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2-aryl-propionamide derivatives useful as bradykinin receptor antagonists and pharmaceutical compositions containing them

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(54) Title: 2-ARYL-PROPIONAMIDE DERIVATIVES USEFUL AS BRADYKININ RECEPTOR ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM

(57) Abstract: (R,S) 2-aryl-propionamide derivatives, or their single enantiomers (R) and (S) are disclosed useful in the treatment or prevention of symptoms and disorders such as pain and inflammation associated with the bradykinin B1 pathway.

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"2-ARYL-PROPIONAMIDE DERIVATIVES USEFUL AS BRADYKININ RECEPTOR ANTAGONISTS AND PHARMACEUTICAL COMPOSITIONS CONTAINING THEM"

Field of the invention

The present invention relates to (R,S) 2-aryl-propionamide derivatives, their single enantiomers (R) and (S) for use in the treatment or prevention of symptoms and disorders such as pain and inflammation associated with the bradykinin B1 pathway.

Background of the invention

The nonapeptide bradykinin (BK) and the physiologically-related decapeptide kallidin (KD) are endogenous vasoactive peptides generated as short-lived components of the kallikrein-kinin system. They play a key role in the regulation of normal physiological processes in the peripheral (PNS) and central (CNS) nervous systems and are effectors of a number of inflammatory responses, including bronchoconstrition, plasma extravasation, release of prostaglandins and leukotrienes, smooth muscle contraction and relaxation and nociception [Austin C.E. et al., *J. Biol. Chem.* (1997) 272, 11420-11425; Hess J.F. et al. *Biochem. Biophys. Res. Commun.* (1992) 184, 260-268]. Under pathophysiological conditions, elevated levels of kinins are rapidly produced from the circulating precursors kininogens by enzymatic action of trypsine-like serine proteases, kallikrein and tissue kallikrein. Kinins exert their action interacting with two cell surface receptors, BKB1R and BKB2R, belonging to the 7TM-GPCR superfamily. Through the $G\alpha_q$ protein subunit they stimulate the phospholipase C-dependent pathway to increase the intracellular free calcium concentration and inositol phosphate formation, while through the $G\alpha_i$ subunit activation they inhibit adenylcyclase and, by consequence, the formation of cAMP. BKB2Rs are constitutively expressed in most cells and tissue types and mediate the most part of acute effects due to BK and KD after their production in plasma and tissues, respectively. BKB1Rs are poorly constitutively expressed under physiological conditions and are induced following inflammatory insults or noxious stimuli, although recent data show the presence of constitutive BKB1Rs in rat and mouse CNS, making BKB1R a particularly attractive drug target.

Overproduction of kinins under pathophysiological conditions is implicated in the pathogenesis of a number of clinically-relevant disorders, including pain, inflammation, hypotension, asthma, colitis, rhinitis, pancreatitis, sepsis and rheumatoid arthritis [Leeb-

Lundberg L.M.F. et al., *Pharmacol. Rev.* (2005) 57, 57, 27-77]. BK is also implicated in peripheral inflammatory processes associated with Alzheimer's disease [Huang H.M. et al., *J. Neurochem.* (1995) 64, 761-766 and Yong Y.I. et al., FASEB J (2003) vol. 17:2319-2321], in multiple sclerosis (Prat A. et al., Neurology (1999), vol.53: 2087) in the growth of several solid tumors[Stewart J.M. *Curr. Pharm.Design* (2003) 9, 2036-2042] and is also thought to play a role in cardiovascular diseases [Heitsch H. *Expert Opin. Investig. Drugs* (2003) 12, 759-770] as evidenced by BKB2R antagonists in alleviating congestive heart failure, hypertension and ischemic heart disease. The BK plays also a key role in chronic inflammatory bowel diseases such as Chron's disease and ulcerative colitis as demonstrated by the presence of bradikinin receptor BR1 and BR2 in the intestine of patients affected by said pathologies (Stadnicki A. et al., Am J Physiol Gastrointest Liver Physiol (2005), vol. 289: G316-G366). Moreover it was demonstrated that high levels of bradykinin may participate in the pathogenesis and symptomatology of interstitial cystitis (Rosamilia A. et al., Journal of Urology Vol. 162, 129-134 July, 1999). The putative role of kinins, specifically BK, in the management of pain and inflammation has been well documented [Marceau F. et al. *Nat. Rev. Drug Discov.* (2004) 3, 845-852] and has provided impetus to the development of potent and selective BK antagonists. The BKB1R is an attractive target to treat inflammation because it is absent in normal tissues in most systems but it is inducible following tissue injury under the control of inflammatory cytokines, mitogen-activated protein kinase (MAPK) pathways and some transcription factors such as nuclear factor κB (NF-κB). BKB1R is more resistant than BKB2R to desensitization [Marceau F. et al. *Pharmacol. Rev.* (1998) 50, 357-386] making BKB1R antagonism more adapted to chronic or persistent inflammatory systems than BKB2R antagonism. More, the proposed protective effect of kinins mediated by the endothelial BKB2Rs on microcirculation in ischemia, diabetes and other pathological situations is a potential concern limited to BKB2R antagonists. On these basis, several research programs, also by industrial organizations, have been developed for the identification of novel non-peptide ligands binding BKB1 receptors replacing classical peptide antagonists. In recent years these efforts have been heightened with the expectation that useful therapeutic agents with anti-inflammatory properties would provide relief from diseases mediated by a BK receptor pathway [Bock M.G. et al. *Current Opinion in Chem. Biol.* (2000) 4, 401-406].

Non peptide BKB1R antagonists have appeared in the literature since the year 2000 and several of the disclosed structures, generated by different laboratories and belonging to different chemical classes, seem to share a possible common pharmacophore determined by the presence of a common moiety "RN-SO_2-phenyl" [Marceau F. *TRENDS Pharmacol. Sc.* (2005) 26, 116-118] that has allowed to derive a hypothesis of docking to the human B1 receptor and suggests structural communities and a preferential molecular mode of action within the selected compounds.

Along the last few years several classes of non peptide BKB1R antagonists have been disclosed. Three main classes have been claimed by several pharmaceutical companies: N-(Arylsulfonyl)aminoacid derivatives [Sanofi WO9725315 (1997); Novartis WO 00075107 (2000) and WO02092556 (2002); Bayer AG WO03007958 (20039; Elan Pharmaceuticals WO03093245 (2003); Lab. Fournier SA FR2840897 (2003); Merck & Co. INC. WO2004/054584 (2004)]; Biaryl derivatives [Pharmacopeia Inc. WO0105783 (2001); Merck & Co. INC. US2004034064 (2004), US2004029920 (2004), US 2004063761 (2004) and finally also US 2006/0111392]; Benzodiazepine derivatives [Merck & Co. INC. WO02099388 (2002)].

The Applicant has found that the single enantiomer R and/or S of specific classes of 2-arylpropionic acid derivatives show inhibitory activity of chemiotaxis of PMN leukocytes induced by IL-8 and/or chemiotaxis of PMN leukocytes and monocytes induced by C5a, rendering these compounds particularly useful: in the treatment of pathologies associated with these mechanisms of action such as: sepsis, psoriasis, ulcerative colitis, rheumatoid arthritis, melanoma, bullous pemphigus and pemphigoid, chronic obstructive pulmonary disease (COPD) and in particular acute respiratory distress syndrome (ARDS), idiopathic fibrosis, glomerulonephritis, and in the prevention and treatment of injury caused by ischemia and reperfusion.

For example:

- WO2006/06399 disclose that the (R)-2-phenylpropionamides and (R)-2-phenylpropionylsulphonamides show a surprising potent inhibitory effect on C5a induced PMN chemotaxis.
- WO02/068377 disclose that the whole class of omega amminoalkylamides of (R)-2-arylpropionic acid show inhibitory effect on C5a induced PMN and monocytes and only a selected class of these compounds also show a strong inhibitory activity of IL-8 induced PMN chemotaxis.

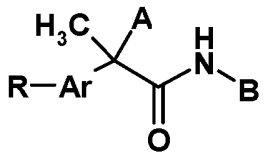
- WO2005/090295 disclose that the 2 (R)-(4-trifluoro-methane-sulphonyloxyphenyl)propionylamides, are able to inhibit the chemotactic activation of neutrophils (PMN leukocytes) induced by the interaction of IL-8 with CXCR1 and CXCR2 membrane receptors.
- WO2005028425 discloses that the 2 arylpropionamides amidine derivatives or the corresponding single (R) or (S) enantiomers exhibit inhibiting activity of the PMN chemiotaxis induced by IL-8.
- WO2008/075184 discloses that the 2 aryl-2-fluoro-propionic acid derivatives or the single R or S enantiomer inhibit chemiotaxis of PMN induced by IL-8.

Summary of the invention

The Applicant has now found that specific 2-arylpropionamide derivatives are also selective B1 bradykinin antagonists. Said compounds are therefore useful in the treatment of pathologies depending on the bradykinin pathways B1 receptor-dependent.

The present invention as claimed herein is described in the following items 1 to 22:

1. Use of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

A is selected from the group consisting of H, CH_3 and F;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl, C_2-C_8-alkenyl or C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl;

-optionally substituted 5 -6-membered heterocyclic residues; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

-$(CH_2)_n$-$(NH)_p$-Y wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

-$(CH_2)_n$-Z-$(CH_2)_{n'}$-A wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from -CONH-, -O-, -NCH_3-, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

-CHR_aR_b, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, -CH_2-NHCOO-C_1-C_4-alkyl, -(COO)C_1-C_4-alkyl;

wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido;

for the preparation of a medicament for the treatment and prevention of diseases and conditions mediated by Bradykinin B1 receptor pathway wherein said diseases and conditions are selected from pain, hyperreactive airways and inflammatory diseases and events associated with airway diseases, inflammatory bowel diseases, inflammatory skin disorders, edema resulting from burns, sprains and fractures, cerebral edema and angioedema, diabetic vasculopathy, diabetic neuropathy, diabetic symptoms associated with insulitis, liver disease, cardiovascular disease, congestive heart failure; myocardial infarct; neurodegenerative diseases, epilepsy, septic shock, headache, migraine, closed

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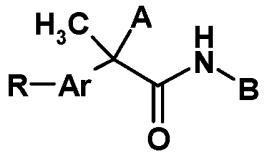
head trauma, cancer, sepsis, gingivitis, osteoporosis, benign hyperplasia and hyperactive bladder, interstitial cystitis,

provided that when A = H or F

said diseases mediated by Bradykinin B1 receptor pathway are different from: rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ulcerative colitis, psoriasis, sepsis, melanoma, and heart ischemia.

2. A method of treatment or prevention of a disease or a condition mediated by Bradykinin B1 receptor pathway comprising administration to a patient in need thereof a pharmaceutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

A is selected from the group consisting of H, CH_3 and F;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl or C_2-C_8-alkenyl, C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl;

-optionally substituted 5 -6-membered heterocyclic residues; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

$-(CH_2)_n-(NH)_p-Y$ wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

$-(CH_2)_n-Z-(CH_2)_{n'}-A$ wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from –CONH-, -O-, $-NCH_3-$, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

$-CHR_aR_b$, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, $-CH_2-NHCOO-C_1-C_4$-alkyl, -(COO)C_1-C_4-alkyl;

wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido;

wherein said disease or condition mediated by Bradykinin B1 receptor pathway is selected from pain, hyperreactive airways and inflammatory diseases and events associated with airway diseases, inflammatory bowel diseases, inflammatory skin disorders, edema resulting from burns, sprains and fractures, cerebral edema and angioedema, diabetic vasculopathy, diabetic neuropathy, diabetic symptoms associated with insulitis liver disease, cardiovascular disease, congestive heart failure; myocardial infarct; neurodegenerative diseases, epilepsy, septic shock, headache, migraine, closed head trauma, cancer, sepsis, gingivitis, osteoporosis, benign hyperplasia and hyperactive bladder, interstitial cystitis,

<u>provided that</u> when A = H or F

said disease mediated by Bradykinin B1 receptor pathway is different from: rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ulcerative colitis, psoriasis, sepsis, melanoma, and heart ischemia.

3. Use of item 1 or method of item 2, wherein Ar is selected from phenyl, thiophene and pyrrole.

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4. Use or method of item 3, wherein said Ar is selected from phenyl substituted by R in position 3 or 4, and thiophen-2-yl.

5. Use of any one of items 1, 3 and 4, or method of any one of items 2 to 4, wherein R is selected from hex-1-en-1-yl, 2-methylpropyl, cyclopropylamino, substituted or unsubstituted phenylcarbonyl, substituted or unsubstituted thiophen-carbonyl, substituted or unsubstituted phenylamino, substituted or unsubstituted 1,3-thiazol-2-yl-amino, substituted or unsubstituted 1,3-oxazol-2-yl-amino, substituted or unsubstituted phenoxy, substituted or unsubstituted naphthalen-1-yloxy, substituted or unsubstituted naphthalen-2-yloxy morpholin-4-yl, piperidin-1-yl, trifluoromethanesulfonyloxy, substituted or unsubstituted phenylsulfonyloxy, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

6. Use of any one of items 1 and 3 to 5, or method of any one of items 2 to 5, wherein B is selected from H, ethyl, 2-methylprop-2-en-1-yl, 2-amino-2-methyl-propyl, substituted or unsubstituted 1*H*-pyrazol-4-yl, substituted or unsubstituted 1*H*-pyrazol-5-yl, substituted or unsubstituted thiophen-3-yl, substituted or unsubstituted 1,3-thiazol-2-yl, pyrimidin-4-yl, substituted or unsubstituted 1-*H*-pyrrol-1-yl, substituted or unsubstituted 4*H*-1,2,4-triazol-4-yl, substituted or unsubstituted pyridine-4-yl, pyrazin-2-yl, substituted or unsubstituted piperydin-4-yl, substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, furan-2-yl-C_1-C_3-alkyl, substituted or unsubstituted piperidin-1-yl-C_1-C_3-alkyl, pyridine-2-yl-amino-C_1-C_3-alkyl, phenylamino-C_1-C_3-alkyl, cyclohexylamino-N-C_1-C_3-alkyl, 1*H*-pyrazol-1-yl-C_1-C_3-alkyl, pyridin-4-yl-C_1-C_3-alkyl, morpholin-4-yl-C_1-C_3-alkyl, pyrrolidin-1-yl-C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, (benzylamino)C_1-C_3-alkyl, (C_1-C_3-alkylamino)-ethyl, -(C_1-C_4-dialkylamino)C_1-C_3-alkyl, 2-(tert-butylamino)-2-oxoethyl; (phenoxy)C_1-C_3alkyl, [(benzyl)(methylamino)]C_1-C_3alkyl, (3,4-dimethylphenoxy)-2-, [(dimethylamino)(4-fluorophenyl)methyl]amino; (*tert*-butoxycarbonyl) aminoethylcarboxy], carbamoyl, furan-2-carbamido, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-

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mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

7. Use of any one of items 1 and 3 to 6, or method of any one of items 2 to 6, wherein the compound of formula (I) is selected from the group consisting of:

4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-fluoro-1-oxo-1-{[2-(pyridin-2-ylamino)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate;

2-fluoro-*N*-(2-sulfamoylthiophen-3-yl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;

2-fluoro-*N*-(2-sulfamoylphenyl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino} phenyl)propanamide;

4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate;

N-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-[5-(phenylcarbonyl)thiophen-2-yl]propanamide;

2-[(3-methoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide;

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(3-fluorophenoxy)phenyl] propanamide;

2-[3-(3-fluorophenoxy)phenyl]-*N*-[2-(phenylamino)ethyl]propanamide;

2-{4-[(2,6-dichlorophenyl)amino]phenyl}-*N*-phenylpropanamide;

2-[3-(cyclopropylamino)phenyl]-N-(pyrimidin-4-yl)propanamide;

2-(3-{[4-(morpholin-4-yl)phenyl]amino}phenyl)N-(pyrimidin-4-yl)propanamide;

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(morpholin-4-yl)ethyl]propanamide;

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(cyclohexylamino)propyl] propanamide;

N-(2-amino-2-methylpropyl)-2-{3-[3-(trifluoromethoxy)phenoxy] phenylpropanamide;

N-[(2-pyrrolidin-1-yl)ethyl]-2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanamide;

3-(1-{[2-(4-fluorophenoxy)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

N-(2-methylprop-2-en-1-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide;

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N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide;
2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide;
2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(pyrimidin-4-yl)propanamide;
2-{3-[hex-1-en-1-yl]phenyl}-*N*-[2-(propan-2-ylamino)ethyl]propanamide;
2-{3-[hex-1-en-1-yl]phenyl}-*N*-(pyrimidin-4-yl)propanamide;
N-(3-ethyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl) propanamide;
N-[2-(*tert*-butylamino)-2-oxoethyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino} phenyl)propanamide;
N-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide;
N-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide;
2-[3-(phenylcarbonyl)phenyl]-*N*-(1,3-thiazol-2-yl)propanamide;
N-cyclohexyl-2-[3-(phenylcarbonyl)phenyl]propanamide;
N-phenyl-2-[3-(phenylcarbonyl)phenyl]propanamide;
N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(phenylcarbonyl)phenyl] propanamide;
2-[4-(2-methylpropyl)phenyl]-*N*-(pyridin-4-yl)propanamide;
N-carbamoyl-2-[4-(2-methylpropyl)phenyl]propanamide;
1-methyl-4-({2-[4-(2-methylpropyl)phenyl]propanoyl}amino)pyrimidin-1-ium iodide;
N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[4-(2-methylpropyl)phenyl] propanamide;
N-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;
N-[2-(3,5-dimethylpiperidin-1-yl)ethyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;
N-[furan-2-yl(morpholin-4-yl)methyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;
N-[2-(furan-2-yl)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide;
4-(1-{[2-(furan-2-yl)propyl]amino}-1-oxopropan-2-yl)phenyl Trifluoromethanesulfonate;
4-[1-oxo-1-(pyridin-4-ylamino)propan-2-yl]phenyl trifluoromethanesulfonate;

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4-(1-{[(dimethylamino)(4-fluorophenyl)methyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(1-{[3-[3-methoxybenzyl(methyl)amino]propyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-[3-(3,4-dimethylphenoxy)-2-hydroxypropyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(3-ethoxypropyl) propanamide;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(1*H*-pyrrol-1-yl) propanamide;

N'-{2-[3-(3-methoxy-5-(trifluoromethyl)phenylamino)phenyl] propanoyl}furan-2-carbohydrazide;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(pyrimidin-4-yl) propanamide;

N-ethyl-2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino} phenyl)propanamide

2-{3-[(3-methoxy-5-(trifluoromethyl)phenyl)amino]phenyl}-*N*-[2-(benzylamino)ethyl]propanamide;

N-(2-amino-2-methylpropyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide;

N-(2-aminocyclohexyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide;

methyl 3-[(tert-butoxycarbonyl)amino]-2-[4-(naphthalen-1-yloxyphenyl)propanoyl] aminopropanoate;

N-[2-(benzylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

N-[3-(dimethylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

N-[3-(cyclohexylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl] propanamide;

N-[2-(acetylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(morpholin-4-yl)ethyl] propanamide;

2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrimidin-4-yl)propanamide;

2-{4-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide;

2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrimidin-4-yl)propanamide;

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2-[3-(naphthalen-1-yloxy)phenyl]-*N*-(pyridin-4-yl)propanamide;
2-{3-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide;
2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrazin-2-yl)propanamide;
2-{3-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide;
2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrazin-2-yl)propanamide;
2-(4-{[(4-chlorophenyl)sulfonyl]amino}phenyl)-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide;
2-{4-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide;
N-(pyridin-4-yl)-2-[4-(quinolin-3-ylamino)phenyl]propanamide;
4-{1-[(3,5-dichloro-2-sulfamoylphenyl)amino]-1-oxopropan-2-yl}phenyl-2-chlorobenzenesulfonate;
or a pharmaceutically acceptable salt thereof.

8. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said pain is selected from central pain syndromes caused by lesions at any level of the nervous system, postsurgical pain syndromes, bone and joint pain, repetitive motion pain, dental pain, cancer pain, myofascial pain, perioperative pain, chronic pain, dysmenorrea, pain associated with angina and inflammatory pain, or pain associated to pancreatitis, cystitis, renal colics, post herpetic neuralgia, nerve injury, osteoarthritis, muscular injury, fibromyalgia, rheumatoid arthritis, rheumatic disease and gout.

9. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said hyperreactive airways diseases and inflammatory events associated with airway disease are selected from the group consisting of: asthma, bronchoconstriction, occupational asthma, viral- or bacterial-exacerbation of asthma, non-allergic asthmas, “wheezy-infant syndrome”, chronic obstructive pulmonary disease and pneumoconiosis.

10. Use or method of item 9, wherein said chronic obstructive pulmonary disease comprises emphysema, ARDS, bronchitis, pneumonia, allergic and vasomotor rhinitis.

11. Use or method of item 9, wherein said pneumoconiosis comprises aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, tabacosis and byssinosis.

12. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said inflammatory bowel disease comprises Crohn’s disease, ulcerative colitis and uveitis.

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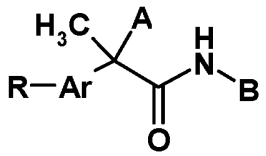
13. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said inflammatory skin disorders are psoriasis and eczema.

14. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said cancer is selected from prostate cancer, pancreatic cancer, glioma, breast cancer, chondrosarcoma, colorectal tumor, brain tumor and myeloma.

15. Use of any one of items 1 and 3 to 7, or method of any one of items 2 to 7, wherein said neurodegenerative diseases are selected from: Alzheimer disease, Parkinson's disease, and multiple sclerosis.

16. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

A is CH_3;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl or C_2-C_8-alkenyl, C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

-linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

$-(CH_2)_n-(NH)_p-Y$ wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

$-(CH_2)_n-Z-(CH_2)_{n'}-A$ wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from –CONH-, -O-, $-NCH_3-$, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy; -(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

$-CHR_aR_b$, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, $-CH_2-NHCOO-C_1-C_4$-alkyl, -(COO)C_1-C_4-alkyl, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

17. The compound of item 16, wherein Ar is selected from phenyl, thiophene and pyrrole.

18. The compound of item 17, wherein said Ar is selected from phenyl substituted by R in position 3 or 4, and thiophen-2-yl.

19. The compound of any one of items 16 to 18, wherein R is selected from hex-1-en-1-yl, 2-methylpropyl, cyclopropylamino, substituted or unsubstituted phenylcarbonyl, substituted or unsubstituted thiophen-carbonyl, substituted or unsubstituted phenylamino, substituted or unsubstituted 1,3-thiazol-2-yl-amino, substituted or unsubstituted 1,3-oxazol-2-yl-amino, substituted or unsubstituted phenoxy, substituted or unsubstituted naphthalen-1-yloxy, substituted or unsubstituted naphthalen-2-yloxy morpholin-4-yl, piperidin-1-yl, trifluoromethanesulfonyloxy, substituted or unsubstituted phenylsulfonyloxy, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

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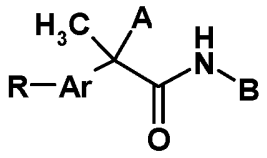
20. The compound of any one of items 16 to 19, wherein B is selected from ethyl, 2-methylprop-2-en-1-yl, 2-amino-2-methyl-propyl, substituted or unsubstituted 1*H*-pyrazol-4-yl, substituted or unsubstituted 1*H*-pyrazol-5-yl, substituted or unsubstituted thiophen-3-yl, substituted or unsubstituted 1,3-thiazol-2-yl, pyrimidin-4-yl, substituted or unsubstituted 1-*H*-pyrrol-1-yl, substituted or unsubstituted 4*H*-1,2,4-triazol-4-yl, substituted or unsubstituted pyridine-4-yl, pyrazin-2-yl, substituted or unsubstituted piperydin-4-yl, substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, furan-2-yl-C_1-C_3-alkyl, substituted or unsubstituted piperidin-1-yl-C_1-C_3-alkyl, pyridine-2-yl-amino-C_1-C_3-alkyl, phenylamino-C_1-C_3-alkyl, cyclohexylamino-N-C_1-C_3-alkyl, 1*H*-pyrazol-1-yl-C_1-C_3-alkyl, pyridin-4-yl-C_1-C_3-alkyl, morpholin-4-yl-C_1-C_3-alkyl, pyrrolidin-1-yl-C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, (benzylamino)C_1-C_3-alkyl, (C_1-C_3-alkylamino)-ethyl, -(C_1-C_4-dialkylamino)C_1-C_3-alkyl, 2-(tert-butylamino)-2-oxoethyl; (phenoxy)C_1-C_3alkyl, [(benzyl)(methylamino)]C_1-C_3alkyl, (3,4-dimethylphenoxy)-2-, [(dimethylamino)(4-fluorophenyl)methyl]amino; (*tert*-butoxycarbonyl) aminoethylcarboxy], carbamoyl, furan-2-carbamido, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

21. A compound of any one of items 16 to 20 selected from the group consisting of: 4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate, 4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate, and pharmaceutically acceptable salts thereof.

22. Pharmaceutical composition comprising the compound according to any one of items 16 to 21, in admixture with pharmaceutically acceptable excipients and/or diluents.

Detailed description of the invention

The present invention as described above at items 1 to 22 relates to (R,S)-2-aryl-propionamides described below which are selective B1 bradykinin antagonists. The (R,S)-2-aryl-propionamide which are selective B1 bradykinin antagonists are the derivatives of formula (I) and their single (R) and (S) enantiomers as well as their pharmaceutically acceptable salts:



(I)

wherein

A is selected from the group consisting of H, CH3 and F;

Ar is a selected from the group consisting of optionally substituted phenyl and 5, 6–membered heteroaryl, said heteroaryl being preferably selected from tiophene and pyrrole;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl or C_2-C_8-alkenyl, C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphtyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl;

-optionally substituted 5 -6-membered heterocyclic residues; and

-X-SO_2R_1, wherein X is selected from NH and O and R1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

-H, linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

-$(CH_2)_n$-$(NH)_p$-Y wherein n is between 0 and 3, p is 0 or 1 and Y is selected from:

-a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

-benzyl, 5-6 membered heteroarylcarbonyl, C_1-C_6-alkyl, linear or branched C_1-C_3-alkylcarbonyl, C_1-C_6-alkoxy and C_1-C_6-alkoxy hydroxy substituted.

-$(CH_2)_n$-Z-$(CH2)_{n'}$-A wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from –CONH-, -O-, -NCH_3-, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-CHR_aR_b, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, -CH_2-NHCOO-C_1-C_4-alkyl, -(COO)C1-C_4-alkyl.

The term "substituted" in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3-alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides.

In the particularly preferred compounds the term "substituted" means substituted by one or more groups independently selected from methyl, ethyl, isopropyl, tert-butyl, Cl, F, hydroxy, methoxy, thiomethyl, trifluoromethyl, trifluoromethoxy, isopropylsulfonyl, sulfonamido, amino.

According to a preferred embodiment of the invention, when Ar is phenyl, R is in position 3 or 4 position of the aromatic ring.

R is preferably selected from the following residues: hex-1-en-1-yl, 2-methylpropyl, cyclopropylamino, substituted or unsubstituted phenylcarbonyl, substituted or unsubstituted tiophen-carbonyl, substituted or unsubstituted phenylamino, substituted or

unsubstituted 1,3-thiazol-2-yl-amino, substituted or unsubstituted 1,3-oxazol-2-yl-amino, substituted or unsubstituted phenoxy, substituted or unsubstituted naphtalen-1-yloxy, substituted or unsubstituted naphtalen-2-yloxy morpholin-4-yl, pyperidin-1-yl, trifluoromethanesulfonyloxy, C1-C4 alkylsulfonylamino, substituted or unsubstituted phenylsulfonylamino, substituted or unsubstituted phenylsulfonyloxy.

B is preferably selected from H, ethyl, 2-methylprop-2-en-1-yl, 2-amino-2-methyl-propyl, substituted or unsubstituted 1*H*-pyrazol-4-yl, substituted or unsubstituted 1*H*-pyrazol-5-yl, substituted or unsubstituted tiophen-3-yl, substituted or unsubstituted 1,3-thiazol-2-yl, pyrimidin-4-yl, substituted or unsubstituted 1-*H*-pyrrol-1-yl, substituted or unsubstituted 4*H*-1,2,4-triazol-4-yl, substituted or unsubstituted pyridine-4-yl, pyrazin-2-yl, substituted or unsubstituted piperydin-4-yl, substituted or unsubstituted phenyl, substituted or unsubstituted ciclohexyl, furan-2-yl-C_1-C_3-alkyl, substituted or unsubstituted piperidin-1-yl-C_1-C_3-alkyl, pyridine-2-yl-amino-C1-C3-alkyl, phenylamino-C_1-C_3-alkyl, cyclohexylamino-N-C_1-C_3-alkyl, 1*H*-pyrazol-1-yl-C_1-C_3-alkyl, pyridin-4-yl-C_1-C_3-alkyl, morpholin-4-yl-C_1-C_3-alkyl, pyrrolidin-1-yl-C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, (benzylamino)C_1-C_3-alkyl, (C_1-C_3-alkylamino)-ethyl, -(C_1-C_4-dialkylamino)C_1-C_3-alkyl, 2-(tert-butylamino)-2-oxoethyl; (phenoxy)C_1-C_3alkyl, [(benzyl)(methylamino)]C_1-C_3alkyl, (3,4-dimethylphenoxy)-2-, [(dimethylamino)(4-fluorophenyl)methyl]amino; (*tert*-butoxycarbonyl) aminoetylcarboxy], carbamoyl, furan-2-carbamido.

