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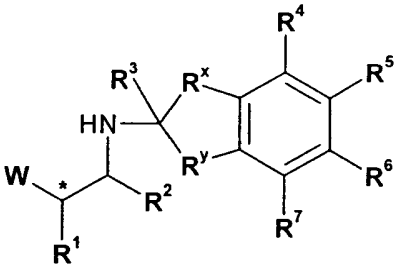

(I)

(57) Abstract: A medicament comprising, separately or together, (A) a compound of formula (I) in free or salt or solvate form, where W, R^x, R^y, R^1, R^2, R^3, R^4, R^5, R^6 and R^7 have the meanings as indicated in the specification, and (B) one or more of compounds selected from the group consisting of A2A agonists, A2B antagonists, antihistamines, caspase inhibitors, ENaC inhibitors, LTB4 antagonists, LTD4 antagonists and serine protease inhibitors, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

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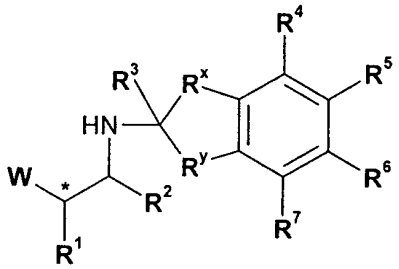
ORGANIC COMPOUNDS

This invention relates to organic compounds and their use as pharmaceuticals, in particular for the treatment of inflammatory or obstructive airways diseases.

In one aspect, the present invention provides a medicament comprising, separately or together,

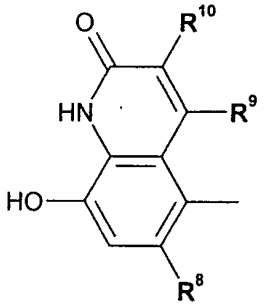
(A) a compound of formula I



I

in free or salt or solvate form, where

W is a group of formula



R^x and R^y are both $-CH_2-$ or $-(CH_2)_2-$;

R^1 is hydrogen, hydroxy, or C_1-C_{10}-alkoxy;

R^2 and R^3 are each independently hydrogen or C_1-C_{10}-alkyl;

R^4, R^5, R^6 and R^7 are each independently hydrogen, halogen, cyano, hydroxy, C_1-C_{10}-alkoxy, C_6-C_{10}-aryl, C_1-C_{10}-alkyl, C_1-C_{10}-alkyl substituted by one or more halogen atoms or one or more hydroxy or C_1-C_{10}-alkoxy groups, C_1-C_{10}-alkyl interrupted by one or more hetero atoms, C_2-C_{10}-alkenyl, trialkylsilyl, carboxy, C_1-C_{10}-alkoxycarbonyl, or $-CONR^{11}R^{12}$ where R^{11} and R^{12} are each independently hydrogen or C_1-C_{10}-alkyl,

or R^4 and R^5, R^5 and R^6, or R^6 and R^7 together with the carbon atoms to which they are attached denote a 5-, 6- or 7-membered carbocyclic ring or a 4- to 10-membered heterocyclic ring; and

R^8, R^9 and R^{10} are each independently hydrogen or C_1-C_4-alkyl; and

(B) one or more of compounds selected from the group consisting of

(i) A_{2A} agonists,

(ii) A_{2B} antagonists,

(iii) antihistamines,

(iv) caspase inhibitors

(v) ENaC inhibitors,

(vi) LTB4 antagonists,

(vii) LTD4 antagonists, and

(viii) serine protease inhibitors;

for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

In another aspect, the present invention provides a method of treating an inflammatory or obstructive airways disease which comprises administering to a subject in need of such treatment effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined.

In a further aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) as hereinbefore defined and (B) as hereinbefore defined, optionally together with at least one pharmaceutically acceptable carrier.

The invention further provides the use of (A) as hereinbefore defined and (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

Terms used in the specification have the following meanings:

"Optionally substituted" as used herein means the group referred to can be substituted at one or more positions by any one or any combination of the radicals listed thereafter.

"Halo" or "halogen" as used herein denotes a element belonging to group 17 (formerly group VII) of the Periodic Table of Elements, which may be, for example, fluorine, chlorine, bromine or iodine. Preferably halo or halogen is fluorine or chlorine.

"C_1-C_{10}-alkyl" as used herein denotes straight chain or branched alkyl that contains one to ten carbon atoms. Preferably, C_1-C_{10}-alkyl is C_1-C_4-alkyl.

"C_1-C_{10}-alkylene" as used herein denotes a straight chain or branched alkylene that contains one to ten carbon atoms. Preferably C_1-C_{10}-alkylene is C_1-C_4 alkylene, especially ethylene or methylethylene.

"C_2-C_{10}-alkenyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon double bonds. Preferably "C_2-C_{10}-alkenyl" is "C_2-C_4-alkenyl".

"C_2-C_{10}-alkynyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon triple bonds. Preferably "C_2-C_{10}-alkynyl" is "C_2-C_4-alkynyl".

"5-, 6 or 7-membered carbocyclic ring" as used herein denotes a carbocyclic group having 5 to 7 ring carbon atoms, either cycloaliphatic, such as a C_5-C_7-cycloalkyl, or aromatic, such as phenyl, which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups.

"C_3-C_{10}-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or more, usually one or two, C_1-C_4-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C_3-C_{10}-cycloalkyl is C_3-C_6-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

"C_1-C_{10}-haloalkyl" as used herein denotes C_1-C_{10}-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.

"C_1-C_{10}-alkylamino" and "di(C_1-C_{10}-alkyl)amino" as used herein denote amino substituted respectively by one or two C_1-C_{10}-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C_1-C_{10}-alkylamino and di(C_1-C_{10}-alkyl)amino are respectively C_1-C_4-alkylamino and di(C_1-C_4-alkyl)amino.

