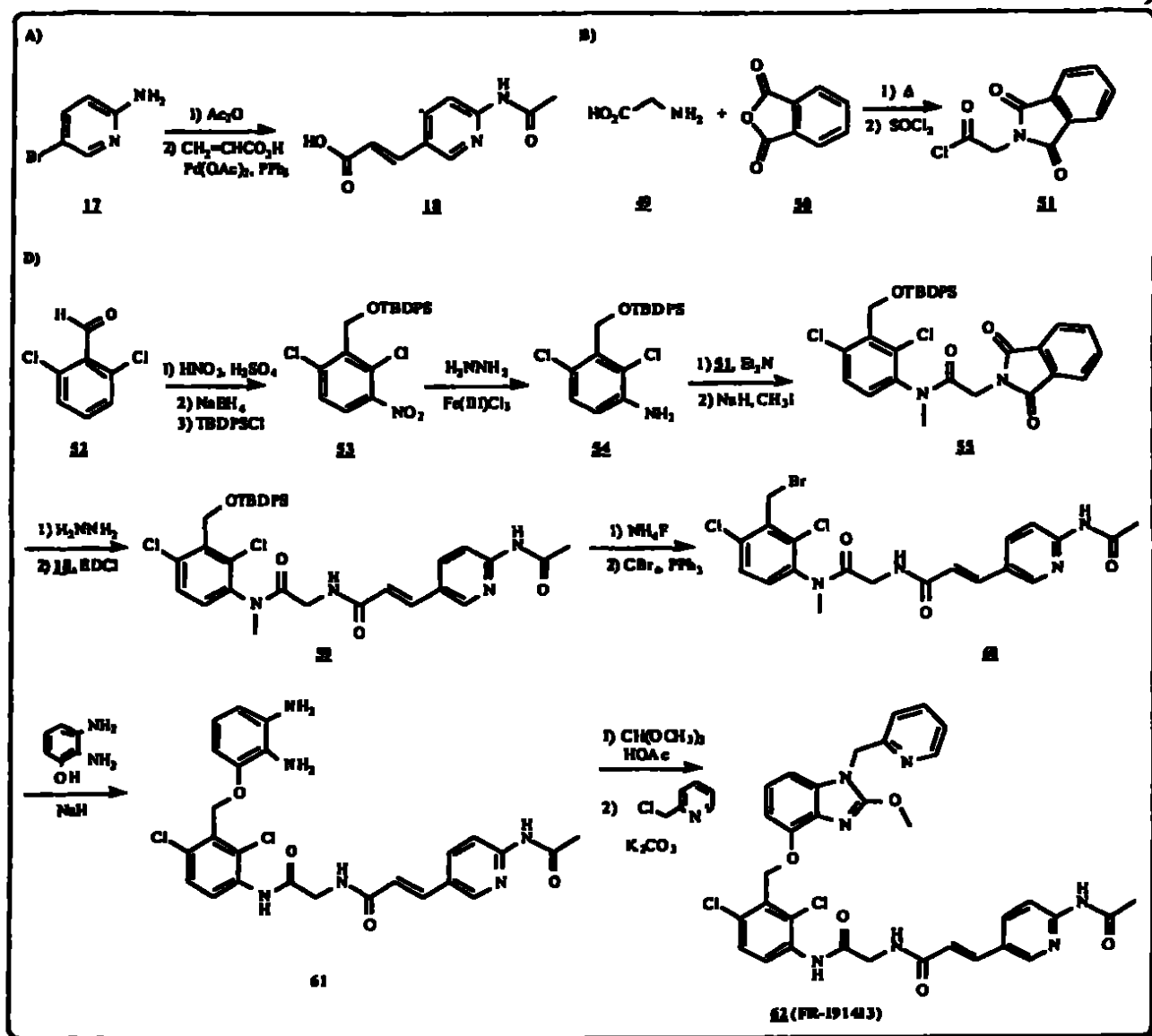
Scheme 6. Synthesis of the quinoline BK B₂ receptor agonist FR-190997 (58) from Fujisawa.

pure antagonist to that of a full agonist. It is worth noting that both the onset and offset rates of action of FR-190997 are markedly slower than those of kinins, indicating a long-lasting BK B₂ receptor desensitization in preparations exposed to FR-190997. *In vivo* the agonist action of FR-190997 has been demonstrated by its ability to induce a hypotensive response in anesthetized SHR after continuous infusion into the abdominal aorta. The duration of the response was prolonged, presumably as a consequence of the compound's resistance to proteolytic degradation. It was also shown, that FR-190997 upon selective infusion into the renal artery effectively, and to a greater extent than BK infused at the same rate, induced natriuresis and diuresis without any influence on urinary potassium excretion in anesthetized rabbits [93]. Similar results were obtained with regard to the induction of edema in the rat paw [94].

FR-191413

Besides the quinoline derivative FR-190997 described above a second promising series of non-peptide BK B₂ receptor agonist with close structural similarity to non-peptide BK B₂ receptor antagonists discovered by researchers at Fujisawa are the 3-(2-pyridylmethyl)-substituted benzimidazoles represented by FR-191413 [89]. One synthetic route to FR-191413 is shown in Scheme 7.

Analogously to the synthesis of FR-190997 the preparation of FR-191413 (62) started from 2,5-dichlorobenzaldehyde, which was converted into the TBDPS-protected benzylic alcohol 55 as common building block in both agonists as already described above (C). Subsequently, compound 55 was acylated with *trans*-3-[6-(acetamido)-

Scheme 7. Synthetic path towards the benzimidazole BK B₂ receptor agonist FR-191413 (62) from Fujisawa.

pyridin-3-yl]acrylic acid 18 (A) after cleavage of its terminal phthaloyl group by treatment with hydrazine monohydrate to afford compound 59. In the subsequent steps 59 was converted into the benzylic bromide 60 by treatment with NH₄F followed by reaction with CBr₄ in the presence of PPh₃, which was then coupled with 2-hydroxy-5-amino-aniline to yield the O-alkylated phenyl diamine derivative 61. Condensation of 61 with tetramethyl orthocarbonate and 3*N*-alkylation of the obtained benzimidazole intermediate finally provided FR-191413 (62) [89].

The pharmacological properties of this BK B₂ receptor agonist have been less intensively evaluated than those of FR-190990. For this compound it has only been reported that it displaced [³H]-BK binding in competition experiments on membranes from GPI and CHO cells transfected with the human BK B₂ receptor with IC₅₀ values of 20.0 nM and 2.60 nM, respectively, and stimulated

prostaglandin E₂ production in WI-38 cells [89]. These data are comparable to those obtained for FR-190997, indicating that FR-191413 is *in vitro* almost equipotent to FR-190997.

CONCLUSION AND PERSPECTIVES

In the last five years substantial progress in the search for non-peptide BK B₂ receptor antagonists has been made by the efforts of several research groups. Starting with the discovery of the unique phosphonium salt WIN-64338 as rather unspecific non-peptide BK B₂ receptor antagonist, other different and more promising series of this novel class of compounds have been identified. The major breakthrough in the search for the long-sought 'third generation' of BK B₂ receptor antagonists, which are active even upon oral administration, was based on the pioneering work of researchers from Fujisawa. Representative members of these

potent antagonists of the human BK B₂ receptor are the imidazo[1,2-*a*]pyridine FR-167344 and the quinoline FR-173657. In depth pharmacological evaluation of these compounds revealed pronounced beneficial efficacy in various animal models of inflammatory diseases upon oral administration. With LF-16.0687 from Fournier and the thiosemicarbazide bradyzide from Novartis further potent non-peptide BK B₂ receptor antagonists with proven *in vivo* efficacy have also been discovered.

From these series drug candidates can be expected in the near future which will have the pharmacokinetic properties required for optimal clinical application in humans to assess the therapeutic potential of this novel class of compounds. Target indications for BK B₂ receptor antagonists could be all those which are caused by excessively increased local kinin concentrations, such as inflammatory diseases and pain. However, any novel development candidates may have to contend with the less convincing results of the phase II clinical trials performed with the 'second generation' of peptide BK B₂ receptor antagonists icatibant and bradycor on the one hand, and perhaps also against a possible interference with the reported beneficial effects of BK on the other hand.

Potent non-peptide BK B₂ receptor agonist have also been discovered recently, again by researchers from Fujisawa. Representative members of the series with close structural similarity to Fujisawa's BK B₂ receptor antagonists are the 4-(2-pyridylmethoxy)-quinoline FR-190997 and 3-(2-pyridylmethyl)-benzimidazole FR-191413. For FR-190997 cardio-vascular and renal efficacy has already been demonstrated *in vivo*.

By mimicking the reported organ- and cardioprotective properties of BK, non-peptide BK B₂ receptor agonist may become valuable drugs for the treatment or even prevention of diseases such as hypertension, myocardial hypertrophy, myocardial infarction, arrhythmias and diabetic nephropathy. However, BK B₂ receptor agonists have to demonstrate efficacy in these diseases without potential concomitant proinflammatory side effects, especially upon chronic administration.

ABBREVIATIONS

ANGII	= Angiotensin II
ACE	= Angiotensin-converting enzyme
BK	= Bradykinin
BSH	= Bisuccinimidobexane
CHO	= Chinese hamster ovary
GPI	= Guinea-pig ileum
PI	= Phosphoinositide
Oic	= L-(3aS7aS)-octahydroindol-2-carboxylic acid

SHR = Spontaneous hypertensive rats

Tic = 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid

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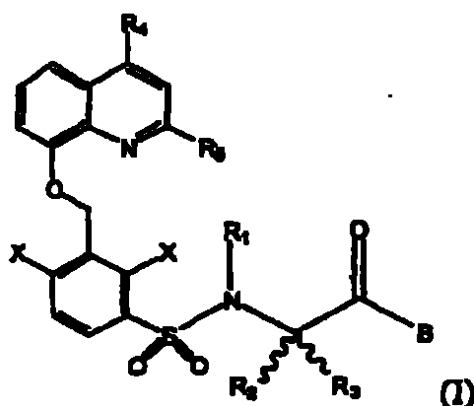
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as specific antagonists of bradykinin (BK) B2 receptor. The compounds
are chemically characterized by the presence of an alpha, alpha-disub-
stituted amino acid at least one amino group, free or salified, or the cor-
responding ammonium quaternary salt. These BK receptor antagonists
are a novel class of medicaments which can be used in all the disorders
in which said receptors are involved.

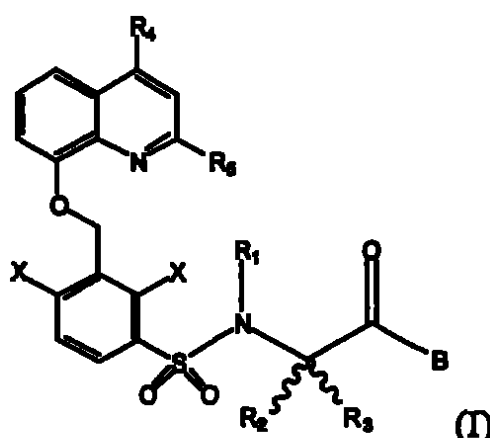
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BASIC NON-PEPTIDE BRADYKININ ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREFROM

FIELD OF THE INVENTION

The present invention relates to non-peptide, basic compounds and the derivatives thereof, having activity as specific antagonists of bradykinin (BK) B2 receptor. The BK receptors antagonists are a novel class of medicaments
5 which can be used in all the conditions in which said receptors are involved.

More particularly, the present invention relates to non-peptide compounds which show high affinity and antagonistic activity towards B2 receptor, having general formula (I):



10

in which

- R_1 is a hydrogen atom or a C_1 - C_4 alkyl group;
- R_2 and R_3 , which can be the same or different, are a C_1 - C_4 alkyl group, or R_2 and R_3 , together with the carbon atom which they are linked to, form a
15 cyclic aliphatic group having 3 to 7 carbon atoms or a heterocyclic aliphatic group having 3 to 7 atoms, one or two of which are selected from the group N, O, S and the others being C atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen atom or a C_1 - C_4 alkyl group;
- 20 - X is selected from the group consisting of halogen, OR_1 , SR_1 , CN,

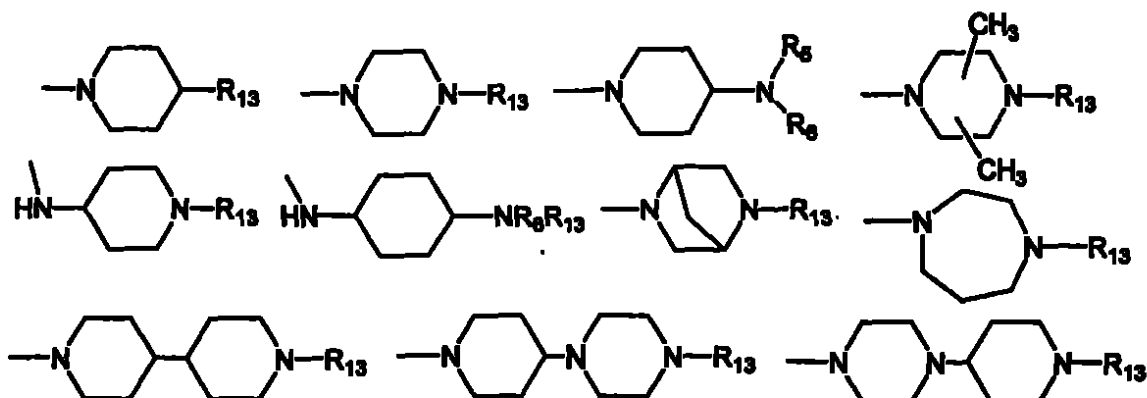
CONFIRMATION COPY

C_1 - C_4 alkyl;

- B has at least one amino group with basic characteristics or a tetraalkylammonium group and can be selected from the group consisting of:

- $NR_6(CH_2)_nNHCOY$, $NR_6(CH_2)_nN(R_6)-Y$, $NR_6(CH_2)_nN(Y)_2$, NR_6Y , $N(Y)_2$,

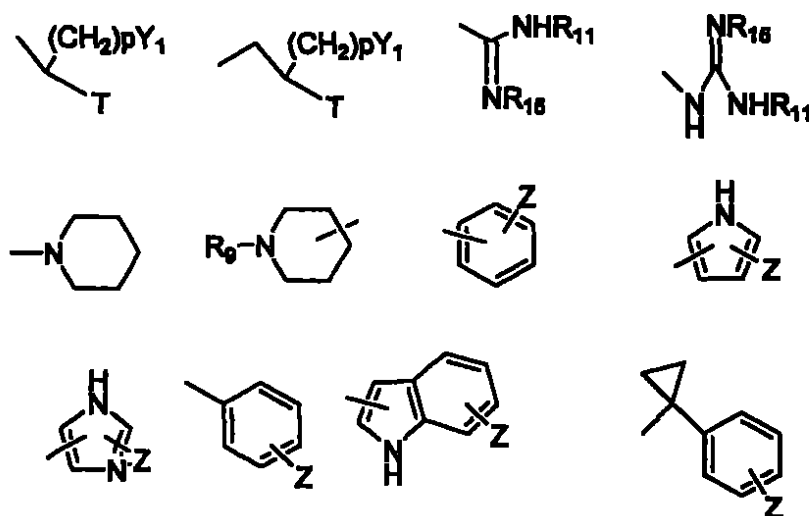
5 $N(Y)(CH_2)_pY_1$ and from the residues:



- R_6 is a hydrogen atom, C_1 - C_6 alkyl;

- $n = 1-12$;

10 - Y is selected from: hydrogen, $(CH_2)_pY_1$, $(CH_2)_pNR_6Y_1$, $(CH_2)_pN(Y_1)_2$, NR_6R_6 , $-NR_6(CH_2)_qY_1$ or from the following residues:



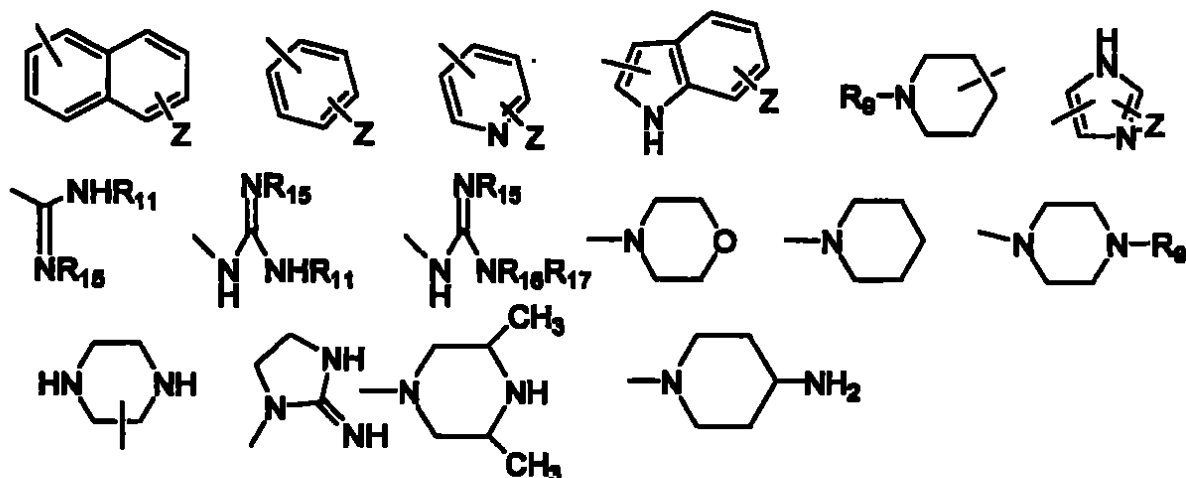
- T is selected from the group of $-NR_7R_8$, $-NR_{14}R_{18}R_{19}$, $-OR_6$;

15 - R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C_1 - C_4 alkyl group, a cyclohexyl group, or NR_7R_8 together are a group selected from :i) guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl or cyclohexyl

groups, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;

- Y_1 is selected from the group consisting of NR_7R_8 , $NR_{14}R_{18}R_{19}$ or from the following residues:

5



- Z is selected from the group consisting of H, C_1 - C_6 alkyl, OR_6 , SR_6 , CF_3 , $OCOR_6$, COR_{10} , $NHCOR_6$, SO_2R_6 , SOR_6 , CO_2R_6 , $N(R_6)_2$, Cl, Br, NO_2 , NH_2 , CN, F, imidazole, phenyl, amidine, guanidine, guanidyl-methyl;

10 - R_9 is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, wherein L is selected from the group of $-OH$, $-NR_5R_6$, $-NR_{14}R_{18}R_{19}$, amidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups;

- R_{10} is selected from the group consisting of OR_6 , NR_6R_{12} ;

15 - R_{11} is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, $-(CH_2)_p-NR_4-(CH_2)_q-L$;

- R_{12} is a hydrogen atom, C_1 - C_6 alkyl, COR_6 ,

- R_{13} is selected from the group consisting of H, C_1 - C_6 alkyl, $-(CH_2)_pW(CH_2)_qY_1$, Y, $-COY$, $-CH_2-Y$;

20 - R_{15} is selected from the group consisting of hydrogen or straight or branched C_1 - C_4 alkyl groups;

- the $-NR_{16}R_{17}$ group is a 5-7 membered nitrogen aliphatic heterocycle

optionally containing another heteroatom selected from O, S, N;

- the $-NR_{14}R_{18}R_{19}$ group is a quaternary ammonium group in which: R_{14} is selected from the group consisting of straight or branched C_1 - C_4 alkyl groups, R_{18} and R_{19} , which can be the same or different, are a straight or branched C_1 - C_4 alkyl group, or $-NR_{18}R_{19}$ is a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- $W = CH_2, O, S, NR_4, N(R_4)_2$;
- $p = 1-6, q = 1-6$.

The present invention also embraces the corresponding pharmacologically acceptable salts with inorganic or organic acids selected from the group of: hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, acetic, trifluoroacetic, propionic, oxalic, malic, maleic, succinic, malonic, aspartic, glutamic acids and possible geometrical isomers, optical isomers, due to the presence of chiral centers, or mixtures thereof, including the racemates. The symbol  means that the configuration of the asymmetric carbon atoms can be either S or R. Amines are known to be mainly in the protonated form at the physiological pHs, i.e. they are in the form of quaternary ammonium, therefore this invention also comprises the analogues in which the amino nitrogen is in the form of tetraalkyl ammonium salt, i.e. the analogues in which a quaternary nitrogen independent on pH is permanently present.

PRIOR ART

Bradykinin (BK) belongs to Kinins and forms, together with Kallidin and T-Kinin, the sub-group of Kinins present in mammals. Kinins play an important role as mediators of pain and inflammation, both in the central and peripheral nervous system. They have peptide nature and bradykinin is, in particular, a nonapeptide ($H-Arg^1-Pro^2-Pro^3-Gly^4-Phe^5-Ser^6-Pro^7-Phe^8-Arg^9-OH$) produced by the body in physiopathological conditions.

Two types of Kinins receptors exist, B1 and B2. The main characteristic of the B1 receptor is that it is more inducible than constitutive. It is expressed in tissues in inflammation or stress conditions. On the other hand, B2 is a constitutive receptor normally present in all tissues and ready to detect the action of the mediator during the inflammatory processes. The cascade of the enzymatic processes which induces Kinins formation and degradation was described in detail in the review by Bhoola et al. (Bhoola H.D., Figueroa C.D., Worthy K., Bioregulation of Kinins: Kallikreins, Kininogens and Kininases, Pharmacological Rev. 1992; 44:4-80). Bradykinin and Kallidin are released from their protein precursors (known as kininogens), by proteolytic enzymes named kininogenases. Among these, the main role is played by Kallikreins which however, once released by the precursor, can exert their action only for a short time as they are quickly destroyed by a series of circulating enzymes and membranes generically defined as Kininases. One of these Kininases cleaves bradykinin at the C-terminal arginine thus forming a des-Arg-BK which acts as B1 receptor agonist.

The activation of bradykinin B1 and B2 receptors induces relaxation of vasal muscles with consequent hypotension, increase in vascular permeability, contraction of smooth muscles of intestine and respiratory tract, stimulation of nociceptive neurons, alteration of ionic epithelial secretion, production of nitroxide and release of cytokines by leukocytes and eicosanoids from different cell types. As a consequence, antagonistic compounds of BK receptors can be considered a novel class of medicaments supposedly active in various disorders. Possible therapeutical applications for said antagonists are inflammatory, allergic and autoimmune disorders, such as asthma and chronic bronchitis (also induced by irritants), allergic, vasomotor and viral rhinitis, obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis),

glomerulonephritis, psoriasis, rash, acute and chronic cystitis; degenerative disorders characterized by fibrosis, such as hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis; thanks to their analgesic activity, in the treatment of both acute and chronic pain, for example in burns, cephalaea, insects bites, chronic pain in cancer patients; in disorders of the cardiovascular apparatus such as septic, allergic and post-traumatic shocks, and hepatic cirrhosis by hepatorenal syndrome; as anticancer and antiangiogenetics; in the treatment of hypotension and of alopecia.

