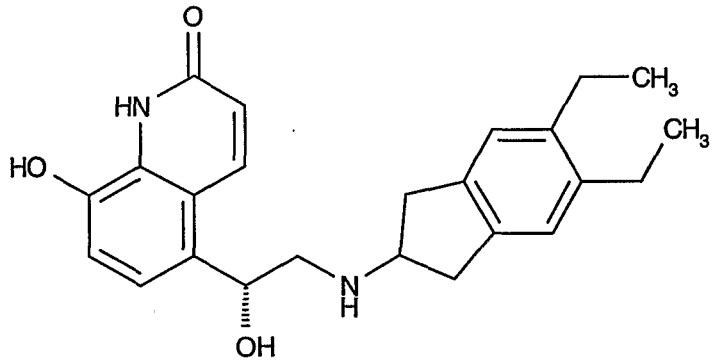
ORGANIC COMPOUNDS

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

in free or pharmaceutically acceptable salt or solvate form and (B) a corticosteroid, 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 pharamceutical 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.

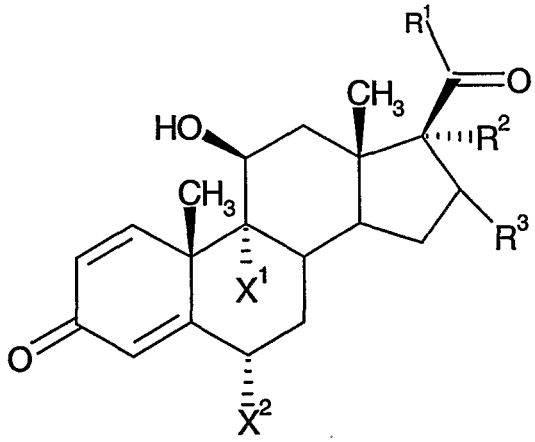
The invention further provides the use of (A) as hereinbefore defined and/or (B) as hereinbefore defined in the preparation of a medicament for combination therapy by simultaneous, sequential or separate administration of (A) and (B) in the treatment of an inflammatory or obstructive airways disease.

The compound of formula I 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 I in free or salt or solvate form. The reactions may be carried out using the procedures hereinafter described in the Examples or analogous procedures. (R)-8-benzyloxy-5-oxiranylcarbostyril may be prepared as described in W095/25104. 5,6-Diethylindan-2-ylamine may be prepared by known methods or analogues thereof, for example as described hereinafter in the Examples.

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 hydriodic 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 succinc 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. A particularly preferred form of the compound of Formula I is the maleate salt.

The corticosteroid (B) may be, for example, of formula

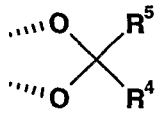


II

or a 1,2-dihydro derivative thereof, where

R^1 is C_1-C_4-alkyl optionally substituted by halogen (preferably chlorine or fluorine), hydroxy, C_1-C_4-alkoxy, acyloxy or by acylthio, or R^1 is C_1-C_4-alkoxy or C_1-C_4-alkylthio optionally substituted by halogen, or R^1 is 5-or 6-membered heterocyclylthio,

either R^2 is acyloxy and R^3 is hydrogen or C_1-C_4-alkyl, or R^2 and R^3 together denote a group of formula



III

where R^4 is C_1-C_4-alkyl or C_3-C_6-cycloalkyl and R^5 is hydrogen or C_1-C_4-alkyl, and X^1 and X^2 are each independently hydrogen, chlorine or fluorine.

C_1-C_4-alkyl as used herein may be methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl or tert-butyl.

C_1-C_4-alkoxy as used herein may be methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, sec-butoxy or tert-butoxy.

C_1-C_4-alkylthio as used herein may be methylthio, ethylthio, n-propylthio, isopropylthio, n-butylthio, isobutylthio, sec-butylthio or tert-butylthio.