"C_1-C_{10}-alkylthio" as used herein denotes straight chain or branched alkylthio having 1 to 10 carbon atoms. Preferably, C_1-C_{10}-alkylthio is C_1-C_4-alkylthio.

"C_1-C_{10}-alkoxy" as used herein denotes straight chain or branched alkoxy that contains 1 to 10 carbon atoms. Preferably, C_1-C_{10}-alkoxy is C_1-C_4-alkoxy.

"C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl" as used herein denotes C_1-C_{10}-alkyl as hereinbefore defined substituted by C_1-C_{10}-alkoxy. Preferably, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl is C_1-C_4-alkoxy-C_1-C_4-alkyl.

"C_1-C_{10}-alkoxycarbonyl" as used herein denotes C_1-C_{10}-alkoxy as hereinbefore defined linked through an oxygen atom thereof to a carbonyl group.

"C_6-C_{10}-aryl" as used herein denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl. Preferably C_6-C_{10}-aryl is C_6-C_8-aryl, especially phenyl.

"C_6-C_{10}-arylsulfonyl" as used herein denotes C_6-C_{10}-aryl as hereinbefore defined linked through a carbon atom thereof to a sulfonyl group. Preferably C_6-C_{10}-arylsulfonyl is C_6-C_8-arylsulfonyl.

"C_7-C_{14}-aralkyl" as used herein denotes alkyl, for example C_1-C_4-alkyl as hereinbefore defined, substituted by aryl, for example C_6-C_{10}-aryl as hereinbefore defined. Preferably, C_7-C_{14}-aralkyl is C_7-C_{10}-aralkyl such as phenyl-C_1-C_4-alkyl, particularly benzyl or 2-phenylethyl.

"C_7-C_{14}-aralkyloxy" as used herein denotes alkoxy, for example C_1-C_4-alkoxy as hereinbefore defined, substituted by aryl, for example C_6-C_{10}-aryl. Preferably, C_7-C_{14}-aralkyloxy is C_7-C_{10}-aralkyloxy such as phenyl-C_1-C_4-alkoxy, particularly benzyloxy or 2-phenylethoxy.
Ar as used herein may be, for example, phenylene which is unsubstituted or substituted by one or more substituents selected from halogen, hydroxy, C_1-C_{10}-alkyl, C_1-C_{10}-alkoxy, C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, phenyl, or C_1-C_{10}-alkyl substituted by phenyl, C_1-C_{10}-alkoxy substituted by phenyl, C_1-C_{10}-alkyl-substituted phenyl and C_1-C_{10}-alkoxy-substituted phenyl. Preferably Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, or C_1-C_4-alkoxy substituted by phenyl. Preferably one substituent in Ar is para to R^1 and optional second and third substituents in Ar are meta to R^1.

"4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, oxazole, isoxazole, thiophene, thiazole, isothiazole, oxadiazole, pyridine,

pyrazine, pyridazine, pyrimidine, piperidine, piperazine, triazine, oxazine, morpholino, quinoline, isoquinoline, naphthyridine, indane or indene. Preferred heterocyclic rings include thiazole, pyrrolidine, piperidine, azacycloheptane and isoxazole.

"4 to 10-membered heterocyclyl-C_1-C_{10}-alkyl" denotes alkyl, for example C_1-C_{10}-alkyl as hereinbefore defined, substituted by a 4- to 10-membered heterocyclic ring as hereinbefore defined. Preferably, 4- to 10-membered heterocyclyl-C_1-C_{10}-alkyl is C_1-C_4-alkyl substituted by a 4- to 8-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom.

"C_1-C_4-alkylsulfonyl" denotes sulfonyl substituted by C_1-C_4-alkyl as hereinbefore defined. "Hydroxy-C_1-C_4-alkyl" denotes C_1-C_4-alkyl as hereinbefore defined substituted by one or more, preferably one, two or three hydroxy groups.

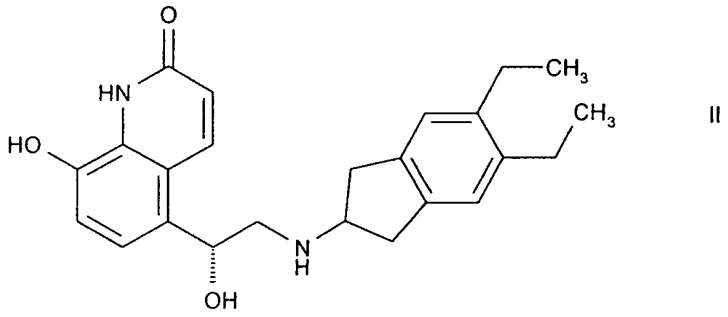
R^{13} and R^{14} together with the carbon atoms to which they are attached as a cycloaliphatic ring may be, for example, a cyclopentane ring, optionally substituted by one or two C_1-C_4-alkyl groups, a cyclohexane ring, optionally substituted by one or two C_1-C_4-alkyl groups, or a cycloheptane ring, preferably a cyclopentane ring.

