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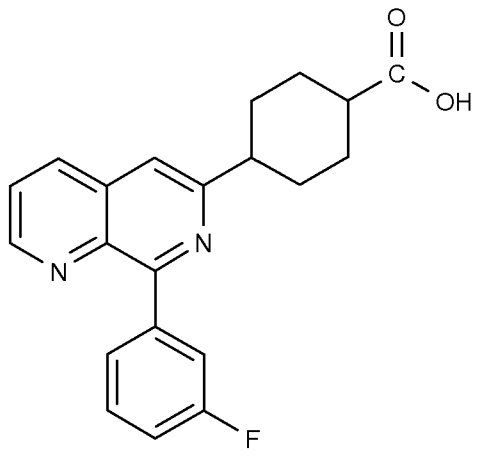

(II)

(57) Abstract: A medicament comprising, separately or together, (A) a compound of formula II in free or salt or solvate form; and (B) one or more of compounds selected from the group consisting of PDE4 inhibitors and PDE5 inhibitors, for simultaneous, sequential or separate administration in the treatment of pulmonary hypertension.

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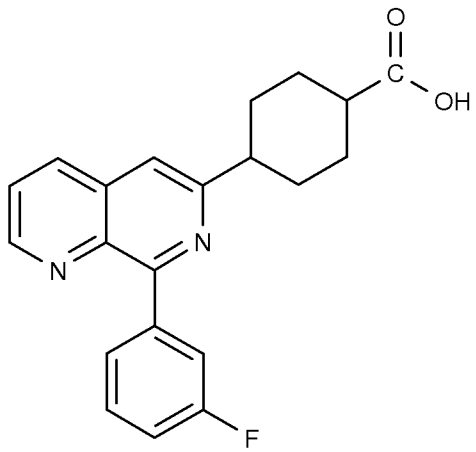
ORGANIC COMPOUNDS

This invention relates to organic compounds and their use as pharmaceuticals, in particular for the treatment of pulmonary hypertension.

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

(A) a compound of formula II



II

in free or salt or solvate form; and

(B) one or more of compounds selected from the group consisting of PDE4 inhibitors and PDE5 inhibitors;

for simultaneous, sequential or separate administration.

In an embodiment of the invention, the medicament is useful in the treatment of pulmonary hypertension.

The compound of formula II, in free or salt form, exhibits cyclic nucleotide phosphodiesterase (PDE) isoenzyme inhibiting activity, selective for type 4 isoenzyme. It possesses anti-inflammatory, anti-airways hyperreactivity and bronchodilator properties. It further possesses immunosuppressive and TNFα secretion inhibitory activities.

Thus, according to the first aspect of the invention, there is provided a medicament which comprises the compound of formula II together with a PDE5 inhibitor and/or a further PDE4 inhibitor.

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

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

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

In an embodiment of the invention as defined above in any aspect, (B) comprises a PDE5 inhibitor.

In an alternative embodiment of the invention as defined above in any aspect, (B) comprises a PDE4 inhibitor.

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

The compound of formula II, in free or salt form, may be prepared as described in WO 03/039544, the contents of which is incorporated herein by reference.

The compound of formula II in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. The compound of formula II can be recovered from reaction mixtures and purified in a conventional manner. Isomers, such as enantiomers, may be obtained in a conventional manner, e.g. by fractional crystallisation or

asymmetric synthesis from correspondingly asymmetrically substituted, e.g. optically active, starting materials.

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

The invention includes all pharmaceutically acceptable isotopically-labelled compounds of formula I wherein one or more atoms are replaced by atoms having the same atomic number, but an atomic mass or mass number different from the atomic mass or mass number usually found in nature. Examples of isotopes suitable for inclusion in the compounds of the invention include isotopes of hydrogen e.g. ^{2}H and ^{3}H, carbon e.g. ^{11}C, ^{13}C and ^{14}C, chlorine e.g. ^{36}Cl, fluorine e.g. ^{18}F, iodine e.g. ^{123}I and ^{125}I, nitrogen e.g. ^{13}N and ^{15}N, oxygen e.g. ^{15}O, ^{17}O and ^{18}O, and sulfur e.g. ^{35}S.

