

(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
18 August 2005 (18.08.2005)

PCT

(10) International Publication Number
WO 2005/074924 A1

(31) International Patent Classification⁷: **A61K 31/428**,
31/58, 31/56, 31/573, A61P 11/06

(74) Agent: **ROTH, Peter, R.**; Novartis AG, Corporate Intellectual Property, CH-4002 Basel (CH).

(21) International Application Number:
PCT/EP2005/001241

(22) International Filing Date: 8 February 2005 (08.02.2005)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
0402797.5 9 February 2004 (09.02.2004) GB

(71) Applicant (for all designated States except AT, US): **NOVARTIS AG** [CH/CH]; Lichtstrasse 35, CH-4056 Basel (CH).

(71) Applicant (for AT only): **NOVARTIS PHARMA GMBH** [AT/AT]; Brunner Strasse 59, A-1230 Vienna (AT).

(72) Inventor; and

(75) Inventor/Applicant (for US only): **FAIRHURST, Robin, Alec** [GB/GB]; Novartis Horsham Research Centre, Wimblehurst Road, Horsham, West Sussex RH12 5AB (GB).

(81) Designated States (unless otherwise indicated, for every kind of national protection available): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

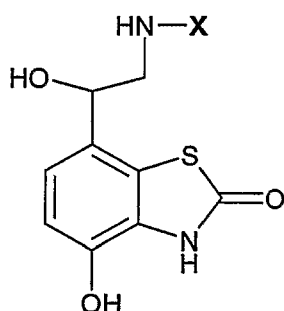
(84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: COMBINATION OF BENZOTHAZOL-2-ONE BETA2 ADRENOCEPTOR AGONISTS AND CORTICOSTEROIDS FOR THE TREATMENT OF RESPIRATORY DISEASES



(I)

(57) Abstract: A medicament comprising, separately or together, (A) a compound of Formula (I) in free or salt or solvate form, wherein X has the meaning as indicated in the specification; and (B) a corticosteroid, for simultaneous, sequential or separate administration in the treatment of an inflammatory obstructive airways disease, the molar ratio of (A) to (B) being from 100:1 to 1:300.

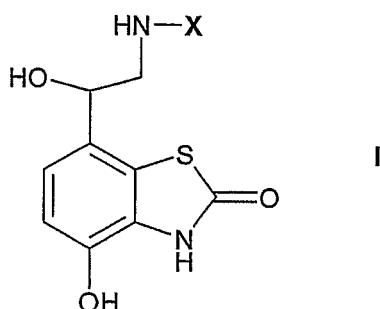


WO 2005/074924 A1

COMBINATION OF BENZOTHIAZOL-2-ONE BETA2 ADRENOCEPTOR AGONISTS AND
CORTICOSTEROIDS FOR THE TREATMENT OF RESPIRATORY DISEASES

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 salt or solvate form, wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_1-C_{10} -alkoxy- C_1-C_{10} -alkyl, phenyl, C_1-C_{10} -alkyl substituted by phenyl, C_1-C_{10} -alkoxy substituted by phenyl, C_1-C_{10} -alkyl-substituted phenyl or by C_1-C_{10} -alkoxy-substituted phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and either R^1 is C_1-C_{10} -alkylene and R^2 is hydrogen, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or halogen or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10} -alkylene optionally substituted by hydroxy, C_1-C_{10} -alkoxy, C_6-C_{10} -aryl or C_7-C_{14} -aralkyl; and

Y is C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_2-C_{10} -alkenyl or C_2-C_{10} -alkynyl optionally substituted by halo, cyano, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or halo- C_1-C_{10} -alkyl; C_3-C_{10} -cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_3-C_{10} -cycloalkyl, C_7-C_{14} -aralkyl, C_7-C_{14} -aralkyloxy or C_6-C_{10} -aryl, where C_3-C_{10} -cycloalkyl, C_7-C_{14} -aralkyl, C_7-C_{14} -aralkyloxy

or C₆-C₁₀-aryl are optionally substituted by halo, hydroxy, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy or halo-C₁-C₁₀-alkyl;

C₆-C₁₀-aryl optionally substituted by halo, hydroxy, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy, C₁-C₁₀-haloalkyl, phenoxy, C₁-C₁₀-alkylthio, C₆-C₁₀-aryl, 4- to 10- membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, or by NR^bR^c where R^b and R^c are each independently C₁-C₁₀-alkyl optionally substituted by hydroxy, C₁-C₁₀-alkoxy or phenyl or R^b may additionally be hydrogen;

phenoxy optionally substituted by C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy or by phenyl optionally substituted by C₁-C₁₀-alkyl or C₁-C₁₀-alkoxy;

a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, said heterocyclic ring being optionally substituted by halo, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy, halo-C₁-C₁₀-alkyl, C₆-C₁₀-aryl, C₇-C₁₄-aralkyl, C₇-C₁₄-aralkyloxy, C₁-C₁₀-alkoxycarbonyl or a 4- to 10-membered heterocyclyl-C₁-C₁₀-alkyl;

-NR^dR^e where R^d is hydrogen or C₁-C₁₀-alkyl and R^e is C₁-C₁₀-alkyl optionally substituted by hydroxy, or R^e is C₆-C₁₀-aryl optionally substituted by halo, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom which ring is optionally substituted by phenyl or halo-substituted phenyl or R^e is C₆-C₁₀-arylsulfonyl optionally substituted by C₁-C₁₀-alkylamino or di(C₁-C₁₀-alkyl)amino;

-SR^f where R^f is C₆-C₁₀-aryl or C₇-C₁₄-aralkyl optionally substituted by halo, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy or C₁-C₁₀-haloalkyl; or

-CONHR^g where R^g is C₁-C₁₀-alkyl, C₃-C₁₀-cycloalkyl or C₆-C₁₀-aryl; 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.

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

In a further 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.

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

Terms used in the specification have the following meanings:

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

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

"C₁-C₁₀-alkyl" as used herein denotes straight chain or branched alkyl that contains one to ten carbon atoms. Preferably, C₁-C₁₀-alkyl is C₁-C₄-alkyl.

"C₁-C₁₀-alkylene" as used herein denotes a straight chain or branched alkylene that contains one to ten carbon atoms. Preferably C₁-C₁₀-alkylene is C₁-C₄ alkylene, especially ethylene or methylethylene.

"C₂-C₁₀-alkenyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon double bonds. Preferably "C₂-C₁₀-alkenyl" is "C₂-C₄-alkenyl".

"C₂-C₁₀-alkynyl" as used herein denotes straight chain or branched hydrocarbon chains that contain two to ten carbon atoms and one or more carbon-carbon triple bonds. Preferably "C₂-C₁₀-alkynyl" is "C₂-C₄-alkynyl".

"C₃-C₁₀-cycloalkyl" as used herein denotes cycloalkyl having 3 to 10 ring carbon atoms, for example a monocyclic group such as a cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl or cyclodecyl, any of which can be substituted by one or

more, usually one or two, C₁-C₄-alkyl groups, or a bicyclic group such as bicycloheptyl or bicyclooctyl. Preferably C₃-C₁₀-cycloalkyl is C₃-C₆-cycloalkyl, for example cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl.

"C₁-C₁₀-haloalkyl" as used herein denotes C₁-C₁₀-alkyl as hereinbefore defined substituted by one or more halogen atoms, preferably one, two or three halogen atoms.

"C₁-C₁₀-alkylamino" and "di(C₁-C₁₀-alkyl)amino" as used herein denote amino substituted respectively by one or two C₁-C₁₀-alkyl groups as hereinbefore defined, which may be the same or different. Preferably C₁-C₁₀-alkylamino and di(C₁-C₁₀-alkyl)amino are respectively C₁-C₄-alkylamino and di(C₁-C₄-alkyl)amino.

"C₁-C₁₀-alkylthio" as used herein denotes straight chain or branched alkylthio having 1 to 10 carbon atoms. Preferably, C₁-C₁₀-alkylthio is C₁-C₄-alkylthio.

"C₁-C₁₀-alkoxy" as used herein denotes straight chain or branched alkoxy that contains 1 to 10 carbon atoms. Preferably, C₁-C₁₀-alkoxy is C₁-C₄-alkoxy.

"C₁-C₁₀-alkoxy-C₁-C₁₀-alkyl" as used herein denotes C₁-C₁₀-alkyl as hereinbefore defined substituted by C₁-C₁₀-alkoxy. Preferably, C₁-C₁₀-alkoxy-C₁-C₁₀-alkyl is C₁-C₄-alkoxy-C₁-C₄-alkyl.

"C₁-C₁₀-alkoxycarbonyl" as used herein denotes C₁-C₁₀-alkoxy as hereinbefore defined linked through an oxygen atom thereof to a carbonyl group.

"C₆-C₁₀-aryl" as used herein denotes a monovalent carbocyclic aromatic group that contains 6 to 10 carbon atoms and which may be, for example, a monocyclic group such as phenyl or a bicyclic group such as naphthyl. Preferably C₆-C₁₀-aryl is C₆-C₈-aryl, especially phenyl.

"C₆-C₁₀-arylsulfonyl" as used herein denotes C₆-C₁₀-aryl as hereinbefore defined linked through a carbon atom thereof to a sulfonyl group. Preferably C₆-C₁₀-arylsulfonyl is C₆-C₈-arylsulfonyl.

"C₇-C₁₄-aralkyl" as used herein denotes alkyl, for example C₁-C₄-alkyl as hereinbefore defined, substituted by aryl, for example C₆-C₁₀-aryl as hereinbefore defined. Preferably, C₇-C₁₄-aralkyl is C₇-C₁₀-aralkyl such as phenyl-C₁-C₄-alkyl, particularly benzyl or 2-phenylethyl.

"C₇-C₁₄-aralkyloxy" as used herein denotes alkoxy, for example C₁-C₄-alkoxy as hereinbefore defined, substituted by aryl, for example C₆-C₁₀-aryl. Preferably, C₇-C₁₄-aralkyloxy is C₇-C₁₀-aralkyloxy such as phenyl-C₁-C₄-alkoxy, particularly benzyloxy or 2-phenylethoxy.

Ar as used herein may be, for example, phenylene which is unsubstituted or substituted by one or more substituents selected from halogen, hydroxy, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy, C₁-C₁₀-alkoxy-C₁-C₁₀-alkyl, phenyl, or C₁-C₁₀-alkyl substituted by phenyl, C₁-C₁₀-alkoxy substituted by phenyl, C₁-C₁₀-alkyl-substituted phenyl and C₁-C₁₀-alkoxy-substituted phenyl. Preferably Ar is phenylene which is unsubstituted or substituted by one or two substituents selected from halogen, C₁-C₄-alkyl, C₁-C₄-alkoxy, or C₁-C₄-alkoxy substituted by phenyl. Preferably one substituent in Ar is para to R¹ and optional second and third substituents in Ar are meta to R¹.

"4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom" as used herein may be, for example, pyrrole, pyrrolidine, pyrazole, imidazole, triazole, tetrazole, thiadiazole, oxazole, isoxazole, thiophene, thiazole, isothiazole, oxadiazole, pyridine, pyrazine, pyridazine, pyrimidine, piperidine, piperazine, triazine, oxazine, morpholino, quinoline, isoquinoline, naphthyridine, indane or indene. Preferred heterocyclic rings include thiazole, pyrrolidine, piperidine, azacycloheptane and isoxazole.

"4 to 10-membered heterocyclyl-C₁-C₁₀-alkyl" denotes alkyl, for example C₁-C₁₀-alkyl as hereinbefore defined, substituted by a 4- to 10-membered heterocyclic ring as hereinbefore defined. Preferably, 4- to 10-membered heterocyclyl-C₁-C₁₀-alkyl is C₁-C₄-alkyl substituted by a 4- to 8-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom.

"C₁-C₄-alkylsulfonyl" denotes sulfonyl substituted by C₁-C₄-alkyl as hereinbefore defined.

"Hydroxy-C₁-C₄-alkyl" denotes C₁-C₄-alkyl as hereinbefore defined substituted by one or more, preferably one, two or three hydroxy groups.

R¹ and R² together with the carbon atoms to which they are attached as a cycloaliphatic ring may be, for example, a cyclopentane ring, optionally substituted by one or two C₁-C₄-alkyl groups, a cyclohexane ring, optionally substituted by one or two C₁-C₄-alkyl groups, or a cycloheptane ring, preferably a cyclopentane ring.

Preferred compounds of formula I in free or salt or solvate form include those wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or by C_1-C_{10} -alkoxy substituted by phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_{10} -alkylene and R^2 is hydrogen,

or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10} -alkylene optionally substituted by hydroxy, C_6-C_{10} -aryl or C_7-C_{14} -aralkyl; and

Y is C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or C_2-C_{10} -alkynyl; C_3-C_{10} -cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10} -alkyl, C_3-C_{10} -cycloalkyl, C_7-C_{14} -aralkyl, C_7-C_{14} -aralkyloxy optionally substituted by halo, or by C_6-C_{10} -aryl optionally substituted by C_1-C_{10} -alkyl or C_1-C_{10} -alkoxy; C_6-C_{10} -aryl optionally substituted by halo, hydroxy, C_1-C_{10} -alkyl, phenoxy, C_1-C_{10} -alkylthio, C_6-C_{10} -aryl, a 4- to 10-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C_1-C_{10} -alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C_1-C_{10} -alkoxy; a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C_1-C_{10} -alkyl, C_6-C_{10} -aryl, C_7-C_{14} -aralkyl, C_1-C_{10} -alkoxycarbonyl or by a 4- to 10-membered heterocycl-C $_1-C_{10}$ -alkyl; $-NR^dR^e$ where R^d is hydrogen or C_1-C_{10} -alkyl and R^e is C_1-C_{10} -alkyl, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom which ring is optionally substituted by halo-substituted phenyl or R^e is C_6-C_{10} -arylsulfonyl optionally substituted by di(C_1-C_{10} -alkyl)amino; $-SR^f$ where R^f is C_6-C_{10} -aryl or C_7-C_{14} -aralkyl optionally substituted by halo or C_1-C_{10} -haloalkyl; or $-CONHR^g$ where R^g is C_3-C_{10} -cycloalkyl or C_6-C_{10} -aryl.

Especially preferred compounds of formula I in free or salt or solvate form include those wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, C_1-C_4 -alkyl, C_1-C_4 -alkoxy or by C_1-C_4 -alkoxy substituted by phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and

either R^1 is C_1-C_4 -alkylene and R^2 is hydrogen,

or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring, especially a 5-membered cycloaliphatic ring;

R^a is a bond or C₁-C₄-alkylene optionally substituted by hydroxy, C₆-C₈-aryl or C₇-C₁₀-aralkyl; and

Y is C₁-C₄-alkyl, C₁-C₄-alkoxy or C₂-C₄-alkynyl; C₃-C₆-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₇-C₁₀-aralkyl, C₇-C₁₀-aralkyloxy optionally substituted by halo, or by C₆-C₈-aryl optionally substituted by C₁-C₄-alkyl or C₁-C₄-alkoxy; C₆-C₈-aryl optionally substituted by halo, hydroxy, C₁-C₄-alkyl, phenoxy, C₁-C₄-alkylthio, C₆-C₈-aryl, a 4- to 8-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C₁-C₄-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C₁-C₄-alkoxy; a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C₁-C₄-alkyl, C₆-C₈-aryl, C₇-C₁₀-aralkyl, C₁-C₄-alkoxycarbonyl or by a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or sulphur atom which ring is optionally substituted by halo-substituted phenyl or R^e is C₆-C₈-arylsulfonyl optionally substituted by di(C₁-C₄-alkyl)amino; -SR^f where R^f is C₆-C₈-aryl or C₇-C₁₀-aralkyl optionally substituted by halo or C₁-C₄-haloalkyl; or -CONHR^g where R^g is C₃-C₆-cycloalkyl or C₆-C₈-aryl.