When R^1 is acyloxy-substituted C_1-C_4-alkyl, the acyloxy group may be, for example, C_1-C_{20}-alkylcarbonyloxy, e.g. acetyloxy, n-propionyloxy, isopropionyloxy or hexadecanoyloxy, or C_3-C_6-cycloalkylcarbonyloxy, e.g. cyclohexylcarbonyloxy. When R^1 is acylthio-substituted C_1-C_4-alkyl, the acylthio group may be, for example, C_1-C_4-alkylcarbonylthio, e.g. acetylthio or n-propionylthio. When R^1 is 5-or-6-membered heterocyclylthio, the heterocyclyl group may be an O-heterocyclyl group, for example a furanonyl group.

When R^2 is acyloxy, it may be, for example, C_1-C_4-alkylcarbonyloxy, e.g. acetyloxy, n-propionyloxy, or n-butyroyloxy, C_3-C_6-cycloalkylcarbonyloxy e.g. cyclopropylcarbonyloxy, or 5-or 6-membered heterocyclylcarbonyloxy e.g. furoyloxy.

When R^3 is C_1-C_4-alkyl it may be in the alpha or beta conformation, more usually in the alpha conformation.

When R^2 and R^3 together denote a group of formula III, R^4 as C_3-C_6-cycloalkyl may be, for example, cyclohexyl.

Corticosteroids of formula I and their 1,2-dihydro derivatives include beclamethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide, flunisolide, rofleponide palmitate, butixocort propionate and

icometasone enbutate. In particularly preferred emodiments of the invention, the corticosteroid (B) is budesonide, fluticasone propionate or mometasone furoate.

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. 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 US3991761, while a suitable MDPI device is that described in WO97/20589.

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 20µg to 2000µg, for example from 20 to 1500µg, from 20 to 1000µg, preferably from

50 to 800μg, e.g. from 100 to 600μg or from 100 to 500μg. A suitable daily dose of steriod (B) for inhalation may be from 20μg to 5000μg, for example from 20 to 4000μg, from 50 to 3000μg, from 50 to 2000μg, from 50 to 1000μg, from 50 to 500μg, from 50 to 400μg, from 50 to 300μg, from 50 to 200μg or from 50 to 100μg. Where (B) is budesonide, a suitable daily dose may be from 25 to 4800μg, for example from 25 to 4000μg, from 25 to 3200μg, from 25 to 2400μg, from 25 to 1600μg, from 50 to 4800μg, from 50 to 4000μg, from 50 to 3200μg, from 50 to 2400μg, from 50 to 1600μg, from 100 to 4000μg, from 100 to 3200μg, from 100 to 2400μg, from 100 to 1600μg, from 100 to 800μg, from 100 to 400μg, from 200 to 4000μg, from 200 to 1600μg, from 200 to 800μg or from 200 to 400μg, 100 to 1600μg being preferred. Where (B) is mometasone furoate, a suitable daily dose may be from 50μg to 2000μg, for example from 100 to 200μg, from 100 to 1600μg, from 100 to 1000μg or from 100 to 800μg, preferably from 200 to 500μg, for instance from 200 to 400μg. Where (B) is fluticasone propionate, a suitable daily dose may be for inhalation may be from 25 to 2000μg, for example from 25 to 1500μg, from 25 to 1000μg, from 25 to 500μg, from 25 to 250μg, from 50 to 1500μg, from 50 to 1000μg, from 50 to 500μg, from 50 to 250μg, from 100 to 1500μg, from 100 to 1000μg, from 100 to 500μg, from 100 to 250μg, from 200 to 1500μg, from 200 to 1000μg or from 200 to 500μg, 100 to 1000μg being preferred.

