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(54) Title: COMPOSITIONS COMPRISING AN ANTIMUSCARINIC AND A LONG-ACTING BETA-AGONIST

(57) Abstract: The invention relates to a composition comprising a combination of a salt of 3-[[[(3-fluorophenyl)[(3,4,5-trifluorophenyl)methyl]amino]carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azoniabicyclo[2.2.2]octane, and a long-acting phenylalkylamino beta2-agonist. The invention also relates to pharmaceutical formulations and kit thereof, and to their use in the treatment of an inflammatory or obstructive airways disease.

WO 2009/090010 A1

COMPOSITIONS COMPRISING AN ANTIMUSCARINIC AND A LONG-ACTING BETA-AGONIST

FIELD OF THE INVENTION

The invention relates to a composition comprising a combination of a salt of 3-[[[(3-fluorophenyl)[(3,4,5-trifluorophenyl)methyl]amino]carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azoniabicyclo[2.2.2]octane, and a long-acting phenylalkylamino beta$_2$–agonist.

The invention also relates to pharmaceutical formulations and kit thereof, and to their use in the prevention and/or treatment of an inflammatory or obstructive airways disease.

BACKGROUND TO THE INVENTION

Quaternary ammonium salts acting as muscarinic receptors antagonists are currently used in therapy to induce bronchodilation for the treatment of respiratory diseases, and in particular inflammatory or obstructive airway diseases such as asthma and chronic obstructive pulmonary disease (COPD).

The use of antimuscarinic drugs with a long-lasting effect is often desirable for treating chronic diseases. This ensures that the concentration of the active substance necessary for achieving the therapeutic effect remains in the lungs for a long time, without the need for the active substance to be administered repeatedly and too frequently.

In particular, it would be desirable to utilize antimuscarinic drugs which are therapeutically effective upon administration by inhalation once a day.

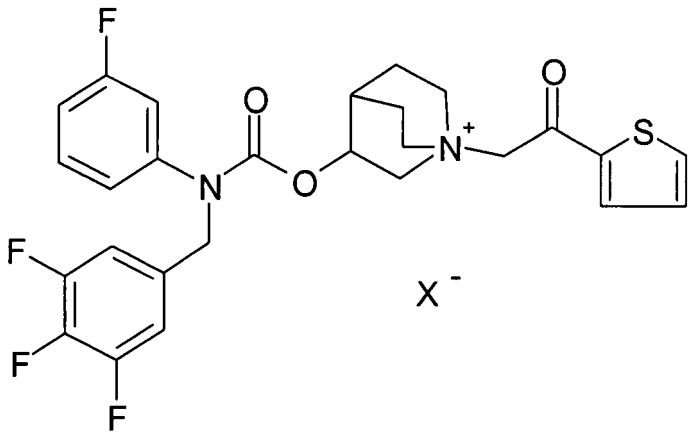
In order to fulfill such a requirement, antimuscarinic drugs shall exhibit good selectivity for M3 muscarinic receptors, and slow dissociation from them.

Recently, tiotropium bromide, the first drug in a new generation of antimuscarinic drugs, has been reported to have a very slow dissociation from

M3 receptors, which behaviour is thought to account for its long lasting activity. However tiotropium bromide still retains slow dissociation kinetics for the M2 muscarinic receptors. Since M2 receptors are a major population in the cardiac muscle, a therapy with said drug might be accompanied by undesired cardiac side effects.

The quaternary ammonium salt of 3-[[[(3-fluorophenyl)[(3,4,5-trifluoro phenyl)methyl]amino]carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azonia-bicyclo[2.2.2]octane (hereinafter referred to as compound **1**) is a novel compound which has been disclosed in the co-pending Patent Application no. PCT/EP2007/057585, incorporated herein by reference.

Compound **1** has the following chemical structure:



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wherein X^- is a pharmaceutically acceptable anion, preferably selected from the group consisting of chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate.

In particular the chloride salt of active compound **1** proved to be equieffective to tiotropium bromide in terms of receptor potency and duration of action, but significantly short-acting on the M2 receptors.

Therefore a salt of compound **1** may provide significant therapeutic

benefit in the treatment of respiratory diseases such as asthma and COPD, when administered by inhalation.

In particular said active drug could provide antimuscarinic-based pharmaceutical compositions having a rapid onset of action and a long-lasting effect so that they could be administered once a day with a great improvement of the compliance of patients. Moreover said pharmaceutical compositions may be safer with respect to those of the prior art.

It has now been found that the treatment of inflammatory or obstructive diseases of the respiratory tract using compound **1** in combination with a long-acting beta$_2$-agonist provides an unexpectedly beneficial therapeutic effect, particularly a synergistic effect.

SUMMARY OF THE INVENTION

One aspect of the present invention provides a composition comprising a pharmaceutically acceptable salt of 3-[[[(3-fluorophenyl)[(3,4,5-trifluoro phenyl)methyl]amino]carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azonia-bicyclo[2.2.2]octane (compound **1**) in combination with a long-acting phenylalkylamino beta$_2$-agonist (compound **2**) or a pharmaceutically acceptable salt thereof.

In a preferred embodiment of the invention the composition comprises the compound **1** in combination with formoterol or carmoterol as compound **2**.

In the compositions mentioned above, the active compounds may be combined in a single preparation or contained in two separate formulations. Pharmaceutical compositions which comprise the compound **1** and a compound **2** in a single preparation are preferred.

Accordingly the present invention relates to a pharmaceutical composition comprising, together, an effective amount of the compound **1** in combination with an effective amount of a compound **2**, and, optionally at least one pharmaceutically acceptable carrier.

The invention also provides a device comprising a pharmaceutical formulation described before.

The invention further provides a kit comprising the compound **1** and a compound **2** in separate unit dosage forms, said forms being suitable for administration of compounds **1** and **2** in effective amounts.

The invention also relates to the use of the compound **1** in combination with a compound **2** as a medicament.

Moreover the invention relates to the use of the compound **1** in combination with a compound **2** in the preparation of a pharmaceutical composition or a kit for the prophylaxis or treatment of an inflammatory or obstructive airways disease, such as asthma or chronic obstructive pulmonary disease (COPD), by separate, simultaneous or sequential administration of the compound **1** and a compound **2**.