More especially preferred compounds of formula I in free or salt or solvate form include: 4-hydroxy-7-(1-hydroxy-2-[2-[4-(4-phenyl-butoxy)-phenyl]-ethylamino]-ethyl)-3H-benzothiazol-2-one; 7-[(R)-2-(1,1-dimethyl-2-phenyl-ethylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one; 4-hydroxy-7-[(R)-1-hydroxy-2-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-ethyl]-3H-benzothiazol-2-one formate; 7-[(R)-2-((1S,2S)-2-benzyloxy-cyclopentylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one; and 7-[(R)-2-((1S,2R)-2-benzyloxy-cyclopentylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one.

In formula I the carbon atom alpha to the phenolic ring carries a hydroxy group and so is asymmetric, so the compound exists in individual optically active isomeric forms or as mixtures thereof, e.g. as racemic or diastereomeric mixtures. Compounds of formula I embrace both individual optically active R and S isomers as well as mixtures, e.g. racemic or diastereomeric mixtures, thereof.

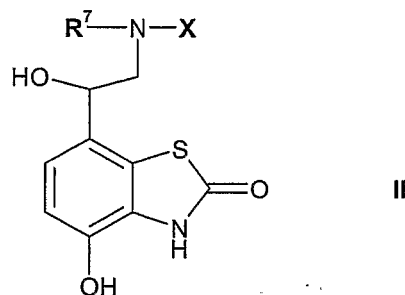
Pharmaceutically acceptable acid addition salts of the compound of formula I include those of inorganic acids, for example, hydrohalic acids such as hydrofluoric acid, hydrochloric acid,

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-hydroxynaphthalene-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.

Pharmaceutically acceptable solvates are generally hydrates.

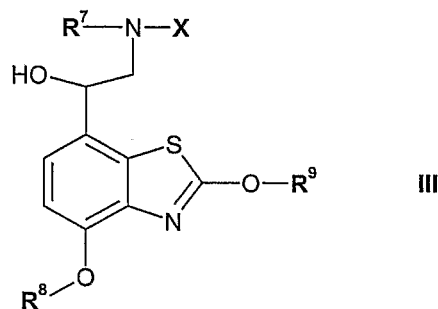
Compounds of formula I in free or salt or solvate form may also be prepared by:

- (i) either (A) reacting a compound of formula II



where X is as hereinbefore defined and R⁷ denotes a protecting group to replace R⁷ by hydrogen,

- or (B) reacting a compound of formula III



where X and R⁷ are as hereinbefore defined and R⁸ and R⁹ each independently denote a protecting group, to convert groups R⁷, R⁸ and R⁹ to hydrogen; and

- (ii) recovering the compound of formula I in free or salt or solvate form.

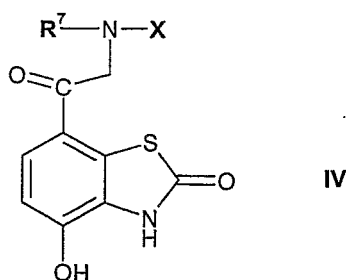
Where reference is made herein to protected functional groups or to protecting groups, the protecting groups may be chosen in accordance with the nature of the functional group, for example as described in *Protective Groups in Organic Synthesis*, T.W. Greene and P.G.M. Wuts, John Wiley & Sons Inc, Third Edition, 1999, which reference also describes procedures suitable for replacement of the protecting groups by hydrogen.

The protecting group R^7 may be, for example, a group chosen from known amine-protecting groups. Preferred protecting groups R^7 include araliphatic groups such as benzyl and trialkylsilyl e.g. trimethylsilyl. Protecting groups R^8 and R^9 may be chosen from known phenolic hydroxy- and alcoholic hydroxy-protecting groups respectively. Preferred groups R^8 and R^9 include C_1 - C_4 -alkyl groups, particularly branched groups such as isopropyl and tert-butyl.

Process variant (A) may be effected, for example, using known procedures for conversion of amine-protecting groups to hydrogen or analogous procedures. For example, where R^7 is a benzyl group it may be converted to hydrogen by hydrogenolysis of the compound of formula II, e.g. with a carboxylic acid such as formic acid, preferably in the presence of a palladium catalyst. This de-protection reaction may be carried out using procedures as described hereinafter in the Examples or analogous procedures.

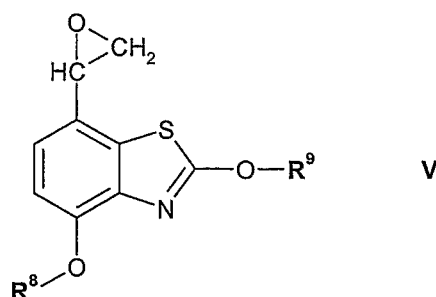
Process variant (B) may be effected using known procedures for conversion of hydroxy-protecting groups to hydrogen or analogous procedures. For example, where, R^8 and R^9 are alkyl groups, R^8 and R^9 may be converted to hydrogen by hydrogenolysis of the compounds of formula IV, e.g. with a carboxylic acid such as formic acid preferably in the presence of a palladium catalyst, for example as hereinbefore described for conversion of R^7 to hydrogen, or by treatment with an acid alone such as formic acid, hydrochloric acid or trifluoroacetic acid, in either case the resulting 2-hydroxybenzothiazole compound being in tautomeric equilibrium with the benzothiazol-2-one form.

Compounds of formula II may be prepared by reduction of a compound of formula IV



where X and R⁷ are as hereinbefore defined. The reduction may be effected using known methods for reduction of ketones to alcohols, or analogous methods, including asymmetric reductions. For example, the compounds of formula IV may be reacted with NaBH₄ in an inert solvent such as an aliphatic alcohol. Suitable reaction temperatures are from -80° C to 100° C, conveniently from -5° C to 5° C. The reduction may be effected using known procedures or analogously as described hereinafter in the Examples.

Compounds of formula III may be prepared by reacting a compound of formula V

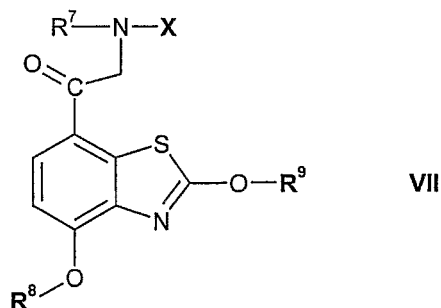


where R⁸ and R⁹ are as hereinbefore defined, with a compound of formula VI



where X and R⁷ are as hereinbefore defined. The reaction of compounds of formulae V and VI may be effected using known procedures for epoxide-amine reactions or analogous procedures. The reaction is optionally effected in an inert organic solvent, conveniently an alcohol such as n-butanol. Suitable reaction temperatures are, for example, from 0° C to solvent reflux temperature. The reaction may be effected conveniently using a procedure as described hereinafter in the Examples, or analogously.

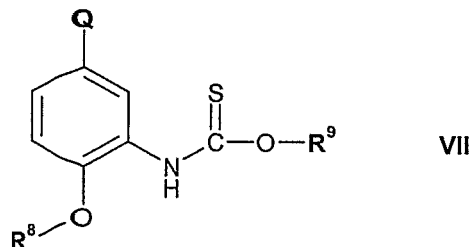
Compounds of formula IV may be prepared by reacting a compound of formula VII



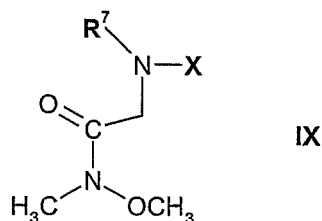
where X, R⁷, R⁸ and R⁹ are as hereinbefore described, with concentrated hydrochloric or hydrobromic acid. The reaction is preferably carried out in an inert organic solvent such as an aliphatic alcohol.

Compounds of formula V and VI may be prepared by known methods or analogously such as hereinafter described in the Examples.

Compounds of formula VII may be prepared by reaction of a compound of formula VIII



where Q is fluorine or chlorine and R^8 and R^9 are as hereinbefore defined, with a strong base, such as an alkyllithium, NaNH_2 or potassium tert-butoxide or a mixture of two or more thereof, and a compound of formula IX

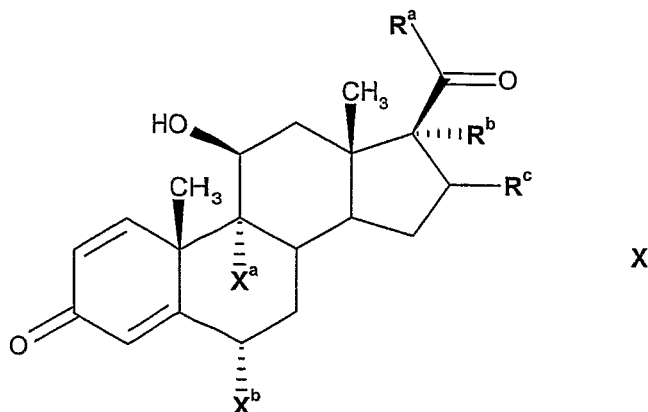


where X and R^7 are as hereinbefore defined. The reaction is preferably effected in an inert organic solvent, for example an ether such as tetrahydrofuran (THF). Suitable reaction temperatures may be, for example, from -80°C to 80°C . The reaction may be effected using a procedure as described hereinafter in the Examples or analogous procedures.

Compounds of formulae VIII and IX may be prepared using known procedures or analogously, such as described hereinafter in the Examples.

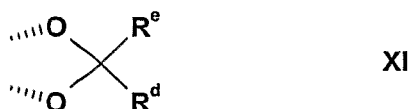
Compounds of formula I in free form may be converted into salt form, and vice versa, in a conventional manner. The compounds in free or salt form can be obtained in the form of hydrates or solvates containing a solvent used for crystallisation. Compounds of formula I can be recovered from reaction mixtures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

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



or a 1,2-dihydro derivative thereof, where

R^a is C_1 - C_4 -alkyl optionally substituted by halogen (preferably chlorine or fluorine), hydroxy, C_1 - C_4 -alkoxy, acyloxy or by C_1 - C_4 -acylthio, or R^a is C_1 - C_4 -alkoxy or C_1 - C_4 -alkylthio optionally substituted by halogen, or R^a is 5- or 6-membered heterocyclylthio, or R^a is C_1 - C_4 -alkylthio optionally substituted by halogen (preferably chlorine or fluorine), either R^b is acyloxy and R^c is hydrogen or C_1 - C_4 -alkyl, or R^b and R^c together denote a group of formula XI



where R^d is C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl and R^e is hydrogen or C_1 - C_4 -alkyl, X^a and X^b are each independently hydrogen, chlorine or fluorine.

When R^a 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^a 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^a is 5- or 6-membered heterocyclylthio, the heterocyclyl group may be an O-heterocyclyl group, for example a furanonyl group.

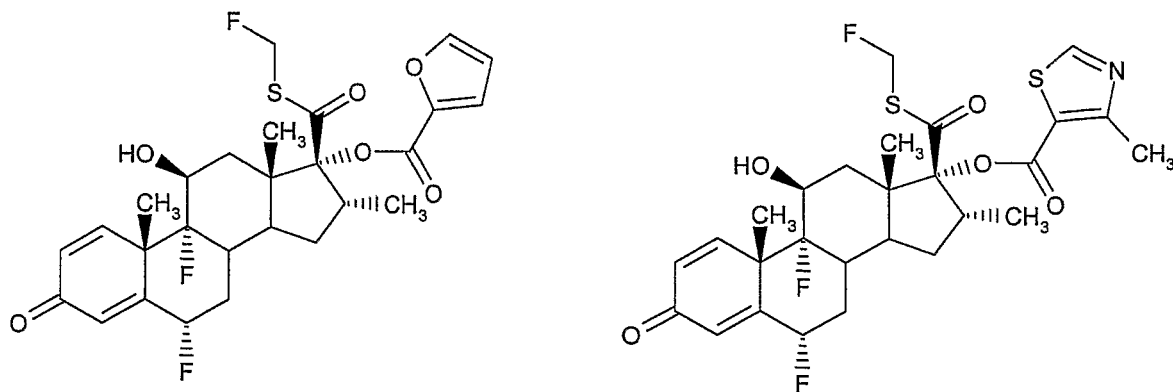
When R^b is acyloxy, it may be, for example, C_1 - C_4 -alkylcarbonyloxy, e.g. acetyloxy, n-propionyloxy, or n-butyroxyloxy, C_3 - C_6 -cycloalkylcarbonyloxy e.g. cyclopropylcarbonyloxy, or 5- or 6-membered heterocyclylcarbonyloxy e.g. furoxyloxy, or when R^b is acyloxy it may be a group $-O-CO-T$ where T is a monovalent cyclic organic group having from 3 to 15 atoms in the ring system. Preferably T is a carbocyclic group or a heterocyclic group having one or more ring hetero atoms selected from nitrogen, oxygen and sulfur.

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

When R^b and R^c together denote a group of formula XI, R^d as C_3 - C_6 -cycloalkyl may be, for example, cyclohexyl.

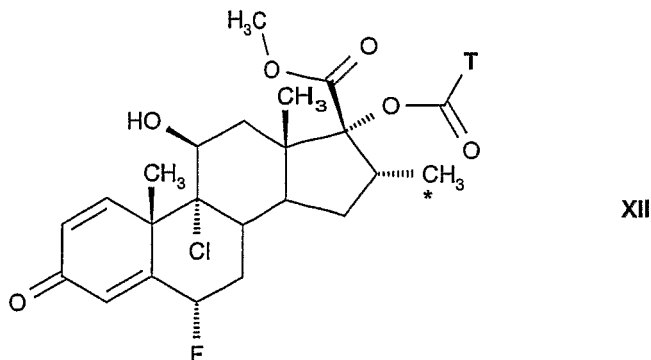
Corticosteroids of formula X and their 1,2-dihydro derivatives include beclamethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide, flunisolide, rofleponide palmitate, butixocort propionate, icometasone enbutate and described in WO 03/042229, WO 03/035668, WO 02/100879, WO 02/088167.

In particularly preferred embodiments of the invention, the corticosteroid (B) is budesonide, fluticasone propionate, mometasone furoate or either of the following compounds:



Budesonide, fluticasone propionate and mometasone furoate and their preparation are described in United States patent specifications US 3929768, US 4335121 and US 4472393 respectively.

Corticosteroids of formula X where R^b is $-O-CO-T$ are preferably compounds of formula XII



where T is a monovalent cyclic organic group having from 3 to 15 atoms in the ring system.

Preferably T is a carbocyclic group or a heterocyclic group having one or more ring hetero atoms selected from nitrogen, oxygen and sulfur.

In one embodiment, T is a cycloaliphatic group having 3 to 8 carbon atoms, for example C₃-C₈-cycloalkyl such as cyclopropyl, methylcyclopropyl, cyclobutyl, methylcyclobutyl, cyclopentyl, cyclohexyl, methylcyclohexyl, dimethylcyclohexyl or cycloheptyl, preferably C₃-C₆-cycloalkyl.

In another embodiment, T is an at least partially saturated heterocyclic group having 5 to 10 ring atoms, of which one or more are ring hetero atoms selected from nitrogen, oxygen and sulfur, preferably having 5 to 7 ring atoms, of which one or two are hetero atoms selected from nitrogen and oxygen, especially a 5-membered heterocyclic group having one ring hetero atom, such as a tetrahydrofuryl or oxotetrahydrofuryl group.

