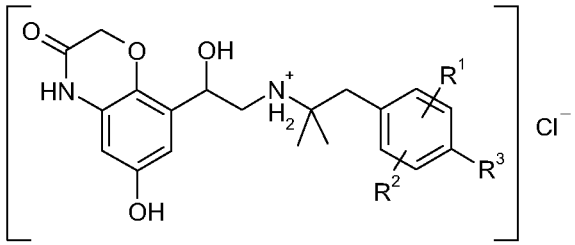
AEROSOLFORMULATION FOR INHALATION

The present invention relates to a propellant-free aerosol formulation which contains one or more compounds of general formula **1**.



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BACKGROUND TO THE INVENTION

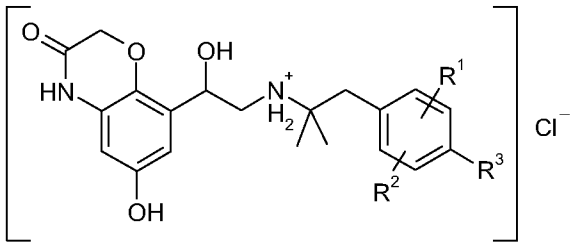
Betamimetics (ß-adrenergic substances) are known from the prior art. For example reference may be made in this respect to the disclosure of WO 04/045618 or US 4,460,581, which proposes betamimetics for the treatment of a range of diseases.

For drug treatment of diseases it is often desirable to prepare medicaments with a longer duration of activity. As a rule, this ensures that the concentration of the active substance in the body needed to achieve the therapeutic effect is guaranteed for a longer period without the need to re-administer the drug at frequent intervals. Moreover, giving an active substance at longer time intervals contributes to the well-being of the patient to a high degree. It is particularly desirable to prepare a pharmaceutical composition which can be used therapeutically by administration once a day (single dose). The use of a drug once a day has the advantage that the patient can become accustomed relatively quickly to regularly taking the drug at certain times of the day.

The object of the present invention is therefore to provide medicament formulations for inhalation which on the one hand confer a therapeutic benefit for example in the treatment of respiratory complaints and in addition are characterised by a longer duration of activity and can thus be used to prepare longer-acting pharmaceutical compositions.

DETAILED DESCRIPTION OF THE INVENTION

To solve the problems mentioned above the present invention proposes the following medicament formulations. The medicament formulations according to the invention are propellant-free medicament formulations, containing as sole active substance 91 to 500 mg per 100 ml solution of one or more compounds of general formula **1**



1

wherein

R^1 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or halogen;

R^2 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or halogen;

R^3 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, OH, -O-C_1-C_4-alkylene-COOH or -O-C_1-C_4-alkylene-COO-C_1-C_4-alkyl,

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof, at least one pharmacologically acceptable acid, optionally other pharmacologically acceptable excipients and/or complexing agents and water as solvent.

Preferred medicament formulations are whose which contain the compounds of general formula **1**, wherein

R^1 denotes hydrogen, methyl, ethyl, fluorine or chlorine;

R^2 denotes hydrogen, methyl, ethyl, fluorine or chlorine;

R^3 denotes hydrogen, methyl, ethyl, propyl, OH, methoxy, ethoxy, fluorine, chlorine, bromine, -O-CH_2-COOH, -O-CH_2-COOmethyl or -O-CH_2-COOethyl,

-O-CH_2-CH_2COOH, -O-CH_2-CH_2COOmethyl or -O-CH_2-CH_2COOethyl,
-O-CH_2-CH_2-CH_2COOH, -O-CH_2-CH_2-CH_2COOmethyl or
-O-CH_2-CH_2-CH_2COOethyl;

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

Preferred medicament formulations are whose which contain the compounds of general formula **1**, wherein

R^1 denotes hydrogen or methyl, preferably hydrogen;

R^2 denotes hydrogen or methyl, preferably hydrogen;

R^3 denotes methyl, OH, methoxy, fluorine, chlorine, bromine, -O-CH_2-COOH or -O-CH_2-COOethyl;

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

Also preferred are medicament formulations which contain the compounds of general formula **1**, wherein

R^3 denotes methoxy, ethoxy, fluorine, chlorine, bromine, -O-CH_2-COOH, -O-CH_2-COOmethyl or -O-CH_2-COOethyl;

and R^1 and R^2 may have the above-mentioned meanings, optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