10 Different peptide and non-peptide antagonists of bradykinin B2 receptor are known in literature.

After the discovery of the first bradykinin B2 receptor antagonist, NPC-567, in 1985, a number of peptide antagonists have been synthesized, many of them, such as Icatibant (HOE-140) and Bradycor (Deltibant, CP-0127), being already in clinical phase.

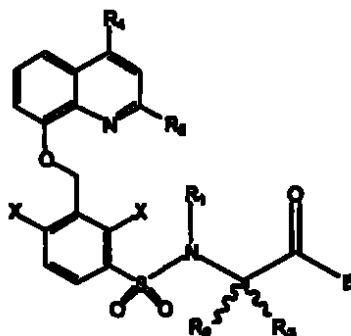
15 The first non-peptide B2 antagonist of bradykinin was synthesized by Sterling Winthrop in 1993, WIN 64338. Said compound, however, showed low binding activity to the human B2 receptor. Very interesting activity has been showed by quinoline and imidazopyridine derivatives claimed by Fujisawa, which starting from 1996, published pharmacological data and
20 studies concerning the novel non-peptide antagonist FR 173657 and the analogues thereof. This compound was of paramount importance in the search for novel non-peptide B2 antagonists due to its selectivity, potency and activity after oral administration. After the publication of Fujisawa patents, similar structures were claimed in patents by Fournier and Hoechst. The
25 compounds by Fournier also have a quinoline linked to dichlorobenzene; a substituted sulfonamide connects this part of the molecule to an aromatic ring (optionally substituted with an amidine) through a basic linker (e.g.: propylenediamine, piperazine). Fournier announced in May 1998 the start of

the clinical phase I for the non-peptide B2 antagonist LF 16.0687 (review: Altamura M. et al., Regulatory Peptides, 1999, 80, 13-26).

In view of the possible advantages of the non-peptide antagonists (enzymatic and metabolic stabilities, high bioavailability) over peptide antagonists, the search for novel non-peptide B2 receptor antagonists is desirable.

DETAILED DISCLOSURE

The present invention aims at providing novel non-peptide antagonists, having a reduced conformational freedom. The present invention discloses novel compounds of non-peptide nature, i.e. straight or cyclic sulfonamido derivatives of α,α -disubstituted amino acids, of general formula (I), wherein R_1 , R_2 , R_3 , R_4 , R_5 , X and B have the meanings defined above.



(I)

The presence of this particular category of amino acids causes limitations in the molecular conformation, thus allowing modulation and optimization of the interaction with the receptor through introduction of suitable pharmacophore groups.

These compounds are characterized both by high affinity and antagonistic activity towards human B2 receptor and remarkable metabolic stability.

The compounds of the present invention are original over the compounds claimed in patent literature (WO 97/24349, WO 98/03503) in the

light of mutagenesis studies, which proved a different interaction with B2 receptor, as well as conformational studies supported by molecular modelling experiments and NMR analysis, which evidenced a defined, different conformation compared with that of analogues non containing α,α -disubstituted amino acids. In particular, a comparative study between the compounds of present invention and the analogues non-containing α,α -disubstituted amino acids, showed that different values of the Φ and Ψ torsion angles are observed already starting from the intermediates.

The present invention also relates to the analogues in which an amine is in the form of a tetraalkyl ammonium compound, which is a similar condition to that of amines at physiological pHs at which their activity is exerted.

In the definitions, C_1 - C_4 alkyl group means a group selected from methyl, ethyl, n-propyl, isopropyl, n-butyl and t-butyl; C_1 - C_6 alkyl group means a group selected from methyl, ethyl, n-propyl, isopropyl, n-butyl, n-pentyl, n-hexyl; cyclic aliphatic group having 3 to 7 carbon atoms means a group selected from cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl; aliphatic heterocyclic group having 3-7 atoms means a group selected from pyrrolidine optionally substituted at the N with a C_1 - C_4 alkyl group, piperidine optionally substituted at the N with a C_1 - C_4 alkyl group, tetrahydrofuran, tetrahydropyran, tetrahydrothiopyran; 5-7 membered aliphatic heterocyclic group means a group selected from pyrrolidine, piperidine, piperazine, morpholine, thiomorpholine, azepine, diazepine, oxazepine.

More particularly, the present invention relates to the compounds of general formula (I) in which:

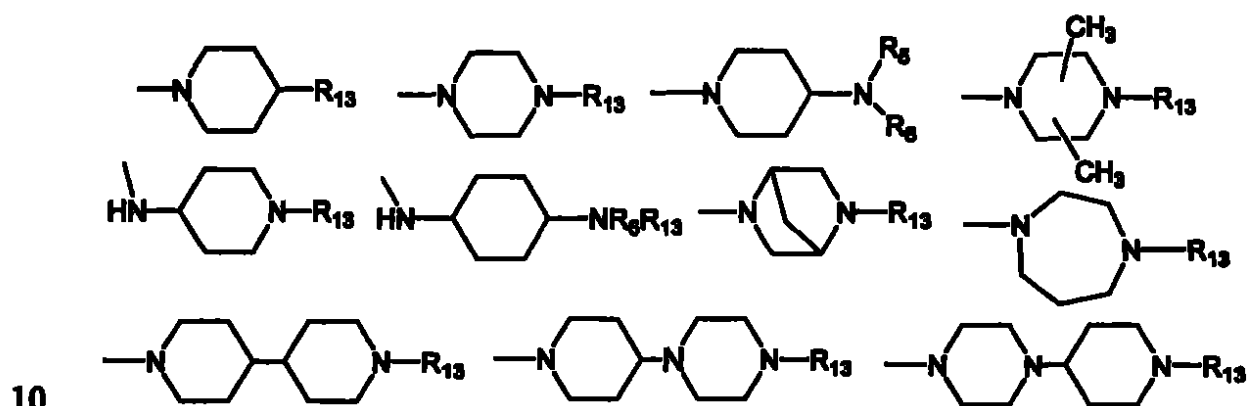
- R_1 is a hydrogen atom or a C_1 - C_4 alkyl group;
- R_2 and R_3 , which can be the same or different, are a C_1 - C_4 alkyl group, or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms or a heterocyclic aliphatic

group having 3 to 7 atoms one or two of which are selected from the group of N, O, S and the other being C atoms;

- R_4 and R_5 , which can be the same or different, are a hydrogen atom or a C_1 - C_4 alkyl group;

5 - X is selected from the group consisting of halogen, OR_1 , SR_1 , CN , C_1 - C_4 alkyl;

- B has at least one amino group with basic characteristics or a tetraalkylammonium and can be selected from the group consisting of:



- R_6 is a hydrogen atom, C_1 - C_6 alkyl;

- Y is selected from: hydrogen, $(CH_2)_p Y_1$, $(CH_2)_p NR_6 Y_1$, $(CH_2)_p N(Y_1)_2$, $NR_5 R_6$, $-NR_6(CH_2)_p Y_1$ or from the following residues:



- T is selected from the group of $-NR_7 R_8$, $-NR_{14} R_{18} R_{19}$, $-OR_6$;

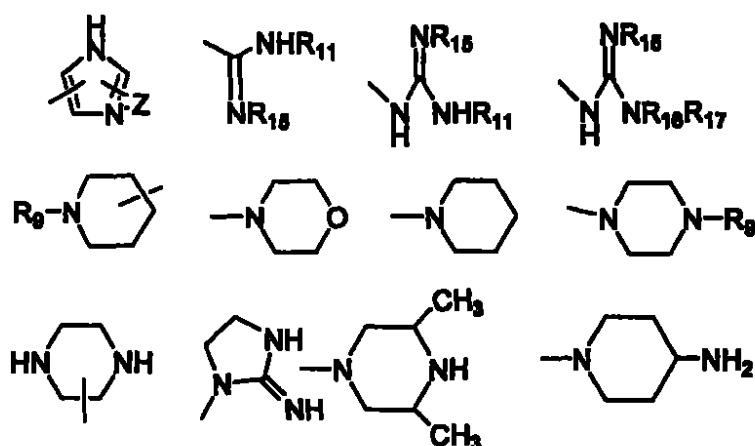
- R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C_1 - C_4 alkyl group, or $NR_7 R_8$ is a group selected from : i) guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, cyclohexyl, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;

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- Y_1 is selected from the group consisting of $NR_7 R_8$, $NR_{14} R_{18} R_{19}$ or from

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the following residues:



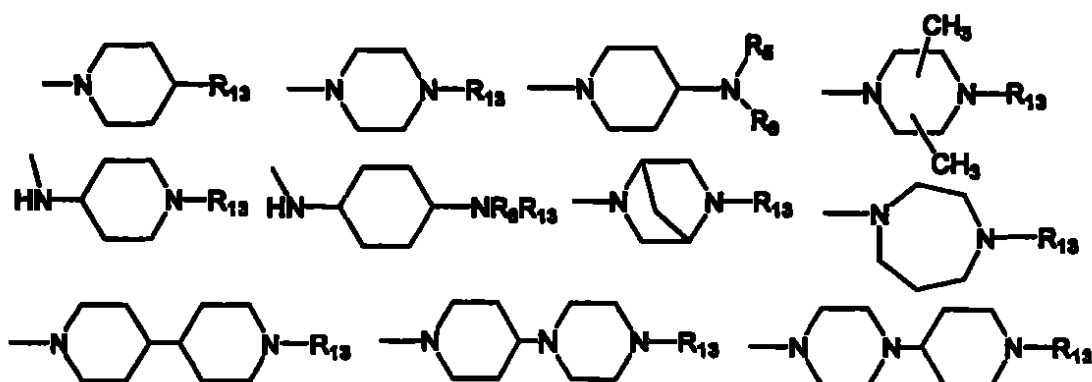
- Z is selected from the group consisting of H, C₁-C₆ alkyl, OR₆, SR₆,
5 CF₃, OCOR₆, COR₁₀, NHCOR₆, SO₂R₆, SOR₆, CO₂R₆, N(R₆)₂, C₁, Br, NO₂,
NH₂, CN, F, imidazole, phenyl, amidine, guanidine, guanidyl-methyl;
- R₉ is selected from the group consisting of hydrogen, -(CH₂)_q-L,
wherein L is selected from the -OH group, -NR₅R₆, -NR₁₄R₁₈R₁₉, amidine
optionally substituted with 1 or 2 C₁-C₄ alkyl groups, guanidine optionally
10 substituted with 1 or 2 C₁-C₄ alkyl groups;
- R₁₀ is selected from the group consisting of OR₆, NR₆R₁₂;
- R₁₁ is selected from the group consisting of hydrogen, -(CH₂)_q-L,
-(CH₂)_p-NR₄-(CH₂)_q-L;
- R₁₂ is a hydrogen atom, C₁-C₆ alkyl, COR₆;
- 15 - R₁₃ is selected from the group consisting of H, C₁-C₆ alkyl,
-(CH₂)_pW(CH₂)_qY₁, Y, -COY, -CH₂-Y;
- R₁₄ is selected from the group consisting of straight or branched C₁-C₄
alkyl groups;
- R₁₅ is selected from the group consisting of hydrogen or straight or
20 branched C₁-C₄ alkyl groups;
- the -NR₁₆R₁₇ group is a 5-7 membered nitrogen aliphatic heterocycle
optionally containing another heteroatom selected from O, S, N;

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- the $-NR_{14}R_{18}R_{19}$ group is a quaternary ammonium group in which: R_{14} is selected from the group consisting of straight or branched C_1 - C_4 alkyl groups, R_{18} and R_{19} , which can be the same or different, are a straight or branched C_1 - C_4 alkyl group, or $-NR_{18}R_{19}$ is a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- $W = CH_2, O, S, NR_4, N(R_4)_2$;
- $p = 1-6, q = 1-6$.

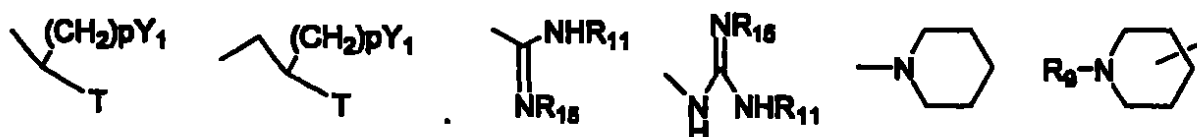
A class of preferred compounds are the compounds of general formula (I), in which:

- 10 - B is selected from the group consisting of the residues:



- Y is selected from: $(CH_2)_pY_1$, $(CH_2)_pNR_5Y_1$, $(CH_2)_pN(Y_1)_2$, NR_5R_6 , or from the following residues:

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in which T is selected from the group of $-NR_7R_8$, $-OR_6$ and the other substituents are as defined above.

- 20 A particularly preferred class of compounds are the compounds in which:

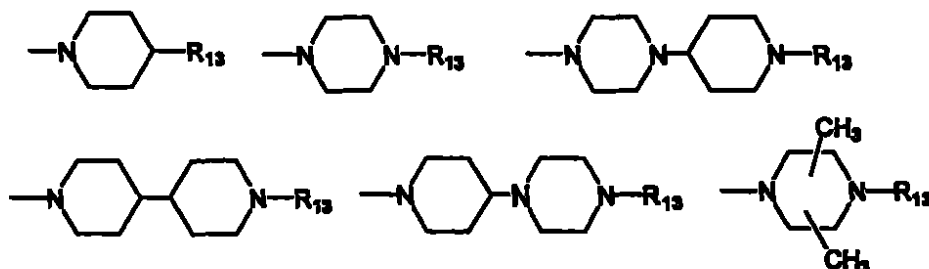
- R_1 is a hydrogen atom or methyl;
- R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to,

form a cyclic aliphatic group having 3 to 7 carbon atoms;

- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl;

- X is a chlorine atom;

5 - B is a group selected from:



in which R_{13} is H, or a $Y = Y_1$ group in which Y_1 is



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- R_{11} is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, $-(CH_2)_p-NR_4-(CH_2)_q-L$ wherein L is selected from $-OH$, $-NR_5R_6$, amidine optionally substituted with 1 or 2 C_1-C_4 alkyl groups, guanidine optionally substituted with 1 or 2 C_1-C_4 alkyl groups;

15 and the other substituents are as defined above.

A further class of particularly preferred compounds of general formula (I) are those in which:

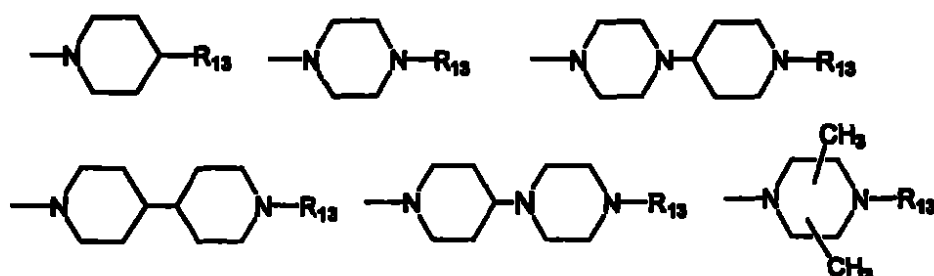
- R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to,

20 form a cyclic aliphatic group having 3 to 7 carbon atoms;

- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl;

- X is a chlorine atom;

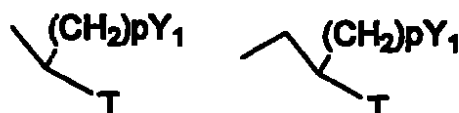
- B contains at least two amino groups with basic characteristics, in the
25 free or salified form, and is selected from the group of:



- in which R_{13} is COY , CH_2Y , $-(\text{CH}_2)_p\text{W}(\text{CH}_2)_q\text{Y}_1$,

- Y is a group $(\text{CH}_2)_p\text{Y}_1$, or is selected from:

5

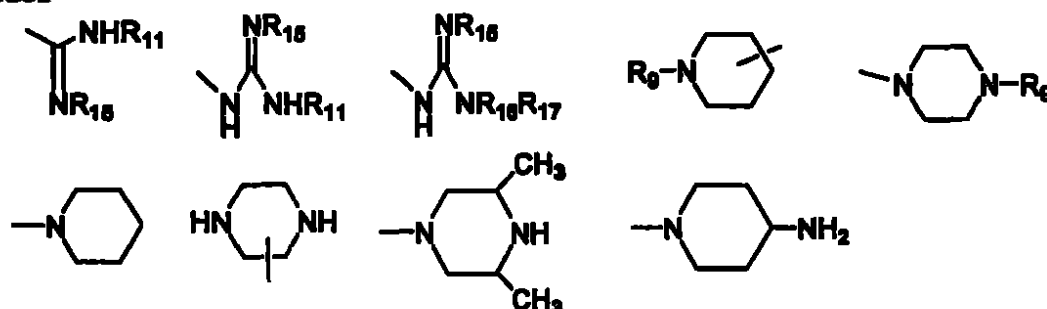


wherein T is selected from $-\text{NR}_7\text{R}_8$, $-\text{OR}_6$;

- R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C_1 - C_4 alkyl group, or NR_7R_8 is a group selected from : i) guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, cyclohexyl, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;

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- Y_1 is selected from the group consisting of $-\text{NR}_7\text{R}_8$ and from the residues



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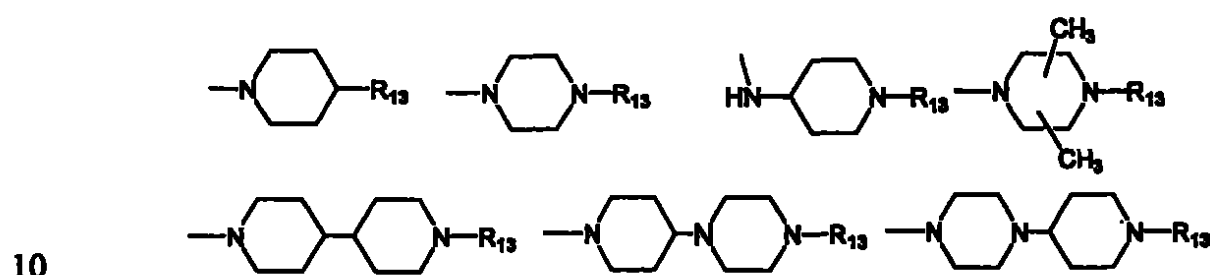
- R_9 is selected from the group consisting of hydrogen, $-(\text{CH}_2)_q\text{L}$, wherein L is selected from the group $-\text{NR}_5\text{R}_6$, amidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups;

20 and the other substituents are as defined above.

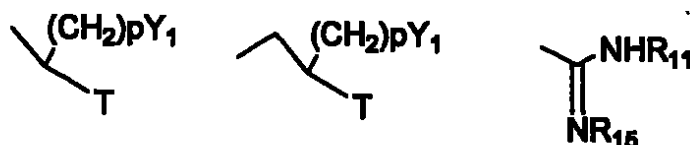
A second class of preferred compounds of general formula (I),

containing at least one tetralkylammonium, are those in which:

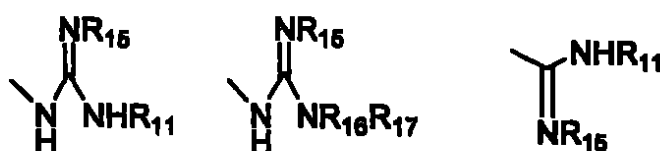
- R_1 is a hydrogen atom or methyl;
- R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to,
- 5 form a cyclic aliphatic group having 3 to 7 carbon atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl;
- X is a chlorine atom;
- B is selected from the group consisting of NR_6Y , and from the residues:



- Y is selected from: Y , COY , $(CH_2)_pY_1$, $NR_6(CH_2)_qY_1$ and from the residues:



- T is selected from the group $-NR_7R_8$, $-NR_{14}R_{18}R_{19}$, $-OR_6$;
- 15 - Y_1 is selected from the group consisting of $-NR_7R_8$, $-NR_7R_8R_{14}$ or from the following residues:

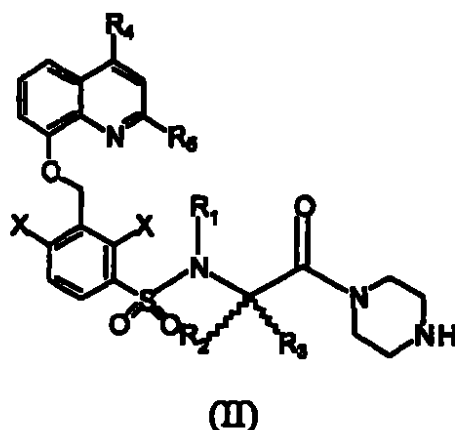


and the other substituents are as defined above.

- 20 The compounds of general formula (I) can be prepared according to well known synthetic routes.