In a further embodiment, T is a carbocyclic or heterocyclic aromatic group having 5 to 15 atoms in the ring system. For example, T may be such an aromatic group in which the ring system is unsubstituted or is substituted by one or more substituents selected from halogen, cyano, C₁-C₄-alkyl, halo-C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, hydroxyl, C₁-C₄-acyl, C₁-C₄-acyloxy, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₁-C₄-acylamino, C₁-C₄-acyl(C₁-C₄-alkyl)-amino, C₁-C₄-alkylsulfonyl(C₁-C₄-alkyl)amino, C₁-C₄-alkoxycarbonyl, or 5-membered heterocyclyl, usually N-heterocyclyl having one or two nitrogen atoms. One preferred class of such aromatic groups is phenyl or naphthyl optionally substituted by one or more, preferably one, two or three, substituents selected from cyano, C₁-C₄-alkyl, halo-C₁-C₄-alkyl, C₁-C₄ alkoxy, halogen, hydroxyl, C₁-C₄-acyloxy, amino, C₁-C₄-alkylamino, di-C₁-C₄-alkylamino, C₁-C₄-acyl-amino, C₁-C₄-acyl(C₁-C₄ alkyl)amino, C₁-C₄ alkylsulfonyl(C₁-C₄ alkyl)amino or C₁-C₄-alkoxy-carbonyl, especially preferred such aromatic groups including phenyl, cyanophenyl, tolyl, dimethylphenyl, ethylphenyl, (trifluoromethyl)phenyl, dimethoxyphenyl, diethoxyphenyl, hydroxyphenyl, (methylamino)phenyl, (methanesulfonylmethylamino)-phenyl and (methoxy-carbonyl)phenyl.

Another preferred class of such aromatic groups 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, C₁-C₄-acyloxy, amino, C₁-C₄-alkylamino, di-(C₁-C₄-alkyl)amino, C₁-C₄-alkyl, hydroxy-C₁-C₄-alkyl, halo-C₁-C₄-alkyl, C₁-C₄-alkoxy, or C₁-C₄-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 C₁-C₄-alkyl (especially methyl or n-butyl).

Another preferred class of such aromatic groups 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, C₁-C₄-alkyl, halo-C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, cyano or hydroxy-C₁-C₄-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), C₁-C₄-alkyl (particularly methyl or ethyl), halo-C₁-C₄-alkyl (particularly trifluoro-methyl), C₁-C₄-alkoxy (particularly methoxy), C₁-C₄-alkylthio (particularly methylthio), cyano or hydroxy-C₁-C₄-alkyl (particularly hydroxymethyl); isoxazolyl, imidazolyl, pyrazolyl, thiazolyl or thiadiazolyl groups optionally substituted by one or two C₁-C₄-alkyl groups; and benzofuryl, benzothienyl and benzofurazanyl groups.

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

Especially preferred compounds of formula XII 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.

The compounds of formula XII and salts thereof where T contains a basic group may be prepared using the procedures described in international patent application WO 02/00679.

The corticosteroid (B) may, for example, also be a non-steroidal glucocorticoid receptor agonist, 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 and WO 04/26248.

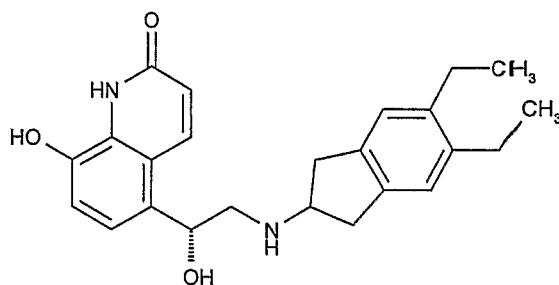
The medicament of the present invention may additionally contain one or more A_{2A} agonists, A_{2B} antagonists, antihistamines, caspase inhibitors, LTB₄ antagonists, LTD₄ antagonists, M₃ antagonists and PDE inhibitors or anti-tussive drug substance.

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. Suitable antihistamine drug substances include cetirizine hydrochloride, acetaminophen, clemastine fumarate, promethazine, loratidine, desloratidine, diphenhydramine and fexofenadine hydrochloride, activastine, astemizole, azelastine, ebastine, epinastine, mizolastine and tefenadine as well as those disclosed in JP 2004107299, WO 03/099807 and WO 04/026841. Suitable caspase inhibitors, including interleukin-1P converting enzyme (ICE) inhibitors, include those that are disclosed in Canadian patent specification 2109646, EP 519748, EP 547699, EP 590650, EP 628550, EP 644197, EP 644198, 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 98/41232, WO 99/06367, WO 99/65451, WO 01/119373, US 5411985, US 5416013, US 5430128, US 5434248, US 5565430, US 5585357, US 5656627, US 5677283, US 6054487, US 6531474, US 20030096737, GB 2,278,276 as well as those disclosed in international patent applications WO 98/10778, WO 98/11109, WO 98/11129 and WO 03/32918. Suitable LTB₄ antagonists include those described in US 5451700. Suitable LTD₄ antagonists include montelukast and zafirlukast. Suitable M₃ antagonists include ipratropium bromide, oxitropium bromide, tiotropium salts, CHF 4226 (Chiesi) and glycopyrrolate, but also those described in EP 424021, US 3714357, US 5171744, 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 04/96800, preferably compounds of the Examples thereof. The M₃ antagonist is most preferably ipratropium bromide, oxitropium bromide or a tiotropium salt. The M₃ antagonist may also be a dual beta-2 adrenoceptor agonist /

muscarinic antagonist such as those disclosed in US 2004/0167167, WO 04/74246 and WO 04/74812. Suitable PDE4 inhibitors include (Ariflo® GSK), Roflumilast (Byk Gulden), V-11294A (Napp), BAY19-8004 (Bayer), SCH-351591 (Schering-Plough), Arofyline (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 04/019945, WO 04/045607 and WO 04/037805.

Although the medicament of the invention contains a compound of formula I that possesses beta-2 adrenoceptor agonist activity the medicament may additionally contain another beta-2 adrenoceptor agonist. Suitable additional such beta-2 adrenoceptor agonists albuterol (salbutamol), metaproterenol, terbutaline, salmeterol fenoterol, procaterol, and especially, formoterol, carmoterol 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 of EP 1440966, JP 05025045, WO 93/18007, WO 99/64035, US 2002/0055651, 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 and WO 04/80964.

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) are in inhalable form. The inhalable form of the medicament 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 (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. The composition may also contain a compound that helps to protect against product performance deterioration due to moisture e.g. magnesium stearate.

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 (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, micro-precipitation, 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 μ l, e.g. 25 to 50 μ l, 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 0642992 A. 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 μ l, 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 (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 (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 US 3991761, while a suitable MDPI device is that described in WO 97/20589.

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

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

A suitable daily dose of the compound (A), particularly as the maleate or trifluoroacetate salt, for inhalation may be from 10 µg to 2000 µg, for example from 10 to 1500 µg, from 10 to 1000 µg, preferably from 20 to 800 µg, e.g. from 20 to 600 µg or from 20 to 500 µg. A suitable daily dose of steroid (B) for inhalation may be from 20 µg to 5000 µg, for example from 20 to 4000 µg, from 50 to 3000 µg, from 50 to 2000 µg, from 50 to 1000 µg, from 50 to 500 µg, from 50 to 400 µg, from 50 to 300 µg, from 50 to 200 µg or from 50 to 100 µg. Where (B) is budesonide, a suitable daily dose may be from 25 to 4800 µg, for example from 25 to 4000 µg, from 25 to 3200 µg, from 25 to 2400 µg, from 25 to 1600 µg, from 50 to 4800 µg, from 50 to 4000 µg, from 50 to 3200 µg, from 50 to 2400 µg, from 50 to 1600 µg, from 100 to 4000 µg, from 100 to 3200 µg, from 100 to 2400 µg, from 100 to 1600 µg, from 100 to 800 µg, from 100 to 400 µg, from 200 to 4000 µg, from 200 to 1600 µg, from 200 to 800 µg or from 200 to 400 µg, 100 to 1600 µg being preferred. Where (B) is mometasone furoate, a suitable daily dose may be from 50 µg to 2000 µg, for example from 100 to 200 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. Where (B) is fluticasone propionate, a suitable daily dose may be for inhalation may be from 25 to 2000 µg, for example from 25 to 1500 µg, from 25 to 1000 µg, from 25 to 500 µg, from 25 to 250 µg, from 50 to 1500 µg, from 50 to 1000 µg, from 50 to 500 µg, from 50 to 250 µg, from 100 to 1500 µg, from 100 to 1000 µg, from 100 to 500 µg, from 100 to 250 µg, from 200 to 1500 µg, from 200 to 1000 µg or from 200 to 500 µg, 100 to 1000 µg being preferred.

A suitable unit dose of compound (A), particularly as the maleate or trifluoroacetate salt, may be from 10 to 2000 µg, for example from 10 to 1500 µg, from 10 to 1000 µg, preferably from 20 to 800 µg, from 20 to 600 µg or from 20 to 500 µg. A suitable unit dose of budesonide may be from 25 to 2400 µg, for example from 50 to 2400 µg, from 50 to 2000 µg, from 50 to 1600 µg, from 50 to 800 µg, from 50 to 400 µg, from 50 to 200 µg, from 100 to 1600 µg, from 100 to 800 µg, from 100 to 400 µg, from 100 to 200 µg, from 200 to 1600 µg, from 200 to 800 µg or from 200 to 400 µg, 100 to 400 µg being preferred. A suitable unit dose of mometasone furoate for inhalation may be from 25 to 2000 µg, for example from 50 µg to 1500 µg, from 50 to 1000 µg, from 50 to 800 µg, from 50 to 400 µg, from 50 to 200 µg, from 50 to 100 µg, from 100 to 800 µg, from 100 to 400 µg or from 100 to 200 µg, 100 to 400 µg being preferred. A suitable unit dose of fluticasone propionate for inhalation may be from 25 to 1000 µg, for example from 25 to 500 µg, from 25 to 250 µg, from 25 to 200 µg, from 50 to 1000 µg, from 50 to 500 µg, from 50 to 250 µg, from 50 to 200 µg, from 100 to 1000 µg,

from 100 to 500 μg , from 100 to 250 μg , from 100 to 200 μg , from 150 to 500 μg or from 150 to 250 μg , 100 to 500 μg 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 50 mg, for example 5 mg, 10 mg, 15 mg, 20 mg, 25 mg, 30 mg, 35 mg, 40 mg, 45 mg or 50 mg.

In another preferred embodiment of the invention, the medicament of the invention is a pharmaceutical composition which is a dry powder for administration from a reservoir of a multi-dose dry powder inhaler adapted to deliver, for example, 3 mg to 25 mg of powder containing a unit dose of (A) and (B) per actuation, for example, where (A) is in the form of the maleate salt, a powder comprising, by weight, 20 to 2000 parts, for example 60 to 1000 parts, 100 to 500 parts, or 100 to 300 parts of (A); 25 to 800 parts, e.g. 25 to 500 parts, 50 to 400 parts, or 100 to 400 parts of (B); and 2000 to 25000 parts, e.g. 4000 to 15000 parts or 4000 to 10000 parts of a pharmaceutically acceptable carrier as hereinbefore described.

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

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

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute/adult lung injury (ALI), adult/acute respiratory distress syndrome (ARDS), cystic fibrosis, 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.

Preparation Example 1: Compound E1

4-hydroxy-7-(1-hydroxy-2-[2-[4-(4-phenyl-butoxy)-phenyl]-ethylamino]-ethyl)-3H-benzothiazol-2-one

Palladium black (0.2 g) is added portion-wise to a solution of 7-[2-(benzyl-[2-[4-(4-phenyl-butoxy)-phenyl]-ethyl]-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one (0.29 g) in formic acid (10 ml) at room temperature. After 1 hour the catalyst is removed by filtration and the filtrate partitioned between $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ and aqueous NaHCO_3 . Evaporation of the $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ layers and recrystallisation from hexane / $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ gives the title compound. MS (ES+) 479.

Preparation Example 2: Compound E2

7-[(R)-2-(1,1-Dimethyl-2-phenyl-ethylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

A solution of (R)-1-(4-tert-Butoxy-2-isopropoxy-benzothiazol-7-yl)-2-(1,1dimethyl-2-phenyl-ethylamino)-ethanol in formic acid (10 ml) is stirred at room temperature. The reaction is shown to be complete by LCMS after 48 hours. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C 18, 0-50% methylcyanide in water (0.1% TFA)) gives the title compound. MS (ES+) *m/e* 359 (MH⁺).

Preparation Example 3: Compound E3

4-Hydroxy-7-[(R)-1-hydroxy-2-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethylamino]-ethyl]-3H-benzothiazol-2-one formate

Palladium black (0.4 g) is added portion-wise to a solution of (R)-2-{benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amino}-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (0.40 g) in formic acid (5 ml) at room temperature. After 24 hours the catalyst is removed by filtration. Evaporation of the formic acid and purification by reverse phase chromatography (ISOLUTE FLASH C18, 0-50% methylcyanide in water (0.1% formic acid)) gives the title compound. MS (ES+) *m/e* 385 (MH⁺).

Preparation Example 4: Compound E4

7-[(R)-2-((1S,2S)-2-Benzyloxy-cyclopentylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

(R)-2-((1S,2S)-2-Benzyloxy-cyclopentylamino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (10 g, 20 mmol) is dissolved in isopropanol (100 ml). 1M HCl (50 ml) is added and the reaction mixture is heated at 80°C for 24 hours. The isopropanol is removed *in vacuo* and

the residue is partitioned between ethyl acetate (50 ml) and sat. NaHCO₃. The organic layer is washed with brine (50 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The title compound is purified by crystallisation from ethanol. MS (ES+) *m/e* 401 (MH⁺).

Preparation Example 5: Compound E5

Example 154: 7-[(R)-2-((1S,2R)-2-Benzoyloxy-cyclopentylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

(R)-2-((1S,2R)-2-Benzoyloxy-cyclopentylamino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol (460 mg, 0.92 mmol) is dissolved in isopropanol (5 ml). 1M HCl (2.5 mL) is added and the reaction mixture is heated at 80°C for 24 hours. The isopropanol is removed *in vacuo* and the residue is partitioned between ethyl acetate (50 ml) and sat. NaHCO₃. The organic layer is washed with brine (50 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the title compound. MS (ES+) *m/e* 401 (MH⁺).

Preparation of intermediate compounds

Certain compounds that are used to prepare compounds of the Examples that are not readily commercially available are prepared as follows:

Tert-butoxy-5-fluoro-phenylamine

A suspension of platinum oxide (17 g) in a solution of 1-tert-butoxy-4-fluoro-2-nitro-benzene (225 g, prepared by procedure T. F. Woiwode et al *J. Org. Chem.* 1998, 63, 9594.) in CH₃OH (1.5 l) is stirred under an atmosphere of hydrogen for 18 hours. Filtration through Celite™ filter material and evaporation gives the title compound. ¹⁹F nmr (CDCl₃, 376 MHz); -43.4.