Throughout this specification and in the claims that follow, unless the context requires otherwise, the word "comprise", or variations such as "comprises" or "comprising", should be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

Preferred compounds of formula I include those wherein
R^8, R^9 and R^{10} are each H, R^1 is OH, R^2 and R^3 are each H and
(i) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each CH_3O- and R^5 and R^6 are each H;
(ii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3CH_2-;
(iii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3-;
(iv) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each CH_3CH_2- and R^5 and R^6 are each H;
(v) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 together denote $-(CH_2)_4-$;
(vi) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 together denote $-O(CH_2)_2O-$;
(vii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each $CH_3(CH_2)_3-$;
(viii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each $CH_3(CH_2)_2-$;

(ix) R^x and R^y are both $-(CH_2)_2-$, R^4, R^5, R^6 and R^7 are each H; or
(x) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3OCH_2-.
These include 8-hydroxy-5-[1-hydroxy-2-(indan-2-ylamino)-ethyl]-1H-quinolin-2-one, 5-[2-(5,6-dimethoxy-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-3-methyl-1H-quinolin-2-one, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-methoxy-methoxy-6-methyl-1H-quinolin-2-one, 5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-6-methyl-1H-quinolin-2-one, 8-hydroxy-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-3,4-dihydro-1H-quinolin-2-one, 5-[(R)-2-(5,6-diethyl-2-methyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one, (S)-5-[2-(4,7-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one hydrochloride, 5-[(R)-1-hydroxy-2-(6,7,8,9-tetrahydro-5H-benzocyclohepten-7-ylamino)-ethyl]- 8-hydroxy-1H-quinolin-2-one hydrochloride, (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]- 8-hydroxy-1H-quinolin-2-one maleate, (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]- 8-hydroxy-1H-quinolin-2-one hydrochloride, (R)-8-hydroxy-5-[(S)-1-hydroxy-2-(4,5,6,7-tetramethyl-indan-2-ylamino)-ethyl]-1H-quinolin-2-one, 8-hydroxy-5-[(R)-1-hydroxy-2-(2-methyl-indan-2-ylamino)-ethyl]-1H-quinolin-2-one, 5-[2-(5,6-diethyl-indan-2-ylamino)-ethyl]-8-hydroxy-1H-quinolin-2-one, 8-hydroxy-5-[(R)-1-hydroxy-2-(2-methyl-2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naphthalen-2-ylamino)-ethyl]-1H-quinolin-2-one, and 5-[(S)-2-(2,3,5,6,7,8-hexahydro-1H-cyclopenta[b]naph-thalen-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one.

An especially preferred compound of formula I is a compound of formula II



II

in free or pharmaceutically acceptable salt or solvate form, especially the maleate salt, namely (R)-5-[2-(5,6-diethyl-indan-2-ylamino)-1-hydroxyethyl]-8-hydroxy-1H-quinolin-2-one maleate.

Compounds of formula I in free or salt or solvate form may be prepared by using the procedures described in international patent application WO 2000/075114, the contents of which is incorporated herein by reference.

The compound of formula II may be prepared in free or salt or solvate form by reacting (R)-8-benzyloxy-5-oxiranylcarbostyril with 5,6-diethylindan-2-ylamine to give 8-benzyloxy-5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-IH-quinolin-2-one, subjecting the latter to a deprotecting reaction to replace the benzyl group by hydrogen, and recovering the resultant compound of formula II in free or salt or solvate form. Such a process is described in WO 2004/76422, the contents of which is incorporated herein by reference. (R)-8-benzyloxy-5-oxiranylcarbostyril may be prepared as described in W0 1995/25104. 5,6-Diethyl-indan-2-ylamine may be prepared as described in WO 2003/76387.

Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

Pharmaceutically acceptable salts of the compound of formula I may be acid addition salts, including those of inorganic acids, for example hydrohalic acids such as hydrofluoric acid, hydrochloric acid, hydrobromic acid or hydroiodic acid, nitric acid, sulfuric acid, phosphoric acid; and organic acids such as formic acid, acetic acid, propionic acid, butyric acid, benzoic acid, o-hydroxybenzoic acid, p-hydroxybenzoic acid, p-chlorobenzoic acid, diphenylacetic acid, triphenylacetic acid, 1-hydroxynaphthalene-2-carboxylic acid, 3-hydroxynaphthalene-2-carboxylic acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as fumaric acid, maleic acid or succinic acid, and sulfonic acids such as methanesulfonic acid or benzenesulfonic acid. These salts may be prepared from compounds of formula I by known salt-forming procedures. Pharmaceutically acceptable solvates are generally hydrates.

An A_{2A} agonist is a substance or agent that activates the human adenosine A_{2A} receptor. Such compounds are useful in the treatment of conditions which respond to the activation of the adenosine A_{2A} receptor, particularly inflammatory or allergic conditions. Their properties as A_{2A} agonists may be demonstrated using the method described by L. J. Murphree *et al* in *Molecular Pharmacology* 61, 455-462 (2002). Suitable A2a agonists include those described in EP 409595A2, EP 1052264, EP 1241176, WO 94/17090, WO 96/02543, WO 96/02553, WO 98/28319, WO 99/24449, WO 99/24450, WO 99/24451, WO 99/38877, WO 99/41267, WO

99/67263, WO 99/67264, WO 99/67265, WO 99/67266, WO 00/23457, WO 00/77018, WO 00/78774, WO 01/23399, WO 01/27130, WO 01/27131, WO 01/60835, WO 01/94368, WO 02/00676, WO 02/22630, WO 02/96462, WO 03/086408, WO 04/039762, WO 04/039766, WO 04/045618 and WO 04/046083.

An A_{2B} antagonist is a substance or agent that inhibits adenosine A_{2B} receptor activation. In general they selectively inhibit activation of the A_{2B} receptor over the adenosine A_1 and A_{2A} receptors. Their inhibitory properties may be demonstrated in the adenosine A_{2B} receptor reporter gene assay that is described in WO 02/42298. Suitable A_{2B} antagonists are described in WO 02/42298 and WO 03/042214.

Histamine is formed *in vivo* by the decarboxylation of histidine. It is released during allergic reactions such as hay fever and causes smooth muscle to contract and capillaries to dilate. Antihistamines inhibit the actions of histamine by blocking its site of action. Suitable antihistamine drug substances include cetirizine hydrochloride, levocetirizine, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, dimetinden, ebastine, epinastine, levocabastine, mizolastine and tefenadine as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841.

