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(54) **Title:** ORGANIC COMPOUNDS COMPRISING A GLYCOPYRRONIUM SALT

(57) **Abstract:** Medicaments comprising (A) an antimuscarinic agent and (B) a corticosteroid for the treatment of inflammatory or obstructive airways diseases.

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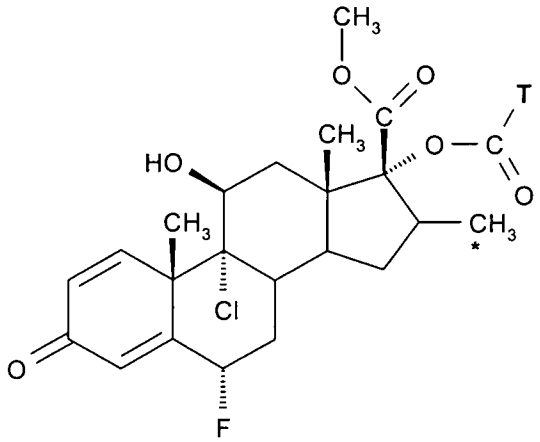
ORGANIC COMPOUNDS COMPRISING A GLYCOPYRRONIUM SALT

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

In a first aspect, the present invention provides a medicament comprising, separately or together (A) a glycopyrronium salt and (B) a compound of formula I



I

where T is a monovalent cyclic organic group having from 3 to 15 atoms in the ring system, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

Glycopyrronium bromide, or glycopyrrolate, is an antimuscarinic agent that is currently administered by injection to reduce secretions during anaesthesia and or taken orally to treat gastric ulcers. Schroeckenstein et al *J . Allergy Clin. Immunol.* 1998; 82(1): 115-119 discloses the use of glycopyrrolate in an aerosol formulation for treating asthma where a single administration of a metered dose achieved bronchodilation for up to 12 hours. More recently international patent application WO 2001/76575 discloses glycopyrrolate can be formulated for pulmonary delivery in controlled release formulation that permits the antimuscarinic agent to exert its pharmacological effect over a period greater than 12 hours.

Compounds of formula I are anti-inflammatory corticosteroids that are disclosed in international patent application WO 02/00679.

It has now surprisingly been found that a significant unexpected therapeutic benefit, particularly a synergistic therapeutic benefit, in the treatment of inflammatory or obstructive airways diseases can be obtained by combination therapy using a glycopyrronium salt and a

compound of formula I. For instance, it is possible using this combination therapy to reduce the dosages of one or both of the two active ingredients required for a given therapeutic effect considerably compared with those required using treatment with the active ingredients alone, thereby minimising possibly undesirable side effects. In particular, it has been found that these combinations induce an anti-inflammatory activity which is significantly greater than that induced by glycopyrronium bromide or a compound of formula I alone. The amount of a compound of formula I in particular needed for a given anti-inflammatory effect may be significantly reduced when used in admixture with glycopyrronium bromide, 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 combination therapy of the invention, particularly using compositions containing glycopyrronium bromide and a compound of formula I, 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. Using the combination therapy of the invention, medicaments which provide improved control of obstructive or inflammatory airways diseases, or a reduction in exacerbations of such diseases, may be prepared. Using compositions of the invention, medicaments which can be used on demand in rescue treatment of obstructive or inflammatory airways diseases, or which reduce or eliminate the need for treatment with short-acting rescue medicaments such as salbutamol or terbutaline, may be prepared; thus medicaments based on compositions of the invention facilitate the treatment of an obstructive or inflammatory airways disease with a single medicament.

Accordingly, in a second aspect, the present invention provides a pharmaceutical composition comprising a mixture of effective amounts of (A) a glycopyrronium salt and (B) a compound of formula I, optionally together with at least one pharmaceutically acceptable carrier.

In a third 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) a glycopyrronium salt and (B) a compound of formula I.

The invention further provides the use of (A) a glycopyrronium salt and (B) a compound of formula I 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:

"C_1-C_4-alkyl" denotes straight chain or branched C_1-C_4-alkyl, which may be methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, iso-butyl or tert-butyl.

"C_1-C_4-alkylamino" denotes amino substituted by C_1-C_4-alkyl as hereinbefore defined.

"(Di-C_1-C_4-alkyl)amino" denotes amino disubstituted by C_1-C_4-alkyl as hereinbefore defined.

"Halo-C_1-C_4-alkyl" denotes C_1-C_4-alkyl as hereinbefore defined substituted by one or more, preferably one, two or three halogen atoms, preferably fluorine or chlorine atoms.