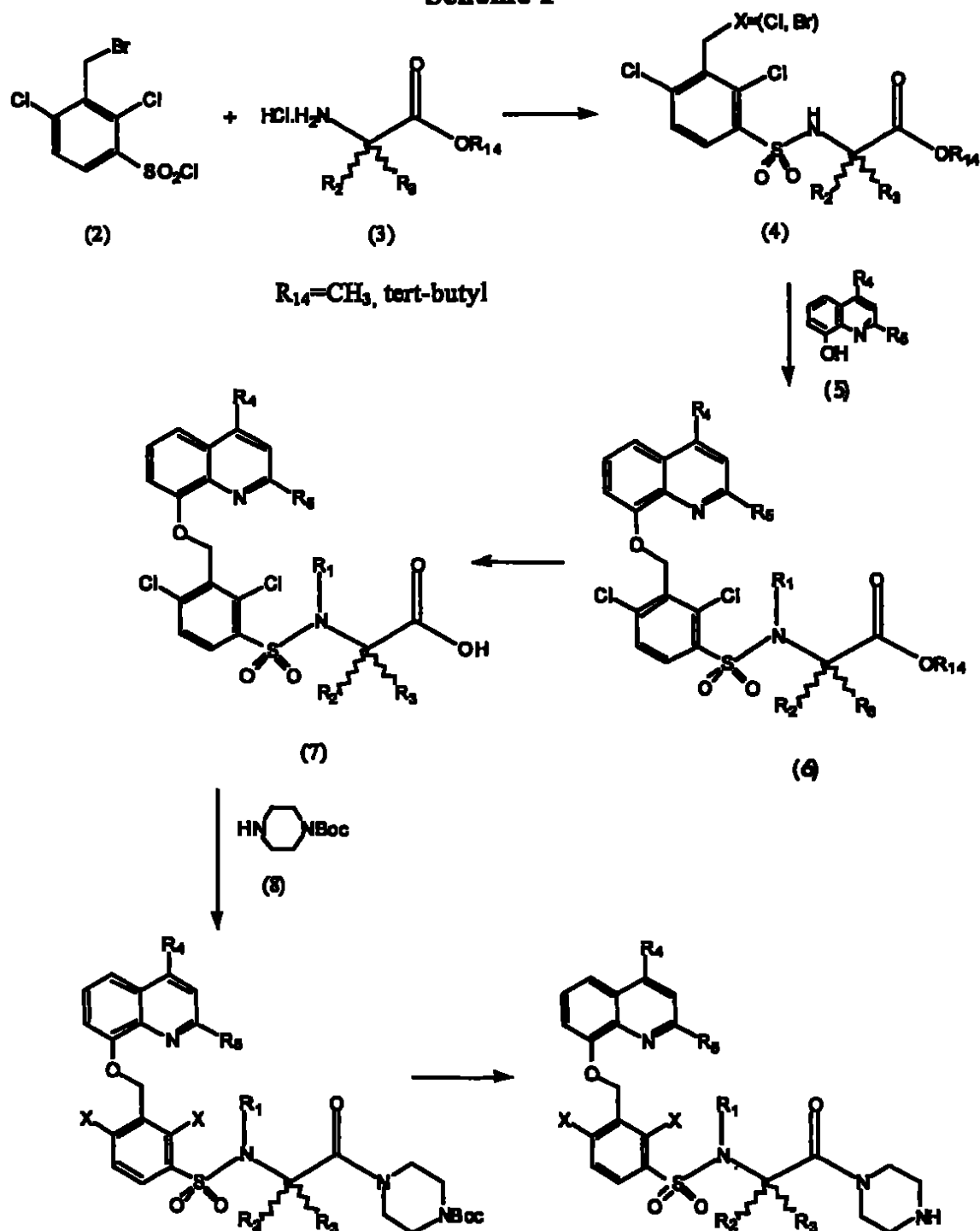
By way of example, and particularly interesting for the purposes of the

invention, the compounds of general formula (I) as defined above in which B is the group $-\text{N} \begin{array}{c} \diagup \diagdown \\ \diagdown \diagup \end{array} \text{N}-\text{COY}$, can be prepared by condensation, in the presence
 5 of a suitable condensing agent, of the intermediate of general formula (II)



with an acylating group, such as 2,6-diaminohexanoic acid, which is
 10 commercially available. Compound (1) (intermediate of general formula (II) in which $R_1 = \text{H}$) can be prepared according to the scheme reported in the following.

Scheme 1



Compound (1) is obtained through a series of reactions shown in Scheme 1. The first step relates consists in the formation of the sulfonamido
 5 bond (4) obtained by condensation of intermediates (2) and (3). This reaction is carried out at room temperature, preferably in acetonitrile/water (2:1), in the presence of NaHCO_3 . Said reaction takes place with chlorine - bromine exchange on the benzyl position: the resulting products mixture is used as

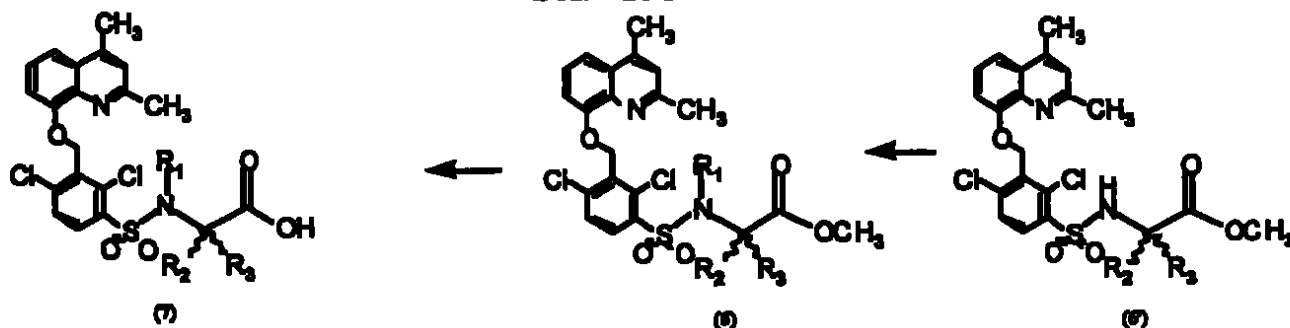
such as for the subsequent step. The halogen derivatives mixture is then reacted with a disubstituted hydroxyquinoline (5), in the presence of potassium carbonate (K_2CO_3) and potassium iodide (KI), in acetone under reflux, to obtain the ether derivative (6). The methyl ester of formula (6) in which $R_{14}=CH_3$, is hydrolysed in basic conditions to carboxylic acid (7), which is then condensed with Boc-piperazine (8), to afford intermediate (9). Said condensation reaction is carried out according to a procedure known in the peptide synthesis, using hydroxybenzotriazole to activate the carboxylic component, a condensing agent such as 1-ethyl-3-(3'-dimethylpropyl)carbodiimide and an amount of tertiary amine, diisopropylethylamine, corresponding to three equivalents compared with the condensing agent. Finally, compound (1) is obtained by cleaving the Boc group from intermediate (9), with a hydrochloric acid solution (4N) in dioxane and isolating the free amine instead of the hydrochloride.

Compound of formula (2) is prepared as described in J. Fluorine Chemistry, 2000, 101:85-89.

Compound of formula (5), i.e. 2,4-dimethyl-8-hydroxyquinoline ($R_4=R_5=CH_3$), is prepared as disclosed in WO9640639.

In case R_1 is an alkyl group, in particular methyl, alkylation of the sulfonamido group of compound (6) is carried out; by way of example, the preparation of intermediate (7) in which $R_1 = \text{methyl}$, is shown in scheme 2.

Scheme 2



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The sulfonamido nitrogen can be alkylated in dimethylformamide using methyl iodide as alkylating agent and potassium carbonate (K_2CO_3) as base.

All compounds of general formula (I) can be obtained suitably changing the procedure of scheme 2, by means of conventional acylation or alkylation reactions on the nitrogen atom in intermediates such as compound (1) or the analogues thereof.

The intermediates and final products of the present invention are recovered and purified through conventional procedures, such as extraction, crystallization, chromatography, precipitation and the like.

In case intermediates and final products have an asymmetric carbon atom, when the configuration (R,S) is not specified, the compounds are racemic compounds or racemates.

In the present invention, the following abbreviations are used:

DCM = dichloromethane; MeOH = methanol; THF = tetrahydrofuran;
DMSO = dimethylsulfoxide; DMF = dimethylformamide; AcOEt = ethyl
acetate; AcOH = acetic acid; TFA = trifluoroacetic acid; pTsOH = para-
toluenesulfonic acid; PPA = poliphosphoric acid;
NBS = N₂-bromosuccinimide, bpo = benzoyl peroxide;
Boc = tert-butoxycarbonyl; HOBt = 1-hydroxy-benzotriazole;
HOAt = 1-hydroxy-7-aza-benzotriazole; EDC = 1-ethyl-3-(3'-
dimethylpropyl)carbodiimide; DIPEA = diisopropylethylamine;
TLC = thin-layer chromatography; NMR = nuclear magnetic resonance;
FCC = Flash Column Chromatography; t_R = retention time.

The intermediates and final products of the present invention were characterized by analytic HPLC: column Symmetry 300, C18, 5 μ m, 250x4.6 mm, using A (0.1% TFA in H_2O) and B (0.1% TFA in acetonitrile) as eluents, with a gradient of 20 to 80% B in 20 minutes, λ =220 nm. For the compounds characterized through nuclear magnetic resonance (NMR), the values of

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proton chemical shifts are reported, as well as the signal multiplicity and the number of protons (in brackets).

The compounds of the invention are used in the treatment of all those disorders in which the activation of bradykinin receptor has to be blocked or
5 reduced. They are particularly suitable for the treatment of inflammatory, allergic and autoimmune disorders, such as asthma and chronic bronchitis, allergic, vasomotor and viral rhinitis, obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory diseases of the bowel (Crohn's disease and ulcerative colitis), glomerulonephritis, psoriasis, rash, acute and
10 chronic cystitis, hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis, both acute and chronic pain, septic, allergic and post-traumatic shocks, hepatic cirrhosis by hepatorenal syndrome, hypotension, alopecia, or as anticancer and antiangiogenetics.

For use in therapy, the compounds of the invention will be suitably
15 formulated together with pharmaceutically acceptable carriers/excipients. Preferred are pharmaceutical forms suitable for the oral administration, such as tablets, capsules, granules, powders, solutions, suspensions, syrups or the like. These pharmaceutical preparations can be prepared with conventional procedures using ingredients known in technique, such as ligands,
20 disintegrants, lubricants, fillers, stabilizing agents, diluents, dyes, flavours, wetting agents and other excipients known to those skilled in the art. The oral formulations also comprise protracted-release forms, such as enteric-coated tablets or granules. The solid oral compositions can be prepared with conventional mixing, filling or compression methods. The liquid oral
25 preparations can be in the form of, for example, aqueous or oily suspensions or solutions, emulsions, syrups, or can be presented as dry product for reconstitution with water or other suitable carrier before use.

The dosage can range depending on the age and general conditions of

the patient, nature and severity of the disease or disorder and route and type of administration. As a rule, in case of oral administration to a human adult patient, the compounds of the present invention will be generally administered at a total ranging daily dosage from 1 to 1000 mg, preferably from 5 to 300

5 mg, in a single dose or in subdivided doses.

The following examples illustrate the invention in greater detail.

Example 1

(Intermediate of formula (4) in which $R_2=CH_3$, $R_3=CH_2CH_3$, $R_{14}=CH_3$)

Methyl (R)-2-(2,4-dichloro-3-bromomethyl-benzenesulfonamido)-2-methyl
10 methylbutanoate.

A solution of (R)-methyl 2-(methylamino)-2-methylbutanoate (30 mg, 0.18 mmol) in DMF (2ml) is added with 69 μ l (0.40 mmol) of DIEA; then with 125 mg (0.369 mmol) of 2,4-dichloro-3-bromomethyl-benzensulfonyl chloride (2) at 0°C. The system is left to warm at room temperature; after reacting for
15 approx. 30 minutes, the solution pH changes from basic to strongly acid. The reaction is monitored by TLC: disappearance of the spot of 2,4-dichloro-3-bromomethyl-benzensulfonyl chloride and formation of the final product are observed. DMF is evaporated off under reduced pressure and the reaction crude is purified on chromatographic column (FCC) eluted with 100%
20 chloroform, thereby obtaining 49 mg of product as a colourless oil, in a 63% yield.

HPLC: $t_R=21.84$ min; MS: $[M+NH_4]^+=449.0$; 1H NMR ($CDCl_3$): 8.00 (d, 1H, $J=9.0$ Hz); 7.46 (d, 1H, $J=9.0$ Hz); 4.90 (s, 2H); 3.70 (s, 3H); 2.01-1.88 (m, 1H); 1.82-1.68 (m, 1H); 1.36 (s, 3H); 0.74 (t, 3H, $J=8.4$ Hz).

25 Example 2

(Intermediate of formula (6) in which $R_4=R_5=CH_3$, $R_2=CH_3$, $R_3=CH_2CH_3$, $R_{14}=CH_3$)

Methyl (R)-2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)-benzene-

sulfonamido]-2-methylbutanoate.

A solution of the products obtained as described in example 1 (49 mg, 0.283 mmol), in anhydrous acetone (10 ml) is added with 110 mg (0.283 mmol) of 2,4-dimethyl-8-hydroxyquinoline, 58 mg of KI (0.349 mmol) previously dried over phosphoric anhydride at 75°C, and finally, 80 mg (0.579 mmol) of K₂CO₃. The solution is refluxed for about five hours and a half, until complete disappearance (monitored by HPLC) of the starting products. After cooling at room temperature, the is partitioned between AcOEt (50 ml) and a buffer solution at pH=4 (90 ml). The organic phase is separated and washed with the buffer solution (50 ml); the aqueous phases are combined, and back-extracted with about 50 ml of AcOEt. Finally, the organic phase is washed with water and brine, dried over sodium sulfate, filtered and evaporated to dryness; the crude product is purified by FCC eluting with hexane/AcOEt (2:1), to give 79 mg (yield: 53%) of methyl (R)-2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)benzenesulfonamido]-2-methylbutanoate, as a pale yellow oil.

HPLC : t_R=16.19 min; MS: [M+H]⁺=525.1; ¹H NMR CDCl₃): 8.02 (d, 1H, J=8.6 Hz); 7.60 (d, 1H, J=8.4 Hz); 7.47 (d, 1H, J=8.6 Hz); 7.36 (t, 1H, J=8.0 Hz); 7.21 (t, 1H, J=7.6Hz); 7.11 (s, 1H); 6.00 (s, 1H); 5.66 (dd, 2H, J₁=14.8 Hz, J₂=10.7 Hz); 2.64 (s, 3H); 2.62 (s, 3H); 2.05-1.90 (m, 1H, J=42.3 Hz); 1.83-1.71(m, 1H, J=28.7 Hz); 1.47 (s, 3H); 0.78 (t, 3H, J=7.4 Hz).

The compounds of the examples reported in the following were prepared analogously.

Example 3

(Intermediate of formula (6) in which R₄=R₅=CH₃, R₂=CH₃, R₃=CH₂CH₃, R₁₄=CH₃)

Methyl (S)-2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)-benzenesulfonamido]-2-methylbutanoate.

HPLC : t_R =16.19 min; MS: $[M+H]^+$ =525.0; 1H NMR ($CDCl_3$): 8.01 (d, 1H, J =8.6 Hz); 7.60 (d, 1H, J =8.4 Hz); 7.47 (d, 1H, J =8.6 Hz); 7.37 (t, 1H, J =7.8 Hz); 7.12 (t, 1H, J =7.6 Hz); 6.00 (s, 1H); 5.65 (dd, 2H, J_1 =14.8 Hz, J_2 =10.7 Hz); 3.69 (s, 3H); 2.65 (s, 3H); 2.10-1.89 (m, 1H); 1.83-1.69 (m, 1H);
5 1.37 (s, 3H); 0.78 (t, 3H, J =7.4 Hz).

Example 4

(Intermediate of formula (6) in which $R_4=R_5=CH_3$, $R_2=R_3=CH_3$, $R_{14}=C(CH_3)_3$)
tert-Butyl 2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)-benzene-sulfonamido]-2-methylpropanoate.

10 HPLC : t_R =14.27 min; MS: $[M+H]^+$ =553.1; 1H NMR ($CDCl_3$): 8.05 (d, 1H, J =8.6 Hz); 7.61 (d, 1H, J =8.4 Hz); 7.47 (d, 1H, J =8.6 Hz); 7.38 (t, 1H, J =7.9 Hz); 7.21 (d, 1H, J =7.6 Hz); 7.13 (s, 1H); 6.09 (s, 1H); 5.67 (s, 2H); 2.67 (s, 3H); 2.63 (s, 3H); 1.45 (s, 9H); 1.40 (s, 6H).

Example 5

15 (Intermediate of formula (6) in which $R_4=H$, $R_5=CH_3$, $R_2=CH_3$, $R_3=CH_2CH_3$, $R_{14}=C(CH_3)_3$)

tert-Butyl 2-[2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzene-sulfonamido]-2-methylpropanoate.

MS: $[M+H]^+$ =539.0; 1H NMR ($CDCl_3$): 8.08 (d, 1H, J =8.6 Hz); 8.03 (d,
20 1H, J =8.4 Hz); 7.51 (d, 1H, J =8.6 Hz); 7.46 (d, 1H, J =7.1 Hz); 7.39 (t, 1H, J =7.6 Hz); 7.35-7.23 (m, 2H); 6.12 (s, 1H); 5.71 (s, 2H); 2.75 (s, 3H); 1.48 (s, 9H); 1.43 (s, 6H).

Example 6

(Intermediate of formula (6) in which $R_4=R_5=CH_3$, R_2 and R_3 , together with
25 the carbon atom which they are linked to, form a cyclopentyl, $R_{14}=CH_3$)
Methyl 1-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)] benzene-sulfonamido-1-cyclopentanecarboxylate.

HPLC : t_R =11.16 min; MS: $[M+H]^+$ =537.0; 1H NMR (DMSO): 8.64 (s,

1H), 8.03 (d, 1H, J=8.6 Hz); 7.79-7.29 (m, 5H); 5.59 (s, 2H); 3.56 (s, 3H); 2.89-2.57 (m, 6H); 1.98-1.85 (m, 4H); 1.60-1.48 (m, 2H); 1.48-1.38 (m, 2H).

Example 7

(Intermediate of formula (6) in which $R_4=H$, $R_5=CH_3$, R_2 and R_3 , together
5 with the carbon atom which they are linked to, form a cyclopentyl, $R_{14}=CH_3$)
Methyl 1-[2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)]benzenesulfonamido-1-cyclopentanecarboxylate.

HPLC : $t_R=15.43$ min; MS: $[M+H]^+=523.2$; 1H NMR ($CDCl_3$): 8.07-
8.01 (m, 2H, $J_1=1.6$ Hz, $J_2=8.6$ Hz); 7.54 (d, 1H, J=8.6 Hz); 7.49-7.38 (m,
10 2H); 7.31 (d, 1H, J=8.4 Hz); 7.25 (dd, 1H, $J_1=7.5$ Hz; $J_2=1.2$ Hz); 5.70 (s, 2H);
5.48 (s, 1H); 3.66 (s, 3H); 2.73 (s, 3H); 2.21-2.10 (m, 2H); 2.01-1.91 (m, 2H);
1.75-1.65 (m, 4H).

Example 8

(Intermediate of formula (6') in which $R_1=CH_3$, R_2 and R_3 , together with the
15 carbon atom which they are linked to, form a cyclopentane)
Methyl 1-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)]-1-N'-methyl-
benzenesulfonamido-1-cyclopentanecarboxylate.

A solution of methyl 1-[2,4-dichloro-3-(2,4-dimethyl-8-
quinolinoxymethyl)]benzenesulfonamido-1-cyclopentanecarboxylate (50 mg,
20 0.093 mmol) in 5 ml of DMF is added with CH_3I (19.2 ml, 0.306 mmol) and
29 mg of K_2CO_3 (0.186 mmol), at $0^\circ C$ under nitrogen atmosphere. After
stirring at room temperature for about 3 hours, the reaction mixture is poured
in 50 ml of buffer solution pH= 4.2, then extracted with AcOEt (3X30 ml).
The organic phase is subsequently washed with water and brine, dried over
25 sodium sulfate, filtered and evaporated under reduced pressure to obtain 52
mg (0.093 mmol) of desired product as a brown solid, in a quantitative yield.

HPLC : $t_R=13.56$ min; MS: $[M+H]^+=551.4$; 1H NMR ($CDCl_3$): 8.07 (d,
1H, J=8.6 Hz); 7.64 (d, 1H, J=8.6 Hz); 7.17 (s, 1H); 5.69 (s, 2H); 3.78 (s, 3H);

3.35 (s, 3H); 2.72 (d, 6H, J=44.9Hz); 2.24 (m, 2H); 1.93 (m, 2H); 1.63 (m, 4H).

Example 9

(Intermediate of formula (7) in which $R_4=R_5=CH_3$, $R_2=CH_3$, $R_3=CH_2CH_3$)
Lithium (R)-2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)-benzene-
5 sulfonamido]-2-methylbutanoate.

A solution of the product described in example 4 (79 mg, 0.15 mmol) in THF/MeOH/H₂O (3:2:1, 6 ml) is added with 23 mg (0.96 mmol) of LiOH. The reaction is stirred at room temperature for about 18 hours, then temperature is raised to 45°C for about 27 hours, to promote the hydrolysis reaction. THF and MeOH are then evaporated off under reduced pressure, and the alkaline solution is partitioned between AcOEt (25 ml) and water (25 ml). NaCl is added to break the resulting emulsion, the two phases are separated, the aqueous phase is acidified to pH=4 with 4N HCl, then extracted with AcOEt (25 ml). The organic phase is then washed with brine, dried over sodium sulfate, filtered and dried to afford 64 mg of product as a yellow solid, in an 82% yield.

HPLC t_R =14.36 min; MS: $[M+H]^+=511.0$; ¹H NMR (DMSO): 8.09 (s, 1H); 8.06 (d, 1H, J=8.6 Hz); 7.73 (d, 1H, J=8.6 Hz); 7.64 (d, 1H, J=8.3 Hz); 7.46 (t, 1H, J=7.9 Hz); 7.34 (d, 1H, J=7.6 Hz); 7.27 (s, 1H), 5.51 (dd, 2H, J₁=13.8 Hz, J₂=10.8 Hz); 2.61 (s, 3H); 2.54 (s, 3H); 1.62 (dd, 2H, J₁=14.4 Hz, J₂=7.1 Hz); 1.01 (s, 3H); 0.61 (t, 3H, J=7.1 Hz).

The compounds of the examples reported in the following were prepared analogously.

Example 10

(Intermediate of formula (7) in which $R_4=R_5=CH_3$, $R_2=CH_3$, $R_3=CH_2CH_3$)
Lithium (S)-2-[2,4-dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)-benzene-sulfonamido]-2-methylbutanoate.

HPLC : t_R =14.24 min; ¹H NMR (CDCl₃): 8.09 (d, 1H, J=8.6 Hz);

7.62-7.47 (m, 3H, J=48.5 Hz); 7.15 (s, 1H); 5.62 (d, 1H, J=9.6 Hz); 5.56 (s, 1H); 5.47 (d, 1H, J=9.6 Hz); 2.66 (s, 3H); 2.53 (s, 3H); 1.86-1.64 (m, 2H, J=58.6 Hz); 1.37 (s, 3H); 0.95 (t, 3H, J=7.4 Hz).

Example 11

- 5 (Intermediate of formula (7) in which $R_4=R_5=CH_3$, $R_2=R_3=CH_3$)
2-[2,4-Dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)benzenesulfonamido]-
2-methylpropionic acid.

HPLC : $t_R=9.09$ min; MS: $[M+H]^+=497.0$.

Example 12

- 10 (Intermediate of formula (7) in which $R_4=H$, $R_5=CH_3$, $R_2=R_3=CH_3$)
2-[2,4-Dichloro-3-(2-methyl-8-quinolinoxymethyl)benzenesulfonamido]-2-
methylpropionic acid

HPLC: $t_R=8.34$ min; MS: $[M+H]^+=483.0$, 1H NMR ($CDCl_3$): 8.68 (d, 1H, J=8.6Hz); 8.17 (d, 1H, J=8.7 Hz); 7.83 (t, 1H, J=8.1 Hz); 7.63 (d, 1H, J=8.7); 7.75-7.66 (m, 2H); 5.66 (s, 2H); 5.50 (s, 1H); 2.94 (s, 3H); 1.52 (s, 6H).