1-Tert-butoxy-4-fluoro-2-isothiocyanato-benzene

Carbon disulphide (38.6 ml) is added to a solution of 2-tert-butoxy-5-fluoro-phenylamine (58.8 g) and triethylamine (89.5 ml) in toluene (66 ml) and the reaction mixture stirred at room temperature for 18 hours, then evaporated. Chloroform (200 ml) and triethylamine (44.9 ml) are added to the residue, which is cooled before the addition of ethyl chloroformate (30.8 ml). After 15 minutes at 0°C, the reaction mixture is washed sequentially with aqueous 3N HCl, saturated brine, saturated NaHCO₃ and saturated brine, then evaporated to give the title compound. ¹H nmr (CDCl₃, 400 MHz); 7.10-7.03 (m, 1H), 6.93-6.87 (m, 1H), 6.86-6.80 (m, 1H), 1.43 (s, 9H).

(2-Tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester

A solution of 1-tert-butoxy-4-fluoro-2-isothiocyanato-benzene (50.0 g) and triethylamine (31 ml) in isopropanol (170 ml) is refluxed for 48 hours. Evaporation of the reaction mixture followed by silica gel flash column chromatography, eluent 20:1 hexane: $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ gives the title compound. ^1H nmr (CDCl_3 , 400 MHz); 8.60 (br s, 1H), 7.38 (br s, 1H), 7.50-6.87 (m, 1H), 6.67-6.58 (m, 1H), 5.64-5.50 (m, 1H), 1.43-1.32 (m, 6H), 1.32-1.25 (s, 9H).

2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone

A solution of tert. butyl lithium in pentane (12.3 ml, 1.7 M) is added to a solution of (2-tert-butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (3.20 g) in tetrahydrofuran (10 ml) at -78°C , the solution warmed to -20°C over 1 hour then re-cooled -78°C and a solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-N-methoxy-N-methyl-acetamide in tetrahydrofuran (10 ml) added at -78°C . The reaction mixture is warmed to room temperature and partitioned between aqueous NH_4Cl and $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$. Evaporation of the $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$, gives the title compound. MS (ES+) 665.

7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one

A solution of 2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanone (2.49 g) in isopropanol (20 ml) and concentrated hydrobromic acid (20 ml) is heated at 50°C . After 3 hours the reaction mixture is partitioned between $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ and water, and the $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ layer washed with aqueous NaHCO_3 then brine. Evaporation of the $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ layers and silica gel column chromatography, eluent 4:1 hexane: $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$, gives the title compd. MS (ES+) 567.

7-[2-(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one

NaBH_4 (2.67 g) is added portion-wise to a solution of 7-[(benzyl-{2-[4-(4-phenyl-butoxy)-phenyl]-ethyl}-amino)-acetyl]-4-hydroxy-3H-benzothiazol-2-one (0.40 g) in CH_3OH (15 ml) at 0°C . After 30 minutes the reaction mixture is partitioned between $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ and water. Evaporation of the $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$ layers and silica gel column chromatography, eluent 1:1 hexane: $\text{CH}_3\text{CO}_2\text{CH}_2\text{CH}_3$, gives the title compound. MS (ES+) 569.

1-(4-Tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanone

Tert. butyllithium (22.7 ml, 1.7 M in pentane) is added dropwise to a solution of (2-tert. butoxy-5-fluoro-phenyl)-thiocarbamic acid O-isopropyl ester (5.00 g) in THF (20 ml) at -78°C . This solution is then allowed to warm to -20°C and a dried mixture of lithium chloride (2.12 g) and copper (I) cyanide (2.24 g) in THF (50 ml) is added. After 15 minutes chloroacetyl chloride (4.36 g) is added and the reaction mixture allowed to warm to 0°C . This temperature is maintained for 1 hour and then the reaction mixture is quenched by the addition of saturated aqueous NH_4Cl (5 ml). The reaction mixture is partitioned between ethyl acetate (250 ml) and water (250 ml). The organic layer is washed with water (250 ml) and brine (250 ml), dried over MgSO_4 , filtered and the solvent removed in vacuo. The title compound is obtained by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). MS (ES+) m/e 341 (MH^+).

(R)-1-(4-Tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol

Borane-THF complex, (14.64 ml, 1M in THF) is added dropwise to a solution of (1R, 2S)-(+)-1-amino-2-indanol (0.22 g) in THF (50 ml) and the solution is stirred at room temperature for 15 minutes. A solution of 1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol (5.00 g) in THF (50 ml) is then added dropwise over a period of 1 hour. The reaction mixture is stirred at room temperature for a further 15 minutes and then quenched by the addition of 0.2M H_2SO_4 (5 ml). The reaction mixture is partitioned between ethyl acetate (200 ml) and 0.2M H_2SO_4 (200 ml). The organic layer is washed with water (200 ml) and brine (200 ml), dried over MgSO_4 , filtered and the solvent removed in vacuo to give the title compound. MS (ES+) m/e 344 (MH^+).

4-Tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole

A mixture of (R)-1-(4-tert.butoxy-2-isopropoxy-benzothiazol-7-yl)-2-chloro-ethanol (4.70 g) and potassium carbonate (7.48 g) in acetone (250 ml) is refluxed for 48 hours. The reaction mixture is allowed to cool, filtered and the solvent removed in vacuo to give the title compound. MS (ES+) m/e 308 (MH^+).

(R)-2-(Benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

A solution of 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (3.50 g) and benzyl-[2-(5,6,7,8-tetrahydro-naphthalen-2-yl)-ethyl]-amine (3.03 g) in 1-butanol (25 ml) is stirred at 110°C . The reaction is shown to be complete by TLC after 18 hours. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). ^1H nmr (CDCl_3 , 400 MHz); 7.35-7.20 (m, 5H), 7.00-6.95 (m, 3H), 6.90-6.80 (m, 2H),

5.45 (m, 1H), 4.70 (m, 1H), 3.95 (d, 1H), 3.55 (d, 1H), 2.85 (m, 6H), 2.70 (m, 4H), 1.75 (m, 4H), 1.45 (m, 6H), 1.35 (s, 9H).

(R)-1-(4-tert-Butoxy-2-isopropoxy-benzothiazol-7-yl)-2-(1,1dimethyl-2-phenyl-ethylamino)-ethanol

A solution of phentermine (0.728 g, 4.89 mmol) and N,O-bis(trimethylsilyl)acetamide (0.496 g, 2.44 mmol) in dry DMF (1 ml) is stirred at room temperature for 30 minutes. A solution of 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (0.75 g, 2.44 mmol) in dry DMF (1 ml) is added and the reaction mixture is stirred at 80°C. The reaction is shown to be complete by TLC after 18 hours. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 1:1). MS (ES+) *m/e* 457 (MH⁺).

(R)-2-((1S,2S)-2-Benzyloxy-cyclopentylamino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole (13.2 g, 42.94 mmol) and (1S,2S)-2-Benzyloxy-cyclopentylamine (10.68 g, 55.82 mmol) are placed in a flask with Diglyme (40 ml) and the reaction mixture is heated at 115°C. The reaction is shown to be complete by TLC after 17 hours. The reaction mixture is cooled and partitioned between heptane (200 ml) and water (200 ml). The organic layer is dried over MgSO₄, filtered and the solvent removed *in vacuo*. The title compound is purified by crystallisation from isopropanol. MS (ES+) *m/e* 499 (MH⁺).

(1R,2S)-2-Aminocyclopentanol hydrochloride

The title compound is prepared from by the procedure of Schaus, Scott E.; Larrow, Jay F.; Jacobsen, Eric N. Practical Synthesis of Enantiopure Cyclic 1,2-Amino Alcohols via Catalytic Asymmetric Ring Opening of Meso Epoxides. Journal of Organic Chemistry (1997), 62(12), 4197-4199.

(1S,2R)-2-(2-Hydroxy-cyclopentyl)-isoindole-1,3-dione

(1R,2S)-2-Aminocyclopentanol hydrochloride (10 g, 72.73 mmol), phthalic anhydride (10.76 g, 72.73 mmol) and diisopropylamine (11.26 g, 87.27 mmol) are placed in a flask and heated to 130°C. The reaction is shown to be complete by TLC after 2 hours. The reaction mixture is allowed to cool and is partitioned between ethyl acetate (200 ml) and 2M hydrochloric acid (200 ml). The organic layer is washed with water (1000 ml), sat. NaHCO₃ (100 ml) and brine (100 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate

1:1). ¹H nmr (CDCl₃, 400 MHz); 7.85 (m, 2H), 7.70 (m, 2H), 4.50 (m, 1H), 4.30 (m, 1H), 2.95 (d, 1H), 2.45 (m, 1H), 2.00 (m, 3H), 1.85 (m, 1H), 1.60 (m, 1H).

(1S,2R)-2-(2-Benzoyloxy-cyclopentyl)-isoindole-1,3-dione

(1S,2R)-2-(2-Hydroxy-cyclopentyl)-isoindole-1,3-dione (7.50 g, 32.47 mmol) is dissolved in dry DMF (15 ml) under an atmosphere of argon. The solution is cooled to 0°C and sodium hydride (0.78 g, 32.47 mmol) is added. The reaction mixture is stirred at room temperature for 30 minutes and then cooled on ice. Benzyl bromide (6.11 g, 35.71 mmol) is added dropwise and the reaction mixture is stirred at room temperature for 18 hours. The reaction is shown to be complete by TLC. The reaction mixture is partitioned between ethyl acetate (200 ml) and water (200 ml). The organic layer is washed with brine (100 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo*. The title compound is obtained after purification by flash column chromatography (silica, iso-hexane / ethyl acetate 10:1). ¹H nmr (CDCl₃, 400 MHz); 7.80 (m, 2H), 7.65 (m, 2H), 7.10 (m, 5H), 4.65 (q, 1H), 4.50 (d, 1H), 4.35 (d, 1H), 4.00 (q, 1H), 2.70 (m, 1H), 2.00 (m, 4H), 1.50 (m, 1H).

(1S,2R)-2-Benzoyloxy-cyclopentylamine

(1S,2R)-2-(2-Benzoyloxy-cyclopentyl)-isoindole-1,3-dione 5.50 g, 17.13 mmol) is dissolved in EtOH (175 ml). Acetic acid (3.08 g, 51.40 mmol) and hydrazine monohydrate (2.57 g, 51.40 mmol) are added and the reaction mixture is refluxed for 2 hours, allowed to cool, any solids are filtered off and the solvent removed *in vacuo*. The residue is partitioned between ethyl acetate (100 ml) and 2M hydrochloric acid (100 ml). The aqueous layer is basified to pH12 with 2M NaOH and extracted with ethyl acetate (3 x 50 ml). The organic layer is washed with brine (100 ml), dried over MgSO₄, filtered and the solvent removed *in vacuo* to give the title compound. ¹H nmr (CDCl₃, 400 MHz); 7.80 (m, 2H), 7.65 (m, 2H), 7.10 (m, 5H), 4.65 (q, 1H), 4.50 (d, 1H), 4.35 (d, 1H), 4.00 (q, 1H), 2.70 (m, 1H), 2.00 (m, 4H), 1.50 (m, 1H).

(R)-2-((1S,2R)-2-Benzoyloxy-cyclopentylamino)-1-(4-tert-butoxy-2-isopropoxy-benzothiazol-7-yl)-ethanol

This compound is prepared from (R)-1-(4-tert-butoxy-2-isopropoxybenzothiazol-7-yl)-2-chloro-ethanol and (1S,2R)-2-Benzoyloxy-cyclopentylamine using procedures analogous to those used to prepare 4-tert.butoxy-2-isopropoxy-7-(R)-oxiranyl-benzothiazole MS (ES+) *m/e* 499 (MH⁺).

Examples 1-60

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 or EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound E1 and budesonide 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 below:

<u>Example</u>	<u>Compound E1 (Parts)</u>	<u>Budesonide (Parts)</u>	<u>Lactose (Parts)</u>
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 budesonide with mometasone furoate, and using amounts as shown in the following table:

<u>Example</u>	<u>Compound E1 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
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 WO 97/20589 is prepared by mixing Compound E1 and fluticasone propionate 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 below:

<u>Example</u>	<u>Compound E1 (Parts)</u>	<u>FP (Parts)</u>	<u>Lactose (Parts)</u>
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 136-180

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E1 and fluticasone propionate 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 directly above but also containing 0.5% magnesium stearate by weight.

Examples 181-208

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound E1 and mometasone furoate/ fluticasone propionate, 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:

<u>Ex.</u>	<u>Cpd.E1 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
181	2	10	36500	60750	2500	-	70
182	4	10	3410	6340	230	0.3	-
183	8	10	97000	-	2500	-	90
184	10	10	30500	67000	2500	0.5	100

185	12	10	3150	6550	250	1	-
186	14	10	3700	6050	250	0.8	-
187	16	10	3800	5900	230	0.4	-
188	18	10	4700	5050	250	1	-
189	20	20	3600	6150	225	1	-
190	22	20	3500	6200	230	1	-
191	24	20	98000	-	2500	1	-
192	30	20	3900	5900	250	1	-
193	2	20	30000	67000	2250	0.2	90
194	10	20	3500	6200	250	0.5	-
195	14	20	3200	6500	230	1	-
196	18	20	3100	6200	225	0.8	-
197	20	20	3150	6100	225	1	-
198	24	20	30000	60000	2000	0.8	-

<u>Ex.</u>	<u>Cpd.E1 (Parts)</u>	<u>FP (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
199	4	10	34000	63000	2250	0.3	50
200	8	10	92000	-	2500	0.5	70
201	12	10	3000	5500	200	-	-
202	16	10	2500	5000	200	0.3	-
203	20	10	2000	3000	150	0.2	-
204	30	10	2000	2000	150	0.2	-
205	8	20	20000	25000	1500	0.2	-
206	12	20	2500	2500	200	0.2	-
207	20	20	2000	2000	150	0.2	-
208	30	20	20000	20000	1500	0.2	-

Examples 209-244

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

<u>Example</u>	<u>Compound E1 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
209	100	100	4800
210	200	100	4700
211	300	100	4600
212	400	100	4500
213	500	100	4400
214	600	100	4300
215	700	100	4200
216	800	100	4100
217	2000	100	2900
218	100	200	4700
219	200	200	4600
220	300	200	4500

221	400	200	4400
222	500	200	4300
223	600	200	4200
224	700	200	4100
225	800	200	4000
226	1200	200	3600
227	100	400	4500
228	200	400	4400
229	300	400	4300
230	400	400	4200
231	500	400	4100
232	600	400	4000
233	700	400	3900
234	800	400	3800
235	100	100	9800
236	200	100	9700
237	300	100	9600
238	400	100	9500
239	500	100	9400
240	100	200	9700
241	200	200	9600
242	300	200	9500
243	400	200	9400
244	500	200	9300

Examples 245-280

The procedure of Examples 91-135 is repeated, but replacing fluticasone propionate by mometasone furoate, using amounts as shown in the table directly above and including 0.5% magnesium stearate by weight.