Particularly preferred compounds of the invention are:

4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-(2-fluoro-1-oxo-1-{[2-(pyridin-2-ylamino)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate

2-fluoro-*N*-(2-sulfamoylthiophen-3-yl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

2-fluoro-*N*-(2-sulfamoylphenyl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate

N-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-[5-(phenylcarbonyl)thiophen-2-yl]propanamide

2-{4-[(3-methoxyphenyl)amino]phenyl}-*N*-(1-benzylpiperidin-4-yl)propanamide

2-[(3-methoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(3-fluorophenoxy)phenyl] propanamide

2-[3-(3-fluorophenoxy)phenyl]-*N*-[2-(phenylamino)ethyl]propanamide

2-{4-[(2,6-dichlorophenyl)amino]phenyl}-*N*-phenylpropanamide

2-[3-(cyclopropylamino)phenyl]-N-(pyrimidin-4-yl)propanamide

2-(3-{[4-(morpholin-4-yl)phenyl]amino}phenyl)N-(pyrimidin-4-yl)propanamide

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(morpholin-4-yl)ethyl]propanamide

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(cyclohexylamino)propyl] propanamide

N-(2-amino-2-methylpropyl)-2-{3-[3-(trifluoromethoxy)phenoxy] phenylpropanamide

N-[(2-pyrrolidin-1-yl)ethyl]-2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanamide

3-(1-{[2-(4-fluorophenoxy)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

2-{4-[(propan-2-ylsulfonyl)amino]phenyl}-*N*-(4-tert-butyl-1,3-thiazol-2-yl) propanamide

N-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-{4-[(propan-2-ylsulfonyl)amino] phenylpropanamide

N-(2-methylprop-2-en-1-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(pyrimidin-4-yl)propanamide

2-{3-[hex-1-en-1-yl]phenyl}-*N*-[2-(propan-2-ylamino)ethyl]propanamide

2-{3-[hex-1-en-1-yl]phenyl}-*N*-(pyrimidin-4-yl)propanamide

N-(3-ethyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl) propanamide

N-[2-(*tert*-butylamino)-2-oxoethyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino} phenyl)propanamide

N-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide

N-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide

2-[3-(phenylcarbonyl)phenyl]-*N*-(1,3-thiazol-2-yl)propanamide

N-cyclohexyl-2-[3-(phenylcarbonyl)phenyl]propanamide

N-phenyl-2-[3-(phenylcarbonyl)phenyl]propanamide

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(phenylcarbonyl)phenyl] propanamide

2-[4-(2-methylpropyl)phenyl]-*N*-(pyridin-4-yl)propanamide

N-carbamoyl-2-[4-(2-methylpropyl)phenyl]propanamide

1-methyl-4-({2-[4-(2-methylpropyl)phenyl]propanoyl}amino)pyrimidin-1-ium iodide

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[4-(2-methylpropyl)phenyl] propanamide

N-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

N-[2-(3,5-dimethylpiperidin-1-yl)ethyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

N-[furan-2-yl(morpholin-4-yl)methyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

N-[4-(pyridin-4-ylmethyl)phenyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide

N-[2-(furan-2-yl)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide

4-(1-{[2-(furan-2-yl)propyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-[1-oxo-1-(pyridin-4-ylamino)propan-2-yl]phenyl trifluoromethanesulfonate

4-{1-oxo-1-[4-(pyridin-4-ylmethyl)propan-2-yl]amino}phenyl trifluoromethanesulfonate

4-(1-{[(dimethylamino)(4-fluorophenyl)methyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-(1-{[3-[3-methoxybenzyl(methyl)amino]propyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

4-[3-(3,4-dimethylphenoxy)-2-hydroxypropyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(3-ethoxypropyl) propanamide

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2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(1*H*-pyrrol-1-yl) propanamide

N'-{2-[3-(3-methoxy-5-(trifluoromethyl)phenylamino)phenyl]propanoyl}furan-2-carbohydrazide

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(pyrimidin-4-yl) propanamide

N-ethyl-2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino} phenyl)propanamide

2-{3-[(3-methoxy-5-(trifluoromethyl)phenyl)amino]phenyl}-*N*-[2-(benzylamino)ethyl] propanamide

N-(2-amino-2-methylpropyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl] propanamide

N-(2-aminocyclohexyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl] propanamide

Methyl 3-[(tert-butoxycarbonyl)amino]-2-[4-(naphthalen-1-yloxyphenyl)propanoyl] aminopropanoate

N-[2-(benzylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide

N-[3-(dimethylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide

N-[3-(cyclohexylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl] propanamide

N-[2-(acetylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(morpholin-4-yl)ethyl] propanamide

The above 2-arylpropionamide derivatives show the ability to effectively inhibit bradykinin biological activity due to their nature of selective BKB1R antagonists.

Thus, the present invention relates to the above compounds for use as inhibitors of bradykinin B1 receptor-activated pathway.

As it has already been discussed in the background of the invention this pathway is responsible for the pathogenesis of disorders involving pain and inflammation.

Accordingly, the present invention also relates to the use of the above compounds for prevention and/or treatment of pain and inflammation.

In particular, the present invention relates to the use of the above compounds for the prevention and/or treatment of visceral pain, preferably pancreatitis, cystitis, renal colic; neuropathic pain, preferably post herpetic neuralgia, nerve injury; central pain syndromes caused by lesions at any level of the nervous system and postsurgical pain syndromes;

bone and joint pain, preferably osteoarthritis; repetitive motion pain; dental pain; cancer pain; myofascial pain, preferably muscular injury, fibromyalgia and perioperative pain; chronic pain; dysmenorrea; pain associated with angina and inflammation-related pain, pain of varied origins, preferably pain derived from osteoarthritis, rheumatoid arthritis, rheumatic disease and gout.

The invention also relates to the use of the compounds of the invention for the prevention and/or treatment of hyperreactive airways and inflammatory events associated with airway disease, preferably asthma including allergic asthma, bronchoconstriction, occupational asthma, viral- or bacterial-exacerbation of asthma, other non-allergic asthmas and "wheezy-infant syndrome", chronic obstructive pulmonary disease. Preferably, said chronic obstructive pulmonary disease comprises emphysema, ARDS, bronchitis, pneumonia, allergic and vasomotor rhinitis, and pneumoconiosis.

Preferably, said pneumoconiosis comprises aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, tabacosis and byssinosis.

The present invention also relates to the use of the above compounds for prevention and/or treatment of inflammatory bowel diseases, preferably Crohn's disease and ulcerative colitis and uveitis; inflammatory skin disorders, preferably psoriasis and eczema; edema resulting from burns, sprains and fractures; cerebral edema and angioedema; diabetic vasculopathy; diabetic neuropathy; diabetic retinopathy; diabetic symptoms associated with insulitis; liver disease; multiple sclerosis; cardiovascular disease, preferably atherosclerosis; congestive heart failure; myocardial infarct; neurodegenerative diseases, preferably Parkinson's and Alzheimer's disease, multiple sclerosis; epilepsy; septic shock; headache including cluster headache, migraine; closed head trauma; cancer, preferably prostate cancer, pancreatic cancer, glioma, breast cancer; chondrosarcoma, colorectal tumor, brain tumor and myeloma; sepsis; gingivitis; osteoporosis; benign hyperplasia, hyperactive bladder, interstitial cistitis.

Pharmaceutical compositions comprising a compound of the invention and a suitable carrier thereof, are also within the scope of the present invention.

The compounds of the invention, together with a conventionally employed adjuvant, carrier, diluent or excipient may, in fact, be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids such as solutions, suspensions, emulsions, elixirs, or

capsules filled with the same, all for oral use, or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

When employed as pharmaceuticals, the acids of this invention are typically administered in the form of a pharmaceutical composition. Such compositions can be prepared in a manner well known in the pharmaceutical art and comprise at least one active compound. Generally, the compounds of this invention are administered in a pharmaceutically effective amount. The amount of the compound actually administered will typically be determined by a physician, in the light of the relevant circumstances, including the condition to be treated, the chosen route of administration, the actual compound administered, the age, weight, and response of the individual patient, the severity of the patient's symptoms, and the like.

The pharmaceutical compositions of the invention can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, and intranasal. Depending on the intended route of delivery, the compounds are preferably formulated as either injectable or oral compositions. The compositions for oral administration can take the form of bulk liquid solutions or suspensions, or bulk powders. More commonly, however, the compositions are presented in unit dosage forms to facilitate accurate dosing. The term "unit dosage forms" refers to physically discrete units suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical excipient. Typical unit dosage forms include prefilled, premeasured ampoules or syringes of the liquid compositions or pills, tablets, capsules or the like in the case of solid compositions. In such compositions, the acid compound is usually a minor component (from about 0.1 to about 50% by weight or preferably from about 1 to about 40% by weight) with the remainder being various vehicles or carriers and processing aids helpful for forming the desired dosing form.

Liquid forms suitable for oral administration may include a suitable aqueous or nonaqueous vehicle with buffers, suspending and dispensing agents, colorants, flavors and the like. Liquid forms, including the injectable compositions described herebelow, are

always stored in the absence of light, so as to avoid any catalytic effect of light, such as hydroperoxide or peroxide formation. Solid forms may include, for example, any of the following ingredients, or compounds of a similar nature: a binder such as microcrystalline cellulose, gum tragacanth or gelatine; an excipient such as starch or lactose, a disintegrating agent such as alginic acid, Primogel, or corn starch; a lubricant such as magnesium stearate; a glidant such as colloidal silicon dioxide; a sweetening agent such as sucrose or saccharin; or a flavoring agent such as peppermint, methyl salicylate, or orange flavoring.

Injectable compositions are typically based upon injectable sterile saline or phosphate-buffered saline or other injectable carriers known in the art. As above mentioned, the acid derivative of formula I in such compositions is typically a minor component, frequently ranging between 0.05 to 10% by weight with the remainder being the injectable carrier and the like. The mean daily dosage will depend upon various factors, such as the seriousness of the disease and the conditions of the patient (age, sex and weight). The dose will generally vary from 1 mg or a few mg up to 1500 mg of the compounds of formula (I) per day, optionally divided into multiple administrations. Higher dosages may be administered also thanks to the low toxicity of the compounds of the invention over long periods of time.

The above described components for orally administered or injectable compositions are merely representative. Further materials as well as processing techniques and the like are set out in Part 7 of "Remington's Pharmaceutical Sciences Handbook", 19th Edition, 1995, Mack Publishing Company, Easton, Pennsylvania, which is incorporated herein by reference.

The compounds of the invention can also be administered in sustained release forms or from sustained release drug delivery systems. A description of representative sustained release materials can also be found in the incorporated materials in the Remington's Handbook as above.

The present invention shall be illustrated by means of the following examples which are not construed to be viewed as limiting the scope of the invention.

Materials and methods

The amines of general formula RNH_2 used as reagents in the synthesis of compounds of formula (I) are known products, generally commercially available, or they can be prepared according to methods described in the literature.

The following arylpropionic acids have been already described or are commercially available: 2-[4-(2-methylpropyl)phenyl]propanoic acid, 2-[3-(phenylcarbonyl)phenyl] propanoic acid, 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid, 2-{4-[(propan-2-ylsulfonyl)oxy]phenyl}propanoic acid, 2-fluoro-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid, 2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanoic acid, 2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanoic acid, 2-[3-(thiophen-2-ylcarbonyl)phenyl]propanoic acid, 2-fluoro-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanoic acid.

^{1}H-NMR spectra were recorded on a Bruker ARX 300 spectrometer. LC-MS spectra were recorded on a Surveyor (THERMO FINNIGAN) apparatus coupled with a LCQ DECA XP plus (THERMO FINNIGAN) apparatus and equipped with a C18 Phenomenex Gemini column. The eluent mixture consisted of buffer 10 mM pH 4.2 $HCOO^-$ $NH4^+$/HCOOH and CH_3OH used according the gradient from 90:10 to 10:90.

Synthesis of arylpropionic acids

2-[4-(Naphthalen-1-yloxy)phenyl]propanoic acid (I)

In a 500 cc round-bottomed flask equipped with condenser and magnetic stirrer, at room temperature commercial 2-(4-hydroxyphenyl)propanoic acid (20 g, 0.12 mol) was dissolved in CH_3OH (50ml) and conc. H_2SO_4 (2 mL, 0.05 mol) was added dropwise to the solution. The reaction mixture was left refluxing overnight. After cooling at room temperature, the solution was diluted in CH_2Cl_2 (20 ml) and extracted with a saturated $NaHCO_3$ aqueous solution (3 x 150ml); the collected organic layers were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give pure methyl 2-(4-hydroxyphenyl)propanoate (18 g, 0.10 mol) as orange oil, used for the next step reaction without further purification.

In a 50 ml round-bottomed flask under nitrogen flux, $Cu(OAc)_2$ (0.49 g, 2.7 mmol) and a catalytic amount of 4Å molecular sieves were suspended in dry CH_2Cl_2 (0.1 mL). After stirring for 10 min. pyridine (0.45 ml, 5.4 mol) was added. The nitrogen inlet was removed and substituted by a $CaCl_2$-tube; a solution of methyl-2-(4-hydroxyphenyl)propanoate (0.5 g, 2.7 mmol) in pyridine (0.65 ml, 8.1 mmol) was added, immediately followed by small portions of naphthylboronic acid (0.7 g, 4.5 mmol). The mixture was left stirring at room temperature for 3 days and, at the completion of the reaction, the solvents were evaporated under vacuum. The crude mixture was purified by flash chromatography (petroleum

ether/EtOAc 8:1) to afford the intermediate methyl 2-[4-(naphthalene-1-yloxy)phenyl] propanoate (0.55 g, 1.8 mmol) used for the following step without further purification.

To a suspension of methyl-2-[4-(naphtalen-1-yloxy)phenyl]propanoate (0.5 g, 1.63 mmol) in dioxane (2 mL) at room temperature, 2M NaOH (4 mL, 0.8 mmol) was added dropwise. The resulting dark solution was stirred at room temperature for 8 h, then it was evaporated under vacuum, the crude dissolved in EtOAc (3 mL) and extracted with water (3 x 5 mL). The collected aqueous extracts were then acidified with 10% $_{w/v}$ $KHSO_4$ (2 mL) and back extracted with EtOAc (3 x 5 mL). The collected organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum to give a crude that, after pulping in petroleum ether afforded pure 2-[4-naphthalen-1-yloxy)phenyl]propanoic acid (I) (0.3 g, 1.027 mmol, 63 % yield from the last intermediate) as waxy solid. ^{1}H-NMR ($CDCl_3$): δ 8.2 (d, 1H., J=7.9 Hz), 7.90 (d, 1H, J=7.6 Hz), 7.65 (d, 1H, J=8.1 Hz), 7.6-7.46 (m, 2H), 7.41 (t, 1H, J=8.1 Hz), 7.32 (d, 2H, J=8.1 Hz), 7.1-6.95 (m, 3H), 3.8 (q, 1H, J=7 Hz), 1.55 (d, 3H, J=7 Hz). MS (ESI): m/z $[M+H]^{1+}$ 292 .