Certain isotopically-labelled compounds of formula I, for example those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution studies. The radioactive isotopes tritium (^{3}H) and carbon-14 (^{14}C) are particularly useful for this purpose in view of their ease of incorporation and ready means of detection. Substitution with heavier isotopes such as deuterium (^{2}H) may afford certain therapeutic advantages that result from greater metabolic stability, for example increased *in vivo* half-life or reduced dosage requirements, and hence may be preferred in some circumstances. Substitution with positron emitting isotopes, such as ^{11}C, ^{18}F, ^{15}O, and ^{13}N can be useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labelled compounds of formula I can generally be prepared by conventional techniques known to those skilled in the art or by processes analogous to those described in the

accompanying examples using an appropriate isotopically-labelled reagent in place of the non-labelled reagent previously used.

Pharmaceutically acceptable solvates in accordance with the invention include those wherein the solvent of crystallisation may be isotopically substituted e.g. D_2O, d_6-acetone or d_6-DMSO.

A PDE4 inhibitor is a substance or agent that exhibits cyclic nucleotide phosphodiesterase (PDE) isoenzyme inhibiting activity, selective for type 4 isoenzyme. Such substances possess anti-inflammatory, anti-airways hyperreactivity and bronchodilator properties. They can also possess immunosuppressive and TNFα secretion inhibitory activities. PDE4 inhibition activity may be measured using the PDE4 isoenzyme inhibition assay described in WO 03/39544

Suitable PDE4 inhibitors include 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), and those disclosed in WO 92/19594, WO 93/19749, WO 93/19750, WO 93/19751, WO 98/18796, WO 99/16766, WO 01/13953, WO 03/104204, WO 03/104205, WO 03/39544, WO 04/000814, WO 04/000839, WO 04/005258, WO 04/018450, 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 04/019944, WO 04/019945, WO 04/045607, WO 04/037805, WO 04/063197, WO 04/103998, WO 04/111044, WO 05/012252, WO 05/012253 and WO 05/013995, WO 05/030212, WO 05/030725, WO 05/087744, WO 05/087745, WO 05/087749 and WO 05/090345.

A PDE5 inhibitor is a substance or agent that exhibits cyclic nucleotide phosphodiesterase (PDE) isoenzyme inhibiting activity, selective for type 5 isoenzyme. Such substances are useful in the treatment of sexual dysfunction, including male erectile dysfunction and female sexual dysfunction, premature labour, dysmenorrhoea, benign prostatic hyperplasia, bladder outlet obstruction, incontinence, stable, unstable and variant (Prinzmetal) angina, hypertension, pulmonary hypertension, congestive heart failure, atherosclerosis, conditions of reduced blood vessel patency, e.g. post-percutaneous transluminal coronary angioplasty, peripheral vascular disease, bronchitis, asthma, allergic rhinitis, glaucoma, tinnitus, diseases characterised by disorders of gut motility, e.g. irritable bowel syndrome, pre-eclampsia, Kawasaki's syndrome, nitrate tolerance, multiple sclerosis, peripheral diabetic neuropathy, stroke, Alzheimer's disease,

acute respiratory failure, psoriasis, skin necrosis, cancer, metastasis, baldness, nutcracker oesophagus, anal fissure and hypoxic vasoconstriction. PDE5 inhibition activity may be measured using the PDE5 isoenzyme inhibition assay described in WO 2001/77110.