Examples 281-317

The procedures of Examples 181-208 is repeated, but using the amounts shown in the following table, the ethanol being omitted in some of the Examples:

<u>Ex.</u>	<u>Cpd.E1</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
281	20	20	5000	-	200	0.5	-
282	40	2	2500	2500	-	-	-
283	75	25	1500	3500	500	-	1
284	20	20	3600	6150	225	-	0.5
285	2	20	30000	67000	-	-	-
286	14	20	3200	6500	1500	-	4

287	20	20	3150	6100	1500	4	-
288	10	20	4700	5050	500	-	0.2
289	60	20	10000	10000	-	-	-
290	60	20	10000	10000	200	-	-
291	60	20	10000	10000	-	0.5	-
292	30	20	8000	12000	-	1	1
293	40	20	5000	15000	500	0.5	0.5
294	50	20	9000	11000	400	0.8	0.2
295	20	20	4600	5000	400	0.4	0.2
296	30	10	20000	25000	-	-	-
297	40	10	20000	30000	-	-	-
298	60	10	35000	65000	-	-	-

<u>Ex.</u>	<u>Cpd.E1</u> <u>(Parts)</u>	<u>FP</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
299	20	10	5000	5000	-	-	1
300	10	10	3650	6350	-	-	1
301	30	10	3200	6800	100	0.5	0.5
302	30	20	7400	7600	100	-	-
303	40	20	8300	6700	200	0.5	-
304	60	20	3100	6900	300	1	-
305	10	10	8000	12000	-	-	-
306	50	20	1600	3400	500	2	0.5

<u>Ex.</u>	<u>Cpd.E1</u> <u>(Parts)</u>	<u>Bud</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
307	10	20	5500	4500	-	-	-
308	2	20	3500	6500	-	-	1
309	1	20	2500	7500	-	-	1
310	20	20	3800	6100	100	0.5	-
311	15	20	3300	6600	100	0.5	0.5
312	30	20	3600	5900	500	4	-
313	40	20	4600	4900	500	3	-
314	30	10	3100	6800	100	0.2	0.5
315	40	10	1400	3100	500	0.2	-
316	60	10	8000	12000	-	-	1
317	80	10	30000	70000	-	-	-

Example 318 – 326

The procedure of Examples 181-208 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:

<u>Ex.</u>	<u>Cpd.E1</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>ST</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
318	60	40	10000	10000	300	4	-

319	60	20	8000	12000	200	8	-
320	50	20	12000	8000	400	10	-
321	40	20	5000	5000	600	2.5	1
322	30	20	3500	6500	-	4	2
323	20	20	6000	4000	-	3	3
324	10	20	4500	5500	100	2	1
325	20	10	4100	5900	50	1	2
326	15	5	1550	3450	200	0.5	1

Examples 327-386

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 or EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound E2 and budesonide which have been ground to a mean particle diameter of 1 to 5µm and lactose monohydrate having a particle diameter below 212 µm, the amounts being as shown in the table below:

<u>Example</u>	<u>Compound E2 (Parts)</u>	<u>Budesonide (Parts)</u>	<u>Lactose (Parts)</u>
327	4	100	19880
328	8	100	19860
329	16	100	19820
330	20	100	19800
331	24	100	19780
332	28	100	19760
333	32	100	19740
334	36	100	19720
335	40	100	19700
336	44	100	19680
337	48	100	19660
338	60	100	19600
339	100	100	19400
340	200	100	18900
341	400	100	17900
342	4	100	24880
343	8	100	24860
344	16	100	24820
345	20	100	24800
346	24	100	24780
347	28	100	24760
348	32	100	24740
349	36	100	24720
350	40	100	24700
351	44	100	24680
352	48	100	24660
353	60	100	24600
354	100	100	24400
355	200	100	23900
356	400	100	22900
357	4	200	14780
358	8	200	14760
359	16	200	14720
360	20	200	14700
361	24	200	14680
362	28	200	14660
363	32	200	14640
364	36	200	14620

365	40	200	14600
366	44	200	14580
367	48	200	14560
368	60	200	14500
369	100	200	14300
370	200	200	13800
371	400	200	12800
372	4	200	24780
373	8	200	24760
374	16	200	24720
375	20	200	24700
376	24	200	24680
377	28	200	24660
378	32	200	24640
379	36	200	24620
380	40	200	24600
381	44	200	24580
382	48	200	24560
383	60	200	24500
384	100	200	24300
385	200	200	23800
386	400	200	22800

Examples 387-416

Examples 327-386 are repeated, but replacing budesonide with mometasone furoate, and using amounts as shown in the following table:

<u>Example</u>	<u>Compound E2 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
387	4	100	24880
388	8	100	24860
389	16	100	24820
390	20	100	24800
391	24	100	24780
392	28	100	24760
393	32	100	24740
394	36	100	24720
395	40	100	24700
396	44	100	24680
397	48	100	24660
398	60	100	24600
399	100	100	24400
400	200	100	23900
401	400	100	22900
402	4	200	14780
403	8	200	14760

404	16	200	14720
405	20	200	14700
406	24	200	14680
407	28	200	14660
408	32	200	14640
409	36	200	14620
410	40	200	14600
411	44	200	14580
412	48	200	14560
413	60	200	14500
414	100	200	14300
415	200	200	13800
416	400	200	12800

Examples 417-461

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E2 and fluticasone propionate which have been ground to a mean particle diameter of 1-5 μ m and lactose monohydrate having a particle diameter below 212 μ m, the amounts being as shown in the table below

<u>Example</u>	<u>Compound E2 (Parts)</u>	<u>FP (Parts)</u>	<u>Lactose (Parts)</u>
417	4	100	4880
418	8	100	4860
419	16	100	4820
420	20	100	4800
421	24	100	4780
422	28	100	4760
423	32	100	4740
424	36	100	4720
425	40	100	4700
426	44	100	4680
427	48	100	4660
428	60	100	4600
429	100	100	4400
430	200	100	3900
431	400	100	2900
432	4	200	9780
433	8	200	9760
434	16	200	9720
435	20	200	9700
436	24	200	9680
437	28	200	9660
438	32	200	9640
439	36	200	9620
440	40	200	9600

441	44	200	9580
442	48	200	9560
443	60	200	9500
444	100	200	9300
445	200	200	8800
446	400	200	7800
447	4	250	14730
448	8	250	14710
449	16	250	14670
450	20	250	14650
451	24	250	14630
452	28	250	14610
453	32	250	14590
454	36	250	14570
455	40	250	14550
456	44	250	14530
457	48	250	14510
458	60	250	14450
459	100	250	14250
460	200	250	13750
461	400	250	12750

Examples 462-506

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E2 and fluticasone propionate which have been ground to a mean particle diameter of 1-5 μ m and lactose monohydrate having a particle diameter below 212 μ m, the amounts being as shown in the table directly above but also containing 1.0% magnesium stearate by weight.

Examples 507-534

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound E2 and mometasone furoate/ fluticasone propionate, 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 as follows:

<u>Ex.</u>	<u>Cpd.E2</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
507	0.5	10	36500	60750	2500	-	70

508	1	10	3410	6340	230	0.3	-
509	2	10	97000	-	2500	-	90
510	2.5	10	30500	67000	2500	0.5	100
511	3	10	3150	6550	250	1	-
512	3.5	10	3700	6050	250	0.8	-
513	4	10	3800	5900	230	0.4	-
514	4.5	10	4700	5050	250	1	-
515	5	20	3600	6150	225	1	-
516	5.5	20	3500	6200	230	1	-
517	6	20	98000	-	2500	1	-
518	6.5	20	3900	5900	250	1	-
519	0.5	20	30000	67000	2250	0.2	90
520	2.5	20	3500	6200	250	0.5	-
521	3.5	20	3200	6500	230	1	-
522	4.5	20	3100	6200	225	0.8	-
523	5	20	3150	6100	225	1	-
524	5.5	20	30000	60000	2000	0.8	-

Ex.	Cpd.E2 (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
525	1	10	34000	63000	2250	0.3	50
526	2	10	92000	-	2500	0.5	70
527	3	10	3000	5500	200	-	-
528	4	10	2500	5000	200	0.3	-
529	5	10	2000	3000	150	0.2	-
530	6	10	2000	2000	150	0.2	-
531	2	20	20000	25000	1500	0.2	-
532	3	20	2500	2500	200	0.2	-
533	5	20	2000	2000	150	0.2	-
534	6	20	20000	20000	1500	0.2	-

Examples 535-570

The procedure of Examples 417-461 is repeated, but replacing fluticasone propionate by mometasone furoate, and using amounts as shown in the following table.

Example	Compound E2 (Parts)	MF (Parts)	Lactose (Parts)
535	20	100	4800
536	40	100	4700
537	60	100	4600
538	80	100	4500
539	100	100	4400
540	120	100	4300
541	140	100	4200
542	160	100	4100
543	400	100	2900

544	20	200	4700
545	40	200	4600
546	60	200	4500
547	80	200	4400
548	100	200	4300
549	120	200	4200
550	140	200	4100
551	160	200	4000
552	240	200	3600
553	20	400	4500
554	40	400	4400
555	60	400	4300
556	80	400	4200
557	100	400	4100
558	120	400	4000
559	140	400	3900
560	160	400	3800
561	20	100	9800
562	40	100	9700
563	60	100	9600
564	80	100	9500
565	100	100	9400
566	20	200	9700
567	40	200	9600
568	60	200	9500
569	80	200	9400
570	100	200	9300

Examples 571-606

The procedure of Examples 417-461 is repeated, but replacing fluticasone propionate by mometasone furoate, using amounts as shown in the table directly above and including 1.0% magnesium stearate by weight.

Examples 607-643

The procedures of Examples 507-534 is repeated, but using the amounts shown in the following table, the ethanol being omitted in some of the Examples:

<u>Ex.</u>	<u>Cpd.E2 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
607	5	20	5000	-	200	0.5	-
608	8	2	2500	2500	-	-	-

609	19	25	1500	3500	500	-	1
610	5	20	3600	6150	225	-	0.5
611	0.5	20	30000	67000	-	-	-
612	3.5	20	3200	6500	1500	-	4
613	5	20	3150	6100	1500	4	-
614	2.5	20	4700	5050	500	-	0.2
615	15	20	10000	10000	-	-	-
616	15	20	10000	10000	200	-	-
617	15	20	10000	10000	-	0.5	-
618	7.5	20	8000	12000	-	1	1
619	10	20	5000	15000	500	0.5	0.5
620	12.5	20	9000	11000	400	0.8	0.2
621	5	20	4600	5000	400	0.4	0.2
622	7.5	10	20000	25000	-	-	-
623	10	10	20000	30000	-	-	-
624	15	10	35000	65000	-	-	-

Ex.	Cpd.E2 (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
625	5	10	5000	5000	-	-	1
626	2.5	10	3650	6350	-	-	1
627	7.5	10	3200	6800	100	0.5	0.5
628	7.5	20	7400	7600	100	-	-
629	10	20	8300	6700	200	0.5	-
630	15	20	3100	6900	300	1	-
631	2.5	10	8000	12000	-	-	-
632	12.5	20	1600	3400	500	2	0.5

Ex.	Cpd.E2 (Parts)	Bud (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
633	2.5	20	5500	4500	-	-	-
634	0.5	20	3500	6500	-	-	1
635	0.25	20	2500	7500	-	-	1
636	5	20	3800	6100	100	0.5	-
637	3.75	20	3300	6600	100	0.5	0.5
638	7.5	20	3600	5900	500	4	-
639	10	20	4600	4900	500	3	-
640	7.5	10	3100	6800	100	0.2	0.5
641	10	10	1400	3100	500	0.2	-
642	15	10	8000	12000	-	-	1
643	20	10	30000	70000	-	-	-

Example 644 – 652

The procedure of Examples 507-534 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.E2 (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	ST (Parts)	Lactose (Parts)
644	15	40	10000	10000	300	4	-
645	15	20	8000	12000	200	8	-
646	12.5	20	12000	8000	400	10	-
647	10	20	5000	5000	600	2.5	1
648	7.5	20	3500	6500	-	4	2
649	5	20	6000	4000	-	3	3
650	2.5	20	4500	5500	100	2	1
651	5	10	4100	5900	50	1	2
652	3.75	5	1550	3450	200	0.5	1

Examples 653-712

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 or EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound E3 and budesonide which have been ground to a mean particle diameter of 1 to 5 μ m and lactose monohydrate having a particle diameter below 212 μ m, the amounts being as shown in the table below:

Example	Compound E3 (Parts)	Budesonide (Parts)	Lactose (Parts)
653	20	100	19880
654	40	100	19860
655	80	100	19820
656	100	100	19800
657	120	100	19780
658	140	100	19760
659	160	100	19740
660	180	100	19720
661	200	100	19700
662	220	100	19680
663	240	100	19660
664	300	100	19600
665	500	100	19400
666	1000	100	18900
667	2000	100	17900
668	20	100	24880
669	40	100	24860
670	80	100	24820
671	100	100	24800
672	120	100	24780
673	140	100	24760
674	160	100	24740

675	180	100	24720
676	200	100	24700
677	220	100	24680
678	240	100	24660
679	300	100	24600
680	500	100	24400
681	1000	100	23900
682	2000	100	22900
683	20	200	14780
684	40	200	14760
685	80	200	14720
686	100	200	14700
687	120	200	14680
688	140	200	14660
689	160	200	14640
690	180	200	14620
691	200	200	14600
692	220	200	14580
693	240	200	14560
694	300	200	14500
695	500	200	14300
696	1000	200	13800
697	2000	200	12800
698	20	200	24780
699	40	200	24760
700	80	200	24720
701	100	200	24700
702	120	200	24680
703	140	200	24660
704	160	200	24640
705	180	200	24620
706	200	200	24600
707	220	200	24580
708	240	200	24560
709	300	200	24500
710	500	200	24300
711	1000	200	23800
712	2000	200	22800

Examples 713-742

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

<u>Example</u>	<u>Compound E3</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
713	20	100	24880

714	40	100	24860
715	80	100	24820
716	100	100	24800
717	120	100	24780
718	140	100	24760
719	160	100	24740
720	180	100	24720
721	200	100	24700
722	220	100	24680
723	240	100	24660
724	300	100	24600
725	500	100	24400
726	1000	100	23900
727	2000	100	22900
728	20	200	14780
729	40	200	14760
730	80	200	14720
731	100	200	14700
732	120	200	14680
733	140	200	14660
734	160	200	14640
735	180	200	14620
736	200	200	14600
737	220	200	14580
738	240	200	14560
739	300	200	14500
740	500	200	14300
741	1000	200	13800
742	2000	200	12800

Examples 743-787

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E3 and fluticasone propionate 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 below

<u>Example</u>	<u>Compound E3 (Parts)</u>	<u>FP (Parts)</u>	<u>Lactose (Parts)</u>
743	20	100	4880
744	40	100	4860
745	80	100	4820
746	100	100	4800
747	120	100	4780
748	140	100	4760
749	160	100	4740

750	180	100	4720
751	200	100	4700
752	220	100	4680
753	240	100	4660
754	300	100	4600
755	500	100	4400
756	1000	100	3900
757	2000	100	2900
758	20	200	9780
759	40	200	9760
760	80	200	9720
761	100	200	9700
762	120	200	9680
763	140	200	9660
764	160	200	9640
765	180	200	9620
766	200	200	9600
767	220	200	9580
768	240	200	9560
769	300	200	9500
770	500	200	9300
771	1000	200	8800
772	2000	200	7800
773	20	250	14730
774	40	250	14710
775	80	250	14670
776	100	250	14650
777	120	250	14630
778	140	250	14610
779	160	250	14590
780	180	250	14570
781	200	250	14550
782	220	250	14530
783	240	250	14510
784	300	250	14450
785	500	250	14250
786	1000	250	13750
787	2000	250	12750

Examples 788-832

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E3 and fluticasone propionate which have been ground to a mean particle diameter of 1-5 μm and lactose monohydrate having a particle diameter below 21.2 μm , the amounts being as shown in the table directly above but also containing 0.5% magnesium stearate by weight.