Also preferred are medicament formulations which contain the compounds of general formula **1**, wherein

R^1 and R^2 denotes hydrogen;

R^3 denotes OH, fluorine, chlorine, methoxy, ethoxy,-O-CH_2-COOH, preferably OH, fluorine, chlorine, ethoxy or methoxy,

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

Also preferred are medicament formulations which contain the compounds of general formula **1** as hydrochlorides, which are selected from among:

- 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid;

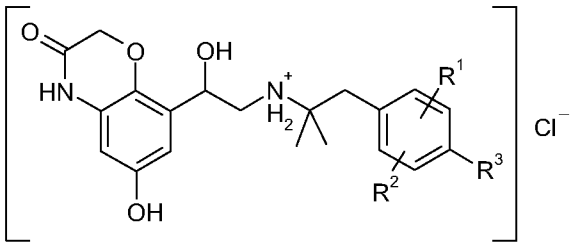
- 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-chloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-bromo-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-3-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-2.6-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-chloro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-chloro-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-chloro-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(2.6-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(2.5-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(4-fluoro-3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3,5-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

- 8-{2-[2-(4-chloro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3,4,5-trifluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;
- 8-{2-[2-(3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one and
- 8-{2-[2-(3,4-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,

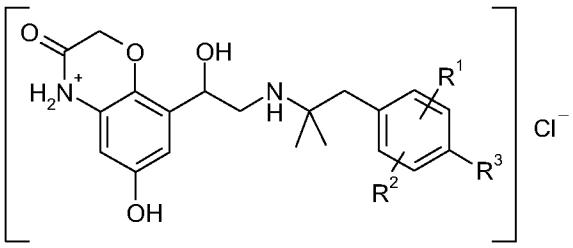
in each case in the form of an acid addition salt with an acid HCl, as well as optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

The compounds according to the invention may be prepared analogously to methods already known in the art. Suitable methods of preparation are known for example from WO 04/045618 or US 4460581, the contents of which are hereby incorporated by reference.

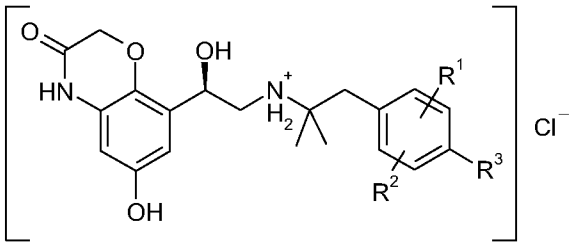
The compounds of formula **1** may optionally be contained in the medicament formulations according to the invention in the form of their tautomers. By tautomerism is meant the occurrence of isomeric compounds which are formed by the displacement of σ or π bonds and may be present in equilibrium. Examples of possible tautomeric forms of the compounds of formula **1** are



or



In another aspect the present invention relates to medicament formulations which contain 91 to 500 mg per 100 ml of solution, of the above-mentioned compounds of formula **1** in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates. Particularly preferred are medicament formulations which contain 91 to 500 mg per 100 ml solution, of the above-mentioned compounds of formula **1** in the form of the enantiomerically pure compounds, while the R-enantiomer of the compounds of formula **1** is of exceptional importance according to the invention. These R-enantiomers can be represented by general formula ***R*-1**



***R*-1**,

wherein the groups R^1, R^2 and R^3 may have the above-mentioned meanings.

In another aspect the present invention relates to the use of the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of respiratory complaints selected from the group comprising obstructive pulmonary diseases of various origins, pulmonary emphysema of various origins, restrictive pulmonary diseases, interstitial pulmonary diseases, cystic fibrosis, bronchitis of various origins, bronchiectasis, ARDS (adult respiratory distress syndrome) and all forms of pulmonary oedema.