Example 13

- (Intermediate of formula (7) in which $R_4=R_5=CH_3$, R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclopentyl)
20 1-[2,4-Dichloro-3-(2,4-dimethyl-8-quinolinoxymethyl)]benzene-sulfonamido-
1-cyclopentanecarboxylic acid.

HPLC: $t_R=9.969$ min; MS: $[M+H]^+=523.0$

Example 14

- (Intermediate of formula (7) in which $R_4=H$, $R_5=CH_3$, R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclopentyl)
25 1-[2,4-Dichloro-3-(2-methyl-8-quinolinoxymethyl)]benzenesulfonamido-1-
cyclopentanecarboxylic acid.

HPLC: eq.: $t_R=13.18$ min(42.6%)- $t_R=13.35$ min(49.4%); MS: $[M]^+$

=507.0; ¹H NMR (DMSO): 12.57 (br s, 1H); 8.45 (s, 1H); 8.20 (d, 1H, J=8.4 Hz); 7.76 (d, 1H, J=8.6 Hz); 7.33-7.58 (m, 4H, J=77.1 Hz); 5.53 (s, 2H); 2.59 (s, 3H); 1.94-1.84 (m, 4H, J=42.3 Hz); 1.60-1.30 (m, 4H, J=92.8 Hz).

Example 15

- 5 Intermediate 4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboxylic acid tert-butyl ester.

A solution in DMF (2 ml) of the product described in example 15 (0.12mmol), is added with 22 mg (0.16 mmol) of HOAt and 29 mg (0.15 mmol) of
10 EDC.HCl. The mixture is stirred at 0°C for about 30 min, then added with 32 mg (0.18 mmol) of tert-butyl-N-(piperazinyl)carbamate diluted in 2 ml of DMF. The mixture is left to warm at room temperature under stirring for 4 hours. The solvent is evaporated off and the product is purified by preparative chromatography using a column Simmetry PrepTM filled with RP-18 10 µm,
15 eluting with a gradient of 90% water in acetonitrile to 50% water in acetonitrile during 40 minutes with a 10 ml/min flow. The fractions corresponding to the desired product are combined and the solvent is evaporated off thereby obtaining 48 mg of the product as a colourless oil in a 58% yield.

- 20 HPLC : t_R=16.68 min; MS: [M+H]⁺=691.5; ¹H NMR (DMSO-d₆) δ: 8.57 (1H, s), 8.02 (1H, d), 7.80 (1H, d), 7.66 (1H, d), 7.48 (1H, t), 7.35 (1H, d), 7.29 (1H, s), 5.54 (2H, s), 2.62 (3H, s), 2.55 (3H, s), 2.04-1.89 (2H, m), 1.82-1.66 (4H, m), 1.41 (9H, s).

Example 16

- 25 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-[1-(piperazine-1-carbonyl)-cyclopentyl]-benzenesulfonamide

A solution of 4N HCl in dioxane (2ml) is dropwise added, at room temperature, to a methanol solution (4 ml) of the intermediate described in

Example 15 (0.072 mmol). The mixture is kept under stirring for about an hour, then evaporated to dryness under reduced pressure; the residue is taken up into a MeOH/ toluene solution, which is then evaporated to yield a white solid. The product is then washed with ethyl ether, filtered, partitioned
5 between AcOEt (25 ml) and a 5% NaHCO₃ aqueous solution (25 ml); the two phases are separated and the organic phase is washed with 25 ml of a 5% NaHCO₃ aqueous solution. The combined aqueous phases are back-extracted with 25 ml of AcOEt, finally the combined organic phases are washed with brine, dried over sodium sulfate, filtered and evaporated, thereby obtaining 25
10 mg a colourless oil in a 66% yield.

HPLC : t_R =8.34 min; MS: $[M+H]^+$ =591.2; ¹H NMR (DMSO-d₆): 8.83 (brs, 2H); 8.64 (s, 1H); 8.02 (d, 1H); 7.82 (d, 1H); 7.6-7.4 (m, 4H); 5.58 (s, 2H); 3.4-2.6 (6H); 1.98 (m, 2H); 1.72 (m, 2H); 1.43 (s, 4H)

Example 17

15 2,4-Dichloro-N-(1,1-dimethyl-2-oxo-2-piperazin-1-yl-ethyl)-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

HPLC : t_R =5.98 min; MS: $[M+H]^+$ =551.1; ¹H NMR (DMSO-d₆): 8.85 (brs, 2H); 8.72 (s, 1H); 8.33 (brs, 1H); 8.07 (d, 1H); 7.82 (d, 1H); 7.63-7.40 (m, 4H); 5.58 (s, 2H); 3.17 (m, 4H); 2.66 (s, 3H); 1.23 (s, 6H)

20 Example 18

N-[2-[4-(2-(S)-Amino-6-dimethylaminohexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide trifluoroacetate.

A solution of 2,6-bis-tert-butyloxycarbonylamino-hexanoic acid (0.060
25 mmol) and HOAt (11 mg, 0.081 mmol) in DMF (1 ml), cooled at 0°C, is added with EDC.HCl (17 mg, 0.089 mmol) in a single portion. After stirring for 30 minutes, the compound described in example 17 (21 mg, 0.037 mmol) dissolved in 2 ml of DMF is added at 0°C and the mixture is kept at this

temperature for a further 30 minutes, then left to warm at room temperature.

After approx. 18 hours, stirring is discontinued and DMF is removed under reduced pressure. The resulting residue is dissolved in 3 ml of a 0.1% TFA aqueous solution and filtered through Anotop 25. The resulting aqueous solution is subjected to preparative chromatography eluting with a gradient of 90% water in acetonitrile to 50% water in acetonitrile during 40 minutes, with a 10 ml/min flow. The fractions containing the product are recovered and combined and the solvent is evaporated off, to obtain 20 mg of product as a colourless oil. The oil is triturated in ethyl ether (3 ml) and filtered under nitrogen. The resulting solid is washed with ethyl ether and dried under nitrogen stream to afford 8.8 mg of white solid (yield 26%). The Boc groups are then removed as in Example 16.

^1H NMR (DMSO- d_6) δ : 9.38-9.26 (1H, brs), 8.72 (1H, s), 8.38-8.26 (1H, brs), 8.19-8.09 (3H, m), 8.07 (1H, d), 7.83 (1H, d), 7.64-7.39 (4H, m), 5.58 (1H, s), 4.52-4.42 (1H, m), 3.04-2.95 (2H, m), 2.80-2.73 (6H, m), 2.69-2.62 (5H, m), 1.77-1.54 (4H, m), 1.43-1.21 (8H, m). HPLC t_R =8.16 min; MS: $[\text{M}+\text{H}]^+=707.2$.

Example 19

N-{2-[4-(6-Guanidinohexyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)benzenesulfonamido-2-methyl-propionamide tris trifluoroacetate HPLC : t_R =6.46 min; MS: $[\text{M}+\text{H}]^+=692.2$.

^1H NMR (DMSO- d_6) δ : 9.38-9.26 (1H, brs), 8.72 (1H, s), 8.38-8.26 (1H, brs), 8.19-8.09 (3H, m), 8.07 (1H, d), 7.83 (1H, d), 7.64-7.39 (4H, m), 5.58 (1H, s), 4.52-4.42 (1H, m), 3.04-2.95 (2H, m), 2.80-2.73 (6H, m), 2.69-2.62 (5H, m), 1.77-1.54 (4H, m), 1.43-1.21 (8H, m).

Example 20

4-{2-[2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine

HPLC : t_R =6.34 min; MS: $[M+H]^+$ =593.3; 1H NMR (DMSO- d_6): 8.71 (s, 1H); 8.06 (d, 1H); 7.82 (d, 1H); 7.6-7.4 (m, 5H); 5.57 (s, 2H); 3.6-3.5 (m, 4H); 2.63 (s, 3H); 1.23 (s, 6H)

Example 21

- 5 N-[2-[4-(2-(S)-Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate.

HPLC : t_R =7.62 min; MS: $[M+H]^+$ =707.1. 1H NMR (DMSO- d_6) δ : 8.73 (1H, s), 8.42-8.32 (1H, brs), 8.26-8.16 (3H, brs), 8.07 (1H, d), 7.82 (1H, d),
 10 7.66-7.00 (7H, m), 5.58 (1H, s), 3.19-3.09 (2H, m), 2.67(3H, s), 1.80-1.45 (4H, m), 1.30-1.21 (6H, m).

Example 22

- N-{2-[4-(6-Aminohexyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris
 15 trifluoroacetate.

HPLC : t_R =6.02 min; MS: $[M+H]^+$ =649.9. 1H NMR (DMSO- d_6) δ : 8.80 (1H, s), 8.08 (1H, d), 7.96-7.80 (3H, m), 7.83 (1H, d), 7.70-7.50 (3H, m), 5.60 (1H, s), 4.58 (2H, m), 3.12-3.03 (2H, m), 3.02-2.84 (1H, m), 2.81-2.69 (2H, m), 1.79 (2H, m), 1.60-1.50 (2H, m), 1.40-1.28 (4H, m), 1.25 (6H, s).

- 20 Example 23

N-{2-[4-(Piperazin-2-yl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris
 trifluoroacetate.

- HPLC : t_R =7.54 min; MS: $[M+H]^+$ =663.0. 1H NMR (DMSO- d_6) δ : 8.69
 25 (1H, s), 8.53-8.31 (2H, m), 8.24-8.02 (1H, m), 8.07 (1H, d), 7.81 (1H, d), 7.69-7.41 (4H, m), 5.59 (2H, s), 3.29-3.19 (2H, m), 2.96-2.81 (2H, m), 2.68 (3H, m), 2.39-2.31 (2H, m), 2.06-1.93 (1H, m), 1.89-1.79 (2H, m), 1.39-1.18 (9H, m).

Example 24

N-{2-[4-(Piperazin-1-ylacetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide bis
5 trifluoroacetate.

HPLC : t_R =7.67 min; MS: $[M+H]^+$ =667.1. 1H NMR (DMSO- d_6) δ : 9.00-8.78 (1H, brs), 8.74 (1H, s), 8.44-8.21 (2H, brs), 8.07 (1H, d), 7.82 (1H, d), 7.67-7.40 (4H, m), 5.57 (1H, s), 3.66-3.45 (4H, m), 3.36-3.18 (3H, m), 3.12-2.98 (3H, m), 2.72-2.61 (3H, m), 1.70-1.60 (2H, m), 1.60-1.51 (1H, m), 1.30-1.21 (7H, m).
10

Example 25

N-{2-[4-2-(Piperidin-4-yl-acetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide bis
trifluoroacetate

15 HPLC: t_R =8.32 min; MS: $[M+H]^+$ =676.1; 1H NMR (DMSO- d_6) δ : 8.69 (1H, s), 8.53-8.31 (2H, m), 8.24-8.02 (1H, m), 8.07 (1H, d), 7.81 (1H, d), 7.69-7.41 (4H, m), 5.59 (2H, s), 3.29-3.19 (2H, m), 2.96-2.81 (2H, m), 2.68 (3H, m), 2.39-2.31 (2H, m), 2.06-1.93 (1H, m), 1.89-1.79 (2H, m), 1.39-1.18 (9H, m).

Example 26

N-{2-[4-[N-(4-Piperidyl)glycyl]-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris
trifluoroacetate

HPLC : t_R =7.42 min; MS: $[M+H]^+$ =691.2. 1H NMR (DMSO- d_6) δ :
25 9.16-9.01 (2H, m), 8.76-8.65 (2H, m), 8.43-8.22 (1H, m), 8.07 (1H, d), 7.82 (1H, d), 7.62-7.37 (4H, m), 5.56 (2H, s), 4.25-4.15 (2H, m), 3.01-2.88 (2H, m), 2.62 (3H, s), 2.27-2.18 (2H, m), 1.80-1.64 (2H, m), 1.25 (6H, s).

Example 27

N-{2-[4-(4-(2-Aminoethyl)piperazin-1-yl)acetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tetra trifluoroacetate

- 5 HPLC t_R =7.59 min; MS: $[M+H]^+$ =720.2; 1H NMR (DMSO- d_6) δ : 8.74 (1H, s), 8.52-8.32 (1H, brs), 8.08 (1H, d), 7.83 (1H, d), 7.79-7.45 (6H, m), 5.58 (2H, s), 3.69-3.55 (2H, m), 3.54-3.41 (2H, m), 3.00-2.90 (2H, m), 2.68 (3H, s), 2.65-2.54 (2H, m), 1.25 (6H, s).

Example 28

- 10 N-{2-[4-(3-(R)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate

- HPLC : t_R =7.42 min; MS: $[M+H]^+$ =721.1; 1H NMR (DMSO- d_6) δ : 8.71 (1H, s), 8.35-8.24 (1H, brs), 8.23-8.02 (3H, m), 8.07 (1H, d), 7.82 (1H, d),
15 7.65-7.37 (5H, m), 5.57 (2H, s), 4.52-4.42 (1H, m), 3.13-3.04 (2H, m), 2.64 (3H, s), 1.76-1.63 (2H, m), 1.56-1.17 (11H, m).

Example 29

- N-{2-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-
20 benzenesulfonamide tris trifluoroacetate

- HPLC: t_R =7.64 min; MS: $[M+H]^+$ =707.1. 1H NMR (DMSO- d_6) δ : 9.59-9.44 (1H, brs), 8.70 (1H, s), 8.24 (1H, brd), 8.06 (1H, d), 7.89-7.76 (4H, m), 7.60-7.28 (5H, m), 5.56 (2H, s), 3.09-3.00 (2H, m), 2.88-2.73 (7H, m), 2.66-2.59 (3H, m), 1.78-1.52 (4H, m), 1.30-1.21 (6H, m).

- 25 **Example 30**

N-{2-[4-(3-(S)-Amino-7-dimethylamino-heptanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate

27

HPLC : $t_R=7.59$ min; MS: $[M+H]^+=721.2$. 1H NMR (DMSO- d_6) δ : 9.52-9.40 (1H, brs), 8.70 (1H, s), 8.27 (1H, brd), 8.06 (1H, d), 7.84-7.71 (3H, m), 7.82 (1H, d), 7.61-7.28 (5H, m), 5.57 (2H, s), 3.04-2.96 (2H, m), 2.80-2.75 (6H, m), 2.63 (3H, s), 1.65-1.53 (4H, m), 1.40-1.30 (2H, m), 1.25 (6H, s).

Example 31

N-(3-Amino-propyl)-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamide tris trifluoroacetate

10 HPLC : $t_R=8.50$ min; MS: $[M+H]^+=650.2$; 1H NMR (DMSO- d_6) δ : 8.70 (1H, s), 8.36-8.27 (1H, m), 8.06 (1H, d), 7.85-7.71 (7H, m), 7.63-7.39 (4H, m), 5.58 (2H, s), 3.30-3.22 (2H, m), 2.90-2.79 (2H, m), 2.64 (3H, s), 1.85-1.74 (2H, m), 1.24 (6H, s).

Example 32

15 N-[2-[4-(2-(S)-Amino-5-dimethylamino-pentanoyl))-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate

HPLC : $t_R=7.28$ min; MS: $[M+H]^+=693.1$. 1H NMR (DMSO- d_6) δ : 9.68-9.40 (1H, m), 8.76 (1H, s), 8.33-8.16 (4H, m), 8.06 (1H, d), 7.83 (1H, d), 20 7.62-7.35 (4H, m), 5.56 (2H, s), 4.60-4.45 (1H, m), 3.12-3.01 (2H, m), 2.79-2.73 (6H, m), 2.62 (3H, s), 1.78-1.59 (4H, m), 1.32-1.19 (6H, m).

Example 33

(S)-N-{2-[1'-(2-Amino-5-guanidino-pentanoyl)-[4,4']bipiperidiny-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

25 HPLC : $t_R=7.96$ min; MS: $[M+H]^+=789.5$; 1H NMR (DMSO- d_6): 8.57 (s, 1H); 8.22 (d, 1H); 8.06 (bs, 2H); 8.05-8.04 (d, 1H); 7.80 (d, 1H); 7.56-7.36 (5H); 5.55 (s, 2H); 3.92-3.84 (m, 1H); 3.11-3.01 (m, 4H); 2.60 (s, 3H);

27

1.80-0.99 (22H)

Example 34

2,4-Dichloro-N-(2-{4-[2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-3,5-dimethyl-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-3-(2-methyl-4a,8a-dihydro-quinolin-8-yloxymethyl)-benzenesulfonamide

HPLC : t_R =5.87 min; MS: $[M+H]^+$ =719.2; 1H NMR (DMSO- d_6): 8.90 (d, 1H); 8.76 (s, 1H); 8.27-8.18 (m, 2H); 8.05 (d, 1H); 7.85 (d, 1H); 7.56-7.36 (3H); 5.57 (s, 2H); 2.62 (s, 3H); 2.00-2.04 (t, 2H); 1.34-1.16 (18H)

Example 35

N-(2-{4-[4-(2-(S)Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-piperidin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

HPLC : t_R =6.65 min; MS: $[M+H]^+$ =790.4; 1H NMR (DMSO- d_6): 8.57 (s, 1H); 8.22 (d, 1H); 8.06 (bs, 2H); 8.05 (d, 1H); 7.80 (d, 1H); 7.56-7.36 (5H); 5.60 (s, 2H); 4.53-4.37 (4H); 2.62 (s, 3H); 1.82-1.45 (8H); 1.28-1.12 (9H)

Example 36

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid [1-(4-piperazin-1-yl-piperidine-1-carbonyl)-cyclopentyl]-amide

HPLC : t_R =5.70 min; MS: $[M+H]^+$ =674.3; 1H NMR (DMSO- d_6): 8.57 (s, 1H); 8.22 (d, 1H); 8.06 (bs, 2H); 8.04 (d, 1H); 7.80 (d, 1H); 7.56-7.36 (5H); 5.60 (s, 2H); 4.53-4.37 (4H); 2.62 (s, 3H); 1.82-1.45 (8H); 1.28-1.12 (9H)

Example 37

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (1-{4-[4-(2-S-amino-6-guanidino-hexanoyl)-piperazin-1-yl]-piperidine-1-carbonyl}-cyclopentyl)-amide

HPLC : t_R =7.29 min; MS: $[M+H]^+$ =844.4; 1H NMR (DMSO- d_6): 8.57 (s, 1H); 8.3-8.1 (bs, 3H); 8.02 (d, 1H); 7.82 (d, 1H); 5.58 (s, 2H); 4.65-4.48 (m, 4H); 3.08 (m, 1H); 2.69 (s, 3H); 2.61 (m, 3H)

Example 38

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid
(1-{4-[4-(2-S-amino-5-guanidino-pentanoyl)-piperazin-1-yl]-piperidine-1-carbonyl}-cyclopentyl)-amide

- 5 HPLC : t_R =7.26 min; MS: $[M+H]^+$ =830.4; 1H NMR (DMSO- d_6): 8.58 (s, 1H); 8.17 (bs, 3H); 8.02 (d, 1H); 7.82 (d, 1H); 5.58 (s, 2H); 4.65-4.28 (m, 5H); 3.11 (m, 1H); 2.69 (s, 3H); 2.61 (m, 3H)

Example 39

- 10 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid
[1-(4-piperidin-4-yl-piperazine-1-carbonyl)-cyclopentyl]-amide

HPLC : t_R =7.59 min; MS: $[M+H]^+$ =674.3; 1H NMR (DMSO- d_6): 8.8-8.3 (bs, 3H); 8.02 (d, 1H); 7.82 (d, 1H); 7.80-7.25 (5H); 5.57 (s, 2H); 4.52 (bs, 2H); 2.92 (m, 4H); 2.66 (s, 3H); 2.59 (s, 3H); 2.30-1.60 (9H); 1.44 (m, 4H)

Example 40

- 15 2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid {2-[4-(2-guanidino-ethyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-amide

HPLC : t_R =5.68 min; MS: $[M+H]^+$ =636.3; 1H NMR (DMSO- d_6): 8.69 (s, 1H); 8.32 (bs, 1H); 8.06 (d, 1H); 7.82 (d, 1H); 7.6-7.4 (7H); 5.57 (s, 2H); 3.6-3.5 (m, 4H); 2.65 (s, 3H)

- 20 **Example 41**

2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (2-{4-[2-S-amino-5-(N',N''-diethyl-guanidino)-pentanoyl]-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-amide

- 25 HPLC : t_R =7.31 min; MS: $[M+H]^+$ =763.4; 1H NMR (DMSO- d_6): 8.71 (s, 1H); 8.22 (m, 3H); 8.05 (d, 1H); 7.82 (d, 1H); 7.57 (d, 1H); 7.52-7.34 (5H); 5.55 (s, 2H); 4.50 (s, 1H); 3.19 (m, 4H); 2.62 (s, 3H); 1.69 (m, 2H); 1.54 (m, 2H); 1.25 (s, 3H); 1.23 (s, 3H); 1.10 (t, 6H)

Example 42

2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (2-{4-[2-R-amino-5-(N',N''-diethyl-guanidino)-pentanoyl]-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-amide

- 5 HPLC : t_R =7.31 min; MS: $[M+H]^+=763.3$; 1H NMR (DMSO- d_6): 8.71 (s, 1H); 8.22 (m, 3H); 8.05 (d, 1H); 7.82 (d, 1H); 7.57 (d, 1H); 7.52-7.34 (5H); 5.55 (s, 2H); 4.50 (s, 1H); 3.19 (m, 4H); 2.62 (s, 3H); 1.69 (m, 2H); 1.54 (m, 2H); 1.25 (s, 3H); 1.23 (s, 3H); 1.10 (t, 6H)

Example 43

- 10 (2S)-N-(1-{4-[2-Amino-6-(N',N''-diethyl-guanidino)-hexanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

- HPLC : t_R =8.47 min; MS: $[M+H]^+=817.2$; 1H NMR (DMSO- d_6): 8.62 (s, 1H); 8.14 (s, 3H); 8.02 (d, 1H); 7.74-7.22 (6H); 5.57 (s, 2H); 4.47 (m, 1H);
15 3.18 (m, 4H); 3.12 (m, 3H); 2.65 (s, 3H); 2.58 (s, 3H); 1.97 (m, 2H); 1.79-1.65 (4H); 1.56-1.25 (8H); 1.10 (t, 6H)

Example 44

- N-(1-{4-[2-(S)Amino-6-(N',N''-diethyl-guanidino)-pentanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide
- 20