A suitable unit dose of compound (A), particularly as the maleate salt, may be from 20 to 2000μg, for example from 20 to 1500μg, from 20 to 1000μg, preferably from 50 to 800μg, from 50 to 600μg or from 50 to 500μg. A suitable unit dose of budesonide may be from 25 to 2400μg, for example from 50 to 2400μg, from 50 to 2000μg, from 50 to 1600μg, from 50 to 800μg, from 50 to 400μg, from 50 to 200μg, from 100 to 1600μg, from 100 to 800μg, from 100 to 400μg, from 100 to 200μg, from 200 to 1600μg, from 200 to 800μg or from 200 to 400μg, 100 to 400μg being preferred. A suitable unit dose of mometasone furoate for inhalation may be from 25 to 2000μg, for example from 50μg to 1500μg, from 50 to 1000μg, from 50 to 800μg, from 50 to 400μg, from 50 to 200μg, from 50 to 100μg, from 100 to 800μg, from 100 to 400μg or from 100 to 200μg, 100 to 400μg being preferred. A suitable unit dose of fluticasone propionate for inhalation may be from 25 to 1000μg, for example from 25 to 500μg, from 25 to 250μg, from 25 to 200μg, from 50 to 1000μg, from 50 to 500μg, from 50 to 250μg, from 50 to 200μg, from 100 to 1000μg, from 100 to 500μg, from 100 to 250μg, from 100 to 200μg, from 150 to 500μg or from 150 to 250μg, 100 to 500μg being preferred. These unit doses may be administered once or twice daily in accordance with the daily doses mentioned hereinbefore. The precise unit and daily dose 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 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 50mg, for example 5mg, 10mg, 15mg, 20mg, 25mg, 30mg, 35mg, 40mg, 45mg or 50mg.

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, 3mg to 25mg 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 inhalaiton 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.

The invention is illustrated by the following Examples, in which parts are by weight unless stated otherwise. In the Examples, Compound A is the compound of formula I in the form of the maleate salt, Bud denotes budesonide, FP denotes fluticasone propionate, MF denotes mometasone furoate and OA denotes oleic acid (surfactant).

Preparation Examples

Preparation 1 - 3-chloro-1-(3,4-diethylphenyl)- 1-propanone

1,2-Diethylbenzene (10.9 g, 74.6 mmol) and propionyl chloride (9.7 g, 74.6 mmol) are added dropwise to $AlCl_3$ (22.3 g, 167.8 mmol) in nitromethane (75 mL) over 30 min. The reaction mixture is stirred at room temperature for 2 hours, after which 70 g of ice and 14 mL concentrated sulphuric acid are added. The aqueous phase is extracted with ether, and the combined organic phases extracted with 2N HCl and saturated aqueous NaCl. The organic

phase is further treated with activated charcoal, magnesium sulphate, and filtered, and the solvent removed *in vacuo*.

1H-NMR ($CDCl_3$) ppm: 7.8 (1H, s, Ar); 7.7 (1H, d, Ar); 7.2 (1H, d, Ar); 3.9 (2H, t, CH_2); 3.4 (2H, t, CH_2); 2.8 (4H, q, CH_2CH_3); 1.2 (6H, m, CH_3).

Preparation 2 – 5,6-diethyl-indan-1-one

3-chloro-1-(3,4-diethylphenyl)- 1-propanone (15.5 g) is dissolved in 66 mL concentrated sulphuric acid and heated to 90 °C for 4 hours. The reaction mixture is cooled, ice (70 g) is added, and the aqueous solution extracted twice with toluene. The organic layer is washed with sodium bicarbonate, saturated aqueous NaCl, and treated with activated charcoal and magnesium suphate. After filtration, the solvent is removed *in vacuo*. The product is purified by flash column chromatography (silica, hexane / ethylacetate 10:1), and further crystallised in hexane.

1H-NMR (CDCl3) ppm: 7.6 (1H, s, Ar); 7.3 (1H, d, Ar); 3.1 (2H, m, CH_2); 2.7 (6H, m, CH_2+CH_2CH_3); 1.2 (6H, m, CH_3).

Preparation 3 - 5,6-Diethyl- indan-1, 2-dione 2-oxime

5,6-diethyl-indan-1-one (5 g, 26 mmol) in methanol (75 mL) is brought to 40 °C, n-butyl nitrite (3.0 g, 28.6 mmol) is added dropwise, followed by the addition of concentrated HCl (1.25 mL). After 1 hour, the reaction is brought to room temperature and the precipitated product filtered off, washed with ice-cold methanol and dried.