- Preferably the medicament formulations according to the invention are used as specified above for preparing a pharmaceutical composition for the treatment of obstructive pulmonary diseases selected from among bronchial asthma, paediatric asthma, severe asthma, acute asthma attacks, chronic bronchitis and chronic obstructive pulmonary disease (COPD), while it is particularly preferable according to the invention to use them for preparing a pharmaceutical composition for the treatment of bronchial asthma or COPD.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of pulmonary emphysema which has its origins in COPD (chronic obstructive pulmonary disease) or α1-proteinase inhibitor deficiency.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of restrictive pulmonary diseases selected from among allergic alveolitis, restrictive pulmonary diseases triggered by work-related noxious substances, such as asbestosis or silicosis, and restriction caused by lung tumours, such as for example lymphangiosis carcinomatosa, bronchoalveolar carcinoma and lymphomas.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of interstitial pulmonary diseases selected from among pneumonia caused by infections, such as for example infection by viruses, bacteria, fungi, protozoa, helminths or other pathogens, pneumonitis caused by various factors, such as for example aspiration and left heart insufficiency, radiation-induced pneumonitis or fibrosis, collagenoses, such as for example lupus erythematodes, systemic scleroderma or sarcoidosis, granulomatoses, such as for example Boeck's disease, idiopathic interstitial pneumonia or idiopathic pulmonary fibrosis (IPF).

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of cystic fibrosis or mucoviscidosis.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of bronchitis, such as for example

- bronchitis caused by bacterial or viral infection, allergic bronchitis and toxic bronchitis.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of bronchiectasis.

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of ARDS (adult respiratory distress syndrome).

- It is also preferable to use the medicament formulations according to the invention for preparing a pharmaceutical composition for the treatment of pulmonary oedema, for example

- toxic pulmonary oedema after aspiration or inhalation of toxic substances and foreign substances.

- Most preferably, the present invention relates to the use of the pharmaceutical formulations according to the invention for preparing a pharmaceutical composition for the treatment of asthma or COPD. Also of particular importance is the above-mentioned use for preparing a pharmaceutical composition for once-a-day treatment of inflammatory and obstructive respiratory complaints, particularly for the once-a-day treatment of asthma or COPD.

Moreover the present invention relates to a process for the treatment of the above-mentioned diseases, characterised in that one or more of the above-mentioned medicament formulations according to the invention are administered in therapeutically effective amounts.

The present invention relates to liquid active substance formulations of these compounds which can be administered by inhalation; the liquid formulations according to the invention have to meet high quality standards. The formulations according to the invention may be inhaled by oral or nasal route. To achieve an optimum distribution of the active substances in the lung it makes sense to use a liquid formulation without propellant gases administered using suitable inhalers. A formulation of this kind may be inhaled both by oral route and by nasal route. Those inhalers which are capable of nebulising a small amount of a liquid

formulation in the dosage needed for therapeutic purposes within a few seconds into an aerosol suitable for therapeutic inhalation are particularly suitable. Within the scope of the invention, preferred nebulisers are those in which an amount of less than 100 microlitres, preferably less than 50 microlitres, most preferably less than 25 microlitres of active substance solution can be nebulised preferably in one puff or two puffs to form an aerosol having an average particle size (or particle diameter) of less than 20 microns, preferably less than 10 microns, so that the inhalable part of the aerosol already corresponds to the therapeutically effective quantity. An apparatus of this kind for the propellant-free administration of a metered amount of a liquid pharmaceutical composition for inhalation is described in detail for example in International Patent Application WO 91/14468 "Atomizing Device and Methods" and also in WO 97/12687, cf. Figures 6a and 6b and the accompanying description. In a nebuliser of this kind a pharmaceutical solution is converted by means of a high pressure of up to 500 bar into an aerosol destined for the lungs, which is sprayed. Within the scope of the present specification reference is expressly made to the entire contents of the literature mentioned above.

In inhalers of this kind the formulations of solutions are stored in a reservoir. It is essential that the active substance formulations used are sufficiently stable when stored and at the same time are such that they can be administered directly, if possible without any further handling, in accordance with their medical purpose. Moreover, they must not contain any ingredients which might interact with the inhaler in such a way as to damage the inhaler or the pharmaceutical quality of the solution or of the aerosol produced. To nebulise the solution a special nozzle is used as described for example in WO 94/07607 or WO 99/16530. Reference is expressly made here to both these publications.

The aim of the invention is to provide an aqueous formulation of 91 to 500 mg per 100 ml solution, of the compound of formula **1** which meets the high standards required to ensure optimum nebulisation of a solution using the inhalers mentioned above. The active substance formulations according to the invention must be of sufficiently high pharmaceutical quality, i.e. they should be pharmaceutically stable over a storage time of some years, preferably at least one year, more preferably two years. These propellant-free

formulations of solutions must also be capable of being nebulised by means of an inhaler under pressure, while the composition delivered in the aerosol produced is within a specified range.