Suitable PDE5 inhibitors include pyrazolopyrimidinones disclosed in EP 463756, EP 526004, WO 94/28902, WO 96/16657 or WO 98/49166; 5-substituted pyrazole [4,3-d]pyrimidin-7-ones disclosed in EP 201188; griseolic acid derivatives disclosed in EP 214708 and EP 319050; 2-phenylpurinone derivatives disclosed in EP 293063; phenylpyridone derivatives disclosed in EP 347027; fused pyrimidine derivatives disclosed in EP 347146; condensed pyrimidine derivatives disclosed in EP 349239; pyrimidopyrimidine derivatives disclosed in EP 351058; purine compounds disclosed in EP 352960; quinazolinone derivatives disclosed in EP 371731; phenylpyrimidone derivatives disclosed in EP 395328; imidazoquin-oxalinone derivatives or their aza analogues disclosed in EP 400583; phenylpyrimidone derivatives disclosed in EP 400799; phenylpyridone derivatives disclosed in EP 428268; pyrimidopyrimidine derivatives disclosed in EP 442204; 4-aminoquinazoline derivatives disclosed in EP 579496; 4,5-dihydro-4-oxo-pyrrolo[1,2-a]quinoxaline derivatives or their aza analogues disclosed in EP 584487; polycyclic guanine derivatives disclosed in WO91/19717; nitrogenous heterocyclic compounds disclosed in WO93/07124; 2-benzyl-polycyclic guanine derivatives disclosed in WO94/19351; quinazoline derivatives disclosed in US 4060615; 6-heterocyclyl pyrazolo [3,4-d]pyrimidin-4-ones disclosed in US 5294612; benzimidazoles disclosed in Japanese Kokai 5-222000; cycloheptimidazoles disclosed in *European Journal of Pharmacology*, vol. 251, (1994), 1; N-containing heterocycles disclosed in WO 94/22855; pyrazolopyrimidine derivatives disclosed in EP 636626; 4-aminopyrimidine derivatives disclosed in EP 640599; imidazoquinazoline derivatives disclosed in EP 668280; anthranilic acid derivatives disclosed in EP 0686625; 4-aminoquinazoline derivatives disclosed in US 5436233; tetracyclic derivatives disclosed in WO 95/19978 (including tadafil); quinazoline compounds disclosed in EP 0669324; fused pyridazine compounds disclosed in EP 722936; imidazoquinoline compounds disclosed in EP 0758653; substituted pyrazoloquinolinamines disclosed in WO 96/28159; substituted pyrazolopyrimidinones disclosed in WO 96/28429; indole derivatives disclosed in WO 96/32379; benzimidazole derivatives disclosed in WO 97/03070; 2-phenyl substituted imidazotriazinone derivatives disclosed in WO 99/24433 (including vardenafil); as well as those described in WO 2001/77110, for example 3-Isobutyl-8-(6-methoxy-isoquinolin-4-ylmethyl)-1-methyl-3,7-dihydro-purine-2,6-dione.

Especially preferred PDE5 inhibitors include 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one (sildenafil,

VIAGRA®, disclosed in WO 94/28902), (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino(2',1':6,1)pyrido (3,4-b)indole-1,4-dione (tadafil, CIALIS®, disclosed in WO 95/19978)), 4-ethoxy-N-propyl-N-(2-hydroxyethyl)-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)benzenesulfonamide (vardenafil, LEVITRA®, disclosed in WO 99/24433), 4-phenyl-methylamino-6-chloro-2-(1-imidazolyl)-quinazoline (disclosed in US 5436233), 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline (disclosed in US 5436233), 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one (disclosed in EP 636626) and 1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one (disclosed in US 5294612).

In the treatment of disorders in accordance with the invention, the compound of formula II, in free form or in pharmaceutically acceptable salt form, may be administered by any appropriate route, for example orally, e.g. in tablet, capsule or liquid form, parenterally, for example in the form of an injectable solution or suspension, or intranasally, for example in the form of an aerosol or other atomisable formulation using an appropriate intranasal delivery device, e.g. a nasal spray such as those known in the art, or by inhalation.

The compound of formula II in free base or acid addition salt form may be administered in a pharmaceutical composition together with a pharmaceutically acceptable diluent or carrier. Such compositions may be as described in WO 03/039544, for example dry powders, tablets, capsules and liquids, but also injection solutions, infusion solutions or inhalation suspensions, which may be prepared using other formulating ingredients and techniques known in the art.