"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.

"C_1-C_4-alkoxy" denotes straight chain or branched C_1-C_4-alkoxy and may be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

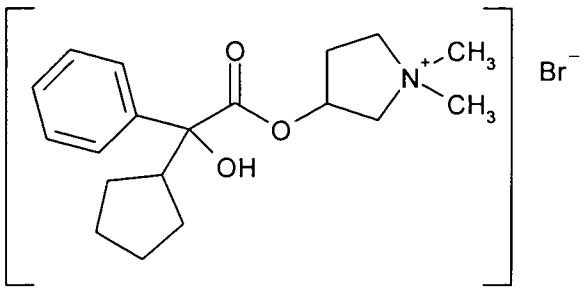
"C_1-C_4-alkylthio" denotes straight chain or branched C_1-C_4-alkylthio and may be methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio or tert-butylthio.

In one aspect, the present invention provides a medicament comprising, separately or together (A) a glycopyrronium salt and (B) a compound of formula I, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease.

Glycopyrronium salts include glycopyrronium bromide, also known as glycopyrrolate, which is known to be an effective antimuscarinic agent. More specifically it inhibits acetyl choline binding to M3 muscarinic receptors thereby inhibiting bronchoconstriction.

Glycopyrrolate is a quaternary ammonium salt. Suitable counter ions are pharmaceutically acceptable counter ions including, for example, fluoride, chloride, bromide, iodide, nitrate, sulfate, phosphate, formate, acetate, trifluoroacetate, propionate, butyrate, lactate, citrate, tartrate, malate, maleate, succinate, benzoate, p-chlorobenzoate, diphenyl-acetate or triphenylacetate, o-hydroxybenzoate, p-hydroxybenzoate, 1-hydroxynaphthalene-2-carboxylate, 3-hydroxynaphthalene-2-carboxylate, methanesulfonate and benzenesulfonate. Its

bromide salt, namely 3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, has the following structural formula



and can be prepared using the procedures described in United States patent US 2956062.

Glycopyrrolate has two stereogenic centres and hence exists in four isomeric forms, namely (3R,2'R)-, (3S,2'R)-, (3R,2'S)- and (3S,2'S)-3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide, as described in United States patent specifications US 6307060 and US 6,613,795. The contents of these patent specifications are incorporated herein by reference. The present invention embraces using one or more of these isomeric forms, especially the 3S,2'R isomer, the 3R,2'R isomer or the 2S,3'R isomer, thus including single enantiomers, mixtures of diastereomers, or racemates, especially (3S,2'R/3R,2'S) -3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

Compounds of formula I are disclosed, together with procedures for their preparation in international patent application WO 02/00679, the contents of which is incorporated herein by reference. These compounds exhibit surprisingly low systemic side effects at therapeutically effective doses and have a long duration of action, with a potential for once-a-day administration.

In one embodiment, T is a heterocyclic aromatic group having a 5-membered heterocyclic ring with one, two or three ring hetero atoms selected from nitrogen, oxygen and sulfur, the heterocyclic ring being unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkyl-thio, cyano or hydroxy-C_1-C_4-alkyl and the heterocyclic ring being optionally fused to a benzene ring. Preferred such heterocyclic aromatic groups include those in which the heterocyclic ring has one nitrogen, oxygen or sulfur atom in the ring or one oxygen and one or two nitrogen atoms in the ring, or one sulfur and one or two nitrogen atoms in the ring, especially a pyrrole, furan, thiophene, oxazole, isoxazole, imidazole, pyrazole, furazan, thiazole or thiadiazole ring. Especially preferred heterocyclic aromatic groups are pyrrolyl, furyl and thienyl groups optionally

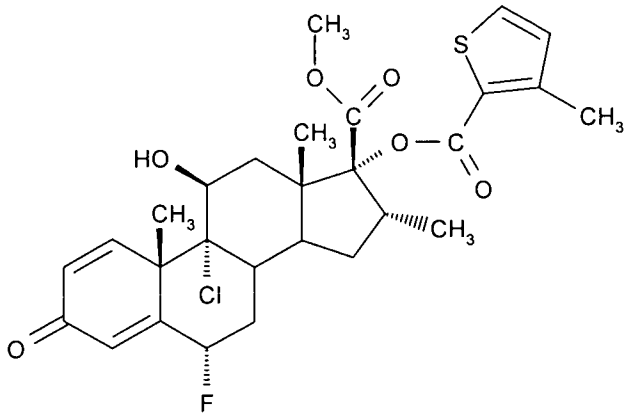
substituted by one or two substituents selected from halogen (particularly chlorine or bromine), C_1-C_4-alkyl (particularly methyl or ethyl), halo-C_1-C_4-alkyl (particularly trifluoro-methyl), C_1-C_4-alkoxy (particularly methoxy), C_1-C_4-alkylthio (particularly methylthio), cyano or hydroxy-C_1-C_4-alkyl (particularly hydroxymethyl); isoxazolyl, imidazolyl, pyrazolyl, thiazolyl or thiadiazolyl groups optionally substituted by one or two C_1-C_4-alkyl groups; and benzofuryl, benzothienyl and benzofurazanyl groups.