2-(3-{[3-Methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)propanoic acid (II)

In a 250 ml round-bottomed flask equipped with condenser, few drops of conc. H_2SO_4 were added to a solution of commercial (3-hydroxyphenyl)acetic acid (25 g, 0.165 mol) in CH_3OH (30 mL), and the resulting mixture was left stirring under reflux for 4 h. After complete disappearance of the starting material (TLC) $CHCl_3$ (30 mL) was added and the organic layer was extracted with 1M NaOH (2 x 20mL), washed with water (2 x 20 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to give pure methyl(3-hydroxyphenyl)acetate (24 g, 0.14 mol) as a brown oil which was used for the next step without any further purification.

In a three necks 250 ml round-bottomed flask equipped with dropping funnel and magnetic stirrer, a solution of methyl(3-hydroxyphenyl)acetate (10g, 0.058 mol) in CH_3OH (50 mL) was cooled to -20°C and triethylamine (12.4 mL, 0.075 mol) was added dropwise; the resulting mixture was left stirring for 30 min. and then trifluoromethanesulfonic anhydride (12.6 mL, 0.075 mol) was added, the ice-water bath removed and the solution stirred for further 2 h. After complete disappearance of the starting material (TLC) the reaction mixture was diluted with 1N HCl (30 mL) and washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to give methyl (3-{[(trifluoromethyl)sulfonyl]oxy}phenyl)acetate (9 g, 0.031 mol) as yellow oil used for the next step without any further purification.

In a 250 ml round-bottomed flask lithium hexamethyldisilazide (1M in THF, 31.4 mL, 0.031 mol) and methyl(3-{[trifluoromethyl)sulfonyl]oxy}phenyl)acetate (8.9 g, 0.03 mol) were dissolved in anhydrous THF (170 ml) under nitrogen atmosphere. After cooling to -78°C and stirring for 20 min, iodomethane (1.86 mL, 0.03 mol) was added dropwise. The resulting mixture was left warming up to room temperature and stirred overnight. An aqueous solution of KH_2PO_4 (30 ml) was added and the aqueous layer extracted with EtOAc (2 x 20 mL). The collected organic extracts were washed with water (2 x 20 ml), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude residue that, after purification by flash chromatography (n-hexane/EtOAc 9:1), afforded methyl 2-(3-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (7.5 g, 0.025 mol, 75% yield) as yellow oil used for the next step.

To a solution of methyl 2-(3-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (0.13 g, 4.3 mmol) and 3-methoxy-5-(trifluoromethyl)aniline (0.1 g, 5.2 mmol) in dry toluene (2 mL) , $Pd_2(dba)_3$ (8 mg, 8.7 mmol), Xantphos (7.5 mg, 1.3 mmol) and K_3PO_4 (0.18 g, 8.7 mmol) were added. The reaction mixture was heated at 150°C and stirred under microwave irradiations. After stirring for 2 h the solvent was evaporated and the residue purified by flash chromatography (n-hexane/EtOAc 9:1) to afford methyl 2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)propanoate (0.8 g, 2.4 mmol, yield 56 %) pure enough for the next step.

In a 100ml round-bottomed flask equipped with condenser and magnetic stirrer, methyl 2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}propanoate (0.73 g, 2.1 mmol) was suspended in 1,4-dioxane (20 mL) at room temperature, 1M NaOH (4.2 mL, 4.2 mmol) was added by dripping and the resulting solution was stirred at room temperature overnight. The solvents were evaporated under vacuum and the crude mixture diluted in EtOAc (10 mL) and extracted with water (3 x 10 mL). The collected aqueous layers were acidified to pH 2 with 1N HCl, washed with brine (2 x 5 mL) and extracted with EtOAc (3 x 10 mL). The organic layer was dried anhydrous Na_2SO_4 and evaporated under reduced pressure to give 2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}-phenyl)propanoic acid (II) (0.72 g, 2.0 mmol, yield 95%) as yellow oil. ^{1}H-NMR (CD_3OD): δ 7.9 (bs, 1H, NH), 7.2 (t, 1H, J=8 Hz), 7.12 (s, 1H), 7.0 (dd, 1H, J^1=7.8 Hz, J^2=1.1 Hz), 6.90 (d, 1H, J=7.8Hz), 6.83 (s, 1H), 6.80 (s, 1H), 6.56 (s, 1H), 3.77 (s, 3H), 3.65 (q, 1H, J=7Hz), 1.43 (d, 3H, J=7Hz). MS (ESI): m/z $[M+H]^{1+}$ 340.

2-(3-{[(Trifluoromethyl)sulphonyl]oxy}phenyl)propanoic acid (III)

In a 500 cc round-bottomed flask equipped with condenser and magnetic stirrer, methyl 2-(3-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (1.2 g, 3.8 mmol) (prepared as above described) was suspended in acetic acid (10 mL) at room temperature and 37% HCl (5 mL) was added by dripping. The resulting solution was refluxed overnight. After cooling at room temperature, the solution was evaporated under vacuum and the crude mixture diluted in CH_2Cl_2 (10 mL) and washed with water (2 x 10 mL); the organic layer was dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give pure 2-(3-{[trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (III) (1.09 g, 3.6 mmol, yield 95%) as colourless oil. ^{1}H-NMR ($CDCl_3$): δ 7.50-7.35 (m, 2H), 7.27 (s, 1H), 7.22 (d, 1H, J=7.3Hz), 3.83 (q, 1H, J=7.3Hz), 1.58 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 299.

2-{4-[(2,3-Dimethoxyphenyl)amino]phenyl}propanoic acid (IV)

Following the same above described procedure for the synthesis of II, but starting from commercial (4-hydroxyphenyl)acetic acid, the intermediate methyl 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate was isolated pure as brown oil and, after treatment with commercial 2,3-dimethoxyaniline in the same conditions previously described and following ester hydrolysis, afforded 2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}propanoic acid (IV) in 25% overall yield as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 9.25 (bs, 1H), 7.60 (t, 1H, J=7Hz), 7.41 (d, 2H, J=8.9Hz), 7.32-7.20 (m, 4H), 3.8 (q, 1H, J=7.3Hz), 1.59 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 302.

2-{3-[3-(Trifluoromethoxy)phenoxy]phenyl}propanoic acid (V)

Commercial (3-hydroxyphenyl)acetic acid was methylated by iodomethane following the procedure above described for I to give the intermediate methyl 2-(3-hydroxyphenyl)propanoate that, following treatment with commercial 3-(trifluoromethoxy)phenylboronic acid in the same conditions previously described for compound (I) afforded 2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanoic acid (V) in 23% overall yield as a colourless oil. ^{1}H-NMR ($CDCl_3$): □ 7.60-7.35 (m, 5H), 7.27 (s, 1H), 7.20-7.0 (m, 2H), 3.83 (q, 1H, J=7.3Hz), 1.58 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 327.

2-{4-[2,6-Dichloro-3-methylphenyl)amino]phenyl}propanoic acid (VI)

Following the same above described procedure for the synthesis of II, but starting from commercial (4-hydroxyphenyl)acetic acid, the intermediate methyl 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate was isolated pure as brown oil and, after treatment with commercial 2,6-dichloro-3-methylaniline in the same conditions

previously described and following ester hydrolysis, afforded 2-{4-[2,6-dichloro-3-methylphenyl)amino]phenyl}propanoic acid (VI) in 28% overall yield as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 8.7 (bs, 1H), 7.41 (d, 2H, J=8.9Hz), 7.20 (d, 2H, J=8.9Hz), 7.02 (d, 1H, J=7.2Hz), 6.80 (d, 1H, J=7.2Hz), 3.8 (q, 1H, J=7.3Hz), 2.3 (s, 3H), 1.59 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 325.

2-(4-{[4-(Morpholin-4-yl)phenyl]amino}phenyl)propanoic acid (VII)

Following the same above described procedure for the synthesis of II, but starting from commercial (4-hydroxyphenyl)acetic acid, the intermediate-methyl-2-(4-{[(trifluoromethyl)-sulfonyl]oxy}phenyl)-propanoate was isolated pure as brown oil and, after treatment with commercial 4-morpholinoaniline in the same conditions previously described and following ester hydrolysis, afforded 2-(4-{[4-(morpholin-4-yl)phenyl]amino}phenyl)propanoic acid (VII) in 34% overall yield as a colourless oil. ^{1}H-NMR ($CDCl_3$): δ 8.5 (bs, 1H), 7.41 (d, 2H, J=8.9Hz), 7.20 (d, 2H, J=8.9Hz), 7.0 (d, 2H, J=7.2Hz), 6.7 (d, 2H, J=7.2Hz), 3.8 (m, 5H), 3.0 (m, 4H), 1.62 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 327.

2-{4-[(2,6-Dichlorophenyl)amino]phenyl}propanoic acid (VIII)

Following the same procedure described for the synthesis of VI, but reacting the intermediate methyl 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate with commercial 2,6-dichloroaniline, 2-{4-[(2,6-dichlorophenyl)amino]phenyl}propanoic acid (VIII) was isolated as a colourless oil in 30% overall yield. ^{1}H-NMR ($CDCl_3$): □ 8.65 (bs, 1H), 7.41 (d, 2H, J=8.9Hz), 7.20 (d, 2H, J=8.9Hz), 7.1 (d, 2H, J=7Hz), 6.90 (t, 1H, J=7Hz), 3.8 (q, 1H, J=7.3Hz), 1.59 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 311.

2-{4-[(Cyclopropylmethyl)amino]phenyl}propanoic acid (IX)

Following the same procedure described for the synthesis of VI, but reacting the intermediate methyl 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate with commercial cyclopropanemethylamine, 2-{4-[(cyclopropylmethyl)amino]phenyl} propanoic acid (IX) was obtained as a colourless oil in 24% overall yield. ^{1}H-NMR ($CDCl_3$): δ 8.65 (bs, 1H), 7.41 (d, 2H, J=8.9Hz), 7.20 (d, 2H, J=8.9Hz), 3.8 (q, 1H, J=7.3Hz), 2.5 (d, 2H, J=7Hz), 1.59 (d, 3H, J=7.3Hz), 0.9 (m, 1H), 0.4 (m, 2H), 0.1 (m, 1H). MS (ESI): m/z $[M+H]^{1+}$ 220.

2-[3-(3-Fluorophenoxy)phenyl]propanoic acid (X)

Following the same procedure described for the synthesis of I, but reacting the intermediate methyl-2-(3-hydroxyphenyl)propanoate with commercial 3-fluorophenylboronic acid, 2-

[3-(3-fluorophenoxy)phenyl]propanoic acid (X) was obtained as a colourless oil in 40% overall yield. ^{1}H-NMR ($CDCl_3$): δ 7.70-7.40 (m, 5H), 7.27 (s, 1H), 7.20-7.00 (m, 2H), 3.83 (q, 1H, J=7.3Hz), 1.58 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 261.

2-{4-[(3-Methoxyphenyl)amino]phenyl}propanoic acid (XI)

Following the same procedure described for the synthesis of VI, but reacting the intermediate methyl 2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate with commercial 3-methoxyaniline, 2-{4-[(3-methoxyphenyl)amino]phenyl}propanoic acid (XI) was obtained as a colourless oil in 25% overall yield. ^{1}H-NMR ($CDCl_3$): δ 8.68 (bs, 1H), 7.41 (d, 2H, J=8.9Hz), 7.20 (d, 2H, J=8.9Hz),7.05 (t, 1H, J=6.8Hz), 6.8-6.6 (m, 3H), 3.8 (q, 1H, J=7.3Hz), 3.70 (s, 3H), 1.59 (d, 3H, J=7.3Hz). MS (ESI): m/z $[M+H]^{1+}$ 272.

2-{4-[3-(Trifluoromethoxy)phenoxy]phenyl}propanoic acid (XII)

Following the same procedure described for the synthesis of I, but reacting the intermediate methyl-2-(4-hydroxyphenyl)propanoate with commercial 3-(trifluoromethoxy)phenylboronic acid, 2-{4-[3-(trifluoromethoxy)phenoxy]phenyl} propanoic acid (XII) was obtained as a colourless oil in 32% overall yield. ^{1}H-NMR ($CDCl_3$): δ7.6-7.40 (m, 3H), 7.35-7.30 (m, 3H), 7.0 (d, 2H, J=8.0Hz), 3.8 (q, 1H, J=7Hz), 1.55 (d, 3H, J=7 Hz). MS (ESI): m/z $[M+H]^{1+}$ 327.

2-Methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (XIII)

In a 250 ml round-bottomed flask lithium hexamethyldisilazide (1M in THF, 5 mL, 6.3 mmol) and methyl2-(4-{[trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (1.4 g, 4.5 mmol) were dissolved in anhydrous THF (5 mL) under nitrogen atmosphere. After cooling to -78°C and stirring for 20 min, iodomethane (0.4 mL, 6.3 mmol) was added by dripping. The resulting mixture was left warming up to room temperature and stirred overnight. An aqueous solution of KH_2PO_4 (30 mL) was added and the aqueous layer extracted with EtOAc (2 x 20 mL). The collected organic extracts were washed with water (2 x 20 mL), dried over anhydrous Na_2SO_4 and evaporated under reduced pressure to give a crude residue that, after purification by flash chromatography (n-hexane/EtOAc 9:1), afforded methyl-2-methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (1.2 g, 4.1 mmol, 93% yield) as colourless oil used for the next step.

In a 500 cc round-bottomed flask equipped with condenser and magnetic stirrer, 37% HCl (5mL) was added by dripping at room temperature to a suspension of methyl-2-methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (1.2 g, 4.1 mmol) in AcOH (10 mL). The resulting solution was refluxed under stirring overnight. After cooling at room

temperature, solvent was evaporated under vacuum and the crude mixture diluted in CH_2Cl_2 (10mL) and the organic phase was washed with water (2 x 10 mL), dried over anhydrous Na_2SO_4 to give 2-methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy} phenyl)propanoic acid (XIII) (1.09 g, 3.5 mmol) as colourless oil in 85% yield. ^{1}H-NMR ($CDCl_3$): δ 7.40 (d, 2H, J=8.5Hz), 7.24 (d, 2H, J=8.5Hz), 1.63 (s, 6H). MS (ESI): m/z $[M+H]^{1+}$ 313.