Finally the invention relates to a method for the prevention and/or treatment of an inflammatory or obstructive airways disease such as asthma or chronic obstructive pulmonary disease (COPD), said method comprising the simultaneous or sequential administration of an effective amount of the compound **1** in combination with a compound **2**.

DEFINITIONS

By 'long–acting $beta_2$-agonist' it is meant a compound that is administered not more frequently than twice a day, preferably once a day.

The terms 'active drug', 'active ingredient', 'active', 'active compound' 'active substance', and 'therapeutic agent' are used as synonymous.

The terms 'muscarinic receptor antagonists', 'antimuscarinic drugs' and 'anticholinergic drugs' are used as synonymous.

By 'daily therapeutically effective dose', hereinafter called 'daily dose', it is meant the quantity of active ingredient administered daily by inhalation and delivered in one or more actuations, preferably one or two actuations

(shots) of the inhaler.

For 'actuation' it is meant the release of the active ingredient from the device by a single activation (e.g. mechanical or breath).

As used herein the term 'substantially pure' means an active ingredient having an optical purity higher than 95% w/w, preferably higher than 98% w/w.

As used herein, the term 'fixed combination' means a combination wherein the active substances are in a fixed amount and quantitative ratio.

As used herein the term 'synergistic' means that the activity of the two compounds is more than would be expected by summing their respective individual activities in a given assay.

FIGURE

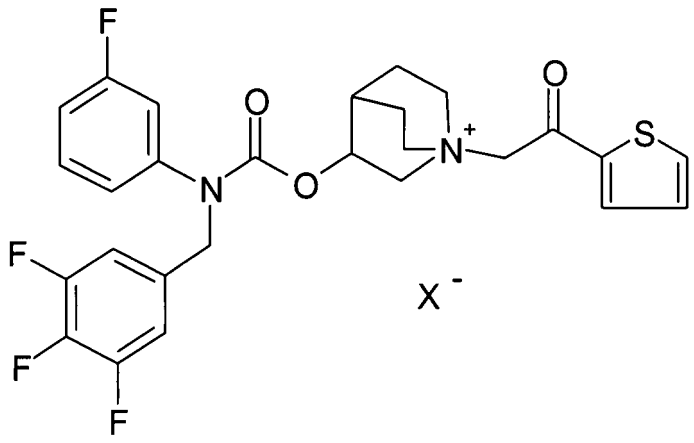
Figure shows the existence of a synergistic action for a preferred embodiment of the present invention.

DETAILED DESCRIPTION OF THE INVENTION

The invention relates to a composition comprising compound **1** in combination with compound **2.**

In particular the invention is directed to a composition comprising a fixed combination of compound **1** and compound **2**.

Within the scope of the present invention, any reference to compound **1** is to be regarded as a reference to a pharmaceutically acceptable salt of 3-[[[(3-fluorophenyl)[(3,4,5-trifluorophenyl)methyl]amino]carbonyl]oxy]-1-[2-oxo-2-(2-thienyl)ethyl]-1-azoniabicyclo[2.2.2]octane, whose formula is reported below:



wherein X^- is a pharmaceutically acceptable anion, preferably selected from the group consisting of chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate.

Compound **1** is preferably used in the form of its chloride salt.

Compound **1** has an asymmetric carbon on the quinuclidine ring, and hence may exist in the form of two optical stereoisomers, (3R)- and (3S)-stereoisomers or a racemic mixture thereof.

In the preferred embodiments compound **1** is in the form of the substantially pure (3R)-enantiomer.

The (3R)-enantiomer of the compound **1** in the form of chloride salt is hereinafter referred to as compound **1'.**

Within the scope of the present invention, any reference to active compound **2** is to be regarded as a reference to a long–acting phenylalkylamino $beta_2$-agonist or a pharmaceutically acceptable salt thereof, also including the relevant enantiomers or mixtures thereof.

Examples of physiologically acceptable acid addition salts of the compound **2** according to the invention are the pharmaceutically acceptable salts which are selected among the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid, or maleic acid.

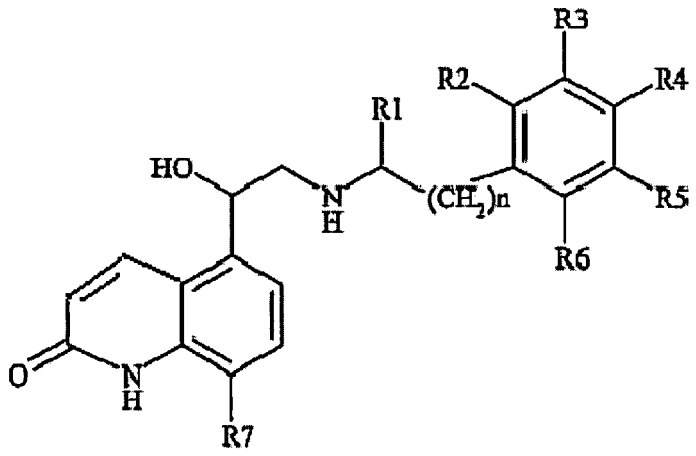
According to the invention, compound **2** may also be present in the form of hydrates or solvates thereof.

The compositions according to the invention may comprise the compound **1** and the compound **2** in ratios ranging from 1:400 to 40:1.

Advantageously the compound **2** is selected from the group consisting of formoterol, hereinafter also indicated as compound **2a**, and salmeterol, hereinafter also indicated as compound **2b**, or salts thereof. The salts of salmeterol and formoterol, also include the relevant enantiomeric salts of (R)-salmeterol, (S)-salmeterol, (R,R)-formoterol, (S,S)-formoterol, (R,S)-formoterol, (S,R)-formoterol, and the mixtures thereof, while the enantiomeric salts of (R)-salmeterol and the racemic mixture (R,R)(S,S)-formoterol are of particular importance.

Formoterol is preferably used in the form of the fumarate salt, more preferably in the form of the dihydrate fumarate salt, hereinafter also indicated as compound **2a'**, while salmeterol is preferably used as the xinafoate salt, hereinafter also indicated as compound **2b'**.