References to the compound of formula **1** always include within the scope of the present invention all the possible amorphous and crystalline modifications of this compound. References to the compound of formula **1** also include within the scope of the present invention all the possible solvates and hydrates which may be formed from this compound.

According to the invention the formulation preferably contains only one compound of formula **1**.

The concentration of the compound of formula **1** in the medicament formulation according to the invention is according to the invention around 91 to 500 mg per 100 ml, preferably around 91 to 400 mg per 100 ml, most preferably 91 to 300 mg per 100 ml. Particularly preferably 100 ml of the formulations according to the invention contain about 91 to about 200 mg of **1**.

The pH of the formulation according to the invention is preferably in a range from 2.0 to 6.5, preferably between 2.2 and 5.0, particularly preferably between about 3.0 and 4.5.

The pH is adjusted by the addition of pharmacologically acceptable acids. Pharmacologically acceptable inorganic acids or organic acids may be used for this purpose. Examples of preferred inorganic acids are selected from the group consisting of hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and phosphoric acid. Examples of particularly suitable organic acids are selected from the group consisting of ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid. Preferred inorganic acids are hydrochloric acid and sulphuric acid, of which hydrochloric acid is particularly preferred according to the invention. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred, of which citric acid is particularly preferred according to the invention. If desired, mixtures of

the abovementioned acids may also be used, particularly in the case of acids which have other properties in addition to their acidifying properties, e.g. those which act as flavourings or antioxidants, such as for example citric acid or ascorbic acid.

If desired, pharmacologically acceptable bases may also be used to titrate the pH precisely. Suitable bases include for example alkali metal hydroxides and alkali metal carbonates. The preferred alkali metal ion is sodium. If bases of this kind are used, care must be taken to ensure that the resulting salts, which are then contained in the finished pharmaceutical formulation, are pharmacologically compatible with the abovementioned acid.

The formulations according to the invention may contain complexing agents as additional ingredients. By complexing agents are meant within the scope of the present invention molecules which are capable of entering into complex bonds. Preferably, these compounds should have the effect of complexing cations, most preferably metal cations. The formulations according to the invention preferably contain editic acid (EDTA) or one of the known salts thereof, e.g. sodium EDTA or disodium EDTA, as complexing agent. Preferably, disodium edetate is used, optionally in the form of its hydrates, more preferably in the form of its dihydrate. If complexing agents are used within the formulations according to the invention, their content is preferably in the range from 5 to 15 mg per 100 ml, particularly preferably in the range from 4 to 14 mg per 100 ml of the formulation according to the invention. Preferably, the formulations according to the invention contain a complexing agent in an amount of about 8 to 12 mg per 100 ml, particularly preferably about 10 mg per 100 ml of the formulation according to the invention.

The remarks made concerning disodium edetate also apply analogously to other possible additives which are comparable to EDTA or the salts thereof, which have complexing properties and can be used instead of them, such as for example nitrilotriacetic acid and the salts thereof.

Other pharmacologically acceptable excipients may also be added to the formulation according to the invention. By adjuvants and additives are meant, in this context, any

pharmacologically acceptable and therapeutically useful substance which is not an active substance, but can be formulated together with the active substance in the pharmacologically suitable solvent, in order to improve the qualities of the active substance formulation. Preferably, these substances have no pharmacological effects or no appreciable or at least no undesirable pharmacological effects in the context of the desired therapy. The adjuvants and additives include, for example, stabilisers, antioxidants and/or preservatives which prolong the shelf life of the finished pharmaceutical formulation, as well as flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride, for example.

The preferred excipients include antioxidants such as ascorbic acid, for example, provided that it has not already been used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins occurring in the human body.

Preservatives can be added to protect the formulation from contamination with pathogenic bacteria. Suitable preservatives are those known from the prior art, particularly benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentrations known from the prior art. Preferably, benzalkonium chloride is added to the formulation according to the invention. The amount of benzalkonium chloride is between 5 mg and 15 mg per 100 ml of the formulation, preferably about 6 to 14 mg per 100 ml, particularly preferably about 8 to 12 mg per 100 ml of the formulation according to the invention, particularly preferably about 10 mg per 100 ml of the formulation according to the invention. Benzalkonium chloride may also be used according to the invention in admixture with other preservatives.