In another embodiment, T is a heterocyclic aromatic group having a 6–membered heterocyclic ring with one, two or three ring heteroatoms, preferably nitrogen, the heterocyclic ring being unsubstituted or substituted by one or more, preferably one, two or three, substituents selected from halogen, cyano, hydroxyl, C_1-C_4-acyloxy, amino, C_1-C_4-alkyl-amino, di-(C_1-C_4-alkyl)amino, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, or C_1-C_4-alkylthio, and the heterocyclic ring being optionally fused to a benzene ring. Preferred such heterocyclic aromatic groups include those in which the heterocyclic group has one or two nitrogen atoms in the ring, especially a pyridine, pyrimidine, pyrazine or pyridazine ring. Especially preferred heterocyclic aromatic groups are pyridyl, pyrimidinyl and pyrazinyl groups, optionally substituted by one or two substituents selected from halogen (particularly chlorine) or C_1-C_4-alkyl (especially methyl or n-butyl).

In compounds of formula I, the indicated methyl group in the 16 position of the cortico-steroid ring system may be in the alpha or beta conformation. 16-α-methyl compounds are preferred.

Especially preferred compounds of formula I are those where the indicated 16-methyl group has the alpha conformation and T is 5-methyl-2-thienyl, N-methyl-2-pyrrolyl, cyclopropyl, 2-furyl, 3-methyl-2-furyl, 3-methyl-2-thienyl, 5-methyl-3-isoxazolyl, 3,5-dimethyl-2-thienyl, 2,5-dimethyl-3-furyl, 4-methyl-2-furyl, 4-(dimethylamino)phenyl, 4-methylphenyl, 4-ethylphenyl, 2-pyridyl, 4-pyrimidyl or 5-methyl-2-pyrazinyl or the indicated 16-methyl group has the beta conformation and R is cyclopropyl.

A particularly preferred compound of formula I is 3-methyl-thiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta-[a]phenanthren-17-yl ester, which has the formula



Compounds of formula I in which T contains a basic group are capable of forming acid addition salts, particularly pharmaceutically acceptable acid addition salts. Pharmaceutically acceptable acid addition salts of the compound of formula I include 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, for example aliphatic monocarboxylic acids such as formic acid, acetic acid, trifluoroacetic acid, propionic acid and butyric acid, aliphatic hydroxy acids such as lactic acid, citric acid, tartaric acid or malic acid, dicarboxylic acids such as maleic acid or succinic acid, aromatic carboxylic acids such as benzoic acid, p-chlorobenzoic acid, diphenylacetic acid or triphenylacetic acid, aromatic hydroxy acids such as o-hydroxybenzoic acid, p-hydroxybenzoic acid, 1-hydroxy-naphthalene-2-carboxylic acid or 3-hydroxynaphthalene-2-carboxylic 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.

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 may be, for example, an atomizable composition such as an aerosol comprising the active ingredients, i.e. (A) and (B) separately or in admixture, in solution or dispersion in a propellant, or a nebulisable 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. 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.

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 (CFC-11), 1,2-dichloro-1,1,2,2 –tetrafluoroethane (CFC-114) or, particularly, 1,1,1,2-tetrafluoroethane (HFA-134a), 1,1,1,2,3,3,3-heptafluoropropane (HFA-227), difluorochloromethane (HCFC-22) 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%, but preferably 0.01 to 0.5% 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 of the medicament is a dry powder, i.e. (A) and (B) are present in a dry powder comprising finely divided (A) and (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, for example lactose monohydrate or anhydrous 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, 3-25 mg of dry powder per actuation.

In the finely divided particulate form of the medicament, and in the aerosol composition where at least one of the active ingredients are 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 500 μm, preferably up to 400 μm, and conveniently has a mean particle diameter of 40 to 300 μm, e.g. 50 to 250 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 nebulised volumes, e.g. 10 to 100 μl, than conventional nebulisers.