Compound **2** may also be a quinolinone derivative of formula **A**:



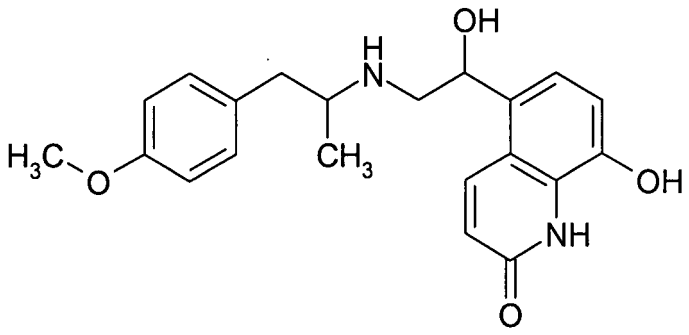
A

wherein

- R_1 is methyl and R_2 is hydrogen or R_1 and R_2 together form a methylene bridge - $(CH_2)_n$- in which n is 1 or 2, preferably 1,

- R_3, R_4, R_5 and R_6 are each independently hydrogen, hydroxy, a straight or branched chain C_1-C_4 alkyl, a straight or branched chain C_1-C_4 alkyl substituted with one or more halogen atoms and/or hydroxy groups, halogen, straight or branched chain C_1-C_4 alkoxy, and
- R_7 is hydrogen, hydroxy, straight or branched chain C_1-C_4 alkyl, straight or branched chain C_1-C_4 alkoxy.

Particularly preferred is the compound wherein R_1 is methyl, R_4 is methoxy, R_2, R_3, R_5, R_6 are hydrogen, R_7 is hydroxy, and n=1, i.e. 8-hydroxy-5-[1-hydroxy-2-[2-(4-methoxyphenyl)-1-methylethyl]amino]ethyl]-2(1H)-quinolinone, hereinafter indicated as compound **2c**.



2c

Compound **2c** has two asymmetric carbons at the position -CH(CH_3)- and at the position -CH(OH)-, respectively,

therefore it may exist in the form of four different stereoisomers, e.g. (R,R)-, (R,S)-, (S,S)-, (S,R)-, or mixtures thereof.

In a preferred embodiment compound **2c** is in the form of the optically pure (R,R)-enantiomer which has been also reported with the name of carmoterol or the experimental codes of TA 2005 and CHF 4226.

More preferably carmoterol is used as the hydrochloride salt, hereinafter indicated as compound **2c'**.

Another preferred quinoline derivative is the compound wherein R_1 and R_2 form a methylene bridge, R_3 and R_6 are H, R_4 and R_5 are ethyl, R_7 is OH, n = 1 which has also been reported with the name of indacaterol or compound **2d**.

Indicaterol is preferably used in the form of maleate salt, hereinafter also indicated as compound **2d'.**

A further long-acting phenylalkylamino $beta_2$-agonist which might be advantageously used in combination with the compound **1** is milveterol (compound **2e**) or a pharmaceutically accepable salt thereof.

The salts of milveterol include the relevant enantiomeric salts (R,R), (S,S), (R,S), (S,R), and the mixtures thereof.

Preferably milveterol is used as hydrochloride salt (compound **2e'**).

Other long-acting phenylalkylamino $beta_2$-agonists which may be used in the combination of the invention are those known with the experimental codes PF-610355 and BI-1744-CL.

In a preferred embodiment of the invention the composition comprises compound **1'** in combination with formoterol fumarate dihydrate.

In another preferred embodiment of the invention the composition comprises compound **1'** in combination with carmoterol hydrochloride.

According to the invention, compounds **1** and **2** may be administered simultaneously or sequentially; the simultaneous administration of compounds **1** and **2** being preferred.

According to the invention, compounds **1** and **2** may be combined in a single preparation or contained in two separate formulations; single preparations, optionally with a pharmaceutically acceptable carrier, are preferred.

According to the invention, compounds **1** and **2** may be used in variable weight ratios.

The ratios may also vary on the basis of the different molecular weights of the various salt forms. The weight ratios specified below were based on compound **1'**, the fumarate dihydrate salt of formoterol (compound **2a'**), the xinafoate salt of salmeterol (compound **2b'**), the hydrochloride salt of carmoterol (compound **2c'**), the maleate salt of indacaterol (compound **2d'**), and the hydrochloride salt of milveterol (compound **2e'**).

For instance, the pharmaceutical compositions according to the invention may comprise the compound **1'** and the compound **2a'** in ratios ranging from 1:30 to 7:1, preferably from 1:25 to 4:1, more preferably from 1:20 to 2:1.

In another embodiment, the compositions may comprise compound **1'** and the compound **2b'** in ratios ranging from 1:60 to 3:1, preferably from 1:50 to 1:1, more preferably from 1:40 to 1:2.

In another embodiment, the compositions may comprise compound **1'** and the compound **2c'** in ratios ranging from 1:10 to 40:1, preferably from 1:8 to 20:1, more preferably from 1:6 to 10:1.

In an further embodiment, the compositions may comprise the compound **1'** and the compound **2d'** in ratios ranging from 1:250 to 1:1, preferably from 1:200 to 2:5, more preferably from 1:150 to 1:5.

In a further embodiment, the compositions may comprise compound **1'** and the compound **2e'** in ratios ranging from 1:40 to 20:1, preferably from 1:20 to 10:1, more preferably from 1:10 to 5:1.

The compositions of the invention may be administered one or more times a day, preferably once a day, and the daily dose of active compounds **1** and **2** may vary depending on the disease and the conditions (weight, sex, age) of the patient.

In one embodiment the daily dose may be reached by a single or double administration.

In another preferred embodiment the daily dose may be reached by a single administration and delivered in one actuation of the inhaler.

In another preferred embodiment the daily dose may be reached by a single administration and delivered in more actuations of the inhaler, preferably two.

In another preferred embodiment the daily dose may be reached by a double administration and delivered in one actuation of the inhaler.

In another preferred embodiment the daily dose may be reached by a double administration and delivered in more actuations of the inhaler, preferably two.