2-{3-[(1-hex-1-en-1-yl]phenyl}propanoic acid (XIV)

To a solution of methyl 2-(3-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoate (prepared as above described for II) (0.52 g, 2.24 mmol) in anhydrous N-methyl-2-pyrrolidinone (6 mL) under nitrogen and vigorous stirring, LiCl (0.285 g, 6.73 mmol), CuI (20 mg, 0.112 mmol), $AsPh_3$ (54 mg, 0.18 mmol), and Pd_2dba_3 (42 mg, 0.04 mmol) were added. After stirring for 10 min, 1-hexenyl-tributyltin (prepared according Labadie J.W. et al. J. Org. Chem., 1983, *105*, 6129-6137) (1.01 g, 2.70 mmol) was added and the reaction mixture left stirring for 5 h at 90°C. After cooling at room temperature, a saturated solution of KF (20 mL) was added and the aqueous layer extracted with Et_2O (3 x 20 mL). The collected organic extracts were washed with water (2 x 20 mL), dried over anhydrous Na_2SO_4 and evaporated under vacuum to give a crude residue that, after purification by flash chromatography (petroleum ether/ EtOAc 8:1), afforded methyl2-{3-[(1-hex-1-en-1-yl]phenyl}propanoate (0.41g, 1.68 mmol, 75% yield) used for the final step of hydrolysis. To the methyl ester was dissolved in CH_3OH (4 mL) a 20% alcoholic solution of KOH (2 mL) was added, and the resulting mixture was left stirring overnight at room temperature. After solvent evaporation the residue was diluted with water (10 mL) and washed with Et_2O (2 x 10 mL), acidified with 1N HCl to pH 2 and extracted with EtOAc (2 x 20 mL). The collected organic extracts were dried over anhydrous Na_2SO_4 and evaporated under vacuum to give a crude residue that, after pulping in petroleum ether (20 mL) and filtration, afforded 2-{3-[(hex-1-en-1-yl]phenyl}propanoic acid (XIV) (0.35 g, 1.51 mmol, 90% yield) as white solid as a 3:1 mixture of E/Z isomers. ^{1}H-NMR ($CDCl_3$): ∟ 7.60-7.45 (m, 2H), 7.35 (s, 1H), 7.22 (d, 1H, J=7.3Hz), 6.50-6.10 (m, 2H), 3.83 (q, 1H, J=7.3Hz), 2.00 (m, 2H), 1.58 (d, 3H, J=7.3Hz), 1.50-1.15 (m, 4H), 0.9 (t, 3H, J=6.9Hz). MS (ESI) : m/z $[M+H]^{1+}$ 233.

General synthesis of amides of formula (I)

Example 1

4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

2-methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (0.88 g, 2.78 mmol) was dissolved in $SOCl_2$ (5 mL) and the resulting solution was left stirring at reflux 3h. After cooling at room temperature, the mixture was evaporated under reduced pressure; the crude acyl chloride was diluted with anhydrous THF (5 mL) and cooled at 0-5°C. Gaseous ammonia was bubbled into the solution up to the complete disappearance of the acid (the reaction was monitored by TLC). The solvent was evaporated under reduced pressure and the residue diluted with CH_2Cl_2 (10 mL) and washed with a saturated solution of $NaHCO_3$ (3 x 10 mL) and H_2O (2 x 10 mL); the organic layer was dried over anhydrous Na_2SO_4 and evaporated under vacuum and the crude pulped in isopropyl ether to give, after filtration, the pure 4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate (0.74 g, 85% yield) as white solid. ^{1}H-NMR ($CDCl_3$) δ 7.75 (d, 2H, J = 7Hz), 7.30 (d, 2H, J = 7Hz), 6.42 (bs, 1H, CONH), 5.47 (bs, 1H, CONH), 1.95 (d, 3H, J = 23Hz).

Example 2

4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

2-methyl-2-(4-{[(trifluoromethyl)sulfonyl]oxy}phenyl)propanoic acid (0.88 g, 2.78 mmol) was dissolved in $SOCl_2$ (5 mL) and the resulting solution was left stirring at reflux 3h. After cooling at room temperature, the mixture was evaporated under reduced pressure; the crude acyl chloride was diluted with dry THF (5 mL) and cooled at 0-5°C. 2-(5-methyl-1H-pyrazol-1-yl)ethanamine (0.76 g, 6.11 mmol) (prepared as described in Attaryan O.S. et al., Russ. J. Gen. Chem., 2008, *78*, 136-138) was added to the mixture, under vigorous stirring. The reaction was monitored by TLC and left stirring at room temperature for 2-4 h; after the complete disappearance of the starting acid the solvent was evaporated under reduced pressure and the residue diluted with CH_2Cl_2 (10 mL) and H_2O (10 mL); the two phases were debated and separated and the organic one was washed with a saturated solution of $NaHCO_3$ (3 x 10 mL) and H_2O (2 x 10 mL), dried over Na_2SO_4 and evaporated under vacuum to give pure 4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate (0.82 g, 70% yield) as colourless oil.

MS (ESI) : m/z $[M+H]^{1+}$ 424 Rt = 1.65 min.

According to the same experimental procedure and using the corresponding above described arylpropionic acids as starting reagents, the following compounds were synthesized:

Example 3

4-(2-fluoro-1-oxo-1-{[2-(pyridin-2-ylamino)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI) : m/z $[M+H]^{1+}$ 436; Rt = 1.67 min.

Example 4

2-fluoro-*N*-(2-sulfamoylthiophen-3-yl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 495; Rt = 3.86 min.

Example 5

2-fluoro-*N*-(2-sulfamoylphenyl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino} phenyl)propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 489; Rt = 3.88 min.

Example 6

4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI) : m/z $[M+H]^{1+}$ 425; Rt = 1.67 min.

Example 7

4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI) : m/z $[M+H]^{1+}$ 417; Rt = 1.64 min.

Example 8

***N*-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-[5-(phenylcarbonyl)thiophen-2-yl]propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 368; Rt = 1.22 min.

Example 9

2-{4-[(3-methoxyphenyl)amino]phenyl}-*N*-(1-benzylpiperidin-4-yl)propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 444; Rt = 9.72 min.

Example 10

2-[(3-methoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide

MS (ESI) : m/z $[M+HCOOH-H]^{1-}$ 409; Rt = 10.55 min.

Example 11

***N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(3-fluorophenoxy)phenyl] propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 353; Rt = 11.34 min.

Example 12

2-[3-(3-fluorophenoxy)phenyl]-*N*-[2-(phenylamino)ethyl]propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 393; Rt = 9.50 min.

Example 13

2-{4-[(2,6-dichlorophenyl)amino]phenyl}-*N*-phenylpropanamide

MS (ESI) : m/z $[M+H]^{1+}$ 439; Rt = 9.84 min.

Example 14

2-[3-(cyclopropylamino)phenyl]-N-(pyrimidin-4-yl)propanamide

MS (ESI) : m/z $[M-H]^{1-}$ 295; Rt = 10.28 min.

Example 15

2-(3-{[4-(morpholin-4-yl)phenyl]amino}phenyl)N-(pyrimidin-4-yl)propanamide

MS (ESI) : m/z $[M-H]^{1-}$ 402; Rt = 10.30 min.

Example 16

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(morpholin-4-yl)ethyl]propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 436; Rt = 9.70 min.

Example 17

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(cyclohexylamino)propyl] propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 460; Rt = 9.72 min.

Example 18

***N*-(2-amino-2-methylpropyl)-2-{3-[3-(trifluoromethoxy)phenoxy] phenylpropanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 397; Rt = 9.73 min.

Example 19

***N*-[(2-pyrrolidin-1-yl)ethyl]-2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 423; Rt = 9.72 min.

Example 20

3-(1-{[2-(4-fluorophenoxy)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI) : m/z $[M+H]^{1+}$ 436 Rt = 1.70 min.

Example 21

2-{4-[(propan-2-ylsulfonyl)amino]phenyl}-*N*-(4-tert-butyl-1,3-thiazol-2-yl) propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 410 Rt = 1.68 min.

Example 22

***N*-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-{4-[(propan-2-ylsulfonyl)amino] phenylpropanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 462 Rt = 1.51 min.

Example 23

***N*-(2-methylprop-2-en-1-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 314; Rt = 10.35 min.

Example 24

***N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 354; Rt = 10.12 min.

Example 25

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 395; Rt = 10.73 min.

Example 26

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(pyrimidin-4-yl)propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 379; Rt = 10.91 min.

Example 27

2-{3-[hex-1-en-1-yl]phenyl}-*N*-[2-(propan-2-ylamino)ethyl]propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 317; Rt = 10.05 min.

Example 28

2-{3-[hex-1-en-1-yl]phenyl}-*N*-(pyrimidin-4-yl)propanamide

MS (ESI) : m/z $[M+H]^{1+}$ 309; Rt = 12.86 min.

Example 29

***N*-(3-ethyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl) propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 408; Rt = 1.28 min.

Example 30

***N*-[2-(*tert*-butylamino)-2-oxoethyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino} phenyl)propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 413; Rt = 1.24 min.

Example 31

***N*-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 491; Rt = 1.30 min.

Example 32

***N*-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 478; Rt = 1.68 min.

Example 33

2-[3-(phenylcarbonyl)phenyl]-*N*-(1,3-thiazol-2-yl)propanamide

^{1}H-NMR ($CDCl_3$) δ 7.90-7.85 (m, 3H), 7.75 (m, 1H), 7.65-7.55 (m, 2H), 7.52-7.45 (m, 3H), 7.40 (d, 1H, J = 3Hz), 6.95 (d, 1H, J = 3Hz), 3.95 (q, 1H, J = 7Hz), 1.70 (d, 3H, J = 7Hz).

Example 34

***N*-cyclohexyl-2-[3-(phenylcarbonyl)phenyl]propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 336; Rt = 11.41 min.

Example 35

***N*-phenyl-2-[3-(phenylcarbonyl)phenyl]propanamide**

MS (ESI) : m/z $[M+H]^{1+}$ 330; Rt = 11.28 min.

Example 36

***N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(phenylcarbonyl)phenyl] propanamide**

MS (ESI) : m/z $[M-H]^{1-}$ 346; Rt = 10.30 min.

Example 37

2-[4-(2-methylpropyl)phenyl]-*N*-(pyridin-4-yl)propanamide

^{1}H-NMR ($CDCl_3$) δ 8.45 (d, 2H, J = 3Hz), 7.40 (d, 2H, J = 3Hz), 7.25 (d, 2H, J = 7Hz), 7.10 (d, 2H, J = 7Hz), 7.05 (bs, 1H, CONH), 3.75 (q, 1H, J = 7Hz), 2.50 (d, 2H, J = 7Hz), 1.90 (m, 1H), 1.60 (d, 3H, J = 7Hz), 0.90 (d, 6H, J = 7Hz).

Example 38

N-carbamoyl-2-[4-(2-methylpropyl)phenyl]propanamide

^{1}H-NMR ($CDCl_3$) δ 8.19-8.03 (bs, 2 H, CONH), 7.25 (d, 2H, J = 7Hz), 7.10 (d, 2H, J = 7Hz), 5.25 (bs, 1H, CONH), 3.64 (q, 1H, J = 7Hz), 2.46 (d, 2H, J = 7Hz), 1.86 (m, 1H), 1.53 (d, 3H, J = 7Hz), 0.91 (d, 6H, J = 7Hz).

Example 39

1-methyl-4-({2-[4-(2-methylpropyl)phenyl]propanoyl}amino)pyrimidin-1-ium iodide

^{1}H-NMR (DMSO-d_6) δ 9.35 (s, 1H), 8.93 (d, 1H, J = 7Hz), 8.45 (d, 1H, J = 7Hz), 7.32 (d, 2H, J = 7Hz), 7.14 (d, 2H, J = 7Hz), 4.10 (q, 1H, J = 7Hz), 4.06 (s, 3H), 2.42 (d, 2H, J = 7Hz), 1.81 (m, 1H), 1.44 (d, 3H, J = 7Hz), 0.85 (d, 6H, J = 7Hz).

Example 40

***N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[4-(2-methylpropyl)phenyl] propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 300; Rt = 11.60 min.

Example 41

***N*-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 424; Rt = 1.59 min.

Example 42

***N*-[2-(3,5-dimethylpiperidin-1-yl)ethyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 455; Rt = 1.73 min.

Example 43

***N*-[furan-2-yl(morpholin-4-yl)methyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 495; Rt = 1.65 min.

Example 44

***N*-[4-(pyridin-4-ylmethyl)phenyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino} phenyl)propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 483; Rt = 1.66 min.

Example 45

***N*-[2-(furan-2-yl)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 424; Rt = 1.68 min.

Example 46

4-(1-{[2-(furan-2-yl)propyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI): m/z $[M+H]^{1+}$ 483; Rt = 1.66 min.

Example 47

4-[1-oxo-1-(pyridin-4-ylamino)propan-2-yl]phenyl trifluoromethanesulfonate

^{1}H-NMR ($CDCl_3$) δ 8.45 (d, 2H, J = 7Hz), 7.45 (m, 4H), 7.30 (d, 2H, J = 7Hz), 3.75 (q, 1H, J = 7Hz), 1.60 (d, 3H, J = 7Hz).

Example 48

4-{1-oxo-1-[4-(pyridin-4-ylmethyl)propan-2-yl]amino}phenyl trifluoromethanesulfonate

MS (ESI): m/z $[M+H]^{1+}$ 465; Rt = 1.30 min.

Example 49

4-(1-{[(dimethylamino)(4-fluorophenyl)methyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI): m/z $[M+H]^{1+}$ 463; Rt = 1.31 min.

Example 50

4-(1-{[3-[3-methoxybenzyl(methyl)amino]propyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI): m/z $[M+H]^{1+}$ 489; Rt = 1.33 min.

Example 51

4-[3-(3,4-dimethylphenoxy)-2-hydroxypropyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate

MS (ESI): m/z $[M+H]^{1+}$ 476; Rt = 1.73 min.

Example 52

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(3-ethoxypropyl) propanamide

MS (ESI): m/z $[M+H]^{1+}$425; Rt = 11.91 min.

Example 53

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(1*H*-pyrrol-1-yl) propanamide

MS (ESI): m/z $[M+H]^{1+}$ 404; Rt = 11.62 min.

Example 54

***N*'-{2-[3-(3-methoxy-5-(trifluoromethyl)phenylamino)phenyl] propanoyl}furan-2-carbohydrazide**

MS (ESI): m/z $[M+H]^{1+}$ 439; Rt = 11.49 min.

Example 55

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(pyrimidin-4-yl) propanamide

MS (ESI): m/z $[M+H]^{1+}$ 417; Rt = 11.78 min.

Example 56

***N*-ethyl-2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino} phenyl)propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 367; Rt = 11.51 min.

Example 57

2-{3-[(3-methoxy-5-(trifluoromethyl)phenyl)amino]phenyl}-*N*-[2-(benzylamino)ethyl]propanamide

MS (ESI): m/z $[M+H]^{1+}$ 472; Rt = 10.05 min.

Example 58

***N*-(2-amino-2-methylpropyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 410; Rt = 9.71 min.

Example 59

***N*-(2-aminocyclohexyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 436; Rt = 9.98 min.

Example 60

methyl 3-[(tert-butoxycarbonyl)amino]-2-[4-(naphthalen-1-yloxyphenyl)propanoyl] aminopropanoate

MS (ESI): m/z $[M+H]^{1+}$ 493; Rt = 12.65 min.

Example 61

***N*-[2-(benzylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 425; Rt = 10.23 min.

Example 62

***N*-[3-(dimethylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 377; Rt = 9.77 min.

Example 63

***N*-[3-(cyclohexylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 431; Rt = 10.45 min.

Example 64

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide

MS (ESI): m/z $[M+H]^{1+}$ 359; Rt = 11.30 min.