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 (MDDPI) 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, typically 0.05-2.0%. 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 suitable MDDPI devices include those described in WO 97/20589 and WO 97/30743.

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

The weight ratio of the glycopyrronium salt to the compound of formula I may be, in general, from 2:1 to 1:2000, for example from 1:1 to 1:1000, from 1:2 to 1:100, or from 1:5 to 1:50. More usually, this ratio is from 1:10 to 1:25, for example from 1:15 to 1:25. The two drugs may be administered separately in the same ratio. Specific examples of this ratio, to the nearest whole number, include 1:10, 1:11, 1:12, 1:13, 1:14, 1:15, 1:16, 1:17, 1:18, 1:19, 1:20, 1:21, 1:22, 1:23, 1:24 and 1:25.

A suitable daily dose of (A) the glycopyrronium salt, particularly as the bromide salt, for inhalation may be from 10 μg to 2000 μg, preferably from 20 to 1000 μg, and especially from 20 to 800 μg, e.g. from 30 to 500 μg.

A suitable daily dose of (B) a compound of formula I for inhalation may be from 50 to 2000 μg, for example from 100 to 2000 μg, from 100 to 1600 μg, from 100 to 1000 μg, or from 100 to 800 μg, preferably from 200 to 500 μg, for instance from 200 to 400 μg.

A suitable unit dose of (A) the glycopyrronium salt, particularly as the bromide salt, for inhalation may be from 10 μg to 2000 μg, preferably from 20 to 1000 μg, and especially from 20 to 800 μg, e.g. from 30 to 500 μg.

A suitable unit dose of (B) a compound of formula I for inhalation may be from 50 to 2000 μg, for example from 100 to 2000 μg, from 100 to 1600 μg, from 100 to 1000 μg, or from 100 to 800 μg, preferably from 200 to 500 μg, for instance from 200 to 400 μg.

These unit doses may be administered once or twice daily in accordance with the daily doses mentioned hereinbefore. A single dose is preferred as this is convenient for the patient and encourages compliance. The precise doses of (A) and (B) used will of course depend on the condition to be treated, the patient and the efficiency of the inhalation device.

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 unit doses of (A) a glycopyrronium salt and (B) a compound of formula I as hereinbefore defined, for example for inhalation from a single capsule inhaler, the capsule suitably containing a unit dose of (A) a glycopyrronium salt and a unit dose of (B) a compound of formula I, 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) a glycopyrronium salt and (B) a compound of formula I per actuation.

In a further preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is an aerosol comprising (A) a glycopyrronium salt and (B) a compound of formula I 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) a glycopyrronium salt and a unit dose of (B) a compound of formula I, or a known fraction of a unit dose of (A) a glycopyrronium salt and a known fraction of a unit dose of (B) a compound of formula I per actuation. Thus if, for example, the

inhaler delivers half of the unit doses of (A) a glycopyrronium salt and (B) a compound of formula I 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) a glycopyrronium salt and (B) a compound of formula I in separate unit dosage forms, said forms being suitable for administration of (A) a glycopyrronium salt and (B) a compound of formula I in effective amounts. Such a kit suitably further comprises one or two inhalation devices for administration of (A) a glycopyrronium salt and (B) a compound of formula I. 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) a glycopyrronium salt and capsules containing a dry powder comprising a dosage unit of (B) a compound of formula I. In another example, the kit may comprise a multi-dose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (A) a glycopyrronium salt and a multi-dose dry powder inhalation device containing in the reservoir thereof a dry powder comprising (B) a compound of formula I. In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising (A) a glycopyrronium salt in a propellant and a metered dose inhaler containing an aerosol comprising (B) a compound of formula I in a propellant.

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) a glycopyrronium salt and (B) a compound of formula I 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) a glycopyrronium salt and (B) 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, 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) a glycopyrronium salt and (B) a compound of formula I, 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 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 or acute 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.

The medicament of the present invention may additionally contain one or more co-therapeutic agents such as anti-inflammatory, bronchodilatory, antihistamine, decongestant or anti-tussive drug substances, particularly in the treatment of obstructive or inflammatory airways diseases such as those mentioned hereinbefore, for example as potentiators of therapeutic activity of such drugs or as a means of reducing required dosaging or potential side effects of such drugs.