The compositions according to the invention are usually administered so that the delivered daily dose of compound **1** is comprised between 1 μg and 20 μg, and that of compound **2** is comprised between 0.5 μg and 400 μg.

Advantageously, when the compound **2** is formoterol, the compositions may deliver a daily dose of compound **1'**, comprised between 1 μg and 20 μg, preferably between 1 μg and 10 μg, more preferably between 1 μg a 5 μg and a daily dose of formoterol, calculated as compound **2a'**, comprised between 3 μg and 24 μg.

In one embodiment the daily dose of compound **2a'** may be comprised between 3 μg and 6 μg.

In another embodiment the daily dose of compound **2a'** may be comprised between 6 μg and 12 μg. In certain further embodiments, the daily dose of compound **2a'** may be comprised between 12 μg and 18 μg or between 18 μg and 24 μg.

According to one embodiment the compositions according to the invention may comprise a quantity of compound **1'** and compound **2a'** such that a daily dose comprised between 1 μg and 20 μg, preferably between 1 and 10 μg, more preferably between 1 and 5 μg of compound **1'** and of 3 μg of

compound **2a'** is delivered.

In another embodiment a daily dose comprised between 1 μg and 20 μg, preferably between 1 and 10 μg, more preferably between 1 and 5 μg of compound **1'** and of 4 μg of **2a'** is delivered.

In a further embodiment, a daily dose comprised between 1 μg and 20 μg, preferably between 1 and 10 μg, more preferably between 1 and 5 μg of compound **1'** and of 6 μg of **2a'** is delivered.

In certain embodiments a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 6 μg, or 8 μg, or 10 μg, or 12 μg, or 15 μg, or 18 μg or 24 μg of **2a'** is delivered.

Advantageously, when the compound **2** is salmeterol, the compositions may deliver a daily dose of compound **1'** comprised between 1 μg and 20 μg, preferably between 1 μg and 10 μg, more preferably between 1 and 5 μg; and a daily dose of salmeterol, calculated as compound **2b'**, comprised between 12 μg and 50 μg. In one embodiment the daily dose of compound **2b'** may be comprised between 12 μg and 25 μg. In another embodiment the daily dose of compound **2b'** may be comprised between 25 μg and 50 μg.

In one embodiment the compositions according to the invention may contain a quantity of compound **1'** and compound **2b'** such that a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 12 μg of compound **2b'** is delivered.

In another embodiment a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 25 μg of **2b'** is delivered.

In a further embodiment, a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 50 μg of **2b'** is delivered.

Advantageously, when the compound **2** is carmoterol the compositions may deliver a daily dose of compound **1'**, comprised between 1 μg and 20 μg, preferably between 1 μg and 10 μg, more preferably between 1 and 5 μg and a

daily dose of carmoterol, calculated as compound **2c'**, comprised between 0.5 μg and 8 μg.

In one embodiment the daily dose of compound **2c'** is comprised between 0.5 μg and 2 μg. In another embodiment the daily dose of compound **2c'** may be comprised between 2 μg and 4 μg. In a further embodiment, the daily dose of compound **2c'** may be comprised between 4 μg and 8 μg.

In certain embodiments daily doses of 1 μg or 2 μg or 4 μg of compound **2c'** may be delivered.

For example, without restricting the scope of the invention thereto, in one embodiment the composition according to the invention may comprise a quantity of compound **1'** and compound **2c'** such that a daily dose of compound **1'** comprised between 2 μg and 5 μg and a daily dose of **2c'** comprised between 1 and 4 μg is delivered.

In a particular embodiment a daily dose of 2 μg of compound **1'** and of 2 μg of **2c'** are delivered. In a further particular embodiment, a daily dose of 2 μg or 5 μg of compound **1'** and of 4 μg of **2c'** is delivered.

Advantageously, when the compound **2** is indacaterol, the compositions may deliver a daily dose of compound **1'**, comprised between 1 μg and 20 μg, preferably between 1 μg and 10 μg, more preferably between 1 and 5 μg and a daily dose of indacaterol, calculated as compound **2d'**, comprised between 25 μg and 200 μg.

In one embodiment the daily dose of compound **2d'** is comprised between 25 μg and 50 μg. In another embodiment the daily dose of compound **2d'** is comprised between 50 μg and 100 μg. In a further embodiment, the daily dose of compound **2d'** is comprised between 100 μg and 200 μg.

In one embodiment the compositions according to the invention may comprise a quantity of compound **1'** and compound **2d'** such that a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 25 μg of **2d'** are

delivered.

In another embodiment a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 50 μg of **2d'** are delivered. In a further embodiment, a daily dose comprised between 2 μg and 5 μg of compound **1'** and of 100 μg or 200 μg of **2d'** are delivered.

Advantageously, when the compound **2** is milveterol, the compositions may deliver a daily dose of compound **1'** comprised between 1 μg and 20 μg, preferably between 1 μg and 10 μg, more preferably between 1 and 5 μg and a daily dose of milveterol, calculated as compound **2e'**, comprised between 1 μg and 20 μg.

The quantities of active substance in the pharmaceutical compositions according to the invention which are administered per single dose can be calculated analogously in case the mentioned salts of the compounds **2** are replaced by other salts.

The pharmaceutical compositions according to the invention may optionally comprise a further active ingredient useful for the prevention and/or treatment of an inflammatory or obstructive airway disease.

According to a particular embodiment, the compositions of the invention may further comprise a corticosteroid, preferably selected from the group consisting of beclometasone dipropionate (BDP), budesonide and epimers thereof, flunisolide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide, rofleponide palmitate. More preferably, the corticosteroid is beclometasone dipropionate or budesonide.

The compositions of the invention may be preferably administered by inhalation. Inhalable preparations include inhalable powders, propellant-containing metering aerosols or propellant-free inhalable formulations.

For administration as a dry powder, single- or multi-dose inhaler device known from the prior art may be utilized, wherein the powder can be filled in

gelatine, plastic or other capsules, cartridges or blister packs or in a reservoir. Said devices are known as dry powder inhalers (DPIs).