When the medicament is to be administered 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 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; as unit doses contained within a disk or other rigid drug carrier; or as unit doses 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 embodiments of the invention as

defined herein, (A), (B) and the carrier are present in amounts to bring the total weight of powder per unit dose (e.g. 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 aerosol vials and procedures for containing within them aerosol compositions under pressure are well known to those skilled in the art of inhalation therapy. For example, an aerosol composition may be administered from a coated can, for example as described in EP-A-0642992. Where the inhalable form of the active ingredient is a nebulizable aqueous, organic or aqueous/organic dispersion, the inhalation device may be a known nebulizer, for example a conventional pneumatic nebulizer such as an airjet nebulizer, or an ultrasonic nebulizer, which may contain, for example, from 1 to 50 ml, commonly 1 to 10 ml, of the dispersion; or a hand-held nebulizer, sometimes referred to as a soft mist or soft spray inhaler, for example an

electronically controlled device such as an AERx (Aradigm, US) or Aerodose (Aerogen), or a mechanical device such as a RESPIMAT (Boehringer Ingelheim) nebulizer which allows much smaller nebulized volumes, e.g. 10 to 100 μl, than conventional nebulizers. Where the inhalable form of the active ingredient is the finely divided particulate form, the inhalation device may be, for example, a dry powder inhalation device adapted to deliver dry powder from a capsule or blister containing a dry powder comprising a dosage unit of (A) and/or (B) or a multidose dry powder inhalation (MDPI) device adapted to deliver, for example, 3-25 mg of dry powder comprising a dosage unit of (A) and/or (B) per actuation. The dry powder composition preferably contains a diluent or carrier, such as lactose, and a compound that helps to protect against product performance deterioration due to moisture e.g. magnesium stearate, typically 0.05-1.5%. Suitable such dry powder inhalation devices are well known. For example, a suitable device for delivery of dry powder in encapsulated form is that described in US 3991761, while a suitable MDPI device is that described in WO 97/20589.

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

The dosage of the compound of formula II in free base or acid addition salt form can depend on various factors, such as the activity and duration of action of the active ingredient, the severity of the condition to be treated, the mode of administration, the species, sex, ethnic origin, age and weight of the subject and/or its individual condition.

In an embodiment of the invention, the recommended daily dose range of the compound of formula II for the conditions described herein lie within the range of from about 1 mg to about 10,000 mg per day, given as a single once-a-day dose, or in divided doses throughout a day. Specifically, a daily dose range should be from about 1 mg to about 5,000 mg per day, more specifically, between about 10 mg and about 2,500 mg per day, between about 100 mg and about 800 mg per day, between about 100 mg and about 1,200 mg per day, or between about 25 mg and about 2,500 mg per day. In managing the patient, the therapy should be initiated at a lower dose, perhaps about 1 mg to about 2,500 mg, and increased if necessary up to about 200 mg to about 5,000 mg per day as either a single dose or divided doses, depending on the patient's global response. In another embodiment of the invention, the compound of formula II is administered from about 1 to about 20 mg/day individually, for example, about 1 mg/day, about 2 mg/day, about 3 mg/day, about 4 mg/day, about 5 mg/day, about 6 mg/day, about 7 mg/day, about 8 mg/day, about 9 mg/day, about 10 mg/day, about 11 mg/day, about 12

mg/day, about 13 mg/day, about 14 mg/day, about 15 mg/day, about 16 mg/day, about 17 mg/day, about 18 mg/day, about 19 mg/day, or about 20 mg/day. In a particular embodiment, 4-[8-(3-Fluorophenyl)-[1,7]naphthyridin-6-yl]-cyclohexanecarboxylic acid is administered in an amount of about 400, 800, 1,200, 2, 500, 5,000 or 10,000 mg a day.