A caspase inhibitor is a substance or agent that inhibits the activity of caspases, a family of enzymes involved in the induction of apoptosis in mammalian cells. The ability of an agent to function as a caspase inhibitor may be determined according to the methodologies disclosed in international patent applications WO 99/06367 and WO 99/65451. Suitable caspase inhibitors, including interleukin- I P converting enzyme (ICE) inhibitors, include those that are disclosed in Canadian patent specification 2109646 (para-nitroanilide peptides), European patent specification EP 519748 (peptidyl derivatives); EP 547 699 (peptidyl derivatives); EP 590 650 (cyclopropene derivatives); EP 628550 (pyridazines); EP 644 197 (peptidic phosphinyloxy-methyl ketones); EP 644198 (alpha- heteroaryloxymethyl ketones); international patent specification WO 93/05071 (peptidyl derivatives); WO 93/14777 (peptidyl derivatives); WO 93/16710 (peptidyl derivatives); WO 94/00154 (peptidyl derivatives); WO 94/03480 (peptidyl 4-amino-2, 2-difluoro-3-oxo-1, 6-hexanedioic acid derivatives); WO 94/21673 (alpha- keto-amide derivatives); WO 95/05152 (substituted ketone derivatives); WO 95/35308 (inhibitors comprising a hydrogen bonding group, a hydrophobic group and an electronegative group); WO 97/22618 (amino acid or di- or tripeptide amide derivatives); WO 97/22619 (N-acylamino compounds), WO 98-41232, WO 99/06367 (isatin sulphonamides);

WO 99/65451, WO 01/119373, United States patent specification US 5411985 (gamma-pyrone-3 -acetic acid compounds); US 5416013 (peptidyl derivatives); US 5430128 (tripeptidyl derivatives); US 5434248 (tripeptidyl compounds); US 5565430 (N,N'-diacylhydrazinoacetic acid compounds); US 5585357 (pyrazolyl derivatives); US 5656627 (inhibitors comprising a hydrogen bonding group, a hydrophobic group and an electronegative group); US 5677283 (pyrazolyl derivatives); US 6054487, US 6531474, US 20030096737 and United Kingdom patent specification GB 2,278,276 (gamma-pyrone-3 -acetic compounds), as well as those disclosed in international patent applications WO 98/10778, WO 98/11109, WO 98/11129 and WO 03/32918.

An ENaC inhibitor is a substance or agent that inhibits the activity of epithelial sodium ion channels. These channels control the fluid that is absorbed into the bloodstream and thus regulate the airway surface liquid volume. If these channels are blocked in some way, fluid will collect in the lumen, which encourages mucus precursors to hydrate and stimulate mucus clearance. ENaC inhibitors can enhance mucus clearance and thus may be used to treat diseases associated with the impairment of mucociliary clearance. Pyrazinecarboxamides such as amiloride, benzamil and dimethyl-amiloride (DMA) are known to block human epithelial sodium channels. Amiloride has been used clinically as a diuretic but its short half life makes it unsuitable for use in treating airway disease. ENaC inhibitor activity can be determined by measuring a change in transepithelial short circuit current using the method described by Baucher et al in *Am. J. Respir. Crit. Care Med.* 150: 221-281 (1994) or by using the assays described in WO 2002/087306 or WO 2004/72645. Suitable ENaC inhibitors include BAY39-9437.

Leukotriene B4 antagonists inhibit the LTB4 receptor. Such compounds are useful in the treatment of conditions which respond to the inhibition of the LTB4 receptor, particularly inflammatory or allergic conditions. Suitable LTB4 antagonists include BIIL 284, CP-195543, DPC11870, LTB4 ethanolamide, LY 293111, LY 255283, CGS025019C, CP-195543, ONO-4057, SB 209247, SC-53228 and those described in US 5451700 and WO 04/108720.

Leukotrienes are products derived from arachidonic acid that act on smooth muscles and can be responsible for respiratory and inflammatory diseases such as asthma and arthritis. Leukotriene D4 antagonists inhibit the LTD4 receptor. Such compounds are useful in the treatment of conditions which respond to the inhibition of the LTD4 receptor, particularly inflammatory or allergic conditions. Suitable LTD4 antagonists include montelukast,

pranlukast, zafirlukast, accolate, SR2640, Wy-48,252, ICI 198615, MK-571, LY-171883, Ro 24-5913 and L-648051.