A diluent or carrier, generally non-toxic and chemically inert to the medicaments, e.g. lactose or any other additive suitable for improving the respirable fraction can be added to the powdered medicament.

Inhalation aerosols containing propellant gas such as hydrofluoroalkanes may contain the active ingredients of the combination of the invention either in solution or in dispersed form. Said propellant-driven formulations may also contain other ingredients such as co-solvents, stabilizers such as inorganic acids, and optionally other excipients.

They are usually administered by inhaler devices known as metered dose inhalers (MDIs).

The propellant-free inhalable formulations comprising the combination of the invention may be in form of solutions or suspensions in an aqueous, alcoholic or hydroalcoholic medium and they may be delivered by jet or ultrasonic nebulizers known from the prior art or by inhaler devices known as soft-mist nebulizers (for example the nebuliser sold under the registered name of Respimat™).

Treatment of inflammatory or obstructive airways diseases in accordance with the invention may be symptomatic or prophylactic. Inflammatory or obstructive airways diseases to which the claimed combinations are 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. 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. Prophylactic benefit in asthma may in particular be apparent in subjects prone to "morning dipping". "Morning dipping" is a recognized asthmatic syndrome, common to a substantial percentage of asthmatics and characterized by asthma attack, e. g., between the hours of about 4 to 6 a.m., i. e. at a time normally substantially distant form any previously administered symptomatic asthma therapy.

Other inflammatory or obstructive airways diseases and conditions to which the present invention is applicable include acute lung injury (ALI), adult respiratory distress syndrome (ARDS), chronic obstructive pulmonary, airways or lung disease (COPD, COAD or COLD) including chronic bronchitis and emphysema, bronchiolitis, 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.

In particular, the combination of the invention is useful for the prevention and/or treatment of the chronic obstructive pulmonary disease (COPD), including chronic bronchitis and emphysema, bronchiolitis, and

bronchiectasis, as in COPD patients, the antimuscarinic drugs relieve the airways constriction due to the vagal cholinergic tone.

The invention further provides a pharmaceutical kit comprising the active compound **1** and an active compound **2** in separate unit dosage forms, said forms being suitable for separate, simultaneous or sequential administration of the active compounds **1** and **2** in effective amounts.

Such a kit suitably further comprises one or more inhalation devices for administration of active compounds **1** and **2**.

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 the active compound **1** and capsules containing a dry powder comprising a dosage unit of an active compound **2**.

In another example, the kit may comprise a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising the active compound **1** and a multidose dry powder inhalation device containing in the reservoir thereof a dry powder comprising an active compound **2**.

In a further example, the kit may comprise a metered dose inhaler containing an aerosol comprising the active compound **1** in a propellant, and a metered dose inhaler containing an aerosol comprising an active compound **2**.

The invention is further illustrated by the following examples.

EXAMPLES

Example 1 - Formulations for metered dose inhalers

Different formulations for metered dose inhalers are prepared with the following compositions:

Formulation	***Amounts***		
	Per unit		Daily dose
(a)	mg	% (w/w)	µg
Compound **1'**	1.60	0.017	10
Formoterol fumarate*$2H_2O$	0.96	0.01	6
Ethanol	1113.6	12	
Hydrochloric acid 1 M	0.014	0.00015	
HFA 134a	q.s. to 9280		
(b)			
Compound **1'**	0.31	0.0028	2
Carmeterol hydrochloride (compound **2c'**)	0.31	0.0028	2
Ethanol	1650.0	15	-
Phosphoric acid 15.2 M	0.3	0.0027	-
HFA 134a	q.s. to 11.000		
(c)			
Compound **1'**	1.54	0.016	10
Carmoterol hydrochloride (compound **2c'**)	0.70	0.006	4
Ethanol	1650.0	15	

Phosphoric acid 15.2 M	0.3	0.0027	
HFA 134a	q.s. to 11.000	84.981	
(d)			
Compound **1'**	6.17	0.064	40
Carmoterol hydrochloride (compound **2c'**)	0.70	0.006	4
Ethanol	1650.0	15	
Phosphoric acid 15.2 M	0.3	0.0027	
HFA 134a q.s. to 9.72 ml	q.s. to 11.000	84.933	-

Example 2 - Powder formulations for a dry powder inhalers

Different formulations for dry powder inhalers are prepared with the following compositions:

Formulation	*Amounts*		
	For shot of the inhaler		Daily dose
(a)	mg	% (w/w)	µg
Compound **1'**	0.01	0.1	10
Formoterol fumarate*2H_2O (compound **2a'**)	0.006	0.06	6
Alpha-lactose monohydrate	9.959	99.59	
Magnesium stearate	0.025	0.25	
Total weight	10	100	
(b)			
Compound **1'**	0.01	0.1	10
Carmoterol hydrochloride	0.004	0.04	4

(compound **2c'**)			
Alpha-lactose monohydrate	9.961	99.61	
Magnesium stearate	0.025	0.25	
Total weight	10		

Example 3 – Assessment of the bronchodilation activity of compound 1'

Airway reactivity is measured using barometric plethysmography (Buxco, USA). Male guinea pigs (500-600 g) are individually placed in plexiglass chambers. After an acclimatisation period, animals are exposed to nebulised saline for 1 min to obtain airway baseline reading. This is followed by a 1 min challenge with nebulised acetylcholine (Ach) -2.5 mg/mL.

After 60 min, 5 min nebulisation of vehicle or the compound **1'** in the range 2.5 -250 µM are applied and Ach challenge is then repeated after 2, 5, 24, 48 and 72 hours (h). Recording of pressure fluctuations in the chambers are taken for 5 min after each nebulisation and analysed to calculate Enhanced Pause (Penh). Airway reactivity is expressed as percentage increase in Penh compared with Penh values from the nebulisation of vehicle.

Two hours after the end of nebulisation with compound **1'**, the Ach-induced increase in Penh is dose-dependently inhibited by the compound, with a maximal effect of 99.6 ± 0.4 at 50 µM.

As for the time-course of the effect, compound **1'** shows increasing duration of action with increasing dose.