Preferred formulations contain only benzalkonium chloride, sodium edetate and the acid needed to adjust the pH, in addition to the solvent water and the compounds of formula **1**.

The pharmaceutical formulations according to the invention containing compounds of formula **1** are preferably used in an inhaler of the kind described hereinbefore in order to produce the propellant-free aerosols according to the invention. At this point we should

once again expressly mention the patent documents described hereinbefore, to which reference is hereby made.

As described at the beginning, a further developed embodiment of the preferred inhaler is disclosed in WO 97/12687 (cf. in particular Figures 6a and 6b and the associated passages of description). This nebuliser (Respimat®) can advantageously be used to produce the inhalable aerosols according to the invention. Because of its cylindrical shape and handy size of less than 9 to 15 cm long and 2 to 4 cm wide, the device can be carried anywhere by the patient. The nebuliser sprays a defined volume of the pharmaceutical formulation out through small nozzles at high pressures, so as to produce inhalable aerosols.

The preferred atomiser essentially consists of an upper housing part, a pump housing, a nozzle, a locking clamp, a spring housing, a spring and a storage container, characterised by

- a pump housing fixed in the upper housing part and carrying at one end a nozzle body with the nozzle or nozzle arrangement,
- a hollow piston with valve body,
- a power take-off flange in which the hollow piston is fixed and which is located in the upper housing part,
- a locking clamping mechanism located in the upper housing part,
- a spring housing with the spring located therein, which is rotatably mounted on the upper housing part by means of a rotary bearing,
- a lower housing part which is fitted onto the spring housing in the axial direction.

The hollow piston with valve body corresponds to a device disclosed in WO 97/12687. It projects partially into the cylinder of the pump housing and is disposed to be axially movable in the cylinder. Reference is made particularly to Figures 1-4 - especially Figure 3 - and the associated passages of description in the abovementioned International Patent Application. At the moment of release of the spring the hollow piston with valve body exerts, at its high pressure end, a pressure of 5 to 60 Mpa (about 50 to 600 bar), preferably 10 to 60 Mpa (about 100 to 600 bar) on the fluid, the measured amount of active substance

solution. Volumes of 10 to 50 microlitres are preferred, volumes of 10 to 20 microlitres are more preferable, whilst a volume of 10 to 15 microlitres per actuation is particularly preferred.

The valve body is preferably mounted at the end of the hollow piston which faces the nozzle body.

The nozzle in the nozzle body is preferably microstructured, i.e. produced by micro-engineering. Microstructured nozzle bodies are disclosed for example in WO-99/16530; reference is hereby made to the contents of this specification, especially Figure 1 and the associated description.

The nozzle body consists for example of two sheets of glass and/or silicon securely fixed together, at least one of which has one or more microstructured channels which connect the nozzle inlet end to the nozzle outlet end. At the nozzle outlet end there is at least one round or non-round opening 2 to 10 microns deep and 5 to 15 microns wide, the depth preferably being 4.5 to 6.5 microns and the length being 7 to 9 microns.
If there is a plurality of nozzle openings, preferably two, the directions of spraying of the nozzles in the nozzle body may run parallel to one another or may be inclined relative to one another in the direction of the nozzle opening. In the case of a nozzle body having at least two nozzle openings at the outlet end, the directions of spraying may be inclined relative to one another at an angle of 20 degrees to 160 degrees, preferably at an angle of 60 to 150 degrees, most preferably 80 to 100°. The nozzle openings are preferably arranged at a spacing of 10 to 200 microns, more preferably at a spacing of 10 to 100 microns, still more preferably 30 to 70 microns. A spacing of 50 microns is most preferred. The directions of spraying therefore meet in the region of the nozzle openings.

As already mentioned, the liquid pharmaceutical preparation hits the nozzle body at an entry pressure of up to 600 bar, preferably 200 to 300 bar, and is atomised through the nozzle openings into an inhalable aerosol. The preferred particle sizes of the aerosol are up to 20 microns, preferably 3 to 10 microns.