A serine protease inhibitor is a substance or agent that inhibits a serine protease. Serine proteases include trypsin, matriptase, prostasin (PRSS8), plasmin, tPA, uPA, Xa, IXa, thrombin, tissue factor, compliment factors, tryptase, HNE, kallikrein (plasma and tissue), matriptase and TRMPSS 3 and 4. Serine protease inhibitors also include channel activating protease inhibitors such as antipain, aprotinin, benzamidine, camostat, gabexate, leupeptin, nafamostat, pepstatin A, ribavirin, sepimostat and ulinastatin. Suitable trypsin inhibitors include patamostat mesylate and those compounds generally or specifically described in US 6469036, e.g. RWJ-58643 (J&J), EP 556024, e.g. TO-195 (Torii), US 6469036, e.g. RWJ-56423 (Ortho-McNeil), JP96020570, e.g. TT-S24 (Teikoko Chemical), EP588655 and WO0181314. Matriptase and prostasin (PRSS8) inhibitors are known as trypsin-like serine protease inhibitors. Suitable Xa inhibitors include fondaparin sodium, rivaroxaban, idrapainux sodium, apixaban and otamixaban and those compounds specifically and generally described in US6469036, particularly RWJ-58643 (J&J), US 6022861, US 6211154, particularly MLN-1021 (Millenium), FR2773804, e.g. SR123781 (Sanofi-Aventis), DE 19829964, e.g. tanogitran, US 6469026, WO 00/01704, e.g. BIBR-1109 (Boehringer Ingelheim), DE 19829964, e.g. BIBT-0871, BIBT-1011 and BIBT-0932CL (Boehringer Ingelheim) and DE19816983. Other FactorXa inhibitors for use in the present invention include those compounds specifically disclosed in the review document *Expert Opin. Ther. Patents* (2006) 16(2):119-145, e.g. DX-9065a, DPC-423, Razaxaban, BAY59-7938 and compounds number 5-153. Suitable thrombin inhibitors include argatroban, glycyrrhizin (Ligand), odiparcil, corthrombin, those compounds specifically and generally described in US5523308 (J&J), WO 91/02750, e.g. Hirulog-1 (Biogen), DE 19706229, e.g. dabigratan and dabigratan etexilate, AU 8551553, e.g. efegatran sulfate hydrate, WO 93/11152, e.g. inogatran, US 2003134801, e.g. LB-30870 (LG Chem), Org42675 (Akzo Nobel), EP 559046, e.g. napsagatran, WO 01/070736, e.g. SSR-182289, EP 615978, e.g. S-18326 (Servier), WO 95/13274, e.g. UK-156406 (Pfizer), EP 0918768, e.g. AT-1362 (C&C Research Labs), WO 00/55156, e.g. AT-1459 (C&C Research Labs), JP 1999502203, e.g. BCH-2763 (Nat Res Council of Canada), EP623596, e.g. BMS-189090 (BMS), CA 2151412, e.g. BMS-191032 (BMS), US 5037819, e.g. BMY-43392-1 (BMS), GB 2312674, e.g. CGH-1484A (Novartis), EP 739886, e.g. CI-1028, LB-30057 and PD-172524 (LG Chem), DE 4115468, e.g. CRC-220 (Dade Behring Marburg), AU 8817332, e.g. DuP-714 (BMS), JP 96333287, e.g. F-1070 (Fuji Yakuhin), WO 97/01338, e.g. L-373890, L-374087 and L-375052 (Merck), WO 97/40024, e.g. L-375378 (Merck), WO 98/42342, e.g. L-376062 (Merck), WO 02/51824, e.g. LK-658 and LK-732 (Lek), WO

97/05160, e.g. LR-D/009 (Guidotti), EP 479489, e.g. LY-293435 (Lilly), AU 8945880, e.g. MDL-28050 (Sanofi Avenits), EP 195212, e.g. MDL-73756 (Sanofi Avenits), AU 9059742, e.g. MDL-74063 (Sanofi Avenits), JP 90289598, e.g. Cyclotheonamide A, WO 99/65934, e.g. NAPAP-PS (Organon), EO858464, e.g. Org-37432 (Organon), WO 98/47876, e.g. Org-37476 (Organon), WO 98/07308, e.g. Org-39430 (Organon), EP 217286, e.g. OS-396, CA 2152205, e.g. S-30266 (Adir), EP 792883, e.g. S-31214 and S-31922 (Servier), EP 471651, e.g. SDZ-217766 and SDZ-MTH-958 (Novartis), WO 95/13274, e.g. UK-179094 (Pfizer), WO 97/16444, e.g. UK-285954 (Pfizer), WO 98/01428, e.g. XU-817 (BMS), JP 96020597, US 5510369, WO 97/36580, WO 98/47876, WO98/47876, WO 97/46553, WO 98/42342, WO 97/46553, EP 863755, US 5891909, WO 99/15169, EP 0815103, US 6117888, WO 00/75134, WO 00/75134, WO 01/38323, EP 00944590, WO 02/64140, EP 1117660, EP 0944590 and EP 0944590. Suitable tryptase inhibitors include mast cell tryptase inhibitors such as those compounds specifically and generally described in WO 94/20527, particularly APC-366 (Celera), and the compounds APC-2059 (Bayer), AVE-8923 (Sanofi-Aventis), MOL-6131 (Molecumetics) and M-58539 (Mochida). Suitable kallikrein inhibitors include cetraxate and ecallantide.

Administration of the medicament or pharmaceutical composition as hereinbefore described, i.e. with (A) and (B) in admixture or separate, is preferably by inhalation, i.e. (A) and (B) or the mixture thereof are in inhalable form. The inhalable form of the medicament i.e. of (A) and/or (B) may be, for example, an atomizable composition such as an aerosol comprising the active ingredient, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulizable composition comprising a solution or dispersion of the active ingredient in an aqueous, organic or aqueous/organic medium. For example, the inhalable form of the medicament may be an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant. In another example, the inhalable form is a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium, or a combination of a dispersion of (A) in such a medium with a dispersion of (B) in such a medium.

An aerosol composition suitable for use as the inhalable form of the medicament may comprise the active ingredient in solution or dispersion in a propellant, which may be chosen from any of the propellants known in the art. Suitable such propellants include hydrocarbons such as n-propane, n-butane or isobutane or mixtures of two or more such hydrocarbons, and halogen-substituted hydrocarbons, for example chlorine and/or fluorine-substituted methanes, ethanes,