After inhalation of 250 µM of compound **1'**, effect persists unchanged up to 48 h (83.0 ± 16.1%), while at 72 h a residual activity of 34.8 ± 20.9% is present. Twenty-four hours after 25 and 50 µM compound **1'** inhalation, a significant bronchoprotective effect was observed (63.7 ± 15.1% and 87.1 ± 8.7%, respectively). At 50 µM, a significant inhibition persists up to

48 h (49.2 ± 23.2%). Inhalation of lower concentrations results in an effect that did not exceed the 5 h observation point.

The estimation of lung levels of compound **1'** achieved after nebulisation endowed with a submaximal bronchodilator activity at 2 h after treatment reveals that the its retained dose in the target organ is about 50 μg/kg. If an extrapolation of these results from rat to human is made, it can be predicted that in patients the daily dose might be comprised between 1 and 20 μg, preferably between 1 and 10 μg and more preferably between 1 and 5 μg.

Synergistic activity of fixed dose combination of carmoterol/ compound 1' on carbachol-induced contraction in guinea-pigs trachea

Male guinea-pigs (380–420 g) are used. The investigation conforms to the Guide for the Care and Use of Laboratory Animals published by the US National Institutes of Health (NIH Publication No. 85-23, revised 1996).

The trachea is removed, cleaned and cut into two zig-zag strips, according to Emmerson et al. (J Pharm Pharmacol 1979; 31: 798). A sub-maximal concentration of carbachol ($3x10^{-7}$ M) is then added to the organ bath and when stable contraction is reached, a cumulative concentration-response curve (from $1x10^{-11}$ to $1x10^{-7}$ M) to carmoterol or compound **1'** is generated (n = 12 for each compound). Maximal relaxation is tested by adding a maximal dose of isoproterenol ($3x10^{-7}$ M) at the end of the curve. Data are expressed as percentages of the isoproterenol-induced maximal relaxation.

Isobolographic analysis is used to characterize the pharmacological interaction between carmoterol and compound **1'**.

To estimate the experimental ED_{50}MIX, the dose-effect curve resulting from this second set of experiments (Table 1) is fitted with a mixed logistic model. All computations are carried out resorting to NLMIXED procedure

(SAS/STAT® User's Guide, version 9, 2004. SAS Institute Inc., Cary, NC).

The ED_{50} (95% conf. lim.) for carmoterol is $5.4x10^{-10}$ M ($4.6x10^{-10}$ - $6.4x10^{-10}$ M), whereas the ED_{50} (95% conf. lim.) for compound **1'** is $9.3x10^{-10}$ M ($7.9x10^{-10}$ - $10.9x10^{-10}$ M).

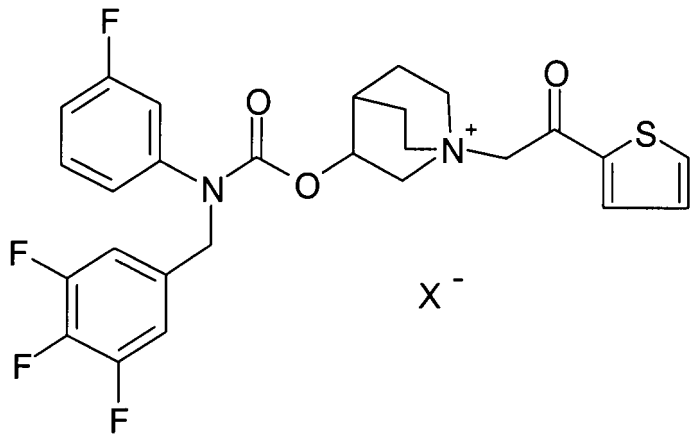
Isobolographic analysis (Figure) shows the existence of a synergistic action between compound **1'** and carmoterol, the $ED_{50}MIX$ observed being significantly lower than the value expected under hypothesis of additivity.

This study shows that the β2-selective agonist carmoterol and the M3-selective antagonist compound **1'** are both potent in antagonizing carbachol-induced contraction in guinea-pig airways. Moreover, in line with their complementary molecular mechanism of action, in the frame of a functional agonism-antagonism, fixed combinations display synergistic effect in the control of cholinergic contraction in guinea-pig trachealis.

CLAIMS

1. A composition comprising:

(a) a pharmaceutically acceptable salt of formula **1**



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wherein:

X^- is a pharmaceutically acceptable anion, and

(b) a long-acting phenylalkylamino $beta_2$–agonist (compound **2**),

or a pharmaceutically acceptable salt or a solvate or hydrate thereof, optionally in the form of the enantiomers, or mixtures of the enantiomers.

2. The composition according to claim 1 wherein the anion is selected from the group consisting of chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate.

3. The composition according to claims 1 or 2 wherein the pharmaceutically acceptable salt of compound **2** is selected form the group consisting of the salts of hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, methanesulfonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

4. The composition according to any one of claims 1 to 3, wherein the

compound **1** and the compound **2** are present in a fixed combination.

5. The composition according to claim 4 wherein the compound **1** and the compound **2** are present in a ratio comprised between 1:400 and 40:1.

6. The composition according to any one of claims 1 to 5 wherein the (3R)-enantiomer of active compound **1** in the form of chloride salt (compound **1'**).

7. The composition according to claim 6 wherein the compound **1'** is administered at a daily dose comprised between 1 μg and 20 μg.

8. The composition according to claim 7 wherein the compound **1'** is administered at a full daily dose comprised between 1 μg and 10 μg.

9. The composition according to claim 8 wherein the compound **1'** is administered at a daily dose comprised between 1 μg and 5 μg.

10. The composition according to any one of claims 1 to 9 wherein the daily dose of compound **2** is comprised between 0.5 μg and 400 μg.

11. The composition according to any one of claims 4 to 10 wherein the compound **2** is formoterol (compound **2a**).

12. The composition according to claim 11 wherein formoterol is in form of fumarate dihydrate (compound **2a'**).

13. The composition according to claim 12 wherein the weight ratio between compound **1'** and compound **2a'** ranges from 1:30 to 7:1.

14. The composition according to claim 12 wherein the weight ratio between compound **1'** and compound **2a'** ranges from 1:25 to 4:1.