Examples 833-860

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound E3 and mometasone furoate/ fluticasone propionate, 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.E3 (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
833	2	10	36500	60750	2500	-	70
834	4	10	3410	6340	230	0.3	-
835	8	10	97000	-	2500	-	90
836	10	10	30500	67000	2500	0.5	100
837	12	10	3150	6550	250	1	-
838	14	10	3700	6050	250	0.8	-
839	16	10	3800	5900	230	0.4	-
840	18	10	4700	5050	250	1	-
841	20	20	3600	6150	225	1	-
842	22	20	3500	6200	230	1	-
843	24	20	98000	-	2500	1	-
844	30	20	3900	5900	250	1	-
845	2	20	30000	67000	2250	0.2	90
846	10	20	3500	6200	250	0.5	-
847	14	20	3200	6500	230	1	-
848	18	20	3100	6200	225	0.8	-
849	20	20	3150	6100	225	1	-
850	24	20	30000	60000	2000	0.8	-

Ex.	Cpd.E3 (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
851	4	10	34000	63000	2250	0.3	50
852	8	10	92000	-	2500	0.5	70
853	12	10	3000	5500	200	-	-
854	16	10	2500	5000	200	0.3	-
855	20	10	2000	3000	150	0.2	-
856	30	10	2000	2000	150	0.2	-
857	8	20	20000	25000	1500	0.2	-
858	12	20	2500	2500	200	0.2	-
859	20	20	2000	2000	150	0.2	-
860	30	20	20000	20000	1500	0.2	-

Examples 861-896

The procedure of Examples 743-787 is repeated, but replacing fluticasone propionate by mometasone furoate, and using amounts as shown in the following table:

<u>Example</u>	<u>Compound E3 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
861	100	100	4800
862	200	100	4700
863	300	100	4600
864	400	100	4500
865	500	100	4400
866	600	100	4300
867	700	100	4200
868	800	100	4100
869	2000	100	2900
870	100	200	4700
871	200	200	4600
872	300	200	4500
873	400	200	4400
874	500	200	4300
875	600	200	4200
876	700	200	4100
877	800	200	4000
878	1200	200	3600
879	100	400	4500
880	200	400	4400
881	300	400	4300
882	400	400	4200
883	500	400	4100
884	600	400	4000
885	700	400	3900
886	800	400	3800
887	100	100	9800
888	200	100	9700
889	300	100	9600
890	400	100	9500
891	500	100	9400
892	100	200	9700
893	200	200	9600
894	300	200	9500
895	400	200	9400
896	500	200	9300

Examples 897-932

The procedure of Examples 743-787 is repeated, but replacing fluticasone propionate by mometasone furoate, using amounts as shown in the table directly above and including 0.5% magnesium stearate by weight.

Examples 933-969

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:

<u>Ex.</u>	<u>Cpd.E3</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
933	20	20	5000	-	200	0.5	-
934	40	2	2500	2500	-	-	-
935	75	25	1500	3500	500	-	1
936	20	20	3600	6150	225	-	0.5
937	2	20	30000	67000	-	-	-
938	14	20	3200	6500	1500	-	4
939	20	20	3150	6100	1500	4	-
940	10	20	4700	5050	500	-	0.2
941	60	20	10000	10000	-	-	-
942	60	20	10000	10000	200	-	-
943	60	20	10000	10000	-	0.5	-
944	30	20	8000	12000	-	1	1
945	40	20	5000	15000	500	0.5	0.5
946	50	20	9000	11000	400	0.8	0.2
947	20	20	4600	5000	400	0.4	0.2
948	30	10	20000	25000	-	-	-
949	40	10	20000	30000	-	-	-
950	60	10	35000	65000	-	-	-

<u>Ex.</u>	<u>Cpd.E3</u> <u>(Parts)</u>	<u>FP</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
951	20	10	5000	5000	-	-	1
952	10	10	3650	6350	-	-	1
953	30	10	3200	6800	100	0.5	0.5
954	30	20	7400	7600	100	-	-
955	40	20	8300	6700	200	0.5	-
956	60	20	3100	6900	300	1	-
957	10	10	8000	12000	-	-	-
958	50	20	1600	3400	500	2	0.5

<u>Ex.</u>	<u>Cpd.E3</u> <u>(Parts)</u>	<u>Bud</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
------------	---------------------------------	------------------------------	----------------------------------	---------------------------------	----------------------------------	-----------------------------	----------------------------------

959	10	20	5500	4500	-	-	-
960	2	20	3500	6500	-	-	1
961	1	20	2500	7500	-	-	1
962	20	20	3800	6100	100	0.5	-
963	15	20	3300	6600	100	0.5	0.5
964	30	20	3600	5900	500	4	-
965	40	20	4600	4900	500	3	-
966	30	10	3100	6800	100	0.2	0.5
967	40	10	1400	3100	500	0.2	-
968	60	10	8000	12000	-	-	1
969	80	10	30000	70000	-	-	-

Example 970 – 978

The procedure of Examples 833-860 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:

<u>Ex.</u>	<u>Cpd.E3 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>ST (Parts)</u>	<u>Lactose (Parts)</u>
970	60	40	10000	10000	300	4	-
971	60	20	8000	12000	200	8	-
972	50	20	12000	8000	400	10	-
973	40	20	5000	5000	600	2.5	1
974	30	20	3500	6500	-	4	2
975	20	20	6000	4000	-	3	3
976	10	20	4500	5500	100	2	1
977	20	10	4100	5900	50	1	2
978	15	5	1550	3450	200	0.5	1

Examples 979-1038

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 or EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound E4 and budesonide 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 below:

<u>Example</u>	<u>Compound E4 (Parts)</u>	<u>Budesonide (Parts)</u>	<u>Lactose (Parts)</u>
979	10	100	19880
980	20	100	19860
981	40	100	19820

982	50	100	19800
983	60	100	19780
984	70	100	19760
985	80	100	19740
986	90	100	19720
987	100	100	19700
988	110	100	19680
989	120	100	19660
990	150	100	19600
991	250	100	19400
992	500	100	18900
993	1000	100	17900
994	10	100	24880
995	20	100	24860
996	40	100	24820
997	50	100	24800
998	60	100	24780
999	70	100	24760
1000	80	100	24740
1001	90	100	24720
1002	100	100	24700
1003	110	100	24680
1004	120	100	24660
1005	150	100	24600
1006	250	100	24400
1007	500	100	23900
1008	1000	100	22900
1009	10	200	14780
1010	20	200	14760
1011	40	200	14720
1012	50	200	14700
1013	60	200	14680
1014	70	200	14660
1015	80	200	14640
1016	90	200	14620
1017	100	200	14600
1018	110	200	14580
1019	120	200	14560
1020	150	200	14500
1021	250	200	14300
1022	500	200	13800
1023	1000	200	12800
1024	10	200	24780
1025	20	200	24760
1026	40	200	24720
1027	50	200	24700
1028	60	200	24680
1029	70	200	24660
1030	80	200	24640
1031	90	200	24620
1032	100	200	24600

1033	110	200	24580
1034	120	200	24560
1035	150	200	24500
1036	250	200	24300
1037	500	200	23800
1038	1000	200	22800

Examples 1039-1068

Examples 979-1038 are repeated, but replacing budesonide with mometasone furoate, and using amounts as shown in the following table:

<u>Example</u>	<u>Compound E4 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
1039	10	100	24880
1040	20	100	24860
1041	40	100	24820
1042	50	100	24800
1043	60	100	24780
1044	70	100	24760
1045	80	100	24740
1046	90	100	24720
1047	100	100	24700
1048	110	100	24680
1049	120	100	24660
1050	150	100	24600
1051	250	100	24400
1052	500	100	23900
1053	1000	100	22900
1054	10	200	14780
1055	20	200	14760
1056	40	200	14720
1057	50	200	14700
1058	60	200	14680
1059	70	200	14660
1060	80	200	14640
1061	90	200	14620
1062	100	200	14600
1063	110	200	14580
1064	120	200	14560
1065	150	200	14500
1066	250	200	14300
1067	500	200	13800
1068	1000	200	12800

Examples 1069-1113

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E4 and fluticasone propionate 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 below:

<u>Example</u>	<u>Compound E4 (Parts)</u>	<u>FP (Parts)</u>	<u>Lactose (Parts)</u>
1069	10	100	4880
1070	20	100	4860
1071	40	100	4820
1072	50	100	4800
1073	60	100	4780
1074	70	100	4760
1075	80	100	4740
1076	90	100	4720
1077	100	100	4700
1078	110	100	4680
1079	120	100	4660
1080	150	100	4600
1081	250	100	4400
1082	500	100	3900
1083	1000	100	2900
1084	10	200	9780
1085	20	200	9760
1086	40	200	9720
1087	50	200	9700
1088	60	200	9680
1089	70	200	9660
1090	80	200	9640
1091	90	200	9620
1092	100	200	9600
1093	110	200	9580
1094	120	200	9560
1095	150	200	9500
1096	250	200	9300
1097	500	200	8800
1098	1000	200	7800
1099	10	250	14730
1100	20	250	14710
1101	40	250	14670
1102	50	250	14650
1103	60	250	14630
1104	70	250	14610
1105	80	250	14590
1106	90	250	14570
1107	100	250	14550

1108	110	250	14530
1109	120	250	14510
1110	150	250	14450
1111	250	250	14250
1112	500	250	13750
1113	1000	250	12750

Examples 1114-1158

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in W0 97/20589 is prepared by mixing Compound E4 and fluticasone propionate 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 directly above but also containing 1.0% magnesium stearate by weight.

Examples 1159-1186

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound E4 and mometasone furoate/ fluticasone propionate, 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:

<u>Ex.</u>	<u>Cpd.E4</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>OA</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
1159	1	10	36500	60750	2500	-	70
1160	2	10	3410	6340	230	0.3	-
1161	4	10	97000	-	2500	-	90
1162	5	10	30500	67000	2500	0.5	100
1163	6	10	3150	6550	250	1	-
1164	7	10	3700	6050	250	0.8	-
1165	8	10	3800	5900	230	0.4	-
1166	9	10	4700	5050	250	1	-
1167	10	20	3600	6150	225	1	-
1168	11	20	3500	6200	230	1	-
1169	12	20	98000	-	2500	1	-
1170	13	20	3900	5900	250	1	-
1171	1	20	30000	67000	2250	0.2	90
1172	5	20	3500	6200	250	0.5	-
1173	7	20	3200	6500	230	1	-
1174	9	20	3100	6200	225	0.8	-

1175	10	20	3150	6100	225	1	-
1176	12	20	30000	60000	2000	0.8	-

Ex.	Cpd.E4 (Parts)	FP (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
1177	2	10	34000	63000	2250	0.3	50
1178	4	10	92000	-	2500	0.5	70
1179	6	10	3000	5500	200	-	-
1180	8	10	2500	5000	200	0.3	-
1181	10	10	2000	3000	150	0.2	-
1182	15	10	2000	2000	150	0.2	-
1183	4	20	20000	25000	1500	0.2	-
1184	6	20	2500	2500	200	0.2	-
1185	10	20	2000	2000	150	0.2	-
1186	15	20	20000	20000	1500	0.2	-

Examples 1187-1222

The procedure of Examples 1069-1113 is repeated, but replacing fluticasone propionate by mometasone furoate, and using amounts as shown in the following table.

Example	Compound E4 (Parts)	MF (Parts)	Lactose (Parts)
1187	50	100	4800
1188	100	100	4700
1189	150	100	4600
1190	200	100	4500
1191	250	100	4400
1192	300	100	4300
1193	350	100	4200
1194	400	100	4100
1195	1000	100	2900
1196	50	200	4700
1197	100	200	4600
1198	150	200	4500
1199	200	200	4400
1200	250	200	4300
1201	300	200	4200
1202	350	200	4100
1203	400	200	4000
1204	600	200	3600
1205	50	400	4500
1206	100	400	4400
1207	150	400	4300
1208	200	400	4200
1209	250	400	4100
1210	300	400	4000

1211	350	400	3900
1212	400	400	3800
1213	50	100	9800
1214	100	100	9700
1215	150	100	9600
1216	200	100	9500
1217	250	100	9400
1218	50	200	9700
1219	100	200	9600
1220	150	200	9500
1221	200	200	9400
1222	250	200	9300

Examples 1223-1258

The procedure of Examples 1069-1113 is repeated, but replacing fluticasone propionate by mometasone furoate, using amounts as shown in the table directly above and including 1.0% magnesium stearate by weight.

Examples 1259-1295

The procedures of Examples 1159-1186 is repeated, but using the amounts shown in the following table, the ethanol being omitted in some of the Examples:

Ex.	Cpd.E4 (Parts)	MF (Parts)	HFA134a (Parts)	HFA227 (Parts)	Ethanol (Parts)	OA (Parts)	Lactose (Parts)
1259	10	20	5000	-	200	0.5	-
1260	20	2	2500	2500	-	-	-
1261	37	25	1500	3500	500	-	1
1262	10	20	3600	6150	225	-	0.5
1263	1	20	30000	67000	-	-	-
1264	7	20	3200	6500	1500	-	4
1265	20	20	3150	6100	1500	4	-
1266	5	20	4700	5050	500	-	0.2
1267	30	20	10000	10000	-	-	-
1268	30	20	10000	10000	200	-	-
1269	30	20	10000	10000	-	0.5	-
1270	15	20	8000	12000	-	1	1
1271	20	20	5000	15000	500	0.5	0.5
1272	25	20	9000	11000	400	0.8	0.2
1273	10	20	4600	5000	400	0.4	0.2
1274	15	10	20000	25000	-	-	-
1275	20	10	20000	30000	-	-	-
1276	30	10	35000	65000	-	-	-

<u>Ex.</u>	<u>Cpd.E4 (Parts)</u>	<u>FP (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1277	10	10	5000	5000	-	-	1
1278	5	10	3650	6350	-	-	1
1279	15	10	3200	6800	100	0.5	0.5
1280	15	20	7400	7600	100	-	-
1281	20	20	8300	6700	200	0.5	-
1282	30	20	3100	6900	300	1	-
1283	5	10	8000	12000	-	-	-
1284	25	20	1600	3400	500	2	0.5

<u>Ex.</u>	<u>Cpd.E4 (Parts)</u>	<u>Bud (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1285	5	20	5500	4500	-	-	-
1286	1	20	3500	6500	-	-	1
1287	0.5	20	2500	7500	-	-	1
1288	10	20	3800	6100	100	0.5	-
1289	7.5	20	3300	6600	100	0.5	0.5
1290	15	20	3600	5900	500	4	-
1291	20	20	4600	4900	500	3	-
1292	15	10	3100	6800	100	0.2	0.5
1293	20	10	1400	3100	500	0.2	-
1294	30	10	8000	12000	-	-	1
1295	40	10	30000	70000	-	-	-

Example 1296 – 1304

The procedure of Examples 1159-1186 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:

<u>Ex.</u>	<u>Cpd.E4 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>ST (Parts)</u>	<u>Lactose (Parts)</u>
1296	30	40	10000	10000	300	4	-
1297	30	20	8000	12000	200	8	-
1298	25	20	12000	8000	400	10	-
1299	20	20	5000	5000	600	2.5	1
1300	15	20	3500	6500	-	4	2
1301	10	20	6000	4000	-	3	3
1302	5	20	4500	5500	100	2	1
1303	10	10	4100	5900	50	1	2
1304	7.5	5	1550	3450	200	0.5	1

Examples 1305-1364

Gelatin capsules suitable for use in a capsule inhaler such as that described in US 3991761 or EP 1270034 are prepared, each capsule containing a dry powder obtained by mixing Compound E5 and budesonide which have been ground to a mean particle diameter of 1 to 5µm and lactose monohydrate having a particle diameter below 212 µm, the amounts being as shown in the table below:

<u>Example</u>	<u>Compound E5 (Parts)</u>	<u>Budesonide (Parts)</u>	<u>Lactose (Parts)</u>
1305	20	100	19880
1306	40	100	19860
1307	80	100	19820
1308	100	100	19800
1309	120	100	19780
1310	140	100	19760
1311	160	100	19740
1312	180	100	19720
1313	200	100	19700
1314	220	100	19680
1315	240	100	19660
1316	300	100	19600
1317	500	100	19400
1318	1000	100	18900
1319	2000	100	17900
1320	20	100	24880
1321	40	100	24860
1322	80	100	24820
1323	100	100	24800
1324	120	100	24780
1325	140	100	24760
1326	160	100	24740
1327	180	100	24720
1328	200	100	24700
1329	220	100	24680
1330	240	100	24660
1331	300	100	24600
1332	500	100	24400
1333	1000	100	23900
1334	2000	100	22900
1335	20	200	14780
1336	40	200	14760
1337	80	200	14720
1338	100	200	14700
1339	120	200	14680
1340	140	200	14660
1341	160	200	14640
1342	180	200	14620

1343	200	200	14600
1344	220	200	14580
1345	240	200	14560
1346	300	200	14500
1347	500	200	14300
1348	1000	200	13800
1349	2000	200	12800
1350	20	200	24780
1351	40	200	24760
1352	80	200	24720
1353	100	200	24700
1354	120	200	24680
1355	140	200	24660
1356	160	200	24640
1357	180	200	24620
1358	200	200	24600
1359	220	200	24580
1360	240	200	24560
1361	300	200	24500
1362	500	200	24300
1363	1000	200	23800
1364	2000	200	22800

Examples 1365-1394

Examples 1305-1364 are repeated, but replacing budesonide with mometasone furoate, and using amounts as shown in the following table:

<u>Example</u>	<u>Compound E5 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
1365	20	100	24880
1366	40	100	24860
1367	80	100	24820
1368	100	100	24800
1369	120	100	24780
1370	140	100	24760
1371	160	100	24740
1372	180	100	24720
1373	200	100	24700
1374	220	100	24680
1375	240	100	24660
1376	300	100	24600
1377	500	100	24400
1378	1000	100	23900
1379	2000	100	22900
1380	20	200	14780
1381	40	200	14760

1382	80	200	14720
1383	100	200	14700
1384	120	200	14680
1385	140	200	14660
1386	160	200	14640
1387	180	200	14620
1388	200	200	14600
1389	220	200	14580
1390	240	200	14560
1391	300	200	14500
1392	500	200	14300
1393	1000	200	13800
1394	2000	200	12800

Examples 1395-1439

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E5 and fluticasone propionate 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 below:

<u>Example</u>	<u>Compound E5 (Parts)</u>	<u>FP (Parts)</u>	<u>Lactose (Parts)</u>
1395	20	100	4880
1396	40	100	4860
1397	80	100	4820
1398	100	100	4800
1399	120	100	4780
1400	140	100	4760
1401	160	100	4740
1402	180	100	4720
1403	200	100	4700
4104	220	100	4680
1405	240	100	4660
1406	300	100	4600
1407	500	100	4400
1408	1000	100	3900
1409	2000	100	2900
1410	20	200	9780
1411	40	200	9760
1412	80	200	9720
1413	100	200	9700
1414	120	200	9680
1415	140	200	9660
1416	160	200	9640
1417	180	200	9620

1418	200	200	9600
1419	220	200	9580
1420	240	200	9560
1421	300	200	9500
1422	500	200	9300
1423	1000	200	8800
1424	2000	200	7800
1425	20	250	14730
1426	40	250	14710
1427	80	250	14670
1428	100	250	14650
1429	120	250	14630
1430	140	250	14610
1431	160	250	14590
1432	180	250	14570
1433	200	250	14550
1434	220	250	14530
1435	240	250	14510
1436	300	250	14450
1437	500	250	14250
1438	1000	250	13750
1439	2000	250	12750

Examples 1440-1484

A dry powder suitable for delivery from the reservoir of the multi-dose inhaler described in WO 97/20589 is prepared by mixing Compound E5 and fluticasone propionate 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 directly above but also containing 0.5% magnesium stearate by weight.

Examples 1485-1512

Aerosol formulations are prepared by dispensing micronised active ingredients, Compound E5 and mometasone furoate/ fluticasone propionate, 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:

<u>Ex.</u>	<u>Cpd.E5 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1485	2	10	36500	60750	2500	-	70
1486	4	10	3410	6340	230	0.3	-
1487	8	10	97000	-	2500	-	90
1488	10	10	30500	67000	2500	0.5	100
1489	12	10	3150	6550	250	1	-
1490	14	10	3700	6050	250	0.8	-
1491	16	10	3800	5900	230	0.4	-
1492	18	10	4700	5050	250	1	-
1493	20	20	3600	6150	225	1	-
1494	22	20	3500	6200	230	1	-
1495	24	20	98000	-	2500	1	-
1496	30	20	3900	5900	250	1	-
1497	2	20	30000	67000	2250	0.2	90
1498	10	20	3500	6200	250	0.5	-
1499	14	20	3200	6500	230	1	-
1500	18	20	3100	6200	225	0.8	-
1501	20	20	3150	6100	225	1	-
1502	24	20	30000	60000	2000	0.8	-

<u>Ex.</u>	<u>Cpd.E5 (Parts)</u>	<u>FP (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1503	4	10	34000	63000	2250	0.3	50
1504	8	10	92000	-	2500	0.5	70
1505	12	10	3000	5500	200	-	-
1506	16	10	2500	5000	200	0.3	-
1507	20	10	2000	3000	150	0.2	-
1508	30	10	2000	2000	150	0.2	-
1509	8	20	20000	25000	1500	0.2	-
1510	12	20	2500	2500	200	0.2	-
1511	20	20	2000	2000	150	0.2	-
1512	30	20	20000	20000	1500	0.2	-

Examples 1513-1548

The procedure of Examples 1395-1439 is repeated, but replacing fluticasone propionate by mometasone furoate, and using amounts as shown in the following table.

<u>Example</u>	<u>Compound E5 (Parts)</u>	<u>MF (Parts)</u>	<u>Lactose (Parts)</u>
1513	100	100	4800
1514	200	100	4700
1515	300	100	4600
1516	400	100	4500
1517	500	100	4400
1518	600	100	4300

1519	700	100	4200
1520	800	100	4100
1521	2000	100	2900
1522	100	200	4700
1523	200	200	4600
1524	300	200	4500
1525	400	200	4400
1526	500	200	4300
1527	600	200	4200
1528	700	200	4100
1529	800	200	4000
1530	1200	200	3600
1531	100	400	4500
1532	200	400	4400
1533	300	400	4300
1534	400	400	4200
1535	500	400	4100
1536	600	400	4000
1537	700	400	3900
1538	800	400	3800
1539	100	100	9800
1540	200	100	9700
1541	300	100	9600
1542	400	100	9500
1543	500	100	9400
1544	100	200	9700
1545	200	200	9600
1546	300	200	9500
1547	400	200	9400
1548	500	200	9300

Examples 1549-1584

The procedure of Examples 1395-1439 is repeated, but replacing fluticasone propionate by mometasone furoate, using amounts as shown in the table directly above and including 0.5% magnesium stearate by weight.

Examples 1585-1621

The procedures of Examples 1485-1512 is repeated, but using the amounts shown in the following table, the ethanol being omitted in some of the Examples:

<u>Ex.</u>	<u>Cpd.E5 (Parts)</u>	<u>MF (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1585	20	20	5000	-	200	0.5	-
1586	40	2	2500	2500	-	-	-
1587	75	25	1500	3500	500	-	1
1588	20	20	3600	6150	225	-	0.5
1589	2	20	30000	67000	-	-	-
1590	14	20	3200	6500	1500	-	4
1591	20	20	3150	6100	1500	4	-
1592	10	20	4700	5050	500	-	0.2
1593	60	20	10000	10000	-	-	-
1594	60	20	10000	10000	200	-	-
1595	60	20	10000	10000	-	0.5	-
1596	30	20	8000	12000	-	1	1
1597	40	20	5000	15000	500	0.5	0.5
1598	50	20	9000	11000	400	0.8	0.2
1599	20	20	4600	5000	400	0.4	0.2
1600	30	10	20000	25000	-	-	-
1601	40	10	20000	30000	-	-	-
1602	60	10	35000	65000	-	-	-

<u>Ex.</u>	<u>Cpd.E5 (Parts)</u>	<u>FP (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1603	20	10	5000	5000	-	-	1
1604	10	10	3650	6350	-	-	1
1605	30	10	3200	6800	100	0.5	0.5
1606	30	20	7400	7600	100	-	-
1607	40	20	8300	6700	200	0.5	-
1608	60	20	3100	6900	300	1	-
1609	10	10	8000	12000	-	-	-
1610	50	20	1600	3400	500	2	0.5

<u>Ex.</u>	<u>Cpd.E5 (Parts)</u>	<u>Bud (Parts)</u>	<u>HFA134a (Parts)</u>	<u>HFA227 (Parts)</u>	<u>Ethanol (Parts)</u>	<u>OA (Parts)</u>	<u>Lactose (Parts)</u>
1611	10	20	5500	4500	-	-	-
1612	2	20	3500	6500	-	-	1
1613	1	20	2500	7500	-	-	1
1614	20	20	3800	6100	100	0.5	-
1615	15	20	3300	6600	100	0.5	0.5
1616	30	20	3600	5900	500	4	-
1617	40	20	4600	4900	500	3	-
1618	30	10	3100	6800	100	0.2	0.5
1619	40	10	1400	3100	500	0.2	-
1620	60	10	8000	12000	-	-	1
1621	80	10	30000	70000	-	-	-

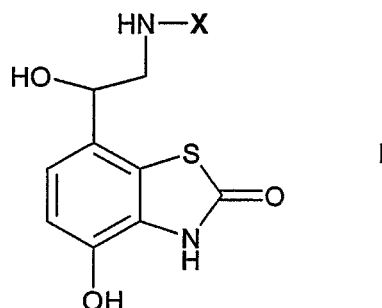
Example 1622 – 1630

The procedure of Examples 1485-1512 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:

<u>Ex.</u>	<u>Cpd.E5</u> <u>(Parts)</u>	<u>MF</u> <u>(Parts)</u>	<u>HFA134a</u> <u>(Parts)</u>	<u>HFA227</u> <u>(Parts)</u>	<u>Ethanol</u> <u>(Parts)</u>	<u>ST</u> <u>(Parts)</u>	<u>Lactose</u> <u>(Parts)</u>
1622	60	40	10000	10000	300	4	-
1623	60	20	8000	12000	200	8	-
1624	50	20	12000	8000	400	10	-
1625	40	20	5000	5000	600	2.5	1
1626	30	20	3500	6500	-	4	2
1627	20	20	6000	4000	-	3	3
1628	10	20	4500	5500	100	2	1
1629	20	10	4100	5900	50	1	2
1630	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 salt or solvate form, wherein

X is $-R^1-Ar-R^2$ or $-R^a-Y$;

Ar denotes a phenylene group optionally substituted by halo, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_1-C_{10} -alkoxy- C_1-C_{10} -alkyl, phenyl, C_1-C_{10} -alkyl substituted by phenyl, C_1-C_{10} -alkoxy substituted by phenyl, C_1-C_{10} -alkyl-substituted phenyl or by C_1-C_{10} -alkoxy-substituted phenyl;

R^1 and R^2 are attached to adjacent carbon atoms in Ar, and
either R^1 is C_1-C_{10} -alkylene and R^2 is hydrogen, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or halogen
or R^1 and R^2 together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C_1-C_{10} -alkylene optionally substituted by hydroxy, C_1-C_{10} -alkoxy, C_6-C_{10} -aryl or C_7-C_{14} -aralkyl; and

Y is C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_2-C_{10} -alkenyl or C_2-C_{10} -alkynyl optionally substituted by halo, cyano, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or halo- C_1-C_{10} -alkyl;
 C_3-C_{10} -cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_3-C_{10} -cycloalkyl, C_7-C_{14} -aralkyl, C_7-C_{14} -aralkyloxy or C_6-C_{10} -aryl, where C_3-C_{10} -cycloalkyl, C_7-C_{14} -aralkyl, C_7-C_{14} -aralkyloxy or C_6-C_{10} -aryl are optionally substituted by halo, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy or halo- C_1-C_{10} -alkyl;

C_6-C_{10} -aryl optionally substituted by halo, hydroxy, C_1-C_{10} -alkyl, C_1-C_{10} -alkoxy, C_1-C_{10} -haloalkyl, phenoxy, C_1-C_{10} -alkylthio, C_6-C_{10} -aryl, 4- to 10- membered heterocyclic

ring having at least one ring nitrogen, oxygen or sulphur atom, or by NR^bR^c where R^b and R^c are each independently $\text{C}_1\text{-C}_{10}$ -alkyl optionally substituted by hydroxy, $\text{C}_1\text{-C}_{10}$ -alkoxy or phenyl or R^b may additionally be hydrogen;

phenoxy optionally substituted by $\text{C}_1\text{-C}_{10}$ -alkyl, $\text{C}_1\text{-C}_{10}$ -alkoxy or by phenyl optionally substituted by $\text{C}_1\text{-C}_{10}$ -alkyl or $\text{C}_1\text{-C}_{10}$ -alkoxy;

a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom, said heterocyclic ring being optionally substituted by halo, $\text{C}_1\text{-C}_{10}$ -alkyl, $\text{C}_1\text{-C}_{10}$ -alkoxy, halo- $\text{C}_1\text{-C}_{10}$ -alkyl, $\text{C}_6\text{-C}_{10}$ -aryl, $\text{C}_7\text{-C}_{14}$ -aralkyl, $\text{C}_7\text{-C}_{14}$ -aralkyloxy, $\text{C}_1\text{-C}_{10}$ -alkoxycarbonyl or a 4- to 10-membered heterocyclyl- $\text{C}_1\text{-C}_{10}$ -alkyl;

$-\text{NR}^d\text{R}^e$ where R^d is hydrogen or $\text{C}_1\text{-C}_{10}$ -alkyl and R^e is $\text{C}_1\text{-C}_{10}$ -alkyl optionally substituted by hydroxy, or R^e is $\text{C}_6\text{-C}_{10}$ -aryl optionally substituted by halo, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen, oxygen or sulphur atom which ring is optionally substituted by phenyl or halo-substituted phenyl or R^e is $\text{C}_6\text{-C}_{10}$ -arylsulfonyl optionally substituted by $\text{C}_1\text{-C}_{10}$ -alkylamino or $\text{di}(\text{C}_1\text{-C}_{10}\text{-alkyl})\text{amino}$;

$-\text{SR}^f$ where R^f is $\text{C}_6\text{-C}_{10}$ -aryl or $\text{C}_7\text{-C}_{14}$ -aralkyl optionally substituted by halo, $\text{C}_1\text{-C}_{10}$ -alkyl, $\text{C}_1\text{-C}_{10}$ -alkoxy or $\text{C}_1\text{-C}_{10}$ -haloalkyl; or

$-\text{CONHR}^g$ where R^g is $\text{C}_1\text{-C}_{10}$ -alkyl, $\text{C}_3\text{-C}_{10}$ -cycloalkyl or $\text{C}_6\text{-C}_{10}$ -aryl; 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 pharmaceutical composition comprising a mixture of effective amounts of (A) and (B) optionally together with at least one pharmaceutically acceptable carrier.