The locking clamping mechanism contains a spring, preferably a cylindrical helical compression spring, as a store for the mechanical energy. The spring acts on the power take-off flange as a spring member the movement of which is determined by the position of a locking member. The travel of the power take-off flange is precisely limited by an upper stop and a lower stop. The spring is preferably tensioned via a stepping-up gear, e.g. a helical sliding gear, by an external torque which is generated when the upper housing part is turned relative to the spring housing in the lower housing part. In this case, the upper housing part and the power take-off flange contain a single- or multi-speed spline gear.

The locking member with the engaging locking surfaces is arranged in an annular configuration around the power take-off flange. It consists for example of a ring of plastics or metal which is inherently radially elastically deformable. The ring is arranged in a plane perpendicular to the axis of the atomiser. After the locking of the spring, the locking surfaces of the locking member slide into the path of the power take-off flange and prevent the spring from being released. The locking member is actuated by means of a button. The actuating button is connected or coupled to the locking member. In order to actuate the locking clamping mechanism the actuating button is moved parallel to the annular plane, preferably into the atomiser, and the deformable ring is thereby deformed in the annular plane. Details of the construction of the locking clamping mechanism are described in WO 97/20590.

The lower housing part is pushed axially over the spring housing and covers the bearing, the drive for the spindle and the storage container for the fluid.

When the atomiser is operated, the upper part of the housing is rotated relative to the lower part, the lower part taking the spring housing with it. The spring meanwhile is compressed and biased by means of the helical sliding gear, and the clamping mechanism engages automatically. The angle of rotation is preferably a whole-number fraction of 360 degrees, e.g. 180 degrees. At the same time as the spring is tensioned, the power take-off

component in the upper housing part is moved along by a given amount, the hollow piston is pulled back inside the cylinder in the pump housing, as a result of which some of the fluid from the storage container is sucked into the high pressure chamber in front of the nozzle.

If desired, a plurality of replaceable storage containers containing the fluid to be atomised can be inserted in the atomiser one after another and then used. The storage container contains the aerosol preparation according to the invention.

The atomising process is initiated by gently pressing the actuating button. The clamping mechanism then opens the way for the power take-off component. The biased spring pushes the piston into the cylinder in the pump housing. The fluid emerges from the nozzle of the atomiser in the form of a spray.

Further details of the construction are disclosed in PCT applications WO 97/12683 and WO 97/20590, to which reference is hereby made.

The components of the atomiser (nebuliser) are made of a material suitable for their function. The housing of the atomiser and – if the function allows – other parts as well are preferably made of plastics, e.g. by injection moulding. For medical applications, physiologically acceptable materials are used.

Figures 6a/b of WO 97/12687 show the Respimat® nebuliser with which the aqueous aerosol preparations according to the invention can advantageously be inhaled. Figure 6a shows a longitudinal section through the atomiser with the spring under tension, Figure 6b shows a longitudinal section through the atomiser with the spring released.

The upper housing part (51) contains the pump housing (52), on the end of which is mounted the holder (53) for the atomiser nozzle. In the holder is the nozzle body (54) and a filter (55). The hollow piston (57) fixed in the power take-off flange (56) of the locking clamping mechanism projects partly into the cylinder of the pump housing. At its end the

hollow piston carries the valve body (58). The hollow piston is sealed off by the gasket (59). Inside the upper housing part is the stop (60) on which the power take-off flange rests when the spring is relaxed. Located on the power take-off flange is the stop (61) on which the power take-off flange rests when the spring is under tension. After the tensioning of the spring, the locking member (62) slides between the stop (61) and a support (63) in the upper housing part. The actuating button (64) is connected to the locking member. The upper housing part ends in the mouthpiece (65) and is closed off by the removable protective cap (66). The spring housing (67) with compression spring (68) is rotatably mounted on the upper housing part by means of the snap-fit lugs (69) and rotary bearings. The lower housing part (70) is pushed over the spring housing. Inside the spring housing is the replaceable storage container (71) for the fluid (72) which is to be atomised. The storage container is closed off by the stopper (73), through which the hollow piston projects into the storage container and dips its end into the fluid (supply of active substance solution). The spindle (74) for the mechanical counter is mounted on the outside of the spring housing. The drive pinion (75) is located at the end of the spindle facing the upper housing part. On the spindle is the slider (76).