1H-NMR (d6-DMSO) ppm: 12.6 (1H, s, OH); 7.4 (1H, s, Ar); 7.3 (1H, d, Ar); 3.6 (2H, s, CH_2); 2.6 (4H, m, CH_2CH_3); 1.1 (6H, m, CH_3).

Preparation 4 – 5,6-Diethyl-indan-2-ylamine hydrochloride

5,6-Diethyl-indan-1, 2-dione 2-oxime (4.5 g) is added to a mixture of acetic acid (150 mL), and concentrated sulphuric acid (4.5 mL). Pd/C 5% (1.5 g) is added, the reaction mixture degassed with nitrogen, and hydrogenated for 5 hours. The catalyst is then removed by filtration, the pH brought to pH 10 with 4M NaOH, and the solution extracted with chloroform. The organic phase is dried with magnesium sulphate, and the solvent removed *in vacuo*. The residue is redisolved in a minimum amount of ether, and HCl saturated ether added. The white precipitate is filtered and dried to yield the HCl salt of 5,6-diethyl-indan-2-ylamine.

1H-NMR (d6-DMSO) ppm: 8.7 (3H, bd s, NH_3); 7.3 (2H, s, Ar); 4.2 (1H, bd s, CH); 3.5 (2H, dd, CH_2); 3.3 (2H, dd, CH_2); 2.8 (4H, q, CH_2CH_3); 1.4 (6H, t, CH_3).

Preparation 5 - 8-benzyloxy-5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one

A solution of (R)-8-benzyloxy-5-oxiranylcarbostyril (5.00g) and 5,6-diethylindan-2-ylamine (3.87g) in n-butanol is heated for 4 hours at 110°C. After cooling to room temperature toluene (100ml) is added and the organic phase is washed with water (3 X 25ml), loaded onto a silica gel chromatography column and eluted with toluene followed by a mixture of toluene: ethanol: ethyl acetate: conc. ammonia (45:10:45:2) to give the title compound.

Preparation 6 – Compound A: 5-[(R)-2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-8-hydroxy-1H-quinolin-2-one maleate

8-benzyloxy-5-[(R)2-(5,6-diethyl-indan-2-ylamino)-1-hydroxy-ethyl]-1H-quinolin-2-one (360mg) is dissolved in methanol (10mL) and the compound is deprotected by adding a catalytic amount of 10% palladium on charcoal and placing the solution under an atmosphere of hydrogen. The reaction is shown to be complete by TLC after 4 hours. The catalyst is filtered off and the solvent is removed *in vacuo*. The product is taken up into isopropanol and a solution of maleic acid in isopropanol added. The title compound is obtained after recrystallisation from ethanol. TLC (silica, dichloromethane / methanol 10:1 R_f = 0.05). ES+ MS *m/e* 393 (MH^+).

Examples 1-60

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 Compound A and budesonide which have been ground to a mean particle diameter of 1 to 5μm and lactose monohydrate having a particle diameter below 212μm, the amounts being as shown in the table below:

Example	Compound A (Parts)	Budesonide (Parts)	Lactose (Parts)
1	20	100	19880
2	40	100	19860
3	80	100	19820
4	100	100	19800
5	120	100	19780
6	140	100	19760
7	160	100	19740

8	180	100	19720
9	200	100	19700
10	220	100	19680
11	240	100	19660
12	300	100	19600
13	500	100	19400
14	1000	100	18900
15	2000	100	17900
16	20	100	24880
17	40	100	24860
18	80	100	24820
19	100	100	24800
20	120	100	24780
21	140	100	24760
22	160	100	24740
23	180	100	24720
24	200	100	24700
25	220	100	24680
26	240	100	24660
27	300	100	24600
28	500	100	24400
29	1000	100	23900
30	2000	100	22900
31	20	200	14780
32	40	200	14760
33	80	200	14720
34	100	200	14700
35	120	200	14680
36	140	200	14660
37	160	200	14640
38	180	200	14620
39	200	200	14600
40	220	200	14580
41	240	200	14560
42	300	200	14500
43	500	200	14300