Example 65

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl] propanamide

MS (ESI): m/z $[M+H]^{1+}$ 403; Rt = 9.82 min.

Example 66

***N*-[2-(acetylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide**

MS (ESI): m/z $[M+H]^{1+}$ 377; Rt = 11.50 min.

Example 67

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(morpholin-4-yl)ethyl] propanamide

MS (ESI): m/z $[M+H]^{1+}$ 405; Rt = 10.28 min.

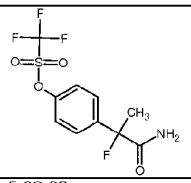
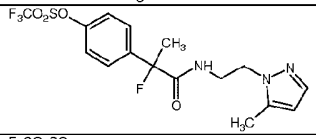
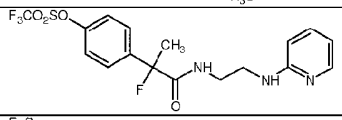
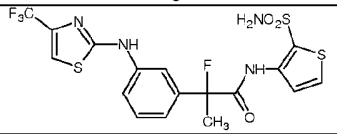
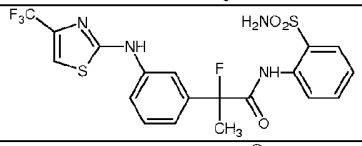
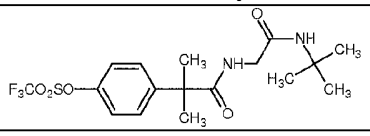
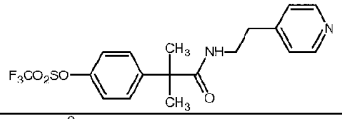
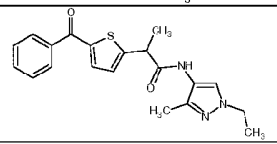
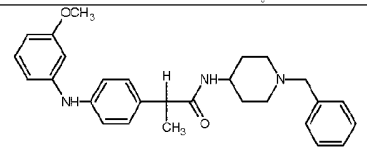
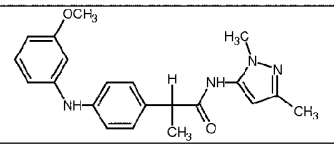
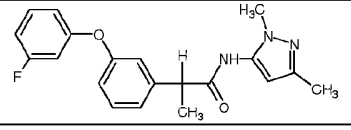
Biological Evaluation

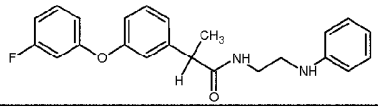
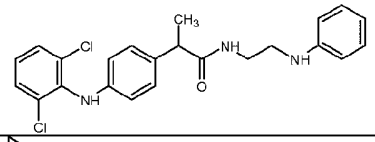
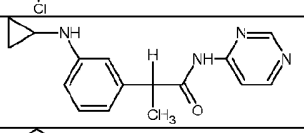
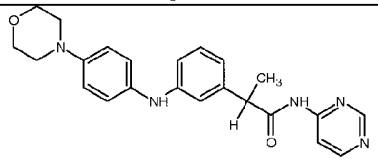
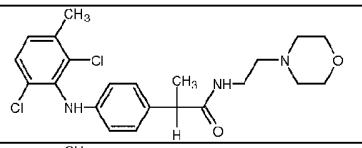
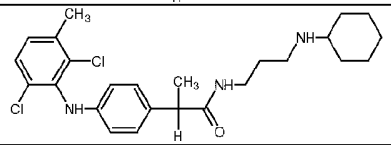
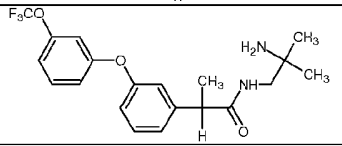
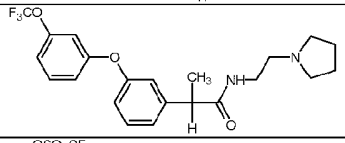
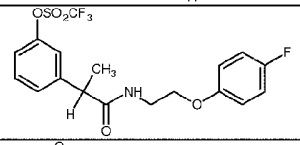
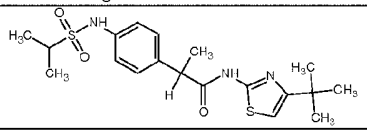
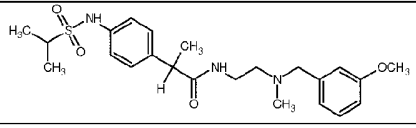
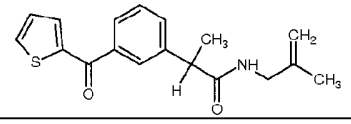
Calcium mobilization assay (FLIPR) – Human (IMR-90) lung fibroblast cells expressing native B1 receptors were harvested by trypsinization and seeded into black wall/clear bottom 96-well plates (Costar 3904; Corning Life Sciences, Acton, MA) at approximately 13,000 cells/well. After 1 day incubation, cells were treated with human IL-1β (0.35 ng/ml) in 10% FBS/MEM for 2 h to up-regulate BKB1 receptors. Induced cells were loaded with fluorescent calcium indicator by incubation with 2.3 μM Fluo-4/acetoxymethyl ester (Invitrogen) at 37°C for 1.5 h in the presence of an anion transport inhibitor (2.5 mM probenecid in 1% FBS/MEM). Extracellular dye was removed by washing with assay buffer (2.5 mM probenecid, 0.1% BSA in 20 mM HEPES/HBSS without bicarbonate or phenol red, pH 7.5) and cell plates were kept in the dark until used. Test compounds were assayed at eight concentrations in triplicate. Addition of test compounds to the cell plate and incubation for 5 min at 35°C, followed by the addition of 2 to 8 nM final BK1 agonist *des*Arg^{10}-kallidin (DAKD, 3 x EC_{50}) was carried out in the fluorimetric imaging plate reader (FLIPR; Molecular Devices) while continuously monitoring calcium-dependent fluorescence.

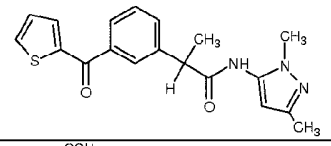
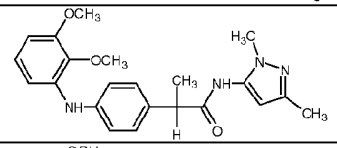
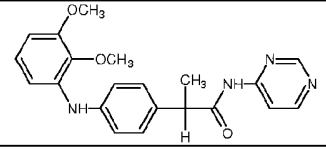
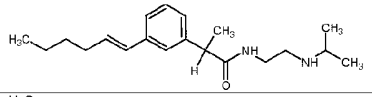
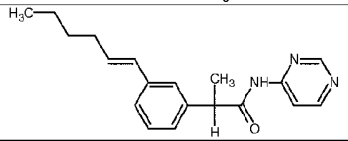
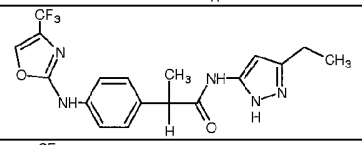
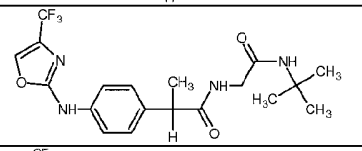
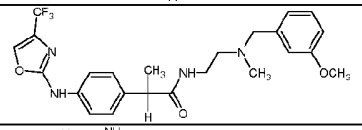
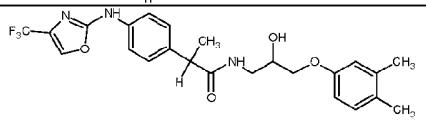
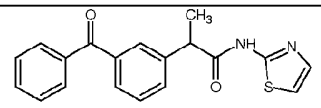
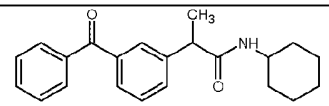
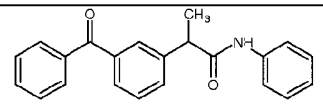
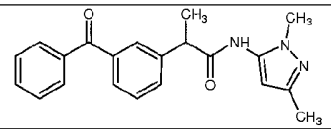
Responses for B2 receptors were measured in IMR-90 cells in an identical manner except that IL-1βtreatment was not necessary and bradykinin (0.7 nM final; 3 x EC_{50}) replaced DAKD as agonist.

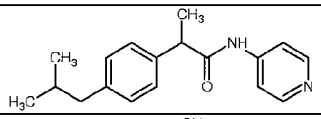
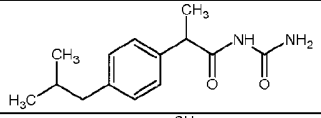
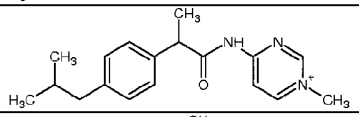
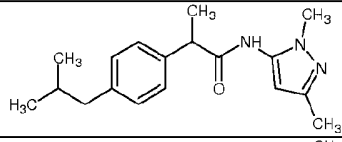
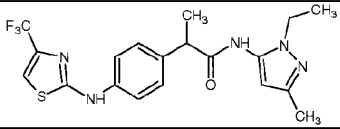
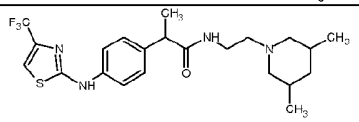
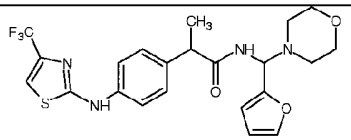
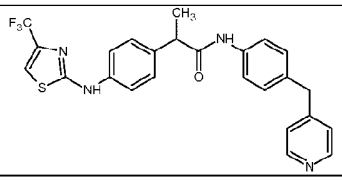
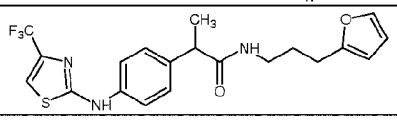
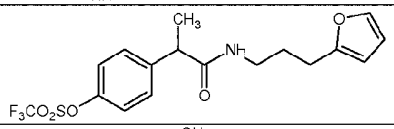
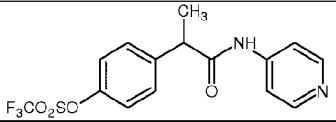
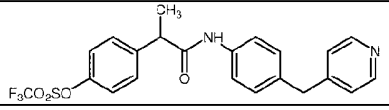
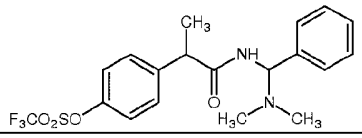
The compounds 1-82 of the invention were tested in the above described assay and found active in inhibiting calcium mobilization in the pIC_{50} range of 4-7 in BKB1 receptors-expressing cells, while the same compounds were found inactive in BKB2 receptors-expressing cells biological assay.

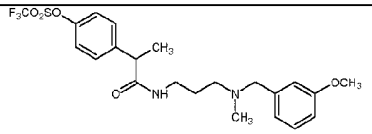
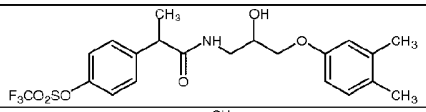
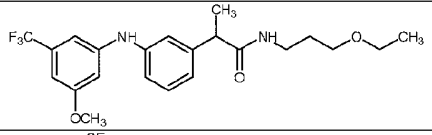
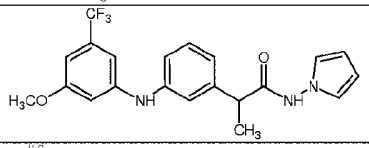
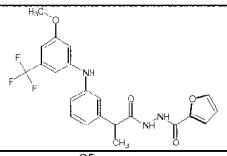
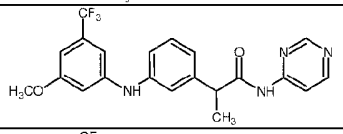
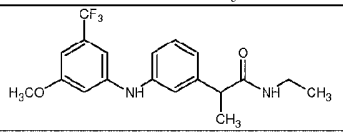
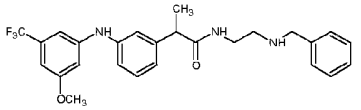
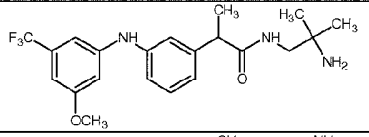
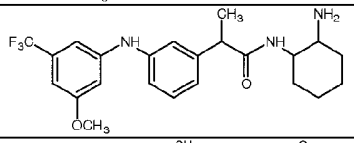
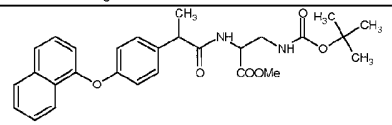
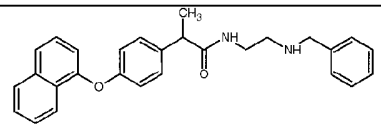
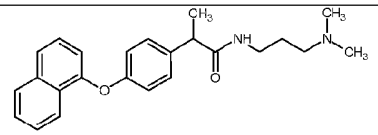
List of the preferred compounds

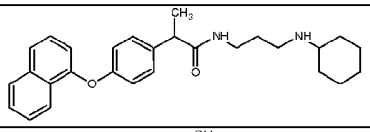
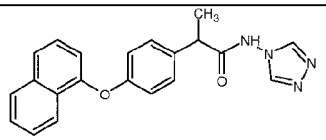
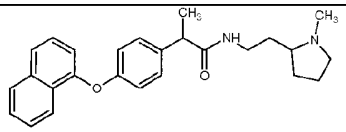
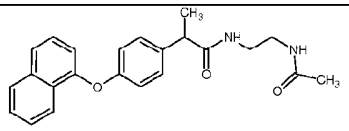
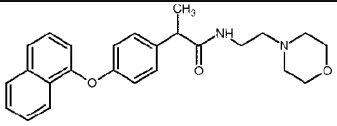
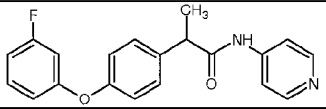
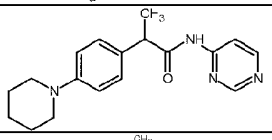
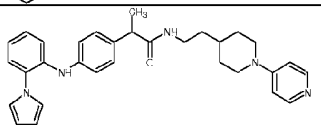
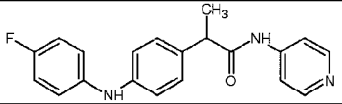
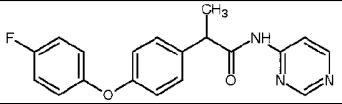
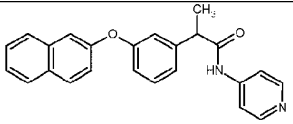
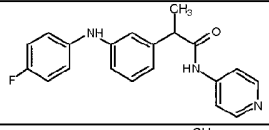
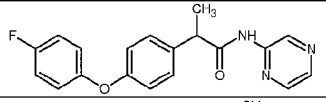
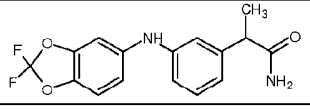
N.	Chemical Structure	Chemical Name	pIC_{50} (hBK)
1		4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	5.19
2		4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	5.21
3		4-(2-fluoro-1-oxo-1-{[2-(pyridin-2-ylamino)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate	4.88
4		2-fluoro-*N*-(2-sulfamoylthiophen-3-yl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	5.37
5		2-fluoro-*N*-(2-sulfamoylphenyl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	5.06
6		4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	4.75
7		4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate	4.94
8		*N*-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-[5-(phenylcarbonyl)thiophen-2-yl]propanamide	5.58
9		2-{4-[(3-methoxyphenyl)amino]phenyl}-*N*-(1-benzylpiperidin-4-yl)propanamide	5.11
10		2-[(3-methoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide	5.10
11		*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(3-fluorophenoxy)phenyl] propanamide	4.95