Administration of (A) and(B) to a patient can occur simultaneously or sequentially by the same or different routes of administration. The suitability of a particular route of administration employed for a particular active agent will depend on the active agent itself (e.g., whether it can be administered orally without decomposing prior to entering the blood stream) and the disease being treated. A preferred route of administration for (A) is oral. Another preferred route of administration for such a compound is parenteral, particularly for patients who are in a peri-transplant period or in an end stage of pulmonary hypertension. Preferred routes of administration for (B) are known to those of ordinary skill in the art such as in *Physicians' Desk Reference* (57th ed., 2003).

The specific amount of (B) will depend on the specific agent used, the type of pulmonary hypertension being treated or managed, the severity and stage of pulmonary hypertension, and the amount(s) of any optional additional active agents concurrently administered to the patient.

This present invention encompasses kits which, when used by the medical practitioner, can simplify the administration of appropriate amounts of active agents to a patient. A typical kit of the invention comprises a dosage form of the compound of formula II, in free or salt form, component (B) and optionally a device or devices for administering (A) and (B) e.g. syringes, drip bags, patches or inhalers.

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

In another embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver, for example, 3 mg to 25 mg of powder containing a unit

dose of (A) and (B) per actuation, for example, where (A) is optionally in the form of a 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 embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is an aerosol comprising (A) and (B), in a propellant as hereinbefore described, optionally together with a surfactant and/or a bulking agent and/or a co-solvent such as ethanol as hereinbefore described, for administration from a metered dose inhaler adapted to deliver an amount of aerosol containing a unit dose of (A) and a unit dose of (B), or a known fraction of a unit dose of (A) and a known fraction of a unit dose of (B), per actuation. Thus if, for example, the inhaler delivers half of the unit doses of (A) and (B) per actuation, the unit doses can be administered by two actuations of the inhaler.

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

The medicaments of the invention are useful in the treatment of pulomonary hypertension.

Treatment of pulmonary hypertension in accordance with the invention may be symptomatic or prophylactic.

Pulmonary hypertension to be treated in accordance with the invention includes primary pulmonary hypertension (PPH); secondary pulmonary hypertension (SPH); familial PPH; sporadic PPH; precapillary pulmonary hypertension; pulmonary arterial hypertension (PAH);

pulmonary artery hypertension; idiopathic pulmonary hypertension; thrombotic pulmonary arteriopathy (TPA); plexogenic pulmonary arteriopathy; functional classes I to IV pulmonary hypertension; and pulmonary hypertension associated with, related to, or secondary to, left ventricular dysfunction, mitral valvular disease, constrictive pericarditis, aortic stenosis, cardiomyopathy, mediastinal fibrosis, anomalous pulmonary venous drainage, pulmonary venoocclusive disease, collagen vasular disease, congenital heart disease, HIV virus infection, drugs and toxins such as fenfluramines, congenital heart disease, pulmonary venous hypertension, chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorder, chronic exposure to high altitude, neonatal lung disease, alveolar-capillary dysplasia, sickle cell disease, other coagulation disorder, chronic thromboemboli, connective tissue disease, lupus, schistosomiasis, sarcoidosis or pulmonary capillary hemangiomatosis.

Pulmonary hypertension to be treated in accordance with the invention is most particularly pulmonary hypertension associated with disorders of the respiratory system and/or hypoxemia, including chronic obstructive pulmonary disease, interstitial lung disease, sleep-disordered breathing, alveolar hypoventilation disorders, chronic exposure to high altitude, neonatal lung disease and alveolar-capillary dysplasia, but especially chronic obstructive pulmonary disease.

The medicaments of the invention are also 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 one or both of the components required for a given therapeutic effect compared with those required using treatment with one of the components 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 one or both of the components needed for a given anti-inflammatory effect may be reduced, thereby reducing the risk of undesirable side effects from the repeated exposure to one or both of the components 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.

EXAMPLES

Compound A1

4-[8-(3-fluorophenyl)-[1,7]naphthyridin-6-yl]-cyclohexanecarboxylic acid

This compound is prepared using the procedures described in international patent application WO 03/039544.