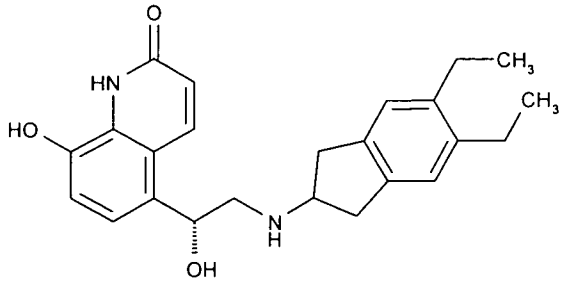
Co-therapeutic agents include A_{2A} agonists, A_{2B} antagonists, antihistamines, beta-2 adrenoceptor agonists, caspase inhibitors, LTB4 antagonists, LTD4 antagonists, PDE4 inhibitors, mucolytics, matrix metal loproteinase inhibitors (MMPi's), leukotrienes, antibiotics, anti neoplastics, peptides, vaccines, nicotine, elastase inhibitors and sodium cromoglycate.

Suitable A_{2A} 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.

Suitable A_{2B} antagonists include those described in WO 02/42298 and WO 03/042214.

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 WO 03/099807, WO 04/026841 and JP 2004107299.

Suitable beta-2 adrenoceptor agonists include albuterol (salbutamol), metaproterenol, terbutaline, salmeterol, fenoterol, procaterol, and especially, formoterol, carmoterol, TA-2005, GSK159797 and pharmaceutically acceptable salts thereof, and compounds (in free or salt or solvate form) of formula I of WO 0075114, which document is incorporated herein by reference, preferably compounds of the Examples thereof, especially a compound of formula



and pharmaceutically acceptable salts thereof, as well as compounds (in free or salt or solvate form) of formula I of WO 04/16601, and also compounds of EP 147719, EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, US 2002/0055651, US 2005/0133417, US 2005/5159448, WO 01/42193, WO 01/83462, WO 02/66422, WO 02/ 70490, WO 02/76933, WO 03/24439, WO 03/42160, WO 03/42164, WO 03/72539, WO 03/91204, WO 03/99764, WO 04/16578, WO 04/22547, WO 04/32921, WO 04/33412, WO 04/37768, WO 04/37773, WO 04/37807, WO 04/39762, WO 04/39766, WO 04/45618 WO 04/46083 , WO 04/80964, EP1460064, WO 04/087142, WO 04/089892, EP 01477167, US 2004/0242622, US 2004/0229904, WO 04/108675, WO 04/108676, WO 05/033121, WO 05/040103, WO 05/044787, WO 05/058867, WO 05/065650, WO 05/066140 and WO 05/07908.

Suitable caspase inhibitors, including interleukin- I P converting enzyme (ICE) inhibitors, include those that are disclosed in CA 2109646, GB 2,278,276EP 519748, EP 547 699, EP 590 650, EP 628550, EP 644 197, EP 644198, US 5411985, US 5416013, US 5430128, US 5434248, US 5565430, US 5585357, US 5656627, US 5677283, US 6054487, US 6531474, US 20030096737, WO 93/05071, WO 93/14777, WO 93/16710, WO 94/00154, WO 94/03480, WO 94/21673, WO 95/05152, WO 95/35308, WO 97/22618, WO 97/22619, WO 98/10778, WO 98/11109, WO 98/11129, WO 98/41232, WO 99/06367, WO 99/65451, WO 01/119373 and WO 03/32918.

Suitable LTB4 antagonists include LY293111, CGS025019C, CP-195543, SC-53228, BIIL 284, ONO 4057, SB 209247 and those described in US 5451700 and WO 04/108720.

Suitable LTD4 antagonists include montelukast and zafirlukast.

Suitable PDE4 inhibitors PDE4 inhibitors such as cilomilast (Ariflo® GlaxoSmithKline), Roflumilast (Byk Gulden),V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofylline (Almirall Prodesfarma), PD189659 / PD168787 (Parke-Davis), AWD-12-281 (Asta Medica), CDC-801 (Celgene), SelCID(TM) CC-10004 (Celgene), VM554/UM565 (Vernalis), T-440 (Tanabe), KW-4490 (Kyowa Hakko Kogyo), GRC 3886 (Oglemilast,

Glenmark), and those described in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/39544, WO 03/104204, WO 03/104205, WO 04/000814, WO 04/000839, WO 04/005258 , WO 04018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/018431, WO 04/018449, WO 04/018450, WO 04/018451, WO 04/018457, WO 04/018465, WO 04/019944, WO 04/019945, WO 04/045607, WO 04/037805, WO 04/063197, WO 04/103998, WO 04/111044, WO 05012252, WO 05012253, WO 05/013995, WO 05/030725, WO 05/030212, WO 05/087744, WO 05/087745, WO 05/087749 and WO 05/090345.