12		2-[3-(3-fluorophenoxy)phenyl]-*N*-[2-(phenylamino)ethyl]propanamide	5.14
13		2-{4-[(2,6-dichlorophenyl)amino]phenyl}-*N*-phenylpropanamide	5.49
14		2-[3-(cyclopropylamino)phenyl]-*N*-(pyrimidin-4-yl)propanamide	5.20
15		2-(3-{[4-(morpholin-4-yl)phenyl]amino}phenyl)N-(pyrimidin-4-yl)propanamide	5.04
16		2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(morpholin-4-yl)ethyl]propanamide	4.92
17		2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(cyclohexylamino)propyl] propanamide	5.27
18		*N*-(2-amino-2-methylpropyl)-2-{3-[3-(trifluoromethoxy)phenoxy] phenylpropanamide	5.68
19		*N*-[(2-pyrrolidin-1-yl)ethyl]-2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanamide	5.11
20		3-(1-{[2-(4-fluorophenoxy)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	4.78
21		2-{4-[(propan-2-ylsulfonyl)amino]phenyl}-*N*-(4-tert-butyl-1,3-thiazol-2-yl)propanamide	5.04
22		*N*-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-{4-[(propan-2-ylsulfonyl)amino] phenylpropanamide	5.09
23		*N*-(2-methylprop-2-en-1-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide	4.66

24		*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide	5.13
25		2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)propanamide	5.51
26		2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(pyrimidin-4-yl)propanamide	5.24
27		2-{3-[hex-1-en-1-yl]phenyl}-*N*-[2-(propan-2-ylamino)ethyl]propanamide	5.07
28		2-{3-[hex-1-en-1-yl]phenyl}-*N*-(pyrimidin-4-yl)propanamide	5.07
29		*N*-(3-ethyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide	5.15
30		*N*-[2-(*tert*-butylamino)-2-oxoethyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide	5.11
31		*N*-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide	5.11
32		*N*-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide	5.08
33		2-[3-(phenylcarbonyl)phenyl]-*N*-(1,3-thiazol-2-yl)propanamide	4.99
34		*N*-cyclohexyl-2-[3-(phenylcarbonyl)phenyl]propanamide	5.07
35		*N*-phenyl-2-[3-(phenylcarbonyl)phenyl]propanamide	5.00
36		*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(phenylcarbonyl)phenyl]propanamide	5.01

37		2-[4-(2-methylpropyl)phenyl]-*N*-(pyridin-4-yl)propanamide	5.86
38		*N*-carbamoyl-2-[4-(2-methylpropyl)phenyl]propanamide	4.70
39		1-methyl-4-({2-[4-(2-methylpropyl)phenyl]propanoyl}amino)pyrimidin-1-ium	4.90
40		*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[4-(2-methylpropyl)phenyl] propanamide	5.68
41		*N*-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	5.0
42		*N*-[2-(3,5-dimethylpiperidin-1-yl)ethyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	5.18
43		*N*-[furan-2-yl(morpholin-4-yl)methyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	4.89
44		*N*-[4-(pyridin-4-ylmethyl)phenyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide	4.94
45		*N*-[2-(furan-2-yl)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl] amino}phenyl)propanamide	4.96
46		4-(1-{[2-(furan-2-yl)propyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	4.86
47		4-[1-oxo-1-(pyridin-4-ylamino)propan-2-yl]phenyl trifluoromethanesulfonate	5.49
48		4-{1-oxo-1-[4-(pyridin-4-ylmethyl)propan-2-yl]amino}phenyl trifluoromethanesulfonate	4.90
49		4-(1-{[(dimethylamino)(4-fluorophenyl)methyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	5.09

50		4-(1-{[3-[3-methoxybenzyl(methyl)amino]propyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	5.44
51		4-[3-(3,4-dimethylphenoxy)-2-hydroxypropyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate	4.94
52		2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(3-ethoxypropyl)propanamide	5.05
53		2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(1*H*-pyrrol-1-yl)propanamide	4.84
54		*N*'-{2-[3-(3-methoxy-5-(trifluoromethyl)phenylamino)phenyl] propanoyl}furan-2-carbohydrazide	5.07
55		2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(pyrimidin-4-yl)propanamide	5.28
56		*N*-ethyl-2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino} phenyl)propanamide	5.11
57		2-{3-[(3-methoxy-5-(trifluoromethyl)phenyl)amino]phenyl}-*N*-[2-(benzylamino)ethyl]propanamide	5.46
58		*N*-(2-amino-2-methylpropyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide	5.23
59		*N*-(2-aminocyclohexyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide	5.16
60		methyl 3-[(tert-butoxycarbonyl)amino]-2-[4-(naphthalen-1-yloxyphenyl)propanoyl]aminopropanoate	4.98
61		*N*-[2-(benzylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide	5.49
62		*N*-[3-(dimethylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide	5.42

63		*N*-[3-(cyclohexylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide	5.41
64		2-[4-(naphthalen-1-yloxy)phenyl]-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide	5.05
65		2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl] propanamide	5.32
66		*N*-[2-(acetylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide	5.18
67		2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(morpholin-4-yl)ethyl] propanamide	5.39
68		2-[4-(3-fluorophenoxy)phenyl]-*N*-(pyridin-4-yl)propanamide	5.21
69		2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrimidin-4-yl)propanamide	4.85
70		*N*-{2-[1-(pyridin-4-yl)piperidin-4-yl]ethyl}-2-(4-{[2-(1*H*-pyrrol-1-yl)phenyl]amino}phenyl)propanamide	6.15
71		2-{4-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide	5.35
72		2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrimidin-4-yl)propanamide	5.47
73		2-[3-(naphthalen-2-yloxy)phenyl]-*N*-(pyridin-4-yl)propanamide	5.55
74		2-{3-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide	6.00
75		2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrazin-2-yl)propanamide	5.92
76		2-{3-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide	5.05

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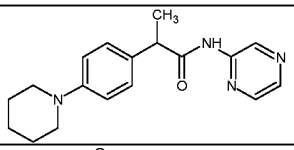
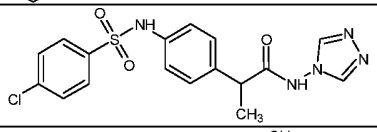
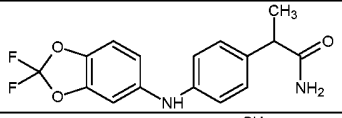
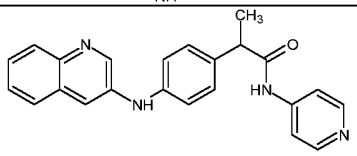
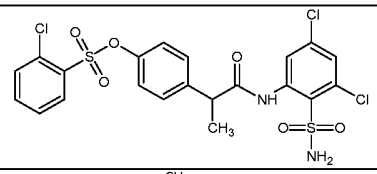
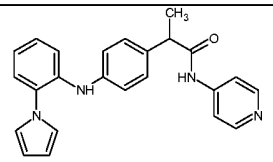
77		2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrazin-2-yl)propanamide	5.36
78		2-(4-{[(4-chlorophenyl)sulfonyl]amino}phenyl)-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide	6.05
79		2-{4-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide	5.87
80		*N*-(pyridin-4-yl)-2-[4-(quinolin-3-ylamino)phenyl]propanamide	5.28
81		4-{1-[(3,5-dichloro-2-sulfamoylphenyl)amino]-1-oxopropan-2-yl}phenyl 2-chlorobenzenesulfonate	5.06
82		2-[4-{[2-(1H-pyrrol-1-yl)phenyl]-N-(pyridin-4-yl)propanamide	5.24

It is to be understood that, if any prior art publication is referred to herein, such reference does not constitute an admission that the publication forms a part of the common general knowledge in the art, in Australia or any other country.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprise" or variations such as "comprises" or "comprising" is used in an inclusive sense, i.e. to specify the presence of the stated features but not to preclude the presence or addition of further features in various embodiments of the invention.

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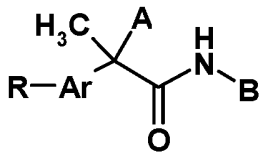
Claims

1. Use of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

A is selected from the group consisting of H, CH_3 and F;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl, C_2-C_8-alkenyl or C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl;

-optionally substituted 5 -6-membered heterocyclic residues; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

-$(CH_2)_n$-$(NH)_p$-Y wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

-$(CH_2)_n$-Z-$(CH_2)_{n'}$-A wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from -CONH-, -O-, -NCH_3-, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

-CHR_aR_b, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic,

substituted or unsubstituted phenyl, dialkylamino, -CH_2-NHCOO-C_1-C_4-alkyl, -(COO)C_1-C_4-alkyl;

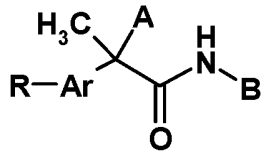
wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido;

for the preparation of a medicament for the treatment and prevention of diseases and conditions mediated by Bradykinin B1 receptor pathway wherein said diseases and conditions are selected from pain, hyperreactive airways and inflammatory diseases and events associated with airway diseases, inflammatory bowel diseases, inflammatory skin disorders, edema resulting from burns, sprains and fractures, cerebral edema and angioedema, diabetic vasculopathy, diabetic neuropathy, diabetic symptoms associated with insulitis, liver disease, cardiovascular disease, congestive heart failure; myocardial infarct; neurodegenerative diseases, epilepsy, septic shock, headache, migraine, closed head trauma, cancer, sepsis, gingivitis, osteoporosis, benign hyperplasia and hyperactive bladder, interstitial cystitis,

provided that when A = H or F

said diseases mediated by Bradykinin B1 receptor pathway are different from: rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ulcerative colitis, psoriasis, sepsis, melanoma, and heart ischemia.

2. A method of treatment or prevention of a disease or a condition mediated by Bradykinin B1 receptor pathway comprising administration to a patient in need thereof a pharmaceutically effective amount of a compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein,

A is selected from the group consisting of H, CH_3 and F;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl or C_2-C_8-alkenyl, C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl;

-optionally substituted 5 -6-membered heterocyclic residues; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

- linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

-$(CH_2)_n$-$(NH)_p$-Y wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

-$(CH_2)_n$-Z-$(CH_2)_{n'}$-A wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from –CONH-, -O-, -NCH_3-, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

-CHR_aR_b, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, -CH_2-NHCOO-C_1-C_4-alkyl, -(COO)C_1-C_4-alkyl;

wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido;

wherein said disease or condition mediated by Bradykinin B1 receptor pathway is selected from pain, hyperreactive airways and inflammatory diseases and events associated with airway diseases, inflammatory bowel diseases, inflammatory skin

disorders, edema resulting from burns, sprains and fractures, cerebral edema and angioedema, diabetic vasculopathy, diabetic neuropathy, diabetic symptoms associated with insulitis liver disease, cardiovascular disease, congestive heart failure; myocardial infarct; neurodegenerative diseases, epilepsy, septic shock, headache, migraine, closed head trauma, cancer, sepsis, gingivitis, osteoporosis, benign hyperplasia and hyperactive bladder, interstitial cystitis,

provided that when A = H or F

said disease mediated by Bradykinin B1 receptor pathway is different from: rheumatoid arthritis, chronic obstructive pulmonary disease (COPD), ulcerative colitis, psoriasis, sepsis, melanoma, and heart ischemia.

3. Use as claimed in claim 1 or method as claimed in claim 2, wherein Ar is selected from phenyl, thiophene and pyrrole.

4. Use or method as claimed in claim 3, wherein said Ar is selected from phenyl substituted by R in position 3 or 4, and thiophen-2-yl.

5. Use as claimed in any one of claims 1, 3 and 4, or method as claimed in any one of claims 2 to 4, wherein R is selected from hex-1-en-1-yl, 2-methylpropyl, cyclopropylamino, substituted or unsubstituted phenylcarbonyl, substituted or unsubstituted thiophen-carbonyl, substituted or unsubstituted phenylamino, substituted or unsubstituted 1,3-thiazol-2-yl-amino, substituted or unsubstituted 1,3-oxazol-2-yl-amino, substituted or unsubstituted phenoxy, substituted or unsubstituted naphthalen-1-yloxy, substituted or unsubstituted naphthalen-2-yloxy morpholin-4-yl, piperidin-1-yl, trifluoromethanesulfonyloxy, substituted or unsubstituted phenylsulfonyloxy, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

6. Use as claimed in any one of claims 1 and 3 to 5, or method as claimed in any one of claims 2 to 5, wherein B is selected from H, ethyl, 2-methylprop-2-en-1-yl, 2-amino-2-methyl-propyl, substituted or unsubstituted 1*H*-pyrazol-4-yl, substituted or unsubstituted 1*H*-pyrazol-5-yl, substituted or unsubstituted thiophen-3-yl, substituted or unsubstituted 1,3-thiazol-2-yl, pyrimidin-4-yl, substituted or unsubstituted 1-*H*-pyrrol-1-yl, substituted or unsubstituted 4*H*-1,2,4-triazol-4-yl, substituted or unsubstituted pyridine-4-yl, pyrazin-2-yl, substituted or unsubstituted piperydin-4-yl, substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, furan-2-yl-C_1-C_3-alkyl, substituted or unsubstituted piperidin-1-yl-C_1-C_3-alkyl, pyridine-2-yl-amino-C_1-C_3-alkyl, phenylamino-C_1-C_3-alkyl, cyclohexylamino-N-C_1-C_3-alkyl, 1*H*-pyrazol-1-yl-C_1-C_3-alkyl, pyridin-4-yl-C_1-C_3-alkyl, morpholin-4-yl-C_1-C_3-alkyl, pyrrolidin-1-yl-C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, (benzylamino)C_1-C_3-alkyl, (C_1-C_3-alkylamino)-ethyl, -(C_1-C_4-dialkylamino)C_1-C_3-alkyl, 2-(tert-butylamino)-2-oxoethyl; (phenoxy)C_1-C_3alkyl, [(benzyl)(methylamino)]C_1-C_3alkyl, (3,4-dimethylphenoxy)-2-, [(dimethylamino)(4-fluorophenyl)methyl]amino; (*tert*-butoxycarbonyl) aminoethylcarboxy], carbamoyl, furan-2-carbamido, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, hydroxy, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