Compound B1

This compound is the PDE4 inhibitor cilomilast.

Compound B2

This compound is the PDE4 inhibitor roflumilast.

Compound B3

This compound is the PDE5 inhibitor sildenafil.

Compound B4

This compound is the PDE5 inhibitor tadafil.

Compound B5

This compound is the PDE5 inhibitor vardenafil.

Examples 1-60

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 and EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound A1 and Compound B1 which have been ground to a mean particle diameter of 1 to 5 μm and lactose monohydrate having a particle diameter below 212 μm, the amounts being as shown in the Table 1 below:

TABLE 1

Example	**Compound A1** (Parts)	**Compound B1** (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 61-105

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in W0 97/20589 is prepared by mixing Compound A1 and Compound B2 which have been ground to a mean particle diameter of 1-5 μm and lactose monohydrate having a particle diameter below 212 μm, the amounts being as shown in the Table 2 below:

TABLE 2

Example	Compound A1 (Parts)	Compound B2 (Parts)	Lactose (Parts)
61	20	100	4880
62	40	100	4860
63	80	100	4820

64	100	100	4800
65	120	100	4780
66	140	100	4760
67	160	100	4740
68	180	100	4720
69	200	100	4700
70	220	100	4680
71	240	100	4660
72	300	100	4600
73	500	100	4400
74	1000	100	3900
75	2000	100	2900
76	20	200	9780
77	40	200	9760
78	80	200	9720
79	100	200	9700
80	120	200	9680
81	140	200	9660
82	160	200	9640
83	180	200	9620
84	200	200	9600
85	220	200	9580
86	240	200	9560
87	300	200	9500
88	500	200	9300
89	1000	200	8800
90	2000	200	7800
91	20	250	14730
92	40	250	14710
93	80	250	14670
94	100	250	14650
95	120	250	14630
96	140	250	14610
97	160	250	14590

98	180	250	14570
99	200	250	14550
100	220	250	14530
101	240	250	14510
102	300	250	14450
103	500	250	14250
104	1000	250	13750
105	2000	250	12750

Examples 106-150

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in W0 97/20589 is prepared by mixing Compound A1 and Compound B3 which have been ground to a mean particle diameter of 1-5 μm and lactose monohydrate having a particle diameter below 212 μm, the amounts being as shown in the Table 2 but also containing 0.5% magnesium stearate by weight.

Examples 151-168

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound A1 and Compound B4, 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 Table 3 below:

TABLE 3

Ex.	Cpd.A1 (Parts)	Cpd.B4 (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
151	2	10	36500	60750	2500	-	70
152	4	10	3410	6340	230	0.3	-
153	8	10	97000	-	2500	-	90
154	10	10	30500	67000	2500	0.5	100

155	12	10	3150	6550	250	1	-
156	14	10	3700	6050	250	0.8	-
157	16	10	3800	5900	230	0.4	-
158	18	10	4700	5050	250	1	-
159	20	20	3600	6150	225	1	-
160	22	20	3500	6200	230	1	-
161	24	20	98000	-	2500	1	-
162	30	20	3900	5900	250	1	-
163	2	20	30000	67000	2250	0.2	90
164	10	20	3500	6200	250	0.5	-
165	14	20	3200	6500	230	1	-
166	18	20	3100	6200	225	0.8	-
167	20	20	3150	6100	225	1	-
168	24	20	30000	60000	2000	0.8	-

Examples 169-178

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound A1 and Compound B5, 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 Table 4 below:

TABLE 4

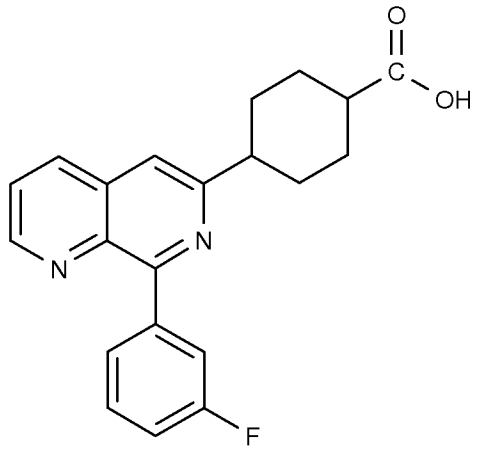
Ex.	Cpd.A1 (Parts)	Cpd.B5 (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
169	4	10	34000	63000	2250	0.3	50
170	8	10	92000	-	2500	0.5	70
171	12	10	3000	5500	200	-	-
172	16	10	2500	5000	200	0.3	-
173	20	10	2000	3000	150	0.2	-
174	30	10	2000	2000	150	0.2	-
175	8	20	20000	25000	1500	0.2	-

176	12	20	2500	2500	200	0.2	-
177	20	20	2000	2000	150	0.2	-
178	30	20	20000	20000	1500	0.2	-

CLAIMS

1. A medicament comprising, separately or together,

(A) a compound of formula II



II

in free or salt or solvate form; and

(B) one or more of compounds selected from the group consisting of PDE4 inhibitors and PDE5 inhibitors;

for simultaneous, sequential or separate administration in the treatment of pulmonary hypertension.

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 Claim 2, in which (B) is a PDE4 inhibitor selected from the group consisting of cilomilast, roflumilast,V-11294A, BAY19-8004, SCH-351591, arofylline, PD189659, PD168787, AWD-12-281, CDC-801, CC-10004, VM554/UM565, T-440 and KW-4490.

4. A medicament according to Claim 1 or Claim 2, in which (B) is a PDE5 inhibitor selected from the group consisting of 5-[2-ethoxy-5-(4-methylpiperazinylsulfonyl)-phenyl]-1-methyl-3-n-propyl-1,6-dihydro-7H-pyrazolo[4,3-d]pyrimidin-7-one, (6R,12aR)-2,3,6,7,12,12a-Hexahydro-2-methyl-6-(3,4-methylenedioxyphenyl)-pyrazino(2',1':6,1)pyrido (3,4-b)indole-1,4-dione, 4-

ethoxy-N-propyl-N-(2-hydroxyethyl)-3-(5-methyl-4-oxo-7-propyl-3,4-dihydroimidazo[5,1-f][1,2,4]triazin-2-yl)benzenesulfonamide, 4-phenyl-methylamino-6-chloro-2-(1-imidazolyl)-quinazoline, 4-phenylmethylamino-6-chloro-2-(3-pyridyl)quinazoline, 1,3-dimethyl-6-(2-propoxy-5-methanesulfonylamidophenyl)-1,5-dihydropyrazolo[3,4-d]pyrimidin-4-one and 1-cyclopentyl-3-ethyl-6-(3-ethoxy-4-pyridyl)-pyrazolo[3,4-d]pyrimidin-4-one.

5. A medicament according to any of claims 1 to 4, wherein (A) and (B) are in a dose form suitable for oral administration.

6. A medicament according to claim 5, wherein (A) and (B) are formulated in a single pharmaceutical composition suitable for oral administration.

7. A medicament according to claim 5 or claim 6, wherein (A) and (B) are in the form of a tablet.

8. A medicament according to any one of claims 1 to 4 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.

9. A medicament according to any one of claims 1 to 4 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 the said medium with a dispersion of (B) in the said medium.

10. A medicament according to any one of claims 1 to 4 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.

11. A pharmaceutical kit comprising (A) as defined in claim 1 and (B) as defined in any one of claims 1 to 4 in separate unit dosage forms, said forms being suitable for administration of (A) and (B) in effective amounts, and optionally a device or devices for administering (A) and (B).

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2008/059576

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61K31/4375 A61P9/12

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, CHEM ABS Data, WPI Data

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

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
15 September 2008	01/10/2008

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	Pilling, Stephen

INTERNATIONAL SEARCH REPORT

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