While (A) the glycopyrronium salt is an antimuscarinic agent, the medicament of the present invention optionally includes one or more other antimuscarinic agents such as ipratropium bromide, oxitropium bromide, tiotropium salts, CHF 4226 (Chiesi), or those described in EP 424021, US 3714357, US 5171744, US 2005/171147, US 2005/182091, WO 01/04118, WO 02/00652, WO 02/51841, WO 02/53564, WO 03/00840, WO 03/33495, WO 03/53966, WO 03/87094, WO 04/018422, WO 04/05285 and WO 05/077361.

While (B) compounds of formula I are a steroid, the medicament of the present invention optionally includes one or more other steroids, for example glucocorticosteroids such as budesonide, beclamethasone dipropionate, fluticasone propionate, mometasone furoate, ciclesonide, or steroids described in WO 02/88167, WO 02/12266, WO 02/100879, WO 03/35668, WO 03/48181, WO 03/62259, WO 03/64445, WO 03/72592, WO 04/39827 and WO 04/66920, or non-steroidal glucocorticoid receptor agonists, such as those described in DE 10261874, WO 00/00531, WO 02/10143, WO 03/82280, WO 03/82787, WO 03/86294, WO 03/104195, WO 03/101932, WO 04/05229, WO 04/18429, WO 04/19935, WO 04/26248 and WO 05/05452.

EXAMPLES

The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise.

In the examples glycopyrrolate is commercially available as a racemate, but can be prepared using the procedures described in US 2956062. Compound B is 3-methyl-thiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxy-carbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-

cyclopenta-[a]phenanthren-17-yl ester and is prepared using the procedures described in WO 02/00679.

Example 1

An aerosol composition suitable for delivery from the canister of a pressurised metered dose inhaler device is prepared by mixing the ingredients listed in Table 1 below. Glycopyrrolate and Compound B are milled to a mean particle diameter of 1-5 μm.

Table 1

Ingredient	% by weight
Glycopyrrolate	0.012
Compound B	0.250
Ethanol (absolute)	2.500
Oleic acid	0.05
HFA 227	60.718
HFA134a	36.470

Example 2

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing the ingredients listed in Table 1 below. Glycopyrrolate and Compound B are milled to a mean particle diameter of 1-5 μm. The lactose monohydrate has a particle diameter below 300 μm.

Table 2

Ingredient	% by weight
Glycopyrrolate	0.5
Compound B	5.00
Lactose monohydrate	94.50

Example 3

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO97/20589 is prepared by mixing 30 parts of glycopyrrolate which has been milled to a mean particle diameter of 1-5 μm in an air-jet mill, 250 parts of Compound B which has been similarly ground to a mean particle diameter of 1-5 μm and 4720 parts of lactose monohydrate having a particle diameter below 300 μm.

Examples 4 - 92

Example 3 is repeated, but using the amounts of the ingredients shown in Table 3 below in place of the amounts used in that Example:

Table 3

Example	Glycopyrrolate (Parts)	Compound B (Parts)	Lactose monohydrate (Parts)
4	25	50	4925
5	25	100	4875
6	25	150	4825
7	25	200	4775
8	12	50	4938
9	12	100	4888
10	12	150	4838
11	12	200	4788
12	12	250	4738
13	50	50	4900
14	50	100	4850
15	50	150	4800
16	50	200	4750
17	50	250	4700
18	100	50	4850
19	100	100	4800
20	100	150	4750
21	100	200	4700
22	100	250	4650
23	200	50	4750
24	200	100	4700
25	200	150	4650
26	200	200	4600
27	200	250	4550
28	400	50	4550
29	400	100	4500
30	400	150	4450
31	400	200	4400
32	400	250	4350
33	12	50	9938
34	12	100	9888
35	12	150	9838
36	12	200	9788
37	12	250	9738
38	25	50	9925
39	25	100	9875
40	25	150	9825
41	25	200	9775
42	25	250	9725
43	50	50	9900
44	50	100	9850
45	50	150	9800