44	1000	200	13800
45	2000	200	12800
46	20	200	24780
47	40	200	24760
48	80	200	24720
49	100	200	24700
50	120	200	24680
51	140	200	24660
52	160	200	24640
53	180	200	24620
54	200	200	24600
55	220	200	24580
56	240	200	24560
57	300	200	24500
58	500	200	24300
59	1000	200	23800
60	2000	200	22800

Examples 61-90

Examples 1-60 are repeated, but replacing the budesonide by mometasone furoate, and using amounts as shown in the following table:

Example	Compound A (Parts)	MF (Parts)	Lactose (Parts)
61	20	100	24880
62	40	100	24860
63	80	100	24820
64	100	100	24800
65	120	100	24780
66	140	100	24760
67	160	100	24740
68	180	100	24720
69	200	100	24700
70	220	100	24680
71	240	100	24660

72	300	100	24600
73	500	100	24400
74	1000	100	23900
75	2000	100	22900
76	20	200	14780
77	40	200	14760
78	80	200	14720
79	100	200	14700
80	120	200	14680
81	140	200	14660
82	160	200	14640
83	180	200	14620
84	200	200	14600
85	220	200	14580
86	240	200	14560
87	300	200	14500
88	500	200	14300
89	1000	200	13800
90	2000	200	12800

Examples 91-135

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in W097/20589 is prepared by mixing Compound A and fluticasone propionate which have been ground to a mean particle diameter of 1-5μm and lactose monohydrate having a particle diameter below 212μm, the amounts being as shown in the table below

Example	Compound A (Parts)	FP (Parts)	Lactose (Parts)
91	20	100	4880
92	40	100	4860
93	80	100	4820
94	100	100	4800
95	120	100	4780
96	140	100	4760
97	160	100	4740

98	180	100	4720
99	200	100	4700
100	220	100	4680
101	240	100	4660
102	300	100	4600
103	500	100	4400
104	1000	100	3900
105	2000	100	2900
106	20	200	9780
107	40	200	9760
108	80	200	9720
109	100	200	9700
110	120	200	9680
111	140	200	9660
112	160	200	9640
113	180	200	9620
114	200	200	9600
115	220	200	9580
116	240	200	9560
117	300	200	9500
118	500	200	9300
119	1000	200	8800
120	2000	200	7800
121	20	250	14730
122	40	250	14710
123	80	250	14670
124	100	250	14650
125	120	250	14630
126	140	250	14610
127	160	250	14590
128	180	250	14570
129	200	250	14550
130	220	250	14530
131	240	250	14510
132	300	250	14450
133	500	250	14250

134	1000	250	13750
135	2000	250	12750

Examples 136-163

Aerosol formulations are prepared by dispensing micronised active ingredients and, if required, lactose as bulking agent into a vial, sealing the vial with a metering valve, injecting the premixed ethanol/propellant and optional surfactant into the vial through the valve and subjecting the vial to ultrasonic energy to disperse the solid particles. The components and amounts used are shown in the following tables:

Ex.	Cpd.A (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
136	2	10	36500	60750	2500	-	70
137	4	10	3410	6340	230	0.3	-
138	8	10	97000	-	2500	-	90
139	10	10	30500	67000	2500	0.5	100
140	12	10	3150	6550	250	1	-
141	14	10	3700	6050	250	0.8	-
142	16	10	3800	5900	230	0.4	-
143	18	10	4700	5050	250	1	-
144	20	20	3600	6150	225	1	-
145	22	20	3500	6200	230	1	-
146	24	20	98000	-	2500	1	-
147	30	20	3900	5900	250	1	-
148	2	20	30000	67000	2250	0.2	90
149	10	20	3500	6200	250	0.5	-
150	14	20	3200	6500	230	1	-
151	18	20	3100	6200	225	0.8	-
152	20	20	3150	6100	225	1	-
153	24	20	30000	60000	2000	0.8	-

Ex.	Cpd.A (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
154	4	10	34000	63000	2250	0.3	50
155	8	10	92000	-	2500	0.5	70

156	12	10	3000	5500	200	-	-
157	16	10	2500	5000	200	0.3	-
158	20	10	2000	3000	150	0.2	-
159	30	10	2000	2000	150	0.2	-
160	8	20	20000	25000	1500	0.2	-
161	12	20	2500	2500	200	0.2	-
162	20	20	2000	2000	150	0.2	-
163	30	20	20000	20000	1500	0.2	-

Examples 164-199

The procedure of Examples 91-135 is repeated, but replacing fluticasone propionate by mometasone furoate, and using amounts as shown in the following table.