15. The composition according to claim 12 wherein the weight ratio between compound **1'** and compound **2a'** ranges from 1:20 to 2:1.

16. The composition according to any one of claims 4 to 10 wherein the compound **2** is salmeterol (compound **2b**).

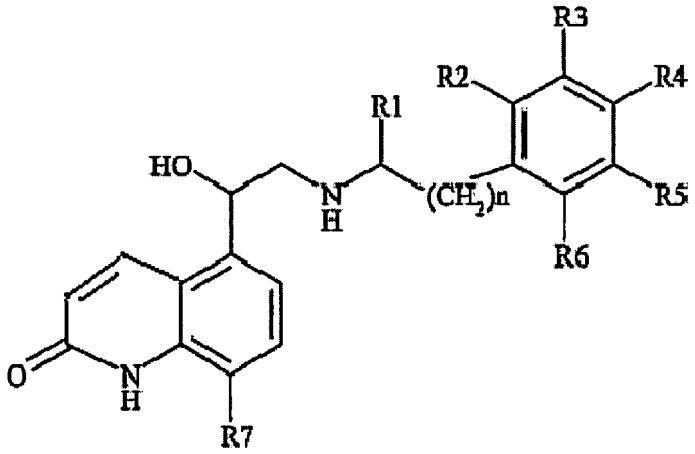
17. The composition according to claim 16 wherein salmeterol is in the form of xinafoate salt (compound **2b'**).

18. The composition according to claim 17 wherein the weight ratio between compound **1'** and compound **2b'** ranges from 1:60 to 3:1.

19. The composition according to claim 17 wherein the weight ratio between compound **1'** and compound **2b'** ranges from 1:50 to 1:1.

20. The composition according to claim 17 wherein the weight ratio between compound **1'** and compound **2b'** ranges from 1:40 to 1:2.

21. The composition according to any one of claims 4 to 10 wherein the compound **2** is a compound of general formula **A**



wherein

- R_1 is methyl and R_2 is hydrogen or R_1 and R_2 together form a methylene bridge
- $(CH_2)_n$- with n is 1 or 2,
- R_3, R_4, R_5 and R_6 are each independently hydrogen, hydroxy, a straight or branched chain C_1-C_4 alkyl, a straight or branched chain C_1-C_4 alkyl substituted with one or more halogen atoms and/or hydroxy groups, halogen, straight or branched chain C_1-C_4 alkoxy, and
- R_7 is hydrogen, hydroxy, straight or branched chain C_1-C_4 alkyl, straight or branched chain C_1-C_4 alkoxy.

22. The composition according to claim 21 wherein the compound **2** is a

compound of general formula **A** wherein R_1 is methyl, R_4 is methoxy, R_2, R_3, R_5, R_6 are hydrogen, R_7 is hydroxy and n=1 (compound **2c**).

23. The composition according to claim 22 wherein the compound **2c** is in the form of the hydrochloride salt (compound **2c'**).

24. The composition according to claim 23 wherein the weight ratio between compound **1'** and compound **2c'** ranges from 1:10 to 40:1.

25. The composition according to claim 23 wherein the weight ratio between compound **1'** and compound **2c'** ranges from 1:8 to 20:1.

26. The composition according to claim 23 wherein the weight ratio between compound **1'** and compound **2c'** ranges from 1:6 to 10:1.

27. The composition according to claim 21 wherein the compound **2** is a compound of general formula **A** wherein R_1 and R_2 together form a methylene bridge, R_3 and R_6 are H, R_4 and R_5 are ethyl, R_7 is OH, n = 1 (compound **2d**).

28. The composition according to claim 27 wherein the compound **2d** is in the form of maleate salt (compound **2d'**).

29. The composition according to claim 28 wherein the weight ratio between compound **1'** and compound **2d'** ranges from 1:250 to 1:1.

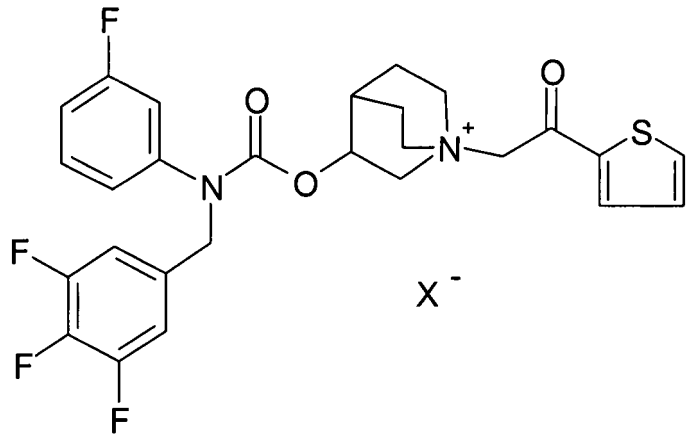
30. The composition according to claim 28 wherein the weight ratio between compound **1'** and compound **2d'** ranges from 1:200 to 2:5.

31. The composition according to claim 28 wherein the weight ratio between compound **1'** and compound **2d'** ranges from 1:150 to 1:5.

32. The composition according to any one of claims 4 to 10 wherein the compound **2** is milveterol or a salt thereof (compound **2e**).

33. A pharmaceutical composition comprising in admixture in a single preparation:

(a) a pharmaceutically acceptable salt of formula **1** as claimed in claim 1 (active compound **1**)



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wherein:

X^- is a pharmaceutically acceptable anion,

(b) a long-acting phenylalkylamino $beta_2$–agonist. **2** (active compound **2**),

or a pharmaceutically acceptable salt or a solvate or hydrate thereof, optionally in the form of the enantiomers, or mixtures of the enantiomers, and a pharmaceutically acceptable carrier.

34. The pharmaceutical composition according to claim 33 wherein the (3R)-enantiomer of active compound **1** in the form of chloride salt (compound **1'**).

35. The pharmaceutical composition according to claim 33 wherein the anion is selected from the group consisting of chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate.

36. The pharmaceutical composition according to claims 33 to 35 further comprising a corticosteroid.

37. The pharmaceutical composition according to claim 36 wherein the corticosteroid is selected form the group consisting of beclometasone dipropionate (BDP), budesonide and epimers thereof, flunisolide, fluticasone propionate, mometasone furoate, ciclesonide, triamcinolone acetonide,

rofleponide palmitate.