46	50	200	9750
47	50	250	9700
48	100	50	9850
49	100	100	9800
50	100	150	9750
51	100	200	9700
52	100	250	9650
53	200	50	9750
54	200	100	9700
55	200	150	9650
56	200	200	9600
57	200	250	9550
58	400	50	9550
59	400	100	9500
60	400	150	9450
61	400	200	9400
62	400	250	9350
63	12	50	14938
64	12	100	14888
65	12	150	14838
66	12	200	14788
67	12	250	14738
68	25	50	14925
69	25	100	14875
70	25	150	14825
71	25	200	14775
72	25	250	14725
73	50	50	14900
74	50	100	14850
75	50	150	14800
76	50	200	14750
77	50	250	14700
78	100	50	14850
79	100	100	14800
80	100	150	14750
81	100	200	14700
82	100	250	14650
83	200	50	14750
84	200	100	14700
85	200	150	14650
86	200	200	14600
87	200	250	14550
88	400	50	14550
89	400	100	14500
90	400	150	14450
91	400	200	14400
92	400	250	14350

Examples 93-181

Example 3 is repeated, but using the amounts of the ingredients shown in Table 3 in place of the amounts used in that Example but also containing 0.5% magnesium stearate by weight.

Examples 182-270

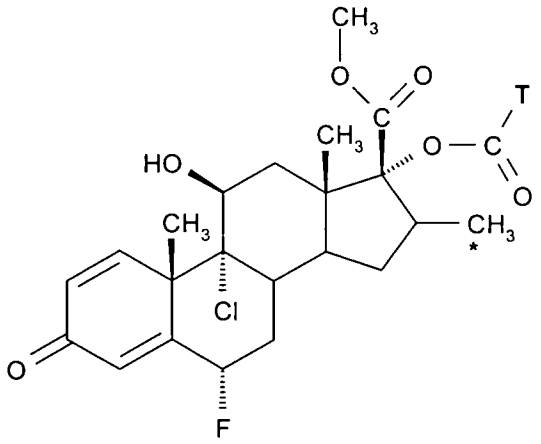
Example 3 is repeated, but using the amounts of the ingredients shown in Table 3 in place of the amounts used in that Example but also containing 1.0% magnesium stearate by weight.

Example 271

Gelatin capsules suitable for use in a capsule inhaler such as that described in US3991761 are prepared, each capsule containing a dry powder obtained by mixing 30 μg of glycopyrrolate which has been milled to a mean particle diameter of 1 to 5 μm in an air jet mill, 250 μg of Compound B which has been similarly milled to a mean particle diameter of 1 to 5μm and 24738 μg of lactose monohydrate having a particle diameter below 300 μm.

CLAIMS

1. A medicament comprising, separately or together (A) a glycopyrronium salt and (B) a compound of formula I



I

where T is a monovalent cyclic organic group having from 3 to 15 atoms in the ring system, 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 wherein the glycopyrronium salt is a racemate or a mixture of diastereomers.

4. A medicament according to claim 1 or 2 wherein the glycopyrronium salt is a single enantiomer.

5. A medicament according to any preceding claim wherein the glycopyrronium salt is glycopyrronium bromide.

6. A medicament according to claim 4 wherein the glycopyrronium salt is (3S,2'R)-3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide or (3R,2'R)-3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

7. A medicament according to claim 3 wherein the glycopyrronium salt is (3S,2'R/3R,2'S)-3-[(cyclopentyl-hydroxyphenylacetyl)oxy]-1,1-dimethylpyrrolidinium bromide.

8. A medicament according to compound according to any preceding claim, in which (B) is a compound of formula I where T is a heterocyclic aromatic group having a 5-membered heterocyclic ring with one, two or three ring hetero atoms selected from nitrogen, oxygen and sulfur, the heterocyclic ring being unsubstituted or substituted by one or two substituents selected from halogen, C_1-C_4-alkyl, halo-C_1-C_4-alkyl, C_1-C_4-alkoxy, C_1-C_4-alkylthio, cyano or hydroxy-C_1-C_4-alkyl, and the heterocyclic ring being optionally fused to a benzene ring.

9. A medicament according to compound according to any one of claims 1 to 7, in which (B) is a compound of formula I where T is a heterocyclic aromatic group having a 6-membered heterocyclic ring with one or two ring nitrogen atoms, the heterocyclic ring being unsubstituted or substituted by one or two substituents selected from halogen, cyano, hydroxyl, C_1-C_4-acyloxy, amino, C_1-C_4 alkylamino, di-(C_1-C_4-alkyl)amino, C_1-C_4-alkyl, hydroxy-C_1-C_4-alkyl, halo-C_1-C_4-alkyl C_1-C_4-alkoxy, or C_1-C_4-alkylthio and the heterocyclic ring being optionally fused to a benzene ring.