7. Use as claimed in any one of claims 1 and 3 to 6, or method as claimed in any one of claims 2 to 6, wherein the compound of formula (I) is selected from the group consisting of:

4-(1-amino-2-fluoro-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-fluoro-1-{[2-(5-methyl-1*H*-pyrazol-1-yl)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-fluoro-1-oxo-1-{[2-(pyridin-2-ylamino)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate;

2-fluoro-*N*-(2-sulfamoylthiophen-3-yl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;

2-fluoro-*N*-(2-sulfamoylphenyl)-2-(3-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino} phenyl)propanamide;

4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate;

N-(1-ethyl-3-methyl-1*H*-pyrazol-4-yl)-2-[5-(phenylcarbonyl)thiophen-2-yl]propanamide;

2-[(3-methoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide;

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(3-fluorophenoxy)phenyl] propanamide;

2-[3-(3-fluorophenoxy)phenyl]-*N*-[2-(phenylamino)ethyl]propanamide;

2-{4-[(2,6-dichlorophenyl)amino]phenyl}-*N*-phenylpropanamide;

2-[3-(cyclopropylamino)phenyl]-N-(pyrimidin-4-yl)propanamide;

2-(3-{[4-(morpholin-4-yl)phenyl]amino}phenyl)N-(pyrimidin-4-yl)propanamide;

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(morpholin-4-yl)ethyl]propanamide;

2-{4-[(2,6-dichloro-3-methylphenyl)amino]phenyl}-*N*-[2-(cyclohexylamino)propyl] propanamide;

N-(2-amino-2-methylpropyl)-2-{3-[3-(trifluoromethoxy)phenoxy] phenylpropanamide;

N-[(2-pyrrolidin-1-yl)ethyl]-2-{3-[3-(trifluoromethoxy)phenoxy]phenyl}propanamide;

3-(1-{[2-(4-fluorophenoxy)ethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

N-(2-methylprop-2-en-1-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide;

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(thiophen-2-ylcarbonyl)phenyl] propanamide;

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(1,3-dimethyl-1*H*-pyrazol-5-yl) propanamide;

2-{4-[(2,3-dimethoxyphenyl)amino]phenyl}-*N*-(pyrimidin-4-yl)propanamide;

2-{3-[hex-1-en-1-yl]phenyl}-*N*-[2-(propan-2-ylamino)ethyl]propanamide;

2-{3-[hex-1-en-1-yl]phenyl}-*N*-(pyrimidin-4-yl)propanamide;

N-(3-ethyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl) propanamide;

N-[2-(*tert*-butylamino)-2-oxoethyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino} phenyl)propanamide;

N-{2-[(3-methoxybenzyl)(methyl)amino]ethyl}-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide;

N-[2-hydroxy-3-(3,4-dimethylphenoxy)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-oxazol-2-yl]amino}phenyl)propanamide;

2-[3-(phenylcarbonyl)phenyl]-*N*-(1,3-thiazol-2-yl)propanamide;

N-cyclohexyl-2-[3-(phenylcarbonyl)phenyl]propanamide;

N-phenyl-2-[3-(phenylcarbonyl)phenyl]propanamide;

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[3-(phenylcarbonyl)phenyl] propanamide;

2-[4-(2-methylpropyl)phenyl]-*N*-(pyridin-4-yl)propanamide;

N-carbamoyl-2-[4-(2-methylpropyl)phenyl]propanamide;

1-methyl-4-({2-[4-(2-methylpropyl)phenyl]propanoyl}amino)pyrimidin-1-ium iodide;

N-(1,3-dimethyl-1*H*-pyrazol-5-yl)-2-[4-(2-methylpropyl)phenyl] propanamide;

N-(1-ethyl-3-methyl-1*H*-pyrazol-5-yl)-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;

N-[2-(3,5-dimethylpiperidin-1-yl)ethyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;

N-[furan-2-yl(morpholin-4-yl)methyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl)propanamide;

N-[2-(furan-2-yl)propyl]-2-(4-{[4-(trifluoromethyl)-1,3-thiazol-2-yl]amino}phenyl) propanamide;

4-(1-{[2-(furan-2-yl)propyl]amino}-1-oxopropan-2-yl)phenyl Trifluoromethanesulfonate;

4-[1-oxo-1-(pyridin-4-ylamino)propan-2-yl]phenyl trifluoromethanesulfonate;

4-(1-{[(dimethylamino)(4-fluorophenyl)methyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-(1-{[3-[3-methoxybenzyl(methyl)amino]propyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

4-[3-(3,4-dimethylphenoxy)-2-hydroxypropyl]amino-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(3-ethoxypropyl) propanamide;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(1*H*-pyrrol-1-yl) propanamide;

N'-{2-[3-(3-methoxy-5-(trifluoromethyl)phenylamino)phenyl] propanoyl}furan-2-carbohydrazide;

2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino}phenyl)-*N*-(pyrimidin-4-yl) propanamide;

N-ethyl-2-(3-{[3-methoxy-5-(trifluoromethyl)phenyl]amino} phenyl)propanamide

2-{3-[(3-methoxy-5-(trifluoromethyl)phenyl)amino]phenyl}-*N*-[2-(benzylamino)ethyl]propanamide;

N-(2-amino-2-methylpropyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide;

N-(2-aminocyclohexyl)-2-[3-{[3-methoxy-5-(trifluoromethyl)phenyl] amino}phenyl]propanamide;

methyl 3-[(tert-butoxycarbonyl)amino]-2-[4-(naphthalen-1-yloxyphenyl)propanoyl] aminopropanoate;

N-[2-(benzylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

N-[3-(dimethylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

N-[3-(cyclohexylamino)propyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(1-methylpyrrolidin-2-yl)ethyl] propanamide;

N-[2-(acetylamino)ethyl]-2-[4-(naphthalen-1-yloxy)phenyl]propanamide;

2-[4-(naphthalen-1-yloxy)phenyl]-*N*-[2-(morpholin-4-yl)ethyl] propanamide;

2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrimidin-4-yl)propanamide;

2-{4-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide;

2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrimidin-4-yl)propanamide;

2-[3-(naphthalen-1-yloxy)phenyl]-*N*-(pyridin-4-yl)propanamide;

2-{3-[(4-fluorophenyl)amino]phenyl}-*N*-(pyridin-4-yl)propanamide;

2-[4-(4-fluorophenoxy)phenyl]-*N*-(pyrazin-2-yl)propanamide;

2-{3-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide;

2-[4-(piperidin-1-yl)phenyl]-*N*-(pyrazin-2-yl)propanamide;

2-(4-{[(4-chlorophenyl)sulfonyl]amino}phenyl)-*N*-(4*H*-1,2,4-triazol-4-yl)propanamide;

2-{4-[(2,2-difluoro-1,3-benzodioxol-5-yl)amino]phenyl}propanamide;

N-(pyridin-4-yl)-2-[4-(quinolin-3-ylamino)phenyl]propanamide;

4-{1-[(3,5-dichloro-2-sulfamoylphenyl)amino]-1-oxopropan-2-yl}phenyl-2-chlorobenzenesulfonate;

or a pharmaceutically acceptable salt thereof.

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8. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said pain is selected from central pain syndromes caused by lesions at any level of the nervous system, postsurgical pain syndromes, bone and joint pain, repetitive motion pain, dental pain, cancer pain, myofascial pain, perioperative pain, chronic pain, dysmenorrea, pain associated with angina and inflammatory pain, or pain associated to pancreatitis, cystitis, renal colics, post herpetic neuralgia, nerve injury, osteoarthritis, muscular injury, fibromyalgia, rheumatoid arthritis, rheumatic disease and gout.

9. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said hyperreactive airways diseases and inflammatory events associated with airway disease are selected from the group consisting of: asthma, bronchoconstriction, occupational asthma, viral- or bacterial-exacerbation of asthma, non-allergic asthmas, “wheezy-infant syndrome”, chronic obstructive pulmonary disease and pneumoconiosis.

10. Use or method as claimed in claim 9, wherein said chronic obstructive pulmonary disease comprises emphysema, ARDS, bronchitis, pneumonia, allergic and vasomotor rhinitis.

11. Use or method as claimed in claim 9, wherein said pneumoconiosis comprises aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, tabacosis and byssinosis.

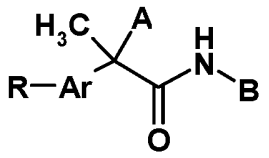
12. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said inflammatory bowel disease comprises Crohn’s disease, ulcerative colitis and uveitis.

13. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said inflammatory skin disorders are psoriasis and eczema.

14. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said cancer is selected from prostate cancer, pancreatic cancer, glioma, breast cancer, chondrosarcoma, colorectal tumor, brain tumor and myeloma.

15. Use as claimed in any one of claims 1 and 3 to 7, or method as claimed in any one of claims 2 to 7, wherein said neurodegenerative diseases are selected from: Alzheimer disease, Parkinson's disease, and multiple sclerosis.

16. A compound of formula (I):



(I)

or a pharmaceutically acceptable salt thereof,

wherein

A is CH_3;

Ar is selected from the group consisting of unsubstituted phenyl and 5, 6-membered heteroaryl;

R is a residue selected from the group consisting of:

-linear or branched C_1-C_6-alkyl or C_2-C_8-alkenyl, C_1-C_4-aminoalkyl,

-3-6 membered cycloalkylamino;

-W-Ar_1 wherein W is selected from O, NH, CO and Ar_1 is selected from the group consisting of optionally substituted phenyl, naphthyl, quinolinyl, benzodioxolyl and 5-6-membered heteroaryl; and

-X-SO_2R_1, wherein X is O and R_1 is selected from linear or branched C_1-C_4 alkyl, C_1-C_4 haloalkyl and optionally substituted phenyl;

B is a residue selected from the group consisting of:

-linear or branched C_1-C_6 alkyl, C_2-C_8-alkenyl, C_1-C_4 alkylamino, carbamoyl;

-$(CH_2)_n$-$(NH)_p$-Y wherein n is between 0 and 3, p is 0 or 1 and Y is selected from: a 5-6 membered ring selected from optionally substituted phenyl, heteroaryl, cycloalkyl and heterocyclic residues;

-$(CH_2)_n$-Z-$(CH_2)_{n'}$-A wherein n is between 0 and 3, n' is between 0 and 1, Z is selected from –CONH-, -O-, -NCH_3-, -CHOH- and A is selected from linear or branched C_1-C_4 alkyl, substituted or unsubstituted phenyl, substituted or unsubstituted phenoxy;

-(benzylamino)C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, furan-2-carbamido;

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$-CHR_aR_b$, wherein R_a and R_b are independently selected from substituted or unsubstituted 5-6 membered heteroaryl, substituted or unsubstituted 5-6 membered heterocyclic, substituted or unsubstituted phenyl, dialkylamino, $-CH_2-NHCOO-C_1-C_4$-alkyl, $-(COO)C_1-C_4$-alkyl, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

17. The compound as claimed in claim 16, wherein Ar is selected from phenyl, thiophene and pyrrole.

18. The compound as claimed in claim 17, wherein said Ar is selected from phenyl substituted by R in position 3 or 4, and thiophen-2-yl.

19. The compound as claimed in any one of claims 16 to 18, wherein R is selected from hex-1-en-1-yl, 2-methylpropyl, cyclopropylamino, substituted or unsubstituted phenylcarbonyl, substituted or unsubstituted thiophen-carbonyl, substituted or unsubstituted phenylamino, substituted or unsubstituted 1,3-thiazol-2-yl-amino, substituted or unsubstituted 1,3-oxazol-2-yl-amino, substituted or unsubstituted phenoxy, substituted or unsubstituted naphthalen-1-yloxy, substituted or unsubstituted naphthalen-2-yloxy morpholin-4-yl, piperidin-1-yl, trifluoromethanesulfonyloxy, substituted or unsubstituted phenylsulfonyloxy, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

20. The compound as claimed in any one of claims 16 to 19, wherein B is selected from ethyl, 2-methylprop-2-en-1-yl, 2-amino-2-methyl-propyl, substituted or unsubstituted 1*H*-pyrazol-4-yl, substituted or unsubstituted 1*H*-pyrazol-5-yl, substituted or unsubstituted thiophen-3-yl, substituted or unsubstituted 1,3-thiazol-2-yl, pyrimidin-4-yl, substituted or unsubstituted 1-*H*-pyrrol-1-yl, substituted or unsubstituted 4*H*-1,2,4-

triazol-4-yl, substituted or unsubstituted pyridine-4-yl, pyrazin-2-yl, substituted or unsubstituted piperydin-4-yl, substituted or unsubstituted phenyl, substituted or unsubstituted cyclohexyl, furan-2-yl-C_1-C_3-alkyl, substituted or unsubstituted piperidin-1-yl-C_1-C_3-alkyl, pyridine-2-yl-amino-C_1-C_3-alkyl, phenylamino-C_1-C_3-alkyl, cyclohexylamino-N-C_1-C_3-alkyl, 1*H*-pyrazol-1-yl-C_1-C_3-alkyl, pyridin-4-yl-C_1-C_3-alkyl, morpholin-4-yl-C_1-C_3-alkyl, pyrrolidin-1-yl-C_1-C_3-alkyl, (C_1-C_6-alkylamino)-C_1-C_3-alkyl, (benzylamino)C_1-C_3-alkyl, (C_1-C_3-alkylamino)-ethyl, -(C_1-C_4-dialkylamino)C_1-C_3-alkyl, 2-(tert-butylamino)-2-oxoethyl; (phenoxy)C_1-C_3alkyl, [(benzyl)(methylamino)]C_1-C_3alkyl, (3,4-dimethylphenoxy)-2-, [(dimethylamino)(4-fluorophenyl)methyl]amino; (*tert*-butoxycarbonyl) aminoethylcarboxy], carbamoyl, furan-2-carbamido, wherein the term substituted in the above definitions means substituted by one or more groups independently selected from linear or branched C_1-C_5-alkyl, halogen, linear or branched C_1-C_5-alkoxy, linear or branched C_1-C_5-mercapto, halo-C_1-C_3-alkyl, halo-C_1-C_3- alkoxy, amino, C_1-C_5-alkylamino, linear or branched C_1-C_5-alkanesulfonamides, sulfonamido.

21. A compound as claimed in any one of claims 16 to 20 selected from the group consisting of: 4-(2-methyl-1-{[2-(*tert*-butylamino)-2-oxoethyl]amino}-1-oxopropan-2-yl)phenyl trifluoromethanesulfonate, 4-(2-methyl-1-oxo-1-{[2-(pyridin-4-yl)ethyl]amino}propan-2-yl)phenyl trifluoromethanesulfonate, and pharmaceutically acceptable salts thereof.

22. Pharmaceutical composition comprising the compound according to any one of claims 16 to 21, in admixture with pharmaceutically acceptable excipients and/or diluents.

23. Use as claimed in claim 1, method as claimed in claim 2, a compound as claimed in claim 16, or a pharmaceutical composition as claimed in claim 22, substantially as herein described with reference to any one of the Examples.