The nebuliser described above is suitable for nebulising the aerosol preparations according to the invention to form an aerosol suitable for inhalation.

If the formulation according to the invention is nebulised using the method described above (Respimat®), the mass expelled, in at least 97%, preferably at least 98% of all the actuations of the inhaler (puffs), should correspond to a defined quantity with a range of tolerance of not more than 25%, preferably 20% of this quantity. Preferably, between 5 and 30 mg, more preferably between 5 and 20 mg of formulation are delivered as a defined mass per puff.

However, the formulation according to the invention can also be nebulised using inhalers other than those described above, for example jet-stream inhalers.

The present invention also relates to an inhalation kit consisting of one of the pharmaceutical preparations according to the invention described above and an inhaler suitable for nebulising this pharmaceutical preparation. The present invention preferably relates to an inhalation kit consisting of one of the pharmaceutical preparations according to the invention described above and the Respimat® inhaler described above.

TERMS AND DEFINITIONS USED

By alkyl groups are meant, unless stated otherwise, branched and unbranched alkyl groups with 1 to 4 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless stated otherwise, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and iso-propyl, butyl includes iso-butyl, sec. butyl and tert.-butyl etc.

By alkylene groups are meant, unless stated otherwise, branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms. Examples include: methylene, ethylene, n-propylene or n-butylene.

By alkyloxy groups (or -O-alkyl groups or alkoxy groups) are meant, unless stated otherwise, branched and unbranched alkyl groups with 1 to 4 carbon atoms which are linked via an oxygen atom. Examples include: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or also butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless stated otherwise, the definitions propyloxy and butyloxy include all the possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and iso-propyloxy, butyloxy includes iso-butyloxy, sec. butyloxy and tert.-butyloxy etc. In some cases within the scope of the present invention the term alkoxy is used instead of the term alkyloxy. The groups methyloxy, ethyloxy, propyloxy or also butyloxy may optionally also be referred to by the terms methoxy, ethoxy, propoxy or butoxy.

Halogen within the scope of the present invention denotes fluorine, chlorine, bromine or iodine. Unless stated otherwise, fluorine, chlorine and bromine are regarded as preferred halogens.

EXPERIMENTAL SECTION

The formulation examples listed hereinafter serve to provide further explanation without restricting the subject matter of the present invention to the compositions described by way of example. Of exceptional importance according to the invention as active substances for the formulation are Examples **1** to **33**, particularly in the form of the R-enantiomers, the preparation of which is known from WO 04/045618 or US4460581.

- **Example 1:** 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-2,6-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 2:** 8-{2-[2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 3:** 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 4:** 6-hydroxy-8-{1-hydroxy-2-[2-(ethyl 4-phenoxy-acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 5:** 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 6:** 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 7:** 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 8:** 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 9:** 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride

- **Example 10:** 8-{2-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 11:** 8-{2-[2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 12:** 8-{2-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 13:** 8-{2-[2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 14:** 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 15:** 8-{2-[2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 16:** 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid-hydrochloride
- **Example 17:** 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 18:** 8-{2-[2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 19:** 8-{2-[2-(4-chloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 20:** 8-{2-[2-(4-bromo-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride-hydrochloride
- **Example 21:** 8-{2-[2-(3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 22:** 8-{2-[2-(4-fluoro-3-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 23:** 8-{2-[2-(4-fluoro-2,6-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 24:** 8-{2-[2-(4-chloro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride

- **Example 25:** 8-{2-[2-(4-chloro-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 26:** 8-{2-[2-(4-chloro-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 27:** 8-{2-[2-(3-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 28:** 8-{2-[2-(2,6-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 29:** 8-{2-[2-(2.5-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 30:** 8-{2-[2-(4-fluoro-3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 31:** 8-{2-[2-(3,5-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 32:** 8-{2-[2-(4-chloro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 33:** 8-{2-[2-(3,4,5-trifluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride
- **Example 34:** 8-{2-[2-(3,4-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one-hydrochloride

II. FORMULATION EXAMPLES

A) Formulation examples according to the invention of the R-enantiomer of compound **Example 1** are composed of 100 ml purified water or water for injections, 10 mg benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 94, 102, 117, 125, 133, 149, 161, 169, 174, 181, 190, 198 or 200 mg of **1**.