38. The pharmaceutical composition according to any one of claims 33 to 37 wherein the pharmaceutical composition is an inhalable aerosol comprising a propellant.

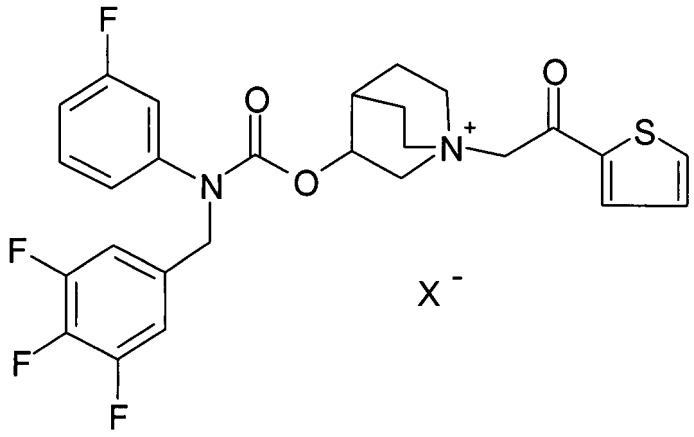
39. The pharmaceutical composition according to any one of claims 33 to 38 wherein the pharmaceutical composition is an inhalable powder.

40. The pharmaceutical composition according to any one of claims 33 to 38 wherein the pharmaceutical composition is an inhalable propellant-free solution or suspension.

41. A device comprising a pharmaceutical composition according to any one of claims 33 to 40.

42. A kit comprising:

a) a therapeutically effective amount of a pharmaceutically acceptable salt of formula **1** (active compound **1**) and, optionally, a pharmaceutically acceptable carrier in a first unit dosage form;



wherein:

X^- is an anion selected from the group consisting of chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate, and

b) a therapeutically effective amount of a long-acting phenylalkylamino

beta$_2$–agonist. **2** (active compound **2)** or a pharmaceutically acceptable salt thereof, and optionally, a pharmaceutically acceptable carrier in a second unit dosage form;

for separate simultaneous or sequential administration in the prevention and/or treatment of an obstructive airways disease.

43. The kit according to claim 42 further comprising one or more inhaler devices.

44. Use of active compound **1'** in combination with an active compound **2** as a medicament.

45. Use of active compound **1'** in combination with an active compound **2** in the preparation of a pharmaceutical composition or a kit for the prophylaxis or treatment, by simultaneous or sequential administration of active compound **1'** and an active compound **2**, of an inflammatory or obstructive airways disease.

46. The use according to claim 44 wherein the disease is asthma.

47. The use according to claim 44 wherein the disease is chronic obstructive pulmonary disease (COPD).

48. The use according to any one of claims 44 to 47 wherein the daily dose of compound **1'** is comprised between 1 μg and 20 μg.

49. The use according to any one of claims 44 to 47 wherein the daily dose of compound **1'** is comprised between 1 μg and 10 μg.

50. The use according to any one of claims 44 to 47 wherein the daily dose of compound **1'** is comprised between 1 μg and 5 μg.

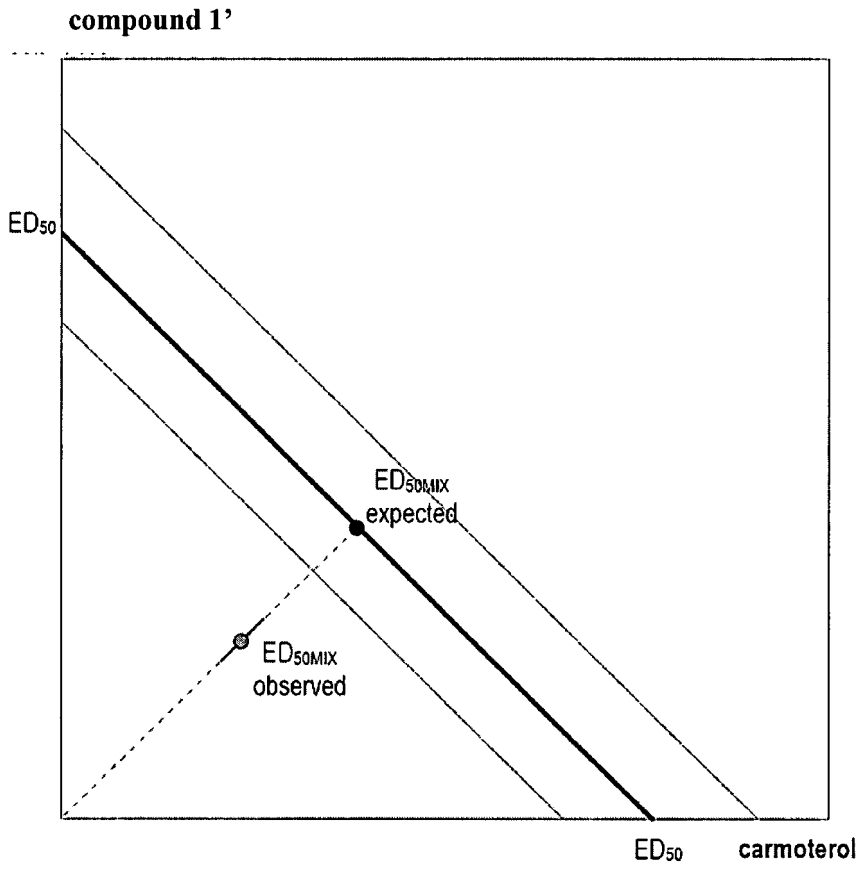

compound 1'
ED50
ED50MIX
expected
ED50MIX
observed
ED50
carmoterol

Figure 1

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2009/000053

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K45/06 A61P11/00

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

B. FIELDS SEARCHED

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

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

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

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

[X] See patent family annex.

* Special categories of cited documents :

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

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

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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
30 April 2009	19/05/2009

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL – 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Stoltner, Anton

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International application No
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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

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