propanes, butanes, cyclopropanes or cyclobutanes, such as dichlorodifluoromethane (CFC 12), trichlorofluoromethane (CFC11), 1,2-dichloro-1,1,2,2 –tetrafluoroethane (CFC114) or, particularly, 1,1,1,2-tetrafluoroethane (HFA134a) and 1,1,1,2,3,3,3-heptafluoropropane (HFA227), or mixtures of two or more such halogen-substituted hydrocarbons. Where the active ingredient is present in suspension in the propellant, i.e. where it is present in particulate form dispersed in the propellant, the aerosol composition may also contain a lubricant and a surfactant, which may be chosen from those lubricants and surfactants known in the art. Other suitable aerosol compositions include surfactant-free or substantially surfactant-free aerosol compositions. The aerosol composition may contain up to about 5% by weight, for example 0.0001 to 5%, 0.001 to 5%, 0.001 to 3%, 0.001 to 2%, 0.001 to 1%, 0.001 to 0.1%, or 0.001 to 0.01% by weight of the active ingredient, based on the weight of the propellant. Where present, the lubricant and surfactant may be in an amount up to 5% and 0.5% respectively by weight of the aerosol composition. The aerosol composition may also contain a co-solvent such as ethanol in an amount up to 30% by weight of the composition, particularly for administration from a pressurised metered dose inhalation device. The aerosol composition may further contain a bulking agent, for example a sugar such as lactose, sucrose, dextrose, mannitol or sorbitol, in an amount, for example, of up to 20%, usually 0.001 to 1%, by weight of the composition.

In another embodiment of the invention, the inhalable form is a dry powder, i.e. (A) and/or (B) are present in a dry powder comprising finely divided (A) and/or (B) optionally together with at least one particulate pharmaceutically acceptable carrier, which may be one or more materials known as pharmaceutically acceptable carriers, preferably chosen from materials known as carriers in dry powder inhalation compositions, for example saccharides, including monosaccharides, disaccharides, polysaccharides and sugar alcohols such as arabinose, glucose, fructose, ribose, mannose, sucrose, trehalose, lactose, maltose, starches, dextran, mannitol or sorbitol. An especially preferred carrier is lactose. The dry powder may be contained as unit doses in capsules of, for example, gelatin or plastic, or in blisters (e.g. of aluminium or plastic), for use in a dry powder inhalation device, which may be a single dose or multiple dose device, preferably in dosage units of (A) and/or (B) together with the carrier in amounts to bring the total weight of powder per capsule to from 5 mg to 50 mg. Alternatively, the dry powder may be contained in a reservoir in a multi-dose dry powder inhalation device adapted to deliver, for example, 3-25mg of dry powder per actuation.

In the finely divided particulate form of the medicament, and in the aerosol composition where the active ingredient is present in particulate form, the active ingredient may have an average

particle diameter of up to about 10 μm, for example 0.1 to 5 μm, preferably 1 to 5 μm. The particulate carrier, where present, generally has a maximum particle diameter up to 300 μm, preferably up to 212 μm, and conveniently has a mean particle diameter of 40 to 100 μm, e.g. 50 to 75 μm. The particle size of the active ingredient, and that of a particulate carrier where present in dry powder compositions, can be reduced to the desired level by conventional methods, for example by grinding in an air-jet mill, ball mill or vibrator mill, sieving, microprecipitation, spray-drying, lyophilisation or controlled crystallisation from conventional solvents or from supercritical media.

The inhalable medicament may be administered using an inhalation device suitable for the inhalable form, such devices being well known in the art. Accordingly, the invention also provides a pharmaceutical product comprising a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described in association with one or more inhalation devices. In a further aspect, the invention provides an inhalation device, or a pack of two or more inhalation devices, containing a medicament or pharmaceutical composition as hereinbefore described in inhalable form as hereinbefore described.

Where the inhalable form of the active ingredient is an aerosol composition, the inhalation device may be an aerosol vial provided with a valve adapted to deliver a metered dose, such as 10 to 100 μl, e.g. 25 to 50 μl, of the composition, i.e. a device known as a metered dose inhaler. Suitable such aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, sometimes referred to as a soft mist or soft spray inhaler, for example an electronically controlled device such as an AERx (Aradigm, US) or Aerodose (Aerogen), or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100 μl, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dry powder comprising a dosage unit of (A) and/or (B) or a multidose dry powder inhalation (MDPI) device adapted to deliver, for

example, 3-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. The dry powder composition preferably contains a diluent or carrier, such as lactose, and a compound that helps to protect against product performance deterioration due to moisture e.g. magnesium stearate. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US 3991761, while a suitable MDPI device is that described in WO 97/20589.

The medicament of the invention is preferably a pharmaceutical composition comprising a mixture of (A) as hereinbefore defined and (B) as hereinbefore defined, preferably together with at least one pharmaceutically acceptable carrier as hereinbefore described.

The molar ratio of the compound (A) to the steroid (B) may be, in general, from 100:1 to 1:300, for example from 50:1 to 1:100 or from 20:1 to 1:50, preferably from 10:1 to 1:20, more preferably from 5:1 to 1:10, from 3:1 to 1:7 or from 2:1 to 1:2. The compound (A) and the steroid (B) may be administered separately in the same ratio.

A suitable daily dose of the compound (A), particularly as the maleate salt, for inhalation may be from 20 μg to 2000 μg, for example from 20 to 1500 μg, from 20 to 1000 μg, preferably from 50 to 800 μg, e.g. from 100 to 600 μg or from 100 to 500 μg.

Where (B) is an A_{2A} agonist, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is an A_{2B} antagonists, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is an antihistamine, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is a caspase inhibitor, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is an ENaC inhibitor, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is a LTB4 antagonist, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is a LTD4 antagonist, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

Where (B) is a serine protease inhibitor, a suitable daily dose for inhalation may be from 20 μg to 5000 μg, for example from 20 to 4000 μg, from 50 to 3000 μg, from 50 to 2000 μg, from 50 to 1000 μg, from 50 to 500 μg, from 50 to 400 μg, from 50 to 300 μg, from 50 to 200 μg or from 50 to 100 μg.