HPLC : t_R =8.97 min; MS: $[M+H]^+=803.2$; 1H NMR (DMSO- d_6): 8.62 (s, 1H); 8.14 (s, 3H); 8.02 (d, 1H); 7.74-7.22 (6H); 5.57 (s, 2H); 4.47 (m, 1H); 3.18 (m, 4H); 3.12 (m, 3H); 2.65 (s, 3H); 2.58 (s, 3H); 1.97 (m, 2H); 1.79-1.65 (4H); 1.56-1.25 (8H); 1.10 (t, 6H)

- 25 **Example 45**

N-[2-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

¹H NMR (DMSO-d₆) δ: 9.58-9.44 (1H, brs), 8.73 (1H, s), 8.27-8.11 (3H, m), 8.07 (1H, d), 7.88-7.36 (5H, m), 5.60 (2H, s), 4.56-4.42 (1H, m), 3.07-2.94 (2H, m), 2.81-2.61 (12H, m), 1.79-1.54 (4H, m), 1.46-1.16 (10H, m). HPLC: t_R = 13.34 min. MS: [M+H]⁺ 721

5 Example 46

N-[2-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

(¹H NMR (DMSO-d₆) δ: 9.54-9.41 (1H, brs), 8.69 (1H, s), 8.06 (1H, d),
10 7.88-7.28 (7H, m), 5.57 (2H, s), 3.08-2.99 (2H, m), 2.88-2.73 (7H, m), 2.72-2.57 (6H, m), 1.76-1.53 (4H, m), 1.30-1.20 (7H, m). HPLC: t_R = 13.56 min. MS: [M+H]⁺ 721

Example 47

N-[2-[4-(3-(S)-Amino-6-dimethylamino-heptanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

(¹H NMR (DMSO-d₆) δ: 9.51-9.37 (1H, brs), 8.69 (1H, s), 8.06 (1H, d),
7.87-7.29 (7H, m), 5.57 (2H, s), 3.05-2.95 (2H, m), 2.86-2.73 (7H, m), 2.73-2.55 (6H, m), 1.67-1.52 (4H, m), 1.43-1.29 (2H, m), 1.24 (6H, s). HPLC:
20 t_R = 13.56 min. MS: [M+H]⁺ 735

Example 48

N-[2-[4-(2-(S)-Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

25 ¹H NMR (DMSO-d₆) δ: 8.72 (1H, s), 8.24-8.12 (3H, m), 8.07 (1H, d), 7.86-6.92 (9H, m), 5.60 (2H, s), 4.54-4.44 (1H, m), 3.19-3.07 (2H, m), 2.79-2.61 (6H, m), 1.77-1.46 (4H, m), 1.29-1.20 (6H, m). HPLC: t_R = 8.32 min. MS: [M+H]⁺ 721

Example 49

N-[2-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

- 5 ¹H NMR (DMSO-d₆) δ: 8.71 (1H, s), 8.24-8.00 (4H, m), 7.88-6.74 (9H, m), 5.59 (2H, s), 4.54-4.40 (1H, m), 3.13-3.03 (2H, m), 2.76-2.59 (6H, m), 1.77-1.62 (2H, m), 1.54-1.43 (2H, m), 1.28-1.22 (6H, m). HPLC: t_R = 8.38 min. MS: [M+H]⁺ 735

Example 50

- 10 N-[2-[4-(2-(S)-Amino-5-dimethylamino-pentanoyl))-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide

- ¹H NMR (DMSO-d₆) δ: 9.53-9.40 (1H, brs), 8.72 (1H, s), 8.29-8.13 (3H, m), 8.06 (1H, d), 7.86-7.31 (4H, m), 5.58 (2H, s), 4.57-4.46 (1H, m),
15 3.12-3.01 (2H, m), 2.80-2.73 (6H, m), 2.73-2.60 (3H, m), 1.80-1.59 (4H, m), 1.33-1.19 (6H, m). HPLC: t_R = 13.44 min. MS: [M+H]⁺ 707

Example 51

N-[2-[4-(2-(R)-Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-

- 20 benzenesulfonamide

¹H NMR (DMSO-d₆) δ: 8.72 (2H, brs), 8.32-8.42 (1H, brs), 8.16-8.22 (3H, brs), 8.17 (1H, d), 7.82 (1H, d), 7.71 (1H, brs), 7.76-6.89 (7H, m), 5.58 (2H, s), 4.49 (1H, brs), 3.13 (1H, brs), 1.63-1.77 (2H, brs), 1.44-1.61 (2H, brs), 1.24 (6H, s). HPLC: t_R = 7.45 min. MS: [M+H]⁺ 709.

- 25 **Example 52**

N-[2-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

¹H NMR (DMSO-d₆) δ: 8.94 (2H, s), 8.71(1H, s), 8.31 (1H, s), 8.08 (1H, d), 7.82 (1H, d), 7.75 (3H, brs), 7.63-7.45 (5H, m), 7.44 (1H, d), 7.35-6.60 (4H, m), 5.67 (2H, s), 3.10 (2H, m), 2.82 (2H, m), 2.63 (3H, s), 1.63-1.49 (4H, m), 1.24 (6H, s).

5 HPLC: t_R = 7.79 min. MS: [M+H]⁺ 721

Example 53

N-[2-[4-(3-(S)-Amino-7-guanidino-heptanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

10 ¹H NMR (DMSO-d₆) δ: 8.95 (2H, s), 8.59 (1H, s), 8.30 (1H, brs), 8.06 (1H, d), 7.82 (1H, d), 7.75 (3H, brs), 7.65-7.38 (6H, m), 7.37-6.73 (3H, m), 5.68 (2H, s), 3.07 (2H, m), 2.80 (1H, m), 2.67 (1H, m), 2.63 (3H, s), 1.63-1.29 (6H, m), 1.29-1.18 (6H, s).

HPLC: t_R = 7.90 min. MS: [M+H]⁺ 735

15 Example 54

N-{2-[4-(4-2-(guanidino)ethyl)piperazin-1-ylacetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide

20 ¹H NMR (DMSO-d₆) δ: 8.62 (1H, brs), 8.25 (1H, brs), 8.23 (1H, d), 8.05 (1H, d), 7.76 (1H, d), 7.60-7.33 (5H, m), 7.18-6.99 (5H, brs), 5.68 (2H, s), 4.06 (2H, brs), 3.58 (2H, brs), 3.34 (2H, m), 3.17 (4H, brs), 2.89 (4H, brs), 2.73 (2H, m), 2.67 (3H, s), 1.31 (6H, s). HPLC: t_R = 7.75 min. MS: [M+H]⁺ 762

Example 55

25 N-[1-[4-(2-(S)-Amino-5-guanidino-pentanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

¹H NMR (DMSO-d₆) d: 8.64 (1H, s), 8.26 (1H, d), 8.15 (2H, brs), 8.05

(1H, d), 7.83 (1H, d), 7.66-7.36 (5H, m), 7.34-6.85 (5H, brs), 5.68 (2H, s), 4.50 (1H, brs), 3.14 (2H, s), 2.63 (3H, s), 2.07-1.38 (12H, m). HPLC: $t_R = 10.63$ min. MS: $[M+H]^+$ 733

Example 56

- 5 N-[1-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 8.64 (1H, s), 8.28 (1H, brs), 8.14 (2H, brs), 8.03 (1H, d), 7.83 (1H, d), 7.63-7.38 (5H, m), 7.37-6.82 (5H, m), 5.68 (2H, s), 4.47 (1H, brs), 3.07 (2H, m), 2.62 (3H, s), 2.04-1.90 (2H, brs), 1.84-1.59 (4H, brs), 1.56-1.37 (8H, m). HPLC: $t_R = 10.98$ min. MS: $[M+H]^+$ 747

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- 15 N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 9.50 (1H, brs), 8.65 (1H, s), 8.26 (1H, d), 8.22-8.11 (2H, m), 8.03 (1H, d), 7.83 (1H, d), 7.62-7.35 (5H, m), 5.68 (2H, s), 4.56-4.41 (1H, brs), 3.09-2.92 (2H, brs), 2.77 (6H, s), 2.62 (3H, s), 2.07-1.24 (16H, m). HPLC: $t_R = 8.19$ min. MS: $[M+H]^+$ 733

- 20 Example 58

N-[1-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 8.65 (1H, s), 8.14 (3H, brs), 8.04 (1H, d), 7.83 (1H, d), 7.81-7.44 (5H, m), 7.39-6.76 (3H, s), 5.50 (2H, s), 4.46 (1H, brs), 3.07 (2H, m), 2.72 (3H, s), 2.67 (3H, s), 2.03-1.91 (2H, m), 1.80-1.61 (4H, m), 1.53-1.25 (10H, m). HPLC: $t_R = 8.80$ min. MS: $[M+H]^+$ 761

Example 59

N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- 5 ¹H NMR (DMSO-d₆) δ: 9.44 (1H, brs), 8.64 (1H, s), 8.23-8.10 (3H, brs), 8.03 (1H, d), 7.83 (1H, d), 7.75 (1H, brs), 7.69-7.33 (8H, m), 5.59 (2H, s), 4.48 (1H, brs), 3.00 (1H, m), 2.78 (6H, s), 2.74-2.58 (4H, m), 2.60 (6H, s), 2.06-1.23 (14H, m). HPLC: t_R = 8.96 min. MS: [M+H]⁺ 747

Example 60

- 10 (R)-N-[4-(2-(S)-amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- ¹H NMR (DMSO-d₆) δ: 8.60 (1H, s), 8.13 (3H, brs), 8.06 (1H, d), 7.82 (1H, d), 7.79-6.70 (8H, m), 5.59 (2H, s), 4.46 (1H, brs), 4.33-3.34 (8H, m),
15 3.07 (2H, m), 2.71 (3H, s), 2.56 (3H, s), 1.86-1.20 (8H, m), 1.09 (3H, s), 0.69 (3H, t). HPLC: t_R = 8.77 min. MS: [M+H]⁺ 749

Example 61

- (R)-N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- 20 ¹H NMR (DMSO-d₆) δ: 9.43 (1H, s), 8.60 (1H, s), 8.15 (3H, brs), 8.05 (1H, d), 7.82 (1H, d), 7.78-7.31 (4H, m), 5.58 (2H, s), 4.47 (1H, s), 3.74 (8H, m), 3.00 (2H, m), 2.77 (6H, s), 2.68 (3H, s), 2.60 (3H, s), 1.87-1.53 (8H, m), 1.10 (3H, s), 0.71 (3H, t). HPLC: t_R = 8.53 min. MS: [M+H]⁺ 735

Example 62

N-{2-[4-(4-2(Guanidino)ethyl)piperazin-1-ylacetyl)-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetra trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.45 (1H, s), 8.02 (1H, d), 7.77 (1H, d), 7.76-7.33 (4H, m), 7.25-7.12 (4H, brs), 5.68 (2H, s), 4.25-4.10 (2H, brs), 3.75-2.76 (16H, m), 2.75 (3H, s), 2.70 (3H, s), 2.10-0.90- (8H, m).

HPLC: t_R = 8.90 min. MS: [M+H]⁺ 802

5 **Example 63**

N-[1-[4-(2-(R)-Amino-6-amino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.42 (1H, s), 8.09 (3H, brs), 8.02 (1H, d), 7.78 (1H, d), 7.72 (1H, d), 7.70 (3H, brs), 7.51 (1H, t), 7.39 (1H, d), 7.34 (1H, s), 5.53 (2H, s), 4.41 (1H, brs), 3.84-3.46 (8H, m), 2.80 (2H, brs), 2.68 (3H, s), 2.62 (3H, s), 1.85-1.23 (14H, m). HPLC: t_R = 8.58 min. MS: [M+H]⁺ 719

Example 64

15 N-[1-[4-(2-(R)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.42 (1H, s), 8.08 (3H, brs), 8.02 (1H, d), 7.79 (1H, d), 7.74 (1H, d), 7.50-7.34 (3H, m), 7.07-6.93 (4H, brs), 5.54 (2H, s), 4.42 (1H, brs), 3.73 (8H, m), 3.11 (2H, m), 2.68 (3H, s), 2.63 (3H, s), 2.08-1.22 (14H, m). HPLC: t_R = 8.74 min. MS: [M+H]⁺ 761

Example 65

N-[2-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

25 ¹H NMR (DMSO-d₆) δ: 8.44 (1H, s), 8.02 (1H, d), 7.79 (1H, d), 7.77-7.67 (3H, m), 7.50 (1H, t), 7.43 (1H, t), 7.37 (1H, d), 7.32 (1H, brs), 7.10-6.90 (4H, brs), 5.61 (2H, s), 3.77-3.41 (9H, m), 3.02 (2H, m), 2.79-2.68 (2H, m), 2.66 (3H, s), 2.59 (3H, s), 2.06-1.37 (12H, m). HPLC: t_R = 9.02 min.

MS: $[M+H]^+$ 761

Example 66

N-[2-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-

5 benzenesulfonamide tris trifluoroacetate

^1H NMR (DMSO- d_6) δ : 9.47 (1H, brs), 8.61 (1H, s), 8.03 (1H, d), 7.82 (1H, d), 7.81 (3H, s), 7.68 (1H, d), 7.51 (1H, t), 7.39 (1H, d), 7.32 (1H, brs), 5.55 (2H, s), 3.52 (8H, m), 3.03-2.84 (2H, brs), 2.76 (3H, s), 2.63 (3H, s), 2.56 (3H, s), 2.03-1.34 (10H, m). HPLC: t_R = 8.85 min. MS: $[M+H]^+$ 747

10 **Example 67**

N-[1-[4-(6-Guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.44 (1H, s), 8.02 (1H, d), 7.79 (1H, d), 7.76-7.32 (5H, m), 7.05-6.84 (4H, brs), 5.55 (2H, s), 3.66-3.47 (8H, m), 3.10 (2H, m), 2.68 (3H, s), 2.52 (3H, s), 2.38-2.32 (2H, m), 2.08-1.23 (14H, m). HPLC: t_R = 10.17 min. MS: $[M+H]^+$ 746

Example 68

N-[2-[4-(2-(S)-Amino-6-amino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.72 (1H, m), 8.37-8.28 (1H, d), 8.18-8.11 (3H, d), 8.07 (1H, d), 7.83 (1H, d), 7.76-7.67 (3H, brs), 7.64-7.40 (4H, m), 5.49 (2H, s), 4.45 (1H, s), 3.65-3.43 (8H, m), 2.83-2.72 (2H, m), 2.65 (3H, s), 1.77-1.31 (6H, m), 1.25 (6H, s). HPLC: t_R = 7.30 min. MS: $[M+H]^+$ 679

Example 69

N-[2-[4-(2-(S)-Guanidino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-

benzenesulfonamide tris trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.44 (1H, s), 8.24 (1H, d), 8.06 (1H, d), 7.79 (1H, d), 7.58 (1H, d), 7.61-7.34 (4H, m), 5.65 (2H, s), 4.78 (1H, m), 3.95-3.46 (8H, m), 3.11 (2H, m), 2.65 (3H, s), 1.79-1.31 (6H, m), 1.28 (6H, s). HPLC:

5 $t_R = 8.04$ min. MS: $[\text{M}+\text{H}]^+$ 763

Example 70

(R)-N-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

10 ^1H NMR (DMSO- d_6) δ : 8.29 (1H, s), 8.64 (1H, d), 7.78 (1H, d), 7.77-7.69 (3H, m), 7.56-7.31 (4H, m), 7.10-6.96 (4H, brs), 5.64 (2H, s), 3.74-3.14 (11H, m), 2.86-2.76 (2H, m), 2.68 (3H, s), 2.62 (3H, s), 1.91-1.53 (6H, m), 1.14 (6H, s). HPLC: $t_R = 9.00$ min. MS: $[\text{M}+\text{H}]^+$ 749

Example 71

15 (R)-N-{2-[4-(4-2(Guanidino)ethyl)piperazin-1-ylacetyl)-piperazin-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetra trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.32 (1H, s), 8.05 (1H, d), 7.78 (1H, d), 7.76-7.33 (5H, m), 7.20-7.07 (4H, m), 5.65 (2H, s), 4.24-4.03 (2H, brs), 3.65-3.68 (8H, m), 3.00-2.77 (4H, m), 2.59 (3H, s), 2.54 (3H, s), 1.92-1.77 (1H, m), 1.75-1.63 (1H, m), 1.13 (3H, s), 0.72 (3H, s).

HPLC: $t_R = 8.94$ min. MS: $[\text{M}+\text{H}]^+$ 790

Example 72

25 (R)-N-[4-(3-(S)-Amino-6-amino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.58 (1H, s), 8.06 (1H, d), 7.87-7.47 (12H, m), 5.60 (2H, m), 2.84-2.57 (11H, m), 1.87-1.64 (2H, m), 1.66-1.58 (4H, brs),

1.09 (3H, brs), 0.69 (3H, t). HPLC: t_R = 8.72 min. MS: $[M+H]^+$ 707

Example 73

(R)-N-[4-(3-(S)-Guanidino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-

5 benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 8.30 (1H, s), 8.05 (1H, d), 7.77 (1H, d), 7.72 (1H, d), 7.58-7.31 (5H, m), 7.14-6.88 (8H, brs), 5.64 (2H, s), 3.97-3.86 (1H, brs), 3.79-3.44 (8H, m), 3.17-3.10 (3H, m), 2.67 (3H, s), 2.66 (2H, m), 2.66 (2H, m), 2.61 (3H, s), 1.90-1.58 (2H, m), 1.58-1.46 (4H, brs), 1.13 (3H, s),
10 0.72 (3H, t). HPLC: t_R = 9.22 min. MS: $[M+H]^{++}$ 396

Example 74

(R)-N-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

15 1H NMR (DMSO- d_6) δ : 9.48-9.37 (1H, brs), 8.57 (1H, s), 8.05 (1H, d), 7.82 (1H, d), 7.83-7.26 (7H, m), 5.58 (1H, m), 3.83-3.56 (8H, m), 3.09-2.97 (2H, m), 2.77 (6H, s), 2.67 (6H, s), 1.87-1.48 (6H, m), 1.08 (3H, s), 0.70 (3H, t). HPLC: t_R = 8.81 min. MS: $[M+H]^+$ 735

Example 75

20 (S)-N-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 8.32 (1H, s), 8.13-8.06 (3H, brs), 8.04 (1H, d), 7.78 (1H, d), 7.76-7.36 (5H, m), 7.09-6.93 (4H, brs), 5.64 (2H, s), 4.47-4.38
25 (1H, brs), 3.96-3.75 (8H, m), 3.12 (2H, m), 2.70 (3H, s), 2.64 (3H, s), 1.91-1.32 (8H, m), 1.14 (3H, s), 0.72 (3H, t). HPLC: t_R = 8.64 min. MS: $[M+H]^+$ 749

Example 76

(S)-N-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- 5 ^1H NMR (DMSO- d_6) δ : 8.32 (1H, s), 8.11-8.03 (3H, brs), 8.04 (1H, d), 7.78 (1H, d), 7.71 (1H, d), 7.50 (1H, t), 7.39 (1H, t), 7.32 (1H, brs), 7.06-6.90 (4H, brs), 5.63 (2H, s), 4.47-4.38 (1H, brs), 3.94-3.48 (8H, m), 3.11 (2H, m), 2.67 (3H, s), 2.59 (3H, s), 1.78-1.32 (6H, m), 1.13 (3H, s), 0.72 (3H, t).
HPLC: t_R = 8.94 min. MS: $[\text{M}+\text{H}]^+$ 749

10 **Example 77**

2,4-Dichloro-N-{1-[4-(3(S),6-diamino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- ^1H NMR (DMSO- d_6) δ : 8.62 (1H, s), 8.04 (1H, d), 7.90-7.32 (12H, m),
15 5.59 (2H, s), 3.58-3.41 (8H, m), 2.86-2.56 (9H, m), 2.03-1.21 (12H, m).
HPLC: t_R = 8.79 min. MS: $[\text{M}+\text{H}]^+$ 719

Example 78

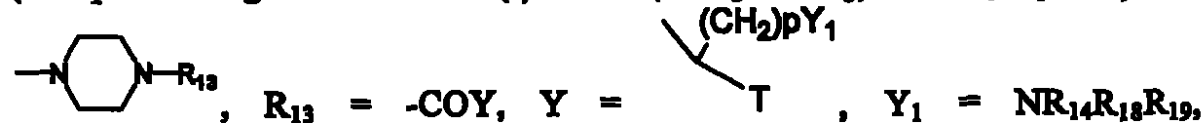
2,4-Dichloro-N-{1-[4-(3(S),6-diguanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide
20 tris trifluoroacetate

^1H NMR (DMSO- d_6) δ : 8.60 (1H, s), 8.03 (1H, d), 7.82 (1H, d), 7.78-6.72 (15H, m), 5.57 (2H, s), 3.95-3.83 (1H, brs), 3.15-2.56 (4H, m), 2.68 (6H, s), 2.03-1.91 (2H, m), 1.79-1.67 (2H, m), 1.54-1.36 (8H, m).

HPLC: t_R = 9.28 min. MS: $[\text{M}+\text{H}]^+$ 803

25 **Example 79**

(Compound of general formula (I) with $R_4 = R_5 = \text{CH}_3$, $X = \text{Cl}$, $R_1 = \text{H}$, $B =$



T = NR₇R₈, p = 4, R₁₄ = R₁₈ = R₁₉ = CH₃, R₇ = R₈ = H)

N-{1-[4-(2-(S)-Amino-6-trimethylammonium-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- 5 ¹H NMR (DMSO-d₆) δ: 8.66 (1H, s), 8.27-8.12 (3H, brs), 8.04 (1H, d), 7.84 (1H, d), 7.81-7.37 (4H, m), 5.60 (2H, s), 4.60-4.42 (1H, brs), 3.70-3.42 (8H, m), 3.24 (2H, m), 3.15 (9H, s), 2.75 (3H, s), 2.67 (3H, s), 2.04-1.93 (2H, m), 1.82-1.22 (14H, m). HPLC: t_R = 8.61 min. MS: [M]⁺ 761

Example 80

- 10 N-(1-{4-[3-(S),6-Bis-(N',N''-dicyclohexyl-guanidino)-hexanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- ¹H NMR (DMSO-d₆) δ: 8.59 (1H, s), 8.02 (1H, d), 7.82 (1H, d), 7.77-6.88 (10H, m), 5.58 (2H, s), 3.52-3.36 (8H, m), 3.26-3.14 (2H, m), 2.82-2.57
15 (6H, m), 2.04-1.90 (2H, m), 1.87-1.00 (52H, m).