Example	Compound A (Parts)	MF (Parts)	Lactose (Parts)
164	100	100	4800
165	200	100	4700
166	300	100	4600
167	400	100	4500
168	500	100	4400
169	600	100	4300
170	700	100	4200
171	800	100	4100
172	2000	100	2900
173	100	200	4700
174	200	200	4600
175	300	200	4500
176	400	200	4400
177	500	200	4300
178	600	200	4200
179	700	200	4100
180	800	200	4000
181	1200	200	3600
182	100	400	4500
183	200	400	4400
184	300	400	4300

185	400	400	4200
186	500	400	4100
187	600	400	4000
188	700	400	3900
189	800	400	3800
190	100	100	9800
191	200	100	9700
192	300	100	9600
193	400	100	9500
194	500	100	9400
195	100	200	9700
196	200	200	9600
197	300	200	9500
198	400	200	9400
199	500	200	9300

Examples 200-236

The procedures of Examples 136-163 is repeated, but using the amounts shown in the following table, the ethanol being omitted in some of the Examples:

Ex.	Cpd.A (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
200	20	20	5000	-	200	0.5	-
201	40	2	2500	2500	-	-	-
202	75	25	1500	3500	500	-	1
203	20	20	3600	6150	225	-	0.5
204	2	20	30000	67000	-	-	-
205	14	20	3200	6500	1500	-	4
206	20	20	3150	6100	1500	4	-
207	10	20	4700	5050	500	-	0.2
208	60	20	10000	10000	-	-	-
209	60	20	10000	10000	200	-	-
210	60	20	10000	10000	-	0.5	-
211	30	20	8000	12000	-	1	1
212	40	20	5000	15000	500	0.5	0.5

213	50	20	9000	11000	400	0.8	0.2
214	20	20	4600	5000	400	0.4	0.2
215	30	10	20000	25000	-	-	-
216	40	10	20000	30000	-	-	-
217	60	10	35000	65000	-	-	-

Ex.	Cpd.A (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
218	20	10	5000	5000	-	-	1
219	10	10	3650	6350	-	-	1
220	30	10	3200	6800	100	0.5	0.5
221	30	20	7400	7600	100	-	-
222	40	20	8300	6700	200	0.5	-
223	60	20	3100	6900	300	1	-
224	10	10	8000	12000	-	-	-
225	50	20	1600	3400	500	2	0.5

Ex.	Cpd.A (Parts)	Bud (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
226	10	20	5500	4500	-	-	-
227	2	20	3500	6500	-	-	1
228	1	20	2500	7500	-	-	1
229	20	20	3800	6100	100	0.5	-
230	15	20	3300	6600	100	0.5	0.5
231	30	20	3600	5900	500	4	-
232	40	20	4600	4900	500	3	-
233	30	10	3100	6800	100	0.2	0.5
234	40	10	1400	3100	500	0.2	-
235	60	10	8000	12000	-	-	1
236	80	10	30000	70000	-	-	-

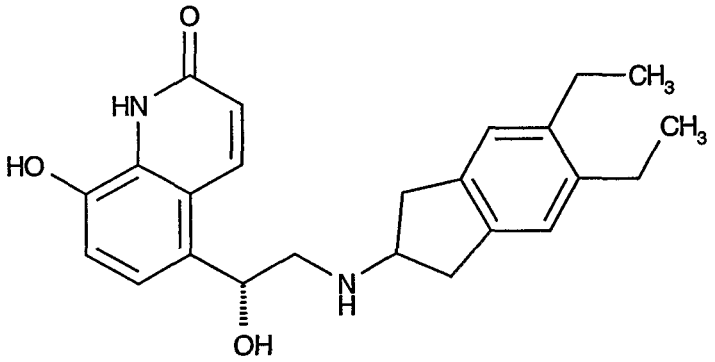
Example 237 – 245

The procedure of Examples 136-163 is repeated, but using sorbitan trioleate (ST) as surfactant in place of oleic acid, the amounts of the ingredients being as shown in the following table:

Ex.	Cpd.A (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	ST (Parts)	Lactose (Parts)
237	60	40	10000	10000	300	4	-
238	60	20	8000	12000	200	8	-
239	50	20	12000	8000	400	10	-
240	40	20	5000	5000	600	2.5	1
241	30	20	3500	6500	-	4	2
242	20	20	6000	4000	-	3	3
243	10	20	4500	5500	100	2	1
244	20	10	4100	5900	50	1	2
245	15	5	1550	3450	200	0.5	1

Claims

1. A medicament comprising, separately or together, (A) a compound of formula



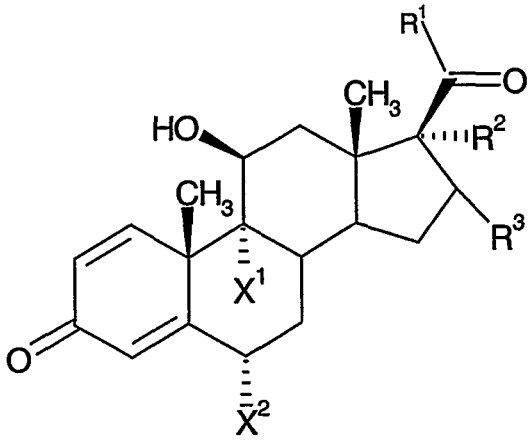
I

in free or pharmaceutically acceptable salt or solvate form and (B) a corticosteroid, for simultaneous, sequential or separate administration in the treatment of an inflammatory or obstructive airways disease, the molar ratio of (A) to (B) being from 100:1 to 1:300.

2. A medicament according to claim 1 which is a pharamceutical 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 in the form of the maleate salt.

4. A medicament according to claim 1, 2 or 3, in which the corticosteroid (B) is of formula

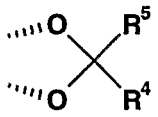


II

or a 1,2-dihydro derivative thereof, where

R^1 is C_1-C_4-alkyl optionally substituted by halogen, hydroxy, C_1-C_4-alkoxy, acyloxy or by acylthio, or R^1 is C_1-C_4-alkoxy or C_1-C_4-alkylthio optionally substituted by halogen, or R^1 is 5- or 6-membered heterocyclylthio,

either R^2 is acyloxy and R^3 is hydrogen or C_1-C_4-alkyl, or R^2 and R^3 together denote a group of formula



III

where R^4 is C_1-C_4-alkyl or C_3-C_6-cycloalkyl and R^5 is hydrogen or C_1-C_4-alkyl, and X^1 and X^2 are each independently hydrogen, chlorine or fluorine.

5. A medicament according to any one of claims 1 to 4, in which the corticosteroid (B) is beclamethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide, flunisolide, rofleponide palmitate, butixocort propionate or icometasone enbutate.

6. A medicament according to claim 5, in which the corticosteroid (B) is budesonide, fluticasone propionate or mometasone furoate.

7. A medicament according to any one of claims 1 to 6 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.

8. A medicament according to any one of claims 1 to 6 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.

9. A medicament according to any one of claims 1 to 6, 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.

10. A medicament according to claim 7 or 9, in which (A) and/or (B) has an average particle diameter up to 10 μm.

11. 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.

12. 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.

13. 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.

14. A medicament according to claim 2, which is an aerosol comprising (A) and (B) in a ratio as hereinbefore specified in claim 1 or 11, 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.

15. A pharmaceutical kit comprising (A) as defined in claim 1 or 3 and (B) as defined in any one of claims 1 and 4 to 6 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).