10. A medicament according to compound according to any one of claims 1 to 7, in which (B) is a compound of formula I where T is 5-methyl-2-thienyl, N-methyl-2-pyrrolyl, cyclopropyl, 2-furyl, 3-methyl-2-furyl, 3-methyl-2-thienyl, 5-methyl-3-isoxazolyl, 3,5-dimethyl-2-thienyl, 2,5-dimethyl-3-furyl, 4-methyl-2-furyl, 4-(dimethylamino)phenyl, 4-methylphenyl, 4-ethyl-phenyl, 2-pyridyl, 4-pyrimidyl or 5-methyl-2-pyrazinyl or the indicated 16-methyl group has the beta conformation and R is cyclopropyl.

11. A medicament according to compound according to claim 8 or 10, in which (B) is 3-methyl-thiophene-2-carboxylic acid (6S,9R,10S,11S,13S,16R,17R)-9-chloro-6-fluoro-11-hydroxy-17-methoxycarbonyl-10,13,16-trimethyl-3-oxo-6,7,8,9,10,11,12,13,14,15,16,17-dodecahydro-3H-cyclopenta-[a]phenanthren-17-yl ester.

12. A medicament according to any preceding claim, which is in inhalable form and is

(i) an aerosol comprising a mixture of (A) and (B) in solution or dispersion in a propellant;

(ii) 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;

(iii) a nebulizable composition comprising a dispersion of (A) and (B) in an aqueous, organic or aqueous/organic medium; or

(iv) a combination of a dispersion of (A) in an aqueous, organic or aqueous/organic medium with a dispersion of (B) in an aqueous, organic or aqueous/organic medium.

13. A medicament according to any one of claims 1 to 11, in which (A) and (B) are present in inhalable form as a dry powder comprising finely divided (A) and (B) optionally together with at least one particulate pharmaceutically acceptable carrier.

14. A medicament according to claim 12 or 13, in which (A) and (B) have an average particle diameter of up to 10 μm.

15. A medicament according to any one of claims 1 to 11, 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; or
an aerosol comprising (A) and (B) 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.

16. A medicament according to any preceding claim, in which the weight ratio of (A) to (B) is from 2:1 to 1:2000.

17. The use of (A) as defined in any one of claims 1, 3, 4, 5, 6 and 7, and (B) a compound of formula I as defined in any one of claims 1, 8, 9, 10 and 11, 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.

18. The use of (A) as defined in any one of claims 1, 3, 4, 5, 6 and 7, and (B) a compound of formula I as defined in any one of claims 1, 8, 9, 10 and 11, in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of asthma or chronic obstructive pulmonary disease.

19. A pharmaceutical kit comprising (A) as defined in any one of claims 1, 3, 4, 5, 6 and 7, and (B) a compound of formula I as defined in any one of claims 1, 8, 9, 10 and 11, 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).

20. A medicament comprising, separately or together (A) a glycopyrronium salt and (B) a compound of formula I as defined in claim 1, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease, substantially as herein described with reference to any one of the Examples.

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/011115

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/40 A61K31/58 A61K9/00 A61P11/06 A61P11/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, EMBASE, BIOSIS, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

*Category**	*Citation of document, with indication, where appropriate, of the relevant passages*	*Relevant to claim No.*
Y	WO 02/00679 A2 (NOVARTIS AG [CH]; NOVARTIS ERFIND VERWALT GMBH [AT]; CUENOUD BERNARD [) 3 January 2002 (2002-01-03) cited in the application page 12; claims	1-20
Y	WO 2004/013156 A (NOVARTIS AG [CH]; NOVARTIS PHARMA GMBH [AT]; JORDINE GUIDO [DE]; MUTZ) 12 February 2004 (2004-02-12) page 5 - page 6; claims	1-20
Y	WO 2005/107872 A2 (ARAKIS LTD [GB]; SNAPE SUSAN [GB]; BANNISTER ROBIN MARK [GB]) 17 November 2005 (2005-11-17) page 6; claims	1-20

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[X] *Further documents are listed in the continuation of Box C.*

[X] *See patent family annex.*

** Special categories of cited documents :*

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

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

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

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

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

"&" document member of the same patent family

Date of the actual completion of the international search	*Date of mailing of the international search report*
19 March 2007	30/03/2007

Name and mailing address of the ISA/	*Authorized officer*
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Zimmer, Barbara

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 2005/074918 A (SOFOTEC GMBH & CO KG [DE]; GOEDE JOACHIM [DE]; MAUS JOACHIM [DE]; CNOT) 18 August 2005 (2005-08-18) page 4 - page 5	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No
PCT/EP2006/011115

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
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