In one preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder in a capsule containing a unit dose of (A) and (B), for example for inhalation from a single capsule inhaler, the capsule suitably containing a unit dose of (A) e.g. as hereinbefore described, and a unit dose of (B), e.g. as hereinbefore described, together with a pharmaceutically acceptable carrier as hereinbefore described in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg, for example 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg.

In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver, for example, 3 mg to 25 mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is in the form of the maleate salt, a powder comprising, by weight, 20 to 2000 parts, for example 60 to 1000 parts, 100 to 500 parts, or 100 to 300 parts of (A); 25 to 800 parts, e.g. 25 to 500 parts, 50 to 400 parts, or 100 to 400 parts of (B); and 2000 to 25000 parts, e.g. 4000 to 15000 parts or 4000 to 10000 parts of a pharmaceutically acceptable carrier as hereinbefore described.
In a further preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is an aerosol comprising (A) and (B), e.g. in a ratio as hereinbefore described, in a propellant as hereinbefore described, optionally together with a surfactant and/or a bulking agent and/or a co-solvent such as ethanol as hereinbefore described, for administration from a metered dose inhaler adapted to deliver an amount of aerosol containing a unit dose of (A) and a unit dose of (B), or a known fraction of a unit dose of (A) and a known fraction of a unit dose of (B), per actuation. Thus if, for example, the inhaler delivers half of the unit doses of (A) and (B) per actuation, the unit doses can be administered by two actuations of the inhaler.

In accordance with the above, the invention also provides a pharmaceutical kit comprising (A) and (B) as hereinbefore defined in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts. Such a kit suitably further comprises one or more inhalation devices for administration of (A) and (B). For example, the kit may comprise one or more dry powder inhalation devices adapted to deliver dry powder from a capsule, together with capsules containing a dry powder comprising a dosage unit of (A) and capsules containing a dry powder comprising a dosage unit of (B). In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) and a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (B). In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising comprising (A) in a propellant and a metered dose inhaler containing an aerosol comprising (B) in a propellant.

The medicaments of the invention are advantageous in the treatment of inflammatory or obstructive airways disease, exhibiting highly effective bronchodilatory and anti-inflammatory properties. For instance, it is possible using the combination therapy of the invention to reduce the dosages of corticosteroid required for a given therapeutic effect compared with those required using treatment with a corticosteroid alone, thereby minimising possibly undesirable

side effects. In particular, these combinations, particularly where (A) and (B) are in the same composition, facilitate achievement of a high anti-inflammatory effect, such that the amount of corticosteroid needed for a given anti-inflammatory effect may be reduced when used in admixture with a compound of formula I, thereby reducing the risk of undesirable side effects from the repeated exposure to the steroid involved in the treatment of inflammatory or obstructive airways diseases. Furthermore, using the combinations of the invention, particularly using compositions containing (A) and (B), medicaments which have a rapid onset of action and a long duration of action may be prepared. Moreover, using such combination therapy, medicaments which result in a significant improvement in lung function may be prepared. In another aspect, using the combination therapy of the invention, medicaments which provide effective control of obstructive or inflammatory airways diseases, or a reduction in exacerbations of such diseases, may be prepared. In a further aspect, using compositions of the invention containing (A) and (B), medicaments which reduce or eliminate the need for treatment with short-acting rescue medicaments such as salbutamol or terbutaline, may be prepared; thus compositions of the invention containing (A) and (B) facilitate the treatment of an obstructive or inflammatory airways disease with a single medicament.

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic treatment. Inflammatory or obstructive airways diseases to which the present invention is applicable include asthma of whatever type or genesis including both intrinsic (non-allergic) asthma and extrinsic (allergic) asthma, mild asthma, moderate asthma, severe asthma, bronchitic asthma, exercise-induced asthma, occupational asthma and asthma induced following bacterial infection. Treatment of asthma is also to be understood as embracing treatment of subjects, e.g. of less than 4 or 5 years of age, exhibiting wheezing symptoms and diagnosed or diagnosable as "wheezy infants", an established patient category of major medical concern and now often identified as incipient or early-phase asthmatics. (For convenience this particular asthmatic condition is referred to as "wheezy-infant syndrome".)

Prophylactic efficacy in the treatment of asthma will be evidenced by reduced frequency or severity of symptomatic attack, e.g. of acute asthmatic or bronchoconstrictor attack, improvement in lung function or improved airways hyperreactivity. It may further be evidenced by reduced requirement for other, symptomatic therapy, i.e. therapy for or intended to restrict or abort symptomatic attack when it occurs, for example anti-inflammatory (e.g. corticosteroid) or bronchodilatory. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognised asthmatic syndrome, common to a substantial percentage of asthmatics and characterised by

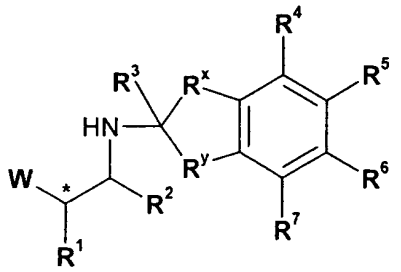
asthma attack, e.g. between the hours of about 4 to 6 am, i.e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD), including chronic bronchitis and emphysema, bronchiectasis and exacerbation of airways hyperreactivity consequent to other drug therapy, in particular other inhaled drug therapy. Further inflammatory or obstructive airways diseases to which the present invention is applicable include pneumoconiosis (an inflammatory, commonly occupational, disease of the lungs, frequently accompanied by airways obstruction, whether chronic or acute, and occasioned by repeated inhalation of dusts) of whatever type or genesis, including, for example, aluminosis, anthracosis, asbestosis, chalicosis, ptilosis, siderosis, silicosis, tobacosis and byssinosis.