HPLC: t_R = 16.91 min. MS: [M+H]⁺ 1131

Example 81

- N-{1-[4-(2-(S)Amino-3-piperidin-4-yl-propionyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-
20 benzenesulfonamide tris trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.65-8.45 (1H, brs), 8.40 (1H, s), 8.38-8.20 (3H, m), 8.02 (1H, d), 7.82 (1H, m), 7.78 (3H, m), 7.72 (1H, d), 5.58 (2H, s), 4.40 (1H, m), 3.80-3.52 (8H, m), 3.40-3.25 (2H, m), 2.89 (6H, s), 2.20-1.28 (15H, m). HPLC: t_R = 8.85 min. MS: [M+H]⁺ 745

- 25 Example 82

 N-{1-[4-(2-Trimethylammonium-acetyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide
 bis trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.27 (1H, s), 8.03 (1H, d), 7.77 (1H, d), 7.74-7.37 (4H, m), 5.69 (2H, s), 4.51 (2H, s), 3.75-3.47 (8H, m), 3.29 (9H, s), 2.70 (3H, s), 2.66 (3H, s), 2.11-2.01 (2H, m), 1.84-1.73 (2H, m), 1.53-1.43 (4H, m). HPLC: t_R = 9.64 min. MS: [M]⁺ 690

5 **Example 83**

N-{1-[4-(4-Trimethylammonium-butanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate

¹H NMR (DMSO-d₆) δ: 8.25 (1H, s), 8.02 (1H, d), 7.82-7.70 (2H, m),
10 7.58-7.33 (3H, m), 5.68 (2H, s), 3.64 (4H, brs), 3.55 (4H, brs), 3.37-3.28 (2H, m), 3.10 (9H, s), 2.69 (3H, s), 2.65 (3H, s), 2.50-2.44 (2H, m), 2.11-1.73 (6H, m), 1.55-1.42 (4H, brs). HPLC: t_R = 9.71 min. MS: [M]⁺ 718

Example 84

N-{1-[4-(3(R)-Hydroxy-4-trimethylammonium-butanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate
15

¹H NMR (DMSO-d₆) δ: 8.27 (1H, s), 8.02 (1H, d), 7.77 (1H, d), 7.76-7.33 (4H, m), 5.68 (2H, s), 4.55-4.47 (1H, m), 3.69-3.49 (8H, m), 3.40 (2H, s), 3.18 (9H, s), 2.58 (3H, s), 2.54 (3H, s), 2.11-2.00 (2H, m), 1.84-1.73 (2H, m),
20 1.51-1.43 (4H, m). HPLC: t_R = 9.44 min. MS: [M]⁺ 734

Example 85

N-[1-[4-(2-(S)-Dimethylamino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

¹H NMR (DMSO-d₆) δ: 9.40 (1H, brs), 8.32 (1H, s), 8.02 (1H, d), 7.77 (1H, d), 7.76-7.33 (4H, m), 5.68 (2H, s), 4.48 (1H, brs), 3.89-3.45 (8H, m), 3.18-3.04 (2H, m), 2.81 (3H, s), 2.79 (3H, s), 2.68 (3H, s), 2.64 (3H, s), 2.09-1.28 (10H, m). HPLC: t_R = 8.65 min. MS: [M+H]⁺ 775
25

Example 86

{5-[(1-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzensulfonylamino]-cyclopentanecarbonyl}-piperidin-4-ylmethyl)-dimethyl-ammonium]-pentyl}-trimethyl-ammonium tris trifluoroacetate

5 HPLC: $t_R = 7.60$ min. MS: $[M+H]^+$ 775.9

Example 87

{5-[(1-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzensulfonylamino]-cyclopentanecarbonyl}-piperidine-4-carbonyl)-amino]-pentyl}-trimethyl-ammonium bis trifluoroacetate salt

10 HPLC: $t_R = 8.20$ min. MS: $[M+H]^+$ 761.8

Example 88

N-[1-[4-(2-(S)-Trimethylammonium-6-trimethylammonium-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

15 1H NMR (DMSO- d_6) δ : 8.32 (1H, s), 8.02 (1H, d), 7.78 (1H, d), 7.73 (1H, d), 7.59-7.31 (3H, m), 5.68 (2H, s), 4.68-4.60 (1H, m), 4.01-3.56 (8H, m), 3.36-3.28 (2H, m), 3.22 (9H, s), 3.08 (9H, s), 2.68 (3H, s), 2.63 (3H, s), 2.13-1.43 (14H, m). HPLC: $t_R = 8.80$ min. MS: $[M]^{++}$ 402

Example 89

20 N-[1-[4-(2-(R)-Trimethylammonium-6-trimethylammonium-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

1H NMR (DMSO- d_6) δ : 8.30 (1H, s), 8.02 (1H, d), 7.81-7.69 (2H, m), 7.52 (1H, t), 7.43-7.34 (2H, m), 5.67 (2H, s), 4.64 (1H, dd), 3.35-3.28 (1H, m), 3.22 (9H, s), 3.07 (9H, s), 2.68 (3H, s), 2.64 (3H, s), 2.12-1.97 (3H, m), 1.84-1.72 (3H, m), 1.54-1.43 (4H, m), 1.41-1.27 (1H, m), 1.27-1.13 (1H, m).

HPLC: $t_R = 7.26$ min. MS: $[M]^{++}$ 402

Example 90

N-[1-[4-(2-(S)-Trimethylammonium-6-amino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate

- 5 ¹H NMR (DMSO-d₆) δ: 8.35 (1H, s), 8.07 (1H, d), 8.01-7.94 (1H, m), 7.87 (2H, s), 7.80 (1H, d), 7.77-7.59 (3H, brs), 5.74 (2H, s), 4.65-4.58 (1H, m), 3.98-3.51 (8H, m), 3.22 (9H, s), 2.91 (6H, s), 2.82-2.80 (2H, m), 2.13-1.41 (14H, m). HPLC: t_R = 8.64 min. MS: [M]⁺ 761

Example 91

- 10 **N-{1-[4-(6-Trimethylammonium-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate**

- ¹H NMR (DMSO-d₆) δ: 8.30 (1H, s), 8.07 (1H, d), 8.02-7.94 (1H, m), 7.91-7.76 (4H, m), 5.74 (2H, s), 3.67-3.50 (8H, m), 3.34-3.26 (2H, m), 3.07
15 (9H, s), 2.92 (3H, s), 2.68 (3H, s), 2.91 (3H, s), 2.43-2.36 (2H, m), 2.12-1.33 (14H, m). HPLC: t_R = 9.99 min. MS: [M]⁺ 746

Example 92

N-(6-Amino-hexyl)-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine

- 20 ¹H NMR (DMSO-d₆) δ: 8.71 (1H, s), 8.37-8.29 (1H, m), 8.07 (1H, d), 7.82 (1H, d), 7.79-7.64 (5H, m), 7.64-7.41 (3H, m), 5.58 (2H, s), 3.22-3.14 (2H, m), 2.84-2.72 (2H, m), 2.65 (3H, s), 1.59-1.46 (4H, m), 1.35-1.27 (4H, m), 1.24 (6H, s). MS: [M+H]⁺ 692; HPLC: t_R = 9.16 min

Example 93

- 25 **N-[2-(3-Amino-propylamino)-ethyl]-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine.**

¹H NMR (DMSO-d₆) δ: 8.92-8.82 (2H, m), 8.73 (1H, s), 8.39-8.29 (1H,

brd), 8.07 (1H, d), 7.98-7.85 (6H, m), 7.82 (1H, d), 7.64-7.41 (4H, m), 5.58 (2H, s), 3.18-3.10 (2H, m), 3.10-3.00 (2H, m), 2.94-2.83 (2H, m), 2.65 (3H, s), 1.96-1.85 (2H, m), 1.25 (6H, s). HPLC: t_R = 8.20 min.; MS: $[M+H]^+$ 693

Example 94

- 5 N-(3-Amino-propyl)-4-{2-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamide bis trifluoroacetate.

1H NMR (DMSO- d_6) δ : 8.57 (1H, s), 8.06 (1H, d), 7.89-7.68 (8H, m), 7.62-7.38 (3H, m), 5.62 (2H, s), 3.32-3.23 (2H, m), 2.92-2.81 (2H, m), 2.69 (3H, s), 2.64 (3H, s), 1.87-1.75 (2H, m), 1.25 (6H, s). HPLC: t_R = 9.36 min.; MS: $[M+H]^+$ 664

Example 95

- 15 N-(6-Amino-hexyl)-4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboxamide bis trifluoroacetate.

1H NMR (DMSO- d_6) δ : 8.41 (1H, s), 8.02 (1H, d), 7.78 (1H, d), 7.76-7.59 (7H, m), 7.54 (1H, t), 7.43 (1H, d), 7.38 (1H, s), 5.64 (2H, s), 3.76-3.65 (4H, m), 3.55-3.47 (4H, m), 3.24-3.15 (2H, m), 2.85-2.75 (2H, m), 2.69 (3H, s), 2.63 (3H, s), 2.08-1.98 (2H, m), 1.82-1.72 (2H, m), 1.60-1.51 (3H, m), 1.49-1.42 (3H, m), 1.40-1.24 (4H, m). HPLC: t_R = 10.54 min.; MS: $[M+H]^+$ 732

Example 96

- 25 N-[2-(3-Amino-propylamino)-ethyl]-4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboxamide bis trifluoroacetate.

1H NMR (DMSO- d_6) δ : 8.97-8.69 (1H, brs), 8.42 (1H, s), 8.02 (1H, d), 7.96-7.74 (5H, m), 7.78 (1H, d), 7.72 (1H, d), 7.51 (1H, t), 7.39 (1H, d), 7.34 (1H, s), 5.64 (2H, s), 3.83-3.68 (4H, m), 3.61-3.51 (4H, m), 3.11-3.02 (2H,

m), 2.97-2.88 (2H, m), 2.67 (3H, s), 2.61 (3H, s), 2.07-1.89 (4H, m), 1.81-1.71 (2H, m), 1.52-1.42 (4H, m). HPLC: $t_R = 9.34$ min.; MS: $[M+H]^+$ 733

Example 97

N-[2-(4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-
5 benzenesulfonylamino]-cyclopentanecarbonyl}-piperazin-1-yl)-ethyl]-4-methyl-piperazine-1-carboxamide bis trifluoroacetate.

^1H NMR (DMSO- d_6) δ : 8.64 (1H, s), 8.27-8.07 (2H, m), 8.03 (1H, d), 7.82 (1H, d), 7.79-7.72 (1H, m), 7.70-7.40 (2H, m), 5.60 (2H, s), 2.84 (3H, s), 2.76-2.60 (5H, m), 2.03-1.92 (2H, m), 1.79-1.68 (2H, m), 1.48-1.39 (4H, m).

10 HPLC: $t_R = 7.04$ min; MS: $[M+H]^+$ 759

Example 98

2,4-Dichloro-N-{1-[4-(2(R),6-diamino-hexyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetra trifluoroacetate.

15 ^1H NMR (DMSO- d_6) δ : 8.53 (1H, s), 8.03 (1H, d), 7.87-7.40 (8H, m), 7.83 (1H, d), 5.60 (2H, s), 2.83-2.56 (8H, m), 2.01-1.92 (2H, m), 1.78-1.64 (2H, m), 1.60-1.32 (10H, m). HPLC: $t_R = 7.00$ min; MS: $[M+H]^+$ 705

Example 99

2,4-Dichloro-N-{1-[4-(2(R),6-diguanidino-hexyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetrahydrochloride.

^1H NMR (DMSO- d_6) δ : 8.81-8.65 (2H, brs), 8.30 (1H, s), 8.03 (1H, d), 7.88-7.63 (3H, m), 7.58-6.91 (13H, m), 5.66 (2H, s), 2.75-2.58 (7H, m), 2.14-1.94 (2H, m), 1.84-1.08 (15H, m). HPLC: $t_R = 7.30$ min; MS: $[M+H]^+$ 789

25 **Example 100**

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-{1-[4-(2-piperazin-1-yl-ethyl)-piperazine-1-carbonyl]-cyclopentyl}-benzenesulfonamide tetra trifluoroacetate.

¹H NMR (DMSO-d₆) δ: 8.75-8.62 (3H, m), 8.04 (1H, d), 7.93-7.56 (4H, m), 5.63 (2H, s), 3.39-3.27 (4H, m), 3.19-3.09 (3H, m), 3.04-2.97 (1H, m), 2.87-2.62 (11H, m), 2.04-1.92 (2H, m), 1.77-1.52 (3H, m), 1.49-1.36 (4H, m).

HPLC: t_R = 7.30 min; MS: [M+H]⁺ 703

5 **Example 101**

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-{1-[4-(2-piperidin-4-yl-ethyl)-piperazine-1-carbonyl]-cyclopentyl}-benzenesulfonamide.

¹H NMR (DMSO-d₆) δ: 8.68 (1H, s), 8.61-8.47 (1H, m), 8.34-8.16 (1H, m), 8.03 (1H, d), 7.93-7.40 (3H, m), 7.84 (1H, d), 7.34-7.17 (2H, m), 5.61 (2H, s), 4.58-4.40 (2H, m), 3.35-3.23 (2H, m), 3.22-3.09 (2H, m), 3.06-2.60 (9H, m), 2.08-1.94 (2H, m), 1.88-1.50 (9H, m), 1.50-1.37 (4H, m), 1.37-1.18 (3H, m). HPLC: t_R = 7.50 min; MS: [M+H]⁺ 702

Example 102

15 {3-[(4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboximidoyl)-amino]-propyl}-trimethyl-ammonium tris trifluoroacetate.

¹H NMR (DMSO-d₆) δ: 8.37-8.26 (1H, m), 8.07-7.98 (1H, m), 7.83-7.66 (4H, m), 7.56-7.46 (1H, m), 7.44-7.31 (2H, m), 5.73-5.64 (2H, m), 3.82-3.71 (4H, m), 3.62-3.52 (5H, m), 3.41-3.26 (4H, m), 3.18-3.06 (9H, m), 2.74-2.60 (6H, m), 2.14-1.96 (5H, m), 1.85-1.73 (2H, m), 1.56-1.43 (4H, m).

HPLC: t_R = 9.90 min; MS: [M]⁺ 732

Example 103

25 4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-N-(3-dimethylamino-propyl)-piperazine-1-carboxamidinium tris trifluoroacetate.

¹H NMR (DMSO-d₆) δ: 9.78-9.40 (1H, brs), 8.35-8.22 (1H, m), 8.06-7.94 (1H, m), 7.82-7.57 (5H, m), 7.57-7.46 (1H, m), 7.46-7.32 (2H, m), 5.71-5.63 (2H, m), 3.80-3.66 (4H, m), 3.59-3.48 (4H, m), 3.36-3.26 (2H, m),

3.15-3.06 (2H, m), 2.86-2.78 (6H, m), 2.73-2.58 (6H, m), 2.12-1.98 (2H, m), 1.98-1.87 (2H, m), 1.83-1.72 (2H, m), 1.54-1.41 (4H, m). HPLC: $t_R = 10.14$ min; MS: $[M+H]^+$ 718

Example 104

- 5 N-(1-{4-[(5-Amino-pentylamino)-methyl]-piperidine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate.

1H NMR (DMSO- d_6) δ : 8.52 (1H, s), 8.47-8.32 (2H, m), 8.03 (1H, d), 7.81 (1H, d), 7.78-7.29 (7H, m), 5.58 (2H, s), 4.44-4.34 (2H, m), 3.06-2.55 (12H, m), 2.02-1.84 (3H, m), 1.82-1.69 (2H, m), 1.68-1.48 (4H, m), 1.48-1.30 (5H, m). HPLC: $t_R = 7.39$ min; MS: $[M+H]^+$ 704

Example 105

- 15 N-{1-[4-(4-Amino-piperidin-1-ylmethyl)-piperidine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate.

1H NMR (DMSO- d_6) δ : 9.62-9.24 (1H, m), 8.53 (1H, s), 8.20-7.99 (2H, m), 8.03 (1H, d), 7.86-7.26 (3H, m), 7.82 (1H, d), 5.59 (2H, s), 4.47-4.31 (2H, m), 3.11-2.92 (4H, m), 2.84-2.57 (6H, m), 2.15-1.88 (5H, m), 1.88-1.51 (5H, m), 1.51-1.32 (4H, m). HPLC: $t_R = 7.22$ min; MS: $[M+H]^+$ 702

- 20 **Example 106**

2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-(1-{4-[(5-methylamino-pentylamino)-methyl]-piperidine-1-carbonyl}-cyclopentyl)-benzenesulfonamide tris trifluoroacetate.

- 25 1H NMR (DMSO- d_6) δ : 8.32 (2H, brs), 8.17 (1H, s), 8.01 (1H, d), 7.79-7.70 (2H, m), 7.50 (1H, t), 7.37 (1H, d), 7.33 (1H, s), 5.66 (2H, s), 4.42-4.33 (2H, m), 2.98-2.74 (8H, m), 2.67 (3H, s), 2.65-2.57 (5H, m), 2.10-1.88 (3H, m), 1.85-1.74 (4H, m), 1.71-1.57 (4H, m), 1.53-1.14 (8H, m).

HPLC: $t_R = 7.56$ min; MS: $[M+H]^+$ 718

Example 107

[4-(S)-Amino-6-(4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazin-1-yl)-6-oxohexyl]-trimethylammonium bis trifluoroacetate.

5 ¹H NMR (DMSO-d₆) δ: 8.27 (1H, s), 8.08-7.99 (1H, m), 7.95-7.72 (4H, m), 7.59-7.51 (1H, m), 7.47-7.37 (2H, m), 5.68 (2H, m), 3.76-3.48 (8H, m), 3.37-3.24 (2H, m), 3.13-3.06 (9H, m), 2.92-2.79 (1H, m), 2.76-2.63 (7H, m), 2.13-1.99 (2H, m), 1.93-1.74 (3H, m), 1.73-1.60 (2H, m), 1.56-1.42 (4H, m).
HPLC: t_R = 10.26 min. MS: [M+H]⁺ 761

10 Biological Activity

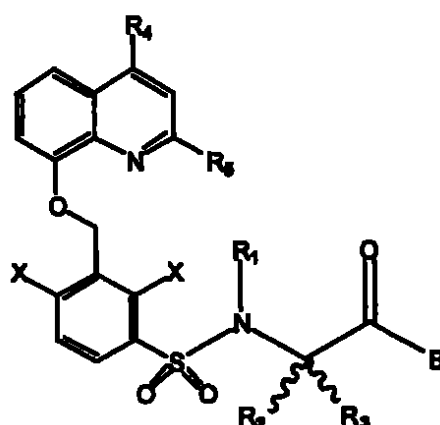
The evaluation of the B2 receptor affinity of the compounds of the present invention was carried out with studies of binding to the human B2 receptor expressed in human fibroblasts W138, following the procedure described by Phagoo et al., Br. J. Pharmacol. (1996) 119: 863-868. In the
15 following the binding values are reported expressed as pKi.

The in vivo activity of the compounds of the present invention was evaluated as effectiveness in inhibiting BK-induced bronchospasm in the guinea pig, following the procedure described by Tramontana et al., J. Pharmacol. Exp. Therap., 296:1051-1057, 2001. The compounds of the
20 present invention show higher potency and longer-lasting action than those of molecules of a similar class which however do not contain alpha,alpha dialkyl amino acids.

	Compound (Example N)	pKi	Compound (Example N)	pKi
5	25	9.27	26	9.3
	31	9.4	29	9.2
	30	9.1	20	9.2
	45	9.2	46	9.3
	48	9.2	51	9.4
10	57	9.0	59	9.0
	93	9.0	61	9.3
	94	9.0	62	9.0
	64	9.2	65	9.1
	66	9.1	67	9.1
15	95	9.3	96	9.1
	68	9.0	70	9.2
	71	9.4	72	9.4
	73	9.2	74	9.1
	98	9.2	80	9.2
20	81	9.2	38	9.3
	39	9.0	100	9.4
	105	9.0	82	9.2
	83	9.4	84	9.2
	85	9.3	106	9.4
25	86	9.4	107	9.7
	88	9.7	90	9.9
	91	9.3	40	9.7
	41	9.3	42	9.4
	43	9.4	44	10.1
	79	9.2		

CLAIMS

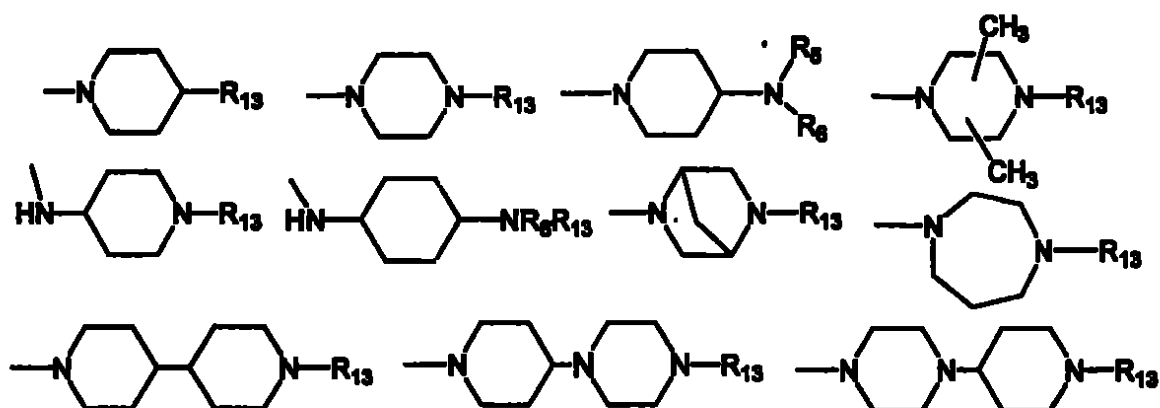
1. Compounds of general formula (I):



(I)