3. A medicament according to claim 1 or 2, in which (A) is a compound of formula I in free or salt or solvate form wherein

X is $-\text{R}^1\text{-Ar-R}^2$ or $-\text{R}^a\text{-Y}$;

Ar denotes a phenylene group optionally substituted by halo, C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy or by C₁-C₁₀-alkoxy substituted by phenyl;

R¹ and R² are attached to adjacent carbon atoms in Ar, and

either R¹ is C₁-C₁₀-alkylene and R² is hydrogen,

or R¹ and R² together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring;

R^a is a bond or C₁-C₁₀-alkylene optionally substituted by hydroxy, C₆-C₁₀-aryl or C₇-C₁₄-aralkyl; and

Y is C₁-C₁₀-alkyl, C₁-C₁₀-alkoxy or C₂-C₁₀-alkynyl; C₃-C₁₀-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C₁-C₁₀-alkyl, C₃-C₁₀-cycloalkyl, C₇-C₁₄-aralkyl, C₇-C₁₄-aralkyloxy optionally substituted by halo, or by C₆-C₁₀-aryl optionally substituted by C₁-C₁₀-alkyl or C₁-C₁₀-alkoxy; C₆-C₁₀-aryl optionally substituted by halo, hydroxy, C₁-C₁₀-alkyl, phenoxy, C₁-C₁₀-alkylthio, C₆-C₁₀-aryl, a 4- to 10-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C₁-C₁₀-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C₁-C₁₀-alkoxy; a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C₁-C₁₀-alkyl, C₆-C₁₀-aryl, C₇-C₁₄-aralkyl, C₁-C₁₀-alkoxycarbonyl or by a 4- to 10-membered heterocyclyl-C₁-C₁₀-alkyl; -NR^dR^e where R^d is hydrogen or C₁-C₁₀-alkyl and R^e is C₁-C₁₀-alkyl, or R^e is a 4- to 10-membered heterocyclic ring having at least one ring nitrogen or oxygen atom which ring is optionally substituted by halo-substituted phenyl or R^e is C₆-C₁₀-arylsulfonyl optionally substituted by di(C₁-C₁₀-alkyl)amino; -SR^f where R^f is C₆-C₁₀-aryl or C₇-C₁₄-aralkyl optionally substituted by halo or C₁-C₁₀-haloalkyl; or -CONHR^g where R^g is C₃-C₁₀-cycloalkyl or C₆-C₁₀-aryl.

4. A medicament according to any preceding claim, in which (A) is a compound of formula I in free or salt or solvate form wherein

X is -R¹-Ar-R² or -R^a-Y;

Ar denotes a phenylene group optionally substituted by halo, C₁-C₄-alkyl, C₁-C₄-alkoxy or by C₁-C₄-alkoxy substituted by phenyl;

R¹ and R² are attached to adjacent carbon atoms in Ar, and

either R¹ is C₁-C₄-alkylene and R² is hydrogen,

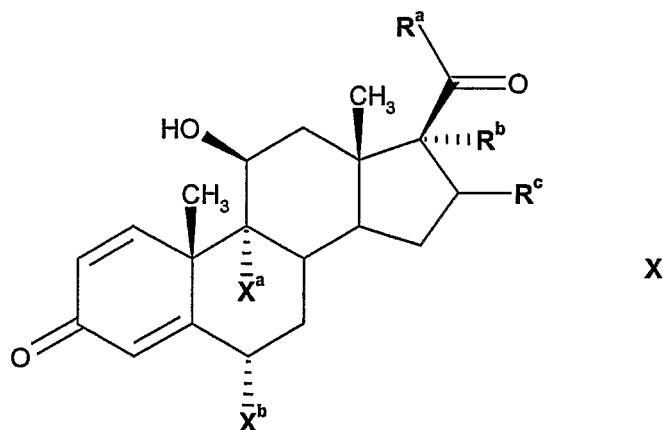
or R¹ and R² together with the carbon atoms in Ar to which they are attached denote a 5-, 6- or 7-membered cycloaliphatic ring, especially a 5-membered cycloaliphatic ring;

R^a is a bond or C₁-C₄-alkylene optionally substituted by hydroxy, C₆-C₈-aryl or C₇-C₁₀-aralkyl; and

Y is C₁-C₄-alkyl, C₁-C₄-alkoxy or C₂-C₄-alkynyl; C₃-C₆-cycloalkyl optionally fused to one or more benzene rings and optionally substituted by C₁-C₆-alkyl, C₃-C₆-cycloalkyl, C₇-C₁₀-aralkyl, C₇-C₁₀-aralkyloxy optionally substituted by halo, or by C₆-C₈-aryl optionally substituted by C₁-C₄-alkyl or C₁-C₄-alkoxy; C₆-C₈-aryl optionally substituted by halo, hydroxy, C₁-C₄-alkyl, phenoxy, C₁-C₄-alkylthio, C₆-C₈-aryl, a 4- to 8-membered heterocyclic ring having at least one ring nitrogen atom, or by NR^bR^c where R^b and R^c are each independently C₁-C₄-alkyl optionally substituted by hydroxy or phenyl or R^b may additionally be hydrogen; phenoxy optionally substituted by C₁-C₄-alkoxy; a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or oxygen atom, said heterocyclic ring being optionally substituted by C₁-C₄-alkyl, C₆-C₈-aryl, C₇-C₁₀-aralkyl, C₁-C₄-alkoxycarbonyl or by a 4- to 8-membered heterocycl- C₁-C₄-alkyl; -NR^dR^e where R^d is hydrogen or C₁-C₄-alkyl and R^e is C₁-C₄-alkyl, or R^e is a 4- to 8-membered heterocyclic ring having at least one ring nitrogen or sulphur atom which ring is optionally substituted by halo-substituted phenyl or R^e is C₆-C₈-arylsulfonyl optionally substituted by di(C₁-C₄-alkyl)amino; -SR^f where R^f is C₆-C₈-aryl or C₇-C₁₀-aralkyl optionally substituted by halo or C₁-C₄-haloalkyl; or -CONHR^g where R^g is C₃-C₆-cycloalkyl or C₆-C₈-aryl.

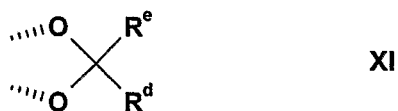
5. A medicament according to any preceding claim, in which (A) is selected from the group consisting of 4-hydroxy-7-(1-hydroxy-2-[2-[4-(4-phenyl-butoxy)-phenyl]-ethylamino]-ethyl)-3H-benzothiazol-2-one; 7-[(R)-2-(1,1-dimethyl-2-phenyl-ethylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzo-thiazol-2-one; 4-hydroxy-7-[(R)-1-hydroxy-2-[2-(5,6,7,8-tetrahydronaphthalen-2-yl)-ethyl-amino]-ethyl]-3H-benzothiazol-2-one formate; 7-[(R)-2-((1S,2S)-2-benzyloxy-cyclopentyl-amino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzo-thiazol-2-one; and 7-[(R)-2-((1S,2R)-2-benzyloxy-cyclopentylamino)-1-hydroxy-ethyl]-4-hydroxy-3H-benzothiazol-2-one.

6. A medicament according to any preceding claim, in which (B) is a compound of formula X



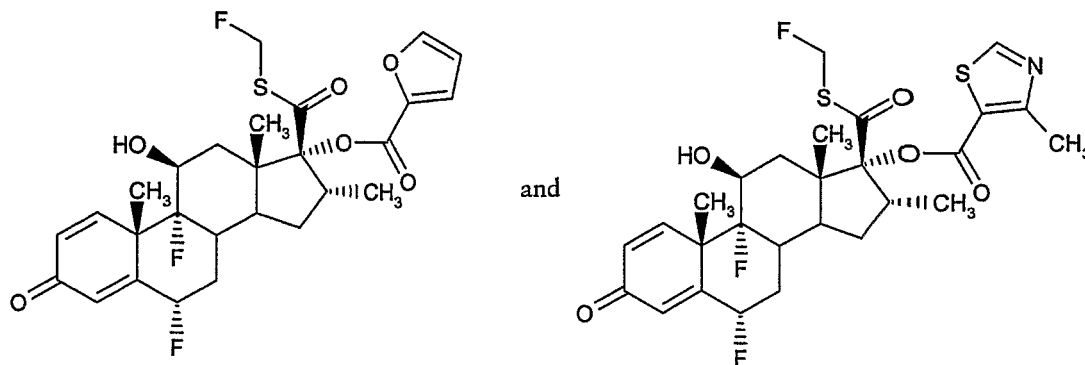
or a 1,2-dihydro derivative thereof, where

R^a is C_1 - C_4 -alkyl optionally substituted by halogen (preferably chlorine or fluorine), hydroxy, C_1 - C_4 -alkoxy, acyloxy or by C_1 - C_4 -acylthio, or R^a is C_1 - C_4 -alkoxy or C_1 - C_4 -alkylthio optionally substituted by halogen, or R^a is 5- or 6-membered heterocyclylthio, or R^a is C_1 - C_4 -alkylthio optionally substituted by halogen (preferably chlorine or fluorine), either R^b is acyloxy and R^c is hydrogen or C_1 - C_4 -alkyl, or R^b and R^c together denote a group of formula XI

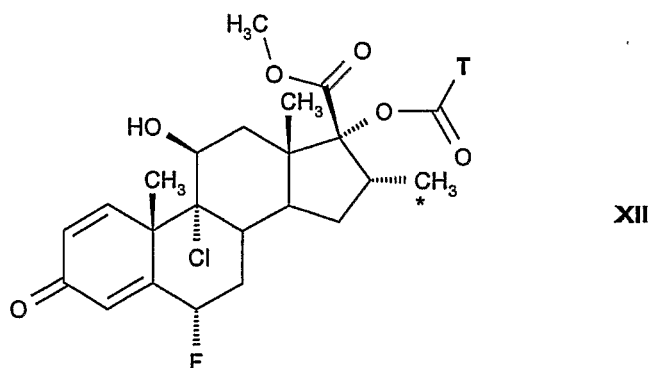


where R^d is C_1 - C_4 -alkyl or C_3 - C_6 -cycloalkyl and R^e is hydrogen or C_1 - C_4 -alkyl, X^a and X^b are each independently hydrogen, chlorine or fluorine.

7. A medicament according to any preceding claim, in which (B) is a compound selected from the group consisting of beclamethasone dipropionate, budesonide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide, flunisolide, rofleponide palmitate, butixocort propionate, icometasone enbutate,



8. A medicament according to any one of claims 1 to 6, in which (B) is a compound of formula XII



where T is a monovalent cyclic organic group having from 3 to 15 atoms in the ring system.

9. A medicament according to claim 8, in which 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, C₁-C₄-alkyl, halo-C₁-C₄-alkyl, C₁-C₄-alkoxy, C₁-C₄-alkylthio, cyano or hydroxy-C₁-C₄-alkyl, and the heterocyclic ring being optionally fused to a benzene ring.
10. A medicament according to claim 8, in which 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, C₁-C₄-alkoxy, amino, C₁-C₄ alkylamino, di-(C₁-C₄-alkyl)amino, C₁-C₄-alkyl, hydroxy-C₁-C₄-alkyl, halo-C₁-C₄-alkyl C₁-C₄-alkoxy, or C₁-C₄-alkylthio and the heterocyclic ring being optionally fused to a benzene ring.
11. A medicament according to claim 8 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.
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; or
 - (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; or
 - (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/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.
14. A medicament according to claim 12 or 13, in which (A) and/or (B) has an average particle diameter up to 10 µm.

15. 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.
16. 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; or
a dry powder comprising, by weight, from 20-2000 parts of (A) in the form of the maleate salt, from 25-800 parts of (B) and 2000-25000 parts of a pharmaceutically acceptable carrier; or
an aerosol comprising (A) and (B) in a ratio as hereinbefore specified in claim 1 or 15, 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.
17. The use of (A) as defined in any preceding claim and (B) as defined in any preceding claim 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 according to claim 17, in which the inflammatory or obstructive airways disease is asthma or chronic obstructive pulmonary disease.
19. A pharmaceutical kit comprising (A) as defined in any one of claims 1, 3, 4 and 5 and (B) as defined in any one of claims 1, 6, 7, 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 compound of formula I as defined in claim; and (B) a corticosteroid, 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/EP2005/001241

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/428 A61K31/58 A61K31/56 A61K31/573 A61P11/06

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)

IPC 7 A61K

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, BIOSIS, EMBASE, WPI Data, CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	WO 99/09018 A (KIRIN BEER KABUSHIKI KAISHA; SUZUKI, HIDEFUMI; SHINDO, KAZUTOSHI; UENO) 25 February 1999 (1999-02-25) claims 1-12 table 5	1-20
Y	SUZUKI H ET AL: "The effects of S1319, a novel marine sponge-derived beta.2-adrenoceptor agonist, on IgE-mediated activation of human cultured mast cells" INFLAMMATION RESEARCH, BIRKHAUSER VERLAG, BASEL, CH, vol. 49, no. 2, 2000, pages 86-94, XP002258317 ISSN: 1023-3830 the whole document	1-20



Further documents are listed in the continuation of box C



Patent family members are listed in annex

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *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
- *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

21 April 2005

Date of mailing of the international search report

29/04/2005

Name and mailing address of the ISA

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

Authorized officer

Giacobbe, S

INTERNATIONAL SEARCH REPORT

International Application No

PCT/EP2005/001241

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SUZUKI H ET AL: "S1319: a novel beta2-adrenoceptor agonist from a marine sponge Dysidea sp" BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, OXFORD, GB, vol. 9, no. 10, 17 May 1999 (1999-05-17), pages 1361-1364, XP004164892 ISSN: 0960-894X the whole document	1-20
Y	----- MCGAVIN J K ET AL: "INHALED BUDESONIDE/FORMOTEROL COMBINATION" DRUGS, ADIS INTERNATIONAL LTD, AT, vol. 61, no. 1, 2001, pages 71-78, XP001013661 ISSN: 0012-6667 the whole document	1-20
Y	----- PALMQVIST M ET AL: "ONSET OF BRONCHODILATION OF BUDESONIDE/FORMOTEROL VS SALMETEROL/FLUTICASONE IN SINGLE INHALERS" PULMONARY PHARMACOLOGY AND THERAPEUTICS, ACADEMIC PRESS, NEW YORK, NY, US, vol. 14, no. 1, 2001, pages 29-34, XP001013120 ISSN: 1094-5539 the whole document	1-20
Y	----- O'CONNOR B ET AL: "DOSE-RANGING STUDY OF MOMETASONE FUROATE DRY POWDER INHALER IN THE TREATMENT OF MODERATE PERSISTENT ASTHMA USING FLUTICASONE PROPIONATE AS AN ACTIVE COMPARATOR" ANNALS OF ALLERGY, ASTHMA & IMMUNOLOGY, ARLINGTON HEIGHTS, IL, US, vol. 86, no. 4, 2001, pages 397-404, XP008012216 ISSN: 1081-1206 abstract	1-20
P,X	----- WO 2004/016601 A (NOVARTIS AG; NOVARTIS PHARMA GMBH; CUENOUD, BERNARD; FAIRHURST, ROBIN,) 26 February 2004 (2004-02-26) the whole document page 18, paragraph 1 - paragraph 3 page 19, line 13 - line 17 page 19, line 21 - line 26 -----	1-20

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP2005/001241

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9909018	A	25-02-1999	WO 9909018 A1	25-02-1999
WO 2004016601	A	26-02-2004	AU 2003255400 A1	03-03-2004
			CA 2493765 A1	26-02-2004
			WO 2004016601 A1	26-02-2004