CLAIMS

1. A medicament comprising, separately or together,

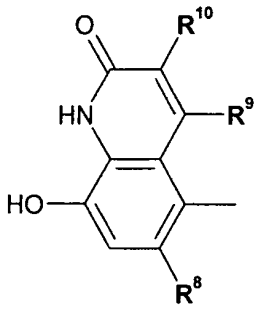
(A) a compound of formula I



I

in free or salt or solvate form, where

W is a group of formula



R^x and R^y are both $-CH_2-$ or $-(CH_2)_2-$;

R^1 is hydrogen, hydroxy, or C_1-C_{10}-alkoxy;

R^2 and R^3 are each independently hydrogen or C_1-C_{10}-alkyl;

R^4, R^5, R^6 and R^7 are each independently hydrogen, halogen, cyano, hydroxy, C_1-C_{10}-alkoxy, C_6-C_{10}-aryl, C_1-C_{10}-alkyl, C_1-C_{10}-alkyl substituted by one or more halogen atoms or one or more hydroxy or C_1-C_{10}-alkoxy groups, C_1-C_{10}-alkyl interrupted by one or more hetero atoms, C_2-C_{10}-alkenyl, trialkylsilyl, carboxy, C_1-C_{10}-alkoxycarbonyl, or $-CONR^{11}R^{12}$ where R^{11} and R^{12} are each independently hydrogen or C_1-C_{10}-alkyl,

or R^4 and R^5, R^5 and R^6, or R^6 and R^7 together with the carbon atoms to which they are attached denote a 5-, 6- or 7-membered carbocyclic ring or a 4- to 10-membered heterocyclic ring; and

R^8, R^9 and R^{10} are each independently hydrogen or C_1-C_4-alkyl; and

(B) one or more of compounds selected from the group consisting of

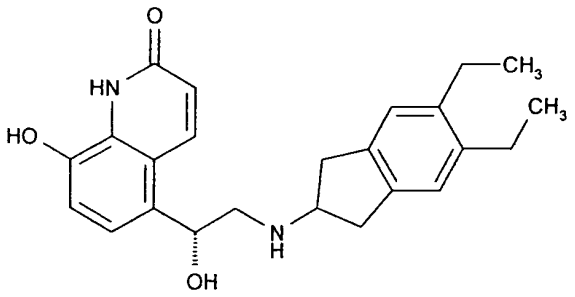
(i) A_{2A} agonists,
(ii) A_{2B} antagonists,
(iii) antihistamines,
(iv) caspase inhibitors
(v) ENaC inhibitors,
(vi) LTB4 antagonists,
(vii) LTD4 antagonists, and
(viii) serine protease inhibitors;

for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

2. A medicament according to claim 1 which is a pharmaceutical composition comprising a mixture of effective amounts of (A) and (B) optionally together with at least one pharmaceutically acceptable carrier.

3. A medicament according to claim 1 or 2, in which (A) is a compound of formula I wherein R^8, R^9 and R^{10} are each H, R^1 is OH, R^2 and R^3 are each H and
(i) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each CH_3O- and R^5 and R^6 are each H;
(ii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3CH_2-;
(iii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3-;
(iv) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each CH_3CH_2- and R^5 and R^6 are each H;
(v) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 together denote $-(CH_2)_4-$;
(vi) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 together denote $-O(CH_2)_2O-$;
(vii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each $CH_3(CH_2)_3-$;
(viii) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each $CH_3(CH_2)_2-$;
(ix) R^x and R^y are both $-(CH_2)_2-$, R^4, R^5, R^6 and R^7 are each H; or
(x) R^x and R^y are both $-CH_2-$, and R^4 and R^7 are each H and R^5 and R^6 are each CH_3OCH_2-.

4. A medicament according to any preceding claim, in which (A) is a compound of formula II



II

in free or pharmaceutically acceptable salt or solvate form.

5. A medicament according to claim 4, in which (A) is the maleate salt.

6. A medicament according to any one of claims 1 to 5 in inhalable form as an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant, or a combination of an aerosol containing (A) in solution or dispersion in a propellant with an aerosol containing (B) in solution or dispersion in a propellant.

7. A medicament according to any one of claims 1 to 5 in the inhalable form as a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium or a combination of a dispersion of (A) in said medium with a dispersion of (B) in said medium.

8. A medicament according to any one of claims 1 to 5, in which (A) and/or (B) are present in inhalable form as a dry powder comprising finely divided (A) and/or (B) optionally together with at least one particulate pharmaceutically acceptable carrier.

9. A medicament according to claim 6 or 8, in which (A) and/or (B) has an average particle diameter up to 10 μm.

10. A medicament according to any one of the preceding claims, in which the molar ratio of (A) to (B) is from 5:1 to 1:10.

11. A medicament according to claim 2, which is a dry powder in a capsule, the capsule containing a unit dose of (A), a unit dose of (B) and a pharmaceutically acceptable carrier in an amount to bring the total weight of dry powder per capsule to between 5 mg and 50 mg.

12. A medicament according to claim 2, which is a dry powder comprising, by weight, from 20 to 2000 parts of (A) in the form of the maleate salt, from 25 to 800 parts of (B) and 2000 to 25000 parts of a pharmaceutically acceptable carrier.

13. A medicament according to claim 2, which is an aerosol comprising (A) and (B) in a ratio as hereinbefore specified in claim 1 or 10, in a propellant, optionally together with a surfactant and/or a bulking agent and/or a co-solvent suitable for administration from a metered dose inhaler adapted to deliver an amount of aerosol containing a unit dose of (A) and a unit dose of (B), or a known fraction of a unit dose of (A) and a known fraction of a unit dose of (B), per actuation.

14. A pharmaceutical kit comprising (A) as defined in any one of claims 1 and 5 and (B) as defined in claim 1 in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts, together with one or more inhalation devices for administration of (A) and (B).