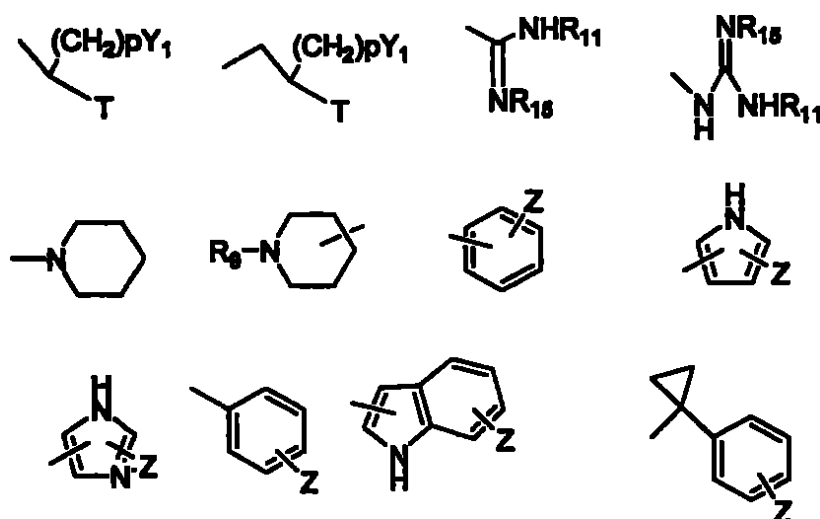
in which

- R_1 is a hydrogen atom or a C_1 - C_4 alkyl group;
- R_2 and R_3 , which can be the same or different, are a C_1 - C_4 alkyl group,
 10 or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms or a heterocyclic aliphatic group having 3 to 7 atoms, one or two of which are selected from the group N, O, S and the others being C atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen atom or a
 15 C_1 - C_4 alkyl group;
- X is selected from the group consisting of halogen, OR_1 , SR_1 , CN, C_1 - C_4 alkyl;
- B has at least one amino group with basic characteristics or a tetraalkylammonium group and can be selected from the group consisting of:
- 20 - $NR_6(CH_2)_nNHCOY$, $NR_6(CH_2)_nN(R_6)-Y$, $NR_6(CH_2)_nN(Y)_2$, NR_6Y , $N(Y)_2$, $N(Y)(CH_2)_pY_1$ and from the residues:

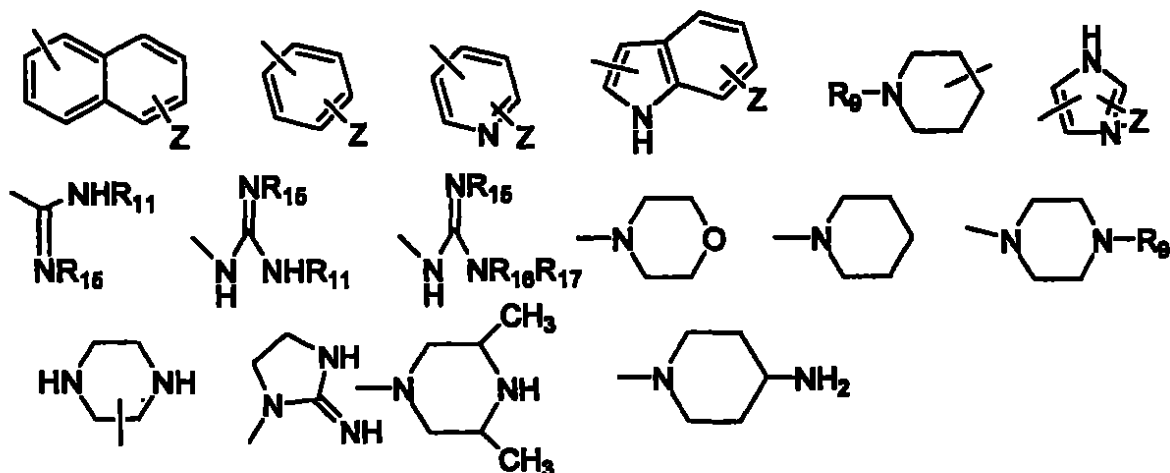


- **R₆ is a hydrogen atom, C₁-C₆ alkyl,**
- **n = 1-12 and**
- **Y is selected from: hydrogen, (CH₂)_pY₁, (CH₂)_pNR₆Y₁, (CH₂)_pN(Y₁)₂,**

5 NR_5R_6 , $-\text{NR}_6(\text{CH}_2)_9\text{Y}_1$ or from the following residues:



- T is selected from the group of $-NR_7R_8$, $-NR_{14}R_{18}R_{19}$, $-OR_6$;
- R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C₁-C₄ alkyl group, a cyclohexyl group, or NR_7R_8 together are a group selected from :i) guanidine optionally substituted with 1 or 2 C₁-C₄ alkyl or cyclohexyl groups, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- Y_1 is selected from the group consisting of NR_7R_8 , $NR_{14}R_{18}R_{19}$ or from the following residues:



- Z is selected from the group consisting of H, C₁-C₆ alkyl, OR₆, SR₆, CF₃, OCOR₆, COR₁₀, NHCOR₆, SO₂R₆, SOR₆, CO₂R₆, N(R₆)₂, Cl, Br, NO₂, NH₂, CN, F, imidazole, phenyl, amidine, guanidine, guanidyl-methyl;
- 5 - R₉ is selected from the group consisting of hydrogen, -(CH₂)_q-L, wherein L is selected from the group of -OH, -NR₃R₆, -NR₁₄R₁₈R₁₉, amidine optionally substituted with 1 or 2 C₁-C₄ alkyl groups, guanidine optionally substituted with 1 or 2 C₁-C₄ alkyl groups;
- R₁₀ is selected from the group consisting of OR₆, NR₆R₁₂;
- 10 - R₁₁ is selected from the group consisting of hydrogen, -(CH₂)_q-L, -(CH₂)_p-NR₄-(CH₂)_q-L;
- R₁₂ is a hydrogen atom, C₁-C₆ alkyl, COR₆,
- R₁₃ is selected from the group consisting of H, C₁-C₆ alkyl, -(CH₂)_pW(CH₂)_qY₁, Y, -COY, -CH₂-Y;
- 15 - R₁₅ is selected from the group consisting of hydrogen or straight or branched C₁-C₄ alkyl groups;
- the -NR₁₆R₁₇ group is a 5-7 membered nitrogen aliphatic heterocycle optionally containing another heteroatom selected from O, S, N;
- the -NR₁₄R₁₈R₁₉ group is a quaternary ammonium group in which: R₁₄
- 20 is selected from the group consisting of straight or branched C₁-C₄ alkyl groups, R₁₈ and R₁₉, which can be the same or different, are a straight or branched C₁-C₄ alkyl group, or -NR₁₈R₁₉ is a 5-7 membered nitrogen

heterocycle optionally containing another heteroatom selected from O, N, S.

- $W = CH_2, O, S, NR_4, N(R_4)_2$

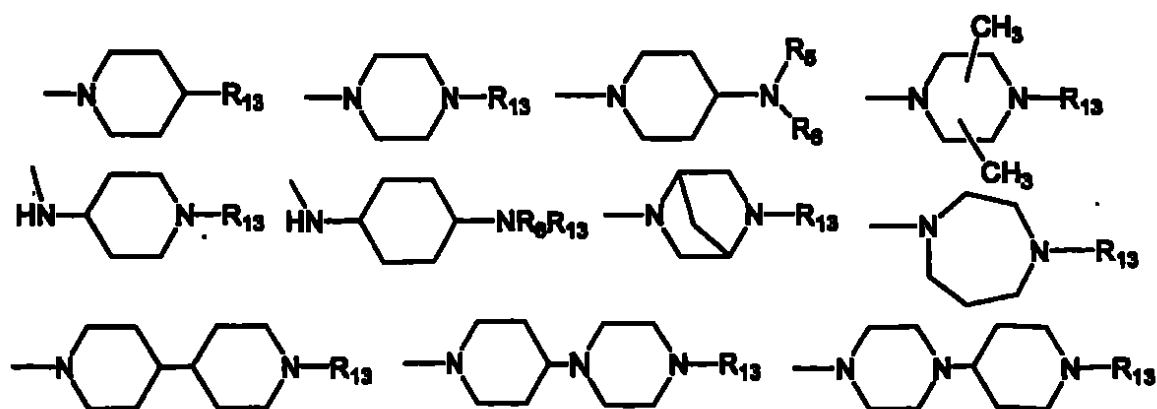
- $p = 1-6, q = 1-6$; and

the pharmacologically acceptable salts thereof with inorganic or organic acids

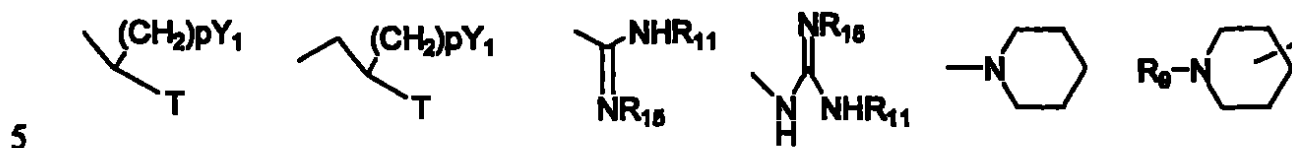
- 5 selected from the group of: hydrochloric, hydrobromic, hydroiodic, sulfuric, phosphoric, acetic, trifluoroacetic, propionic, oxalic, malic, maleic, succinic, malonic, aspartic, glutamic acids and possible optical isomers or their mixtures, including the racemates.

2. Compounds as claimed in claim 1, in which

- 10 - R_1 is a hydrogen atom or a C_1 - C_4 alkyl group;
- R_2 and R_3 , which can be the same or different, are a C_1 - C_4 alkyl group, or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms or a heterocyclic aliphatic group having 3 to 7 atoms one or two of which are selected from the group of
- 15 N, O, S and the other being C atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen atom or a C_1 - C_4 alkyl group;
- X is selected from the group consisting of halogen, OR_1 , SR_1 , CN, C_1 - C_4 alkyl;
- 20 - B has at least one amino group with basic characteristics or a tetraalkylammonium and can be selected from the group consisting of:

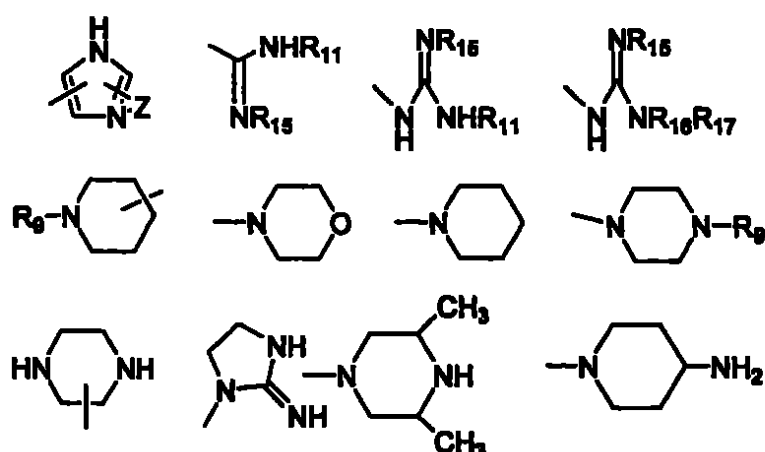


- R_6 is a hydrogen atom, C_1 - C_6 alkyl;
- Y is selected from: hydrogen, $(CH_2)_p Y_1$, $(CH_2)_p NR_6 Y_1$, $(CH_2)_p N(Y_1)_2$, $NR_5 R_6$, $-NR_6(CH_2)_p Y_1$ or from the following residues:



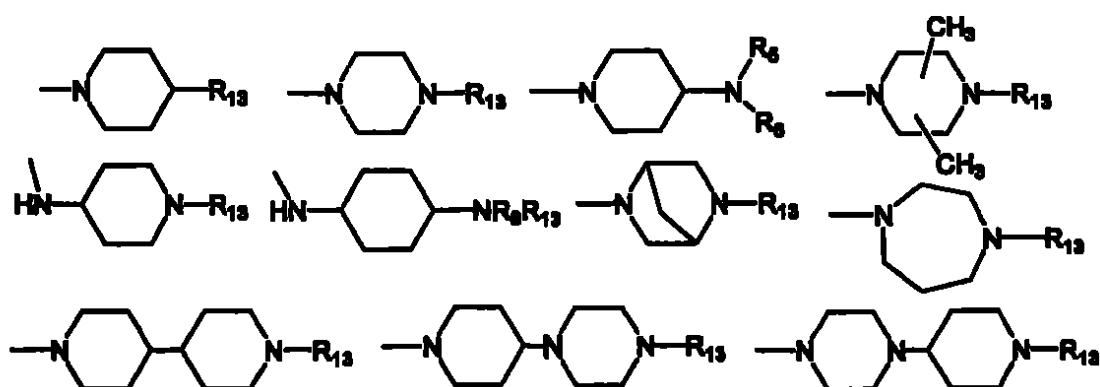
- T is selected from the group of $-NR_7 R_8$, $-NR_{14} R_{18} R_{19}$, $-OR_6$;
- R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C_1 - C_4 alkyl group, or $NR_7 R_8$ is a group selected from : i) guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, cyclohexyl, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- Y_1 is selected from the group consisting of $NR_7 R_8$, $NR_{14} R_{18} R_{19}$ or from the following residues:

15

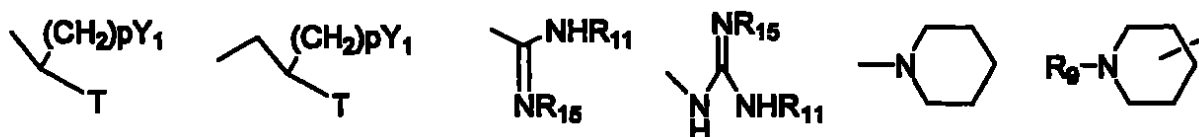


- Z is selected from the group consisting of H, C_1 - C_6 alkyl, OR_6 , SR_6 , CF_3 , $OCOR_6$, COR_{10} , $NHCOR_6$, $SO_2 R_6$, SOR_6 , $CO_2 R_6$, $N(R_6)_2$, C_1 , Br, NO_2 , NH_2 , CN, F, imidazole, phenyl, amidine, guanidine, guanidyl-methyl;
- R_9 is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, wherein L is selected from the $-OH$ group, $-NR_5 R_6$, $-NR_{14} R_{18} R_{19}$, amidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups;

- R_{10} is selected from the group consisting of OR_6 , NR_6R_{12} ;
- R_{11} is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, $-(CH_2)_p-NR_4-(CH_2)_q-L$;
- R_{12} is a hydrogen atom, C_1-C_6 alkyl, COR_6 ;
- 5 - R_{13} is selected from the group consisting of H, C_1-C_6 alkyl, $-(CH_2)_pW(CH_2)_qY_1$, Y , $-COY$, $-CH_2-Y$;
- R_{14} is selected from the group consisting of straight or branched C_1-C_4 alkyl groups;
- R_{15} is selected from the group consisting of hydrogen or straight or
10 branched C_1-C_4 alkyl groups;
- the $-NR_{16}R_{17}$ group is a 5-7 membered nitrogen aliphatic heterocycle optionally containing another heteroatom selected from O, S, N;
- the $-NR_{14}R_{18}R_{19}$ group is a quaternary ammonium group in which: R_{14} is selected from the group consisting of straight or branched C_1-C_4 alkyl
15 groups, R_{18} and R_{19} , which can be the same or different, are a straight or branched C_1-C_4 alkyl group, or $-NR_{18}R_{19}$ is a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- $W = CH_2, O, S, NR_4, N(R_4)_2$;
- $p = 1-6, q = 1-6$.
- 20 3. Compounds as claimed in claim 2, of general formula (I), in which:
- B is selected from the group consisting of the residues:



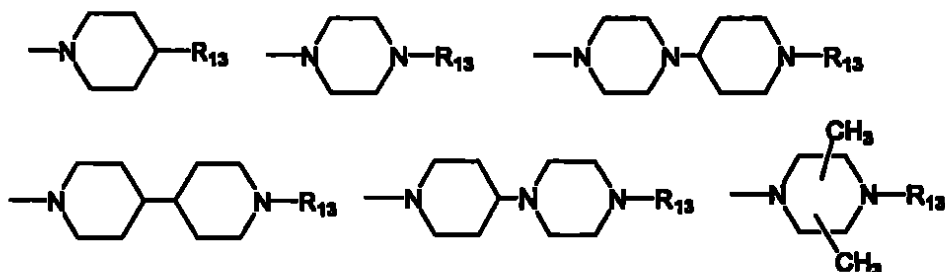
- Y is selected from: $(\text{CH}_2)_p\text{Y}_1$, $(\text{CH}_2)_p\text{NR}_6\text{Y}_1$, $(\text{CH}_2)_p\text{N}(\text{Y}_1)_2$, NR_5R_6 , or from the following residues:



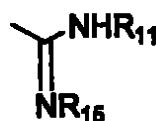
5 in which T is selected from the group of $-\text{NR}_7\text{R}_8$, $-\text{OR}_6$ and the other substituents are as defined in claim 2.

4. Compounds as claimed in claim 3, in which:

- R_1 is a hydrogen atom or methyl;
- R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl;
- X is a chlorine atom;
- 15 - B is a group selected from:



in which R_{13} is H, or a $\text{Y} = \text{Y}_1$ group in which Y_1 is



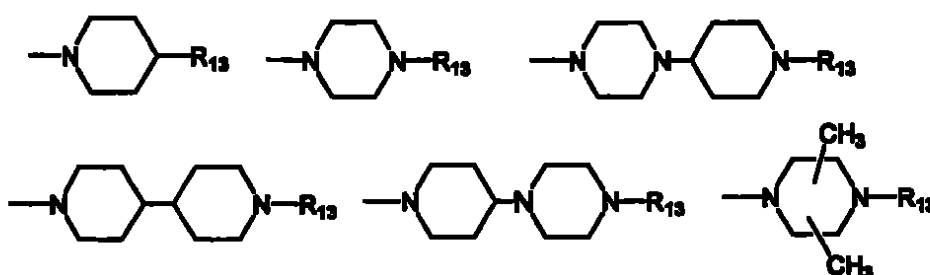
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- R_{11} is selected from the group consisting of hydrogen, $-(\text{CH}_2)_q\text{-L}$, $-(\text{CH}_2)_p\text{-NR}_4\text{-(CH}_2)_q\text{-L}$ wherein L is selected from $-\text{OH}$, $-\text{NR}_5\text{R}_6$, amidine optionally substituted with 1 or 2 $\text{C}_1\text{-C}_4$ alkyl groups, guanidine optionally substituted with 1 or 2 $\text{C}_1\text{-C}_4$ alkyl groups;

and the other substituents are as defined in claim 2.

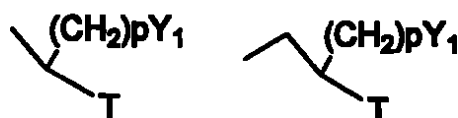
5. Compounds as claimed in claim 3, of general formula (I) in which:

- R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl,
- X is a chlorine atom;
- B contains at least two amino groups with basic characteristics, in the free or salified form, and is selected from the group of:



in which R_{13} is COY , CH_2Y , $-(CH_2)_pW(CH_2)_qY_1$,

- Y is a group $(CH_2)_pY_1$, or is selected from:

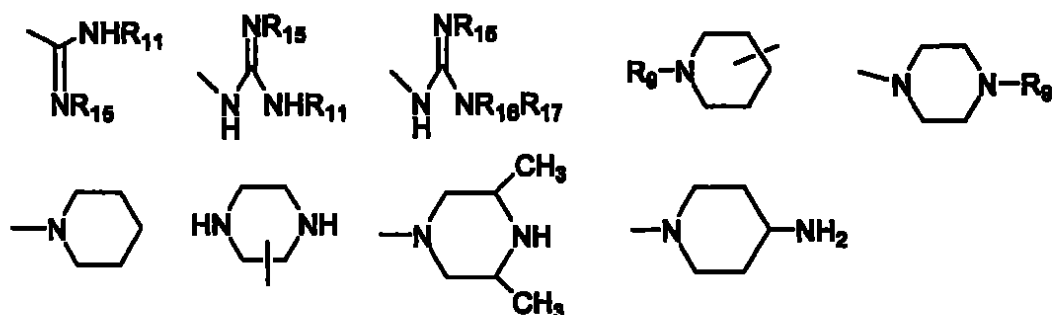


wherein T is selected from $-NR_7R_8$, $-OR_6$;

- R_7 and R_8 , which can be the same or different, are a hydrogen atom, a C_1 - C_4 alkyl group, or NR_7R_8 is a group selected from : i) guanidine optionally substituted with 1 or 2 C_1 - C_4 alkyl groups, cyclohexyl, ii) a 5-7 membered nitrogen heterocycle optionally containing another heteroatom selected from O, N, S;
- Y_1 is selected from the group consisting of $-NR_7R_8$ and from the residues

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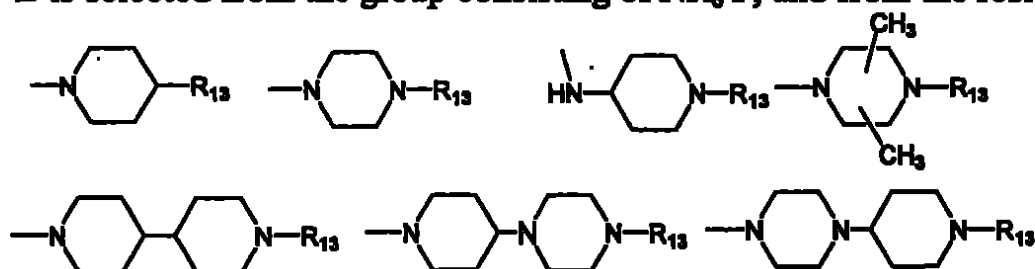
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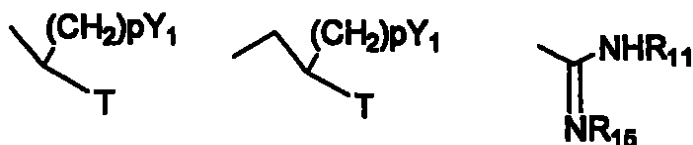
- R_9 is selected from the group consisting of hydrogen, $-(CH_2)_q-L$, wherein L is selected from the group $-NR_5R_6$, amidine optionally substituted with 1 or 2 C_1-C_4 alkyl groups, guanidine optionally substituted with 1 or 2 C_1-C_4 alkyl groups; and the other substituents are as defined in claim 2.

6. Compounds as claimed in claim 2, of general formula (I), containing at least one tetraalkyl ammonium, in which:

- R_1 is a hydrogen atom or methyl;
- 10 - R_2 and R_3 , which can be the same or different, are selected from methyl or ethyl, or R_2 and R_3 , together with the carbon atom which they are linked to, form a cyclic aliphatic group having 3 to 7 carbon atoms;
- R_4 and R_5 , which can be the same or different, are a hydrogen or a methyl;
- 15 - X is a chlorine atom;
- B is selected from the group consisting of NR_6Y , and from the residues:



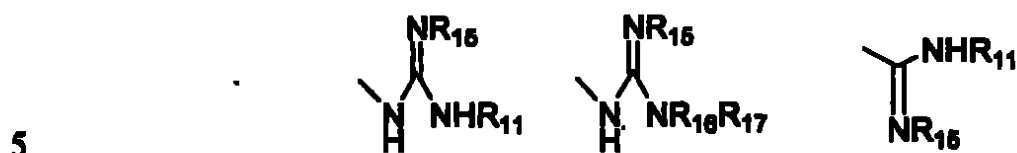
- Y is selected from: Y , COY , $(CH_2)_pY_1$, $NR_6(CH_2)_qY_1$ and from the residues:



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- T is selected from the group -NR₇R₈, -NR₁₄R₁₈R₁₉, -OR₆;
- Y₁ is selected from the group consisting of -NR₇R₈, -NR₇R₈R₁₄ or from the following residues:



and the other substituents are as defined in claim 2.

7. Compounds of general formula (I), as claimed in claims 1 to 6, which are:

- N-[2-[4-(2-(S)-amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonamide trifluoroacetate;
- N-{2-[4-(6-guanidinohexyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)benzenesulfonamido -2-methyl-propionamide tris trifluoroacetate;
- 4-{2-[2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzene-sulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine;
- N-[2-[4-(2-(S)-amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{2-[4-(6-aminohexyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{2-[4-(piperazin-2-yl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{2-[4-(piperazin-1-ylacetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzene-

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- sulfonamide bis trifluoroacetate;
- N-{2-[4-2-(piperidin-4-yl-acetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzene-sulfonamide bis trifluoroacetate;
- 5 - N-{2-[4-[N-(4-piperidyl)glycyl]-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzene-sulfonamide tris trifluoroacetate;
- N-{2-[4-(4-(2-aminoethyl)piperazin-1-yl)acetyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tetra trifluoroacetate;
- 10 - N-{2-[4-(3-(R)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{2-[4-(3-(S)-amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 15 - N-{2-[4-(3-(S)-amino-7-dimethylamino-heptanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 20 - N-(3-Amino-propyl)-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine tris trifluoroacetate;
- N-[2-[4-(2-(S)-amino-5-dimethylamino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-8-quinolinoxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 25 - (S)-N-{2-[1'-(2-Amino-5-guanidino-pentanoyl)-[4,4']bipiperidiny-1-yl]-1,1-dimethyl-2-oxo-ethyl}-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide;

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- 2,4-Dichloro-N-(2-{4-[2-(3,5-dimethyl-piperazin-1-yl)-ethyl]-3,5-dimethyl-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-3-(2-methyl-4a,8a-dihydro-quinolin-8-yloxymethyl)-benzenesulfonamide;
- N-(2-{4-[4-(2-(S)Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-piperidin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid [1-(4-piperazin-1-yl-piperidine-1-carbonyl)-cyclopentyl]-amide;
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (1-{4-[4-(2-S-amino-6-guanidino-hexanoyl)-piperazin-1-yl]-piperidine-1-carbonyl}-cyclopentyl)-amide;
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (1-{4-[4-(2-S-amino-5-guanidino-pentanoyl)-piperazin-1-yl]-piperidine-1-carbonyl}-cyclopentyl)-amide;
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfinic acid [1-(4-piperidin-4-yl-piperazine-1-carbonyl)-cyclopentyl]-amide;
- 2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid {2-[4-(2-guanidino-ethyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl}-amide;
- 2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (2-{4-[2-S-amino-5-(N',N''-diethyl-guanidino)-pentanoyl]-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-amide;
- 2,4-Dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfinic acid (2-{4-[2-R-amino-5-(N',N''-diethyl-guanidino)-pentanoyl]-piperazin-1-yl}-1,1-dimethyl-2-oxo-ethyl)-amide;
- (2S)-N-(1-{4-[2-Amino-6-(N',N''-diethyl-guanidino)-hexanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;

- N-(1-{4-[2-(S)-Amino-6-(N',N''-diethyl-guanidino)-pentanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- N-[2-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- N-[2-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- 10 - N-[2-[4-(3-(S)-Amino-6-dimethylamino-heptanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy methyl)-benzenesulfonamide;
- N-[2-[4-(2-(S)-Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- 15 - N-[2-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- N-[2-[4-(2-(S)-Amino-5-dimethylamino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- 20 - N-[2-[4-(2-(R)-Amino-5-guanidino-pentanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonamide;
- 25 - N-[2-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonamide;
- N-[2-[4-(3-(S)-Amino-7-guanidino-heptanoyl)-piperazin-1-yl]-1,1-

- dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonamide;
- N-{2-[4-(4-2(Guanidino)ethyl)piperazin-1ylacetyl]-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide;
- 5 - N-[1-[4-(2-(S)-Amino-5-guanidino-pentanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-[1-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 10 - N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 15 - N-[1-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 20 - (R)-N-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- (R)-N-[1-[4-(2-(S)-Amino-6-dimethylamino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 25 - N-{2-[4-(4-2(Guanidino)ethyl)piperazin-1ylacetyl]-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-

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- yloxymethyl)-benzenesulfonamide tetra trifluoroacetate;
- N-[1-[4-(2-(R)-Amino-6-amino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
 - 5 - N-[1-[4-(2-(R)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
 - N-[2-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
 - 10 - N-[2-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazin-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
 - N-[1-[4-(6-Guanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate;
 - 15 - N-[2-[4-(2-(S)-Amino-6-amino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
 - 20 - N-[2-[4-(2-(S)-Guanidino-6-guanidino-hexanoyl)-piperazin-1-yl]-1,1-dimethyl-2-oxo-ethyl]-2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonamide tris trifluoroacetate;
 - (R)-N-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy-methyl)-benzenesulfonamide tris trifluoroacetate;
 - 25 - (R)-N-{2-[4-(4-2(Guanidino)ethyl)piperazin-1ylacetyl]-piperazin-1-carbonyl}-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetra trifluoroacetate;

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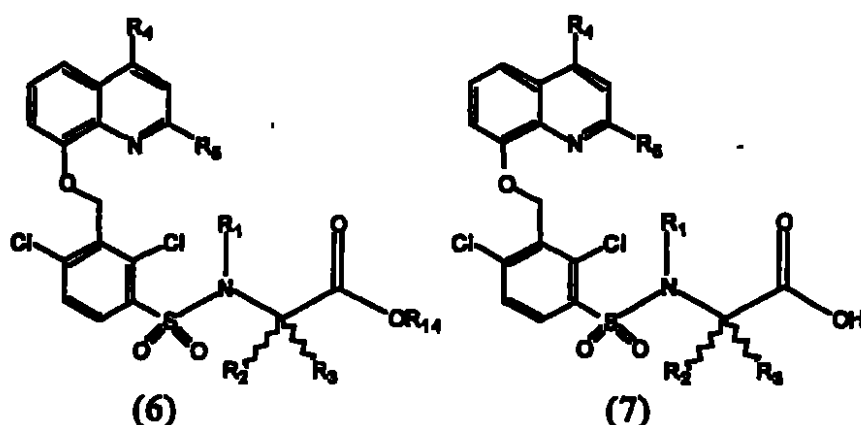
- (R)-N-[4-(3-(S)-Amino-6-amino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- (R)-N-[4-(3-(S)-Guanidino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- (R)-N-[4-(3-(S)-Amino-6-dimethylamino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 10 - (S)-N-[4-(2-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy-methyl)-benzenesulfonamide tris trifluoroacetate;
- (S)-N-[4-(3-(S)-Amino-6-guanidino-hexanoyl)-piperazine-1-carbonyl]-1-methyl-propyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxy-methyl)-benzenesulfonamide tris trifluoroacetate;
- 15 - 2,4-Dichloro-N-{1-[4-(3(S),6-diamino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 2,4-Dichloro-N-{1-[4-(3(S),6-diguanidino-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 20 - N-(1-{4-[3-(S),6-Bis-(N',N''-dicyclohexyl-guanidino)-hexanoyl]-piperazine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 25 - N-{1-[4-(2-(S)Amino-3-piperidin-4-yl-propionyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{1-[4-(2-Trimethylammonium-acetyl)-piperazine-1-carbonyl]-

- cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate;
- 5 - N-{1-[4-(4-Trimethylammonium-butanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate;
- N-{1-[4-(3(R)-Hydroxy-4-trimethylammonium-butanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide bis trifluoroacetate;
- 10 - N-[1-[4-(2-(S)-Dimethylamino-6-dimethylamino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- {5-[(1-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperidin-4-ylmethyl)-dimethyl-ammonium]pentyl}-trimethyl-ammonium tris trifluoroacetate;
- 15 - {5-[(1-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperidine-4-carbonyl)-amino]-pentyl}-trimethyl-ammonium bis trifluoroacetate;
- N-[1-[4-(2-(S)-Trimethylammonium-6-trimethylammonium-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 20 - N-[1-[4-(2-(R)-Trimethylammonium-6-trimethylammonium-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-[1-[4-(2-(S)-Trimethylammonium-6-amino-hexanoyl)-piperazin-1-yl]-cyclopentyl]-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 25 - N-{1-[4-(6-Trimethylammonium-hexanoyl)-piperazine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-

- benzenesulfonamide bis trifluoroacetate;
- N-(6-Amino-hexyl)-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxy-methyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine;
 - 5 - N-[2-(3-Amino-propylamino)-ethyl]-4-{2-[2,4-dichloro-3-(2-methyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-1-carboxamidine;
 - N-(3-Amino-propyl)-4-{2-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-2-methyl-propionyl}-piperazine-10 1-carboxamidine bis trifluoroacetate;
 - N-(6-Amino-hexyl)-4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboxamidine bis trifluoroacetate;
 - N-[2-(3-Amino-propylamino)-ethyl]-4-{1-[2,4-dichloro-3-(2,4-15 dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboxamidine bis trifluoroacetate;
 - N-[2-(4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazin-1-yl)-ethyl]-4-methyl-piperazine-1-carboxamidine bis trifluoroacetate;
 - 20 - 2,4-Dichloro-N-{1-[4-(2(R),6-diamino-hexyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tetra trifluoroacetate;
 - 2,4-Dichloro-N-{1-[4-(2(R),6-diguanidino-hexyl)-piperazine-1-carbonyl]-cyclopentyl}-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-25 benzenesulfonamide tetrahydrochloride
 - 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-{1-[4-(2-piperazin-1-yl-ethyl)-piperazine-1-carbonyl]-cyclopentyl}-benzenesulfonamide tetra trifluoroacetate;

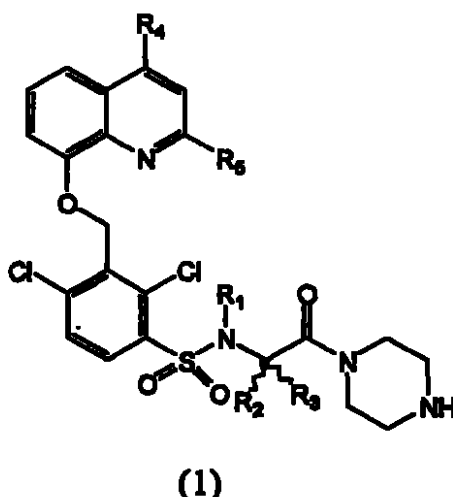
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-{1-[4-(2-piperidin-4-yl-ethyl)-piperazine-1-carbonyl]-cyclopentyl}-benzenesulfonamide;
- {3-[(4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazine-1-carboximidoyl)-amino]propyl}-trimethyl-ammonium tris trifluoroacetate;
- 4-{1-[2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-N-(3-dimethylamino-propyl)-piperazine-1-carboxamidinium tris trifluoroacetate;
- N-(1-{4-[(5-Amino-pentylamino)-methyl]-piperidine-1-carbonyl}-cyclopentyl)-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- N-{1-[4-(4-Amino-piperidin-1-ylmethyl)-piperidine-1-carbonyl]-cyclopentyl}-2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonamide tris trifluoroacetate;
- 2,4-Dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-N-(1-{4-[(5-methylamino-pentylamino)-methyl]-piperidine-1-carbonyl}-cyclopentyl)-benzenesulfonamide tris trifluoroacetate;
- Amino-6-(4-{1-[2,4-dichloro-3-(2,4-dimethyl-quinolin-8-yloxymethyl)-benzenesulfonylamino]-cyclopentanecarbonyl}-piperazin-1-yl)-6-oxohexyl]-trimethyl-ammonium bis trifluoroacetate.

8. Intermediates of general formula (6) or (7)



- 5 in which R_1 can be H or methyl, R_2 and R_3 can be independently methyl, ethyl or, together with the carbon atom which they are linked to, form a cyclopentyl group, and R_{14} is methyl or t-butyl.

9. Intermediates of general formula (1)



10

in which R_1 can be H or methyl, R_2 and R_3 can be independently methyl, ethyl or, together with the carbon atom which they are linked to, form a cyclopentyl group.

- 15 10. Pharmaceutical compositions containing as active ingredient a compound as claimed in any one of claims 1 to 7, together with pharmaceutically acceptable excipients, for the treatment of disorders in which the use of a bradykinin antagonist is needed.

11. The use of a compound as claimed in any one of claims 1 to 7, for the

preparation of pharmaceutical compositions for the treatment of disorders in which the use of a bradykinin antagonist is needed.

12. The use of a compound as claimed in claim 11 for the preparation of pharmaceutical compositions for the treatment of inflammatory, allergic and
5 autoimmune disorders.

13. The use of a compound as claimed in claim 11 for the preparation of pharmaceutical compositions for the treatment of disorders such as asthma and chronic bronchitis, allergic, vasomotor and viral rhinitis, obstructive pulmonary disease (COPD), rheumatoid arthritis, chronic inflammatory
10 diseases of the bowel (Crohn's disease and ulcerative colitis), glomerulonephritis, psoriasis, rash, acute and chronic cystitis, hepatic cirrhosis, glomerulopathies and pulmonary fibrosis, arteriosclerosis, both acute and chronic pain, septic, allergic and post-traumatic shocks, hepatic cirrhosis by hepatorenal syndrome, hypotension, alopecia, or as anticancer and
15 antiangiogenetics.

Internet	Location No
PCT/EP	03/05893

IPC 7 A61K31/47 C07D215/26 C07D401/12 A61P29/00

2. FIELDS SEARCHED

IPC 7 C07D

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

EPO-Internal. WPI Data. PAJ. CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 5 968 951 A (BARTH MARTINE ET AL) 19 October 1999 (1999-10-19) claims 1,11,12	1-13
Y	US 6 063 791 A (BARTH MARTINE ET AL) 16 May 2000 (2000-05-16) claims 1,6	1-13
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	-/-	

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

X Patent family members are listed in annex.

• Special categories of other documents:

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

'8' document member of the same racial family

19 August 2003

09/09/2003

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Berillon, L.

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 03/05893

021

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 140 341 A (SCHOELKENS BERNWARD ET AL) 31 October 2000 (2000-10-31) see abstract and claim 1	1-13

Form PCT/ISA/210 (continuation of second sheet) (July 2002)

021

INTERNATIONAL SEARCH REPORT

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Intern Application No
PCT/EP 03/05893

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BIBDOCID: <WQ____03103871A1_L>

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter Application No
PCT/EP 03/05893

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		ZA 9702129 A	15-09-1997

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(21) International Application Number:
PCT/EP2003/005893

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CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD,
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European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO,
SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM,
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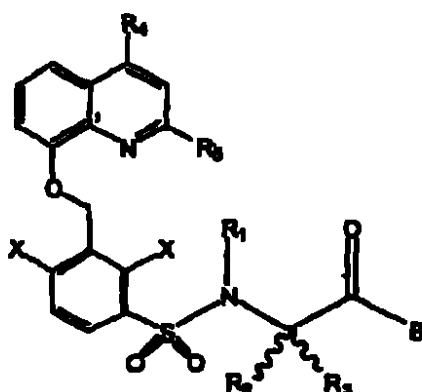
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*For two-letter codes and other abbreviations, refer to the "Guid-
ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: BASIC NON-PEPTIDE BRADYKININ ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREFROM



(I)

(57) Abstract: Non-peptide compounds of formula (I) having activity as specific antagonists of bradykinin (BK) B2 receptor. The compounds are chemically characterized by the presence of an alpha, alpha-disubstituted amino acid at least one amino group, free or saltified, or the corresponding ammonium quaternary salt. These BK receptor antagonists are a novel class of medicaments which can be used in all the disorders in which said receptors are involved.

WO 2003/103671 A1

Fax Confirmation

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REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

PCT/EP2005 / 010412 -
International Application No.(27.09.2005) 27 SEP 2005
International Filing DateEUROPEAN PATENT OFFICE
PCT INTERNATIONAL APPLICATION
Name of receiving Office and "PCT International Application"Applicant's or agent's file reference
(if desired) (12 characters maximum) SCB 969 PCT

Box No. I TITLE OF INVENTION

"NON-PEPTIDE BRADYKININ ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS THEREFROM"

Box No. II APPLICANT

☐ This person is also inventor

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This person is applicant
for the purposes of:☐ all designated
States☒ all designated States except
the United States of America☐ the United States
of America only☐ the States indicated in
the Supplemental Box

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This person is:

☐ applicant only☒ applicant and inventor☐ inventor only (If this check-box is
marked, do not fill in below.)

Applicant's registration No. with the Office

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State (that is, country) of residence:

IT

This person is applicant
for the purposes of:☐ all designated
States☐ all designated States except
the United States of America☒ the United States
of America only☐ the States indicated in
the Supplemental Box☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The person identified below is hereby/has been appointed to act on behalf
of the applicant(s) before the competent International Authorities as:

☒ agent☐ common
representative

Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.)

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<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
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State <i>(that is, country)</i> of nationality: GB	State <i>(that is, country)</i> of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> GIOLITTI, Alessandro Via Vittorio Emanuele II, 239 50134 FIRENZE Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: IT	State <i>(that is, country)</i> of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> MAGGI, Carlo Alberto Via Michelazzi, 43 50141 FIRENZE Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: IT	State <i>(that is, country)</i> of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> QUARTARA, Laura Via delle Cascine, 22 50144 FIRENZE Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: IT	State <i>(that is, country)</i> of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
<i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> ROSSI, Cristina Via E. Berlinguer, 14 00040 POMEZIA (RM) Italy	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality: IT	State <i>(that is, country)</i> of residence: IT
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State <i>(that is, country)</i> of nationality:	State <i>(that is, country)</i> of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATIONS

The filing of this request constitutes under Rule 4.9(a), the designation of all Contracting States bound by the PCT on the international filing date, for the grant of every kind of protection available and, where applicable, for the grant of both regional and national patents.

However,

☐ DE Germany is not designated for any kind of national protection

☐ KR Republic of Korea is not designated for any kind of national protection

☐ RU Russian Federation is not designated for any kind of national protection

(The check-boxes above may be used to exclude (irrevocably) the designations concerned in order to avoid the ceasing of the effect, under the national law, of an earlier national application from which priority is claimed. See the Notes to Box No. V as to the consequences of such national law provisions in these and certain other States.)

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 15 October 2004 (15.10.2004)	MI2004A001983	IT		
item (2)				
item (3)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)).

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

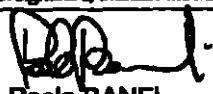
ISA /

Request to use results of earlier search; reference to that search (if an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) on paper, the following number of sheets: request (including declaration sheets) : 5 description (excluding sequence listing and/or tables related thereto) : 17 claims : 3 abstract : 1 drawings : Sub-total number of sheets : 26 sequence listing : tables related thereto : (for both, actual number of sheets if filed on paper, whether or not also filed in electronic form; see (c) below) Total number of sheets : 26 (b) ☐ only in electronic form (Section 801(a)(i)) (i) ☐ sequence listing (ii) ☐ tables related thereto (c) ☐ also in electronic form (Section 801(a)(ii)) (i) ☐ sequence listing (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listing: ☐ tables related thereto: (additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☐ fee calculation sheet : 2. ☐ original separate power of attorney : 3. ☐ original general power of attorney : 4. ☐ copy of general power of attorney; reference number, if any: : 5. ☐ statement explaining lack of signature : 6. ☐ priority document(s) identified in Box No. VI as item(s): : 7. ☐ translation of international application into (language): : 8. ☐ separate indications concerning deposited microorganism or other biological material : 9. ☐ sequence listing in electronic form (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing mentioned in left column : 10. ☐ tables in electronic form related to sequence listing (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : 11. ☒ other (specify): (Request for fax acknowledgement) : (A) C-1 2/68
Figure of the drawings which should accompany the abstract:	Language of filing of the international application: ENGLISH	
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).  Dr. Paolo BANFI 27 September 2005 (27.09.2005)		

For receiving Office use only		
1. Date of actual receipt of the purported international application:	(27.09.2005) 27 SEP 2005	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:		
4. Date of timely receipt of the required corrections under PCT Article 1(2):		
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid	
For International Bureau use only		
Date of receipt of the record copy by the International Bureau:		



No. 07-048163-00000-0000

Fecha: 2007-05-09 15:51:18 Dep. 2020 NUECREACIONE
Tm. 11 PATENTEIYI Eje: 379 FASENACIONALI
Act. 411 PRESENTACION Folios: 127



Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

☒

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente [4]
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud [2]
- ◆ Descripción de la invención [2]
- ◆ Dibujos de ser estos pertinentes [X]
- ◆ Comprobante de pago de las tasas establecidas [4]

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

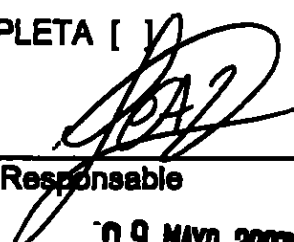
INCOMPLETA []

ESQUEMA DE TRAZADO []

- ◆ Indicación de que se solicita el registro de un Esquema de Trazado []
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud []
- ◆ Representación gráfica del esquema trazado []
- ◆ Comprobante de pago de las tasas establecidas []

COMPLETA []

INCOMPLETA []


Firma Responsable

Fecha

09 MAYO 2007

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@slc.gov.co
www.slc.gov.co
Bogotá, D.C., Colombia

129
921

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
RODRIGUEZ DILIA MARIA

REFERENCIA	Radicación No.	7 46163
	Solicitud internacional	PCT/EP2005/010412
	Fecha inicio fase nacional	15/05/2007
	Trámite	11
	Evento	379
	Actuación	430
	Oficio No.	

8502

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

1. Si fuere el caso, el solicitante debe adjuntar la traducción de los anexos del reporte de examen preliminar internacional (Art. 36.2.b) del tratado PCT.
2. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486. Cuando se trate de documentos otorgados en el extranjero, deben legalizarse de conformidad con lo dispuesto por los artículos 259 y 260 del Código de Procedimiento Civil.
3. La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Unica No.10 de 2001.

Continúa en la página siguiente...

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Radicación No.: 7 46163

Clara C. de Jaimes

CLARA C. DE JAIMES

Jefe de la división de Nuevas Creaciones (E)

El anterior requerimiento fue notificado por fijación en lista de
fecha _____ 13 JUL. 2001
adpall