B) Formulation examples according to the invention of the R-enantiomer of compound **Example 3** are composed of 100 ml purified water or water for injections, 10 mg

benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 91, 94, 99, 102, 110, 117, 125, 133, 138, 143, 149, 155, 161, 169, 174, 178, 181, 186, 190, 198 or 200 mg of **1**.

C) Formulation examples according to the invention of the R-enantiomer of compound **Example 7** are composed of 100 ml purified water or water for injections, 10 mg benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 91, 94, 99, 102, 110, 117, 125, 133, 138, 143, 149, 155, 161, 169, 174, 178, 181, 186, 190, 198 or 200 mg of **1**.

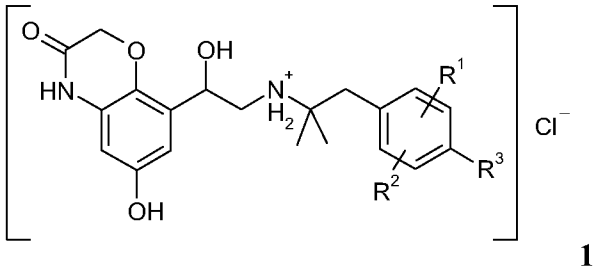
D) Formulation examples according to the invention of the R-enantiomer of compound **Example 9** are composed of 100 ml purified water or water for injections, 10 mg benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 91, 94, 99, 102, 110, 117, 125, 133, 138, 143, 149, 155, 161, 169, 174, 178, 181, 186, 190, 198 or 200 mg of **1**.

E) Formulation examples according to the invention of the R-enantiomer of compound **Example 14** are composed of 100 ml purified water or water for injections, 10 mg benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 91, 94, 99, 102, 110, 117, 125, 133, 138, 143, 149, 155, 161, 169, 174, 178, 181, 186, 190, 198 or 200 mg of **1**.

F) Formulation examples according to the invention of the R-enantiomer of compound **Example 17** are composed of 100 ml purified water or water for injections, 10 mg benzalkonium chloride, 10 mg disodium edetate-dihydrate, 3 mg citric acid and 91, 94, 99, 102, 110, 117, 125, 133, 138, 143, 149, 155, 161, 169, 174, 178, 181, 186, 190, 198 or 200 mg of **1.**

PATENT CLAIMS

1. Medicament formulation, containing as sole active substance 91 to 500 mg per 100 ml solution of one or more compounds of general formula **1**



1

wherein

R^1 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or halogen;

R^2 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy or halogen;

R^3 denotes hydrogen, C_1-C_4-alkyl, C_1-C_4-alkoxy, halogen, OH, -O-C_1-C_4-alkylene-COOH or -O-C_1-C_4-alkylene-COO-C_1-C_4-alkyl,

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof, at least one pharmacologically acceptable acid, optionally other pharmacologically acceptable excipients and/or complexing agents and water as solvent.

2. Medicament formulation according to claim 1, characterised in that it contains one or more compounds of formula **1**, wherein

R^1 denotes hydrogen, methyl, ethyl, fluorine or chlorine;

R^2 denotes hydrogen, methyl, ethyl, fluorine or chlorine;

R^3 denotes hydrogen, methyl, ethyl, propyl, OH, methoxy, ethoxy, fluorine, chlorine, bromine, -O-CH_2-COOH, -O-CH_2-COOmethyl or -O-CH_2-COOethyl, -O-CH_2-CH_2COOH, -O-CH_2-CH_2COOmethyl or -O-CH_2-CH_2COOethyl, -O-CH_2-CH_2-CH_2COOH, -O-CH_2-CH_2-CH_2COOmethyl or -O-CH_2-CH_2-CH_2COOethyl;

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

3. Medicament formulation according to claim 1, characterised in that it contains one or more compounds of formula **1**, wherein

R^1 denotes hydrogen or methyl, preferably hydrogen;

R^2 denotes hydrogen or methyl, preferably hydrogen;

R^3 denotes methyl, OH, methoxy, fluorine, chlorine, bromine, -O-CH_2-COOH or -O-CH_2-COOethyl;

optionally in the form of their tautomers, enantiomers, mixtures of the enantiomers, racemates or solvates thereof.

4. Medicament formulation according to one of claims 1, 2 or 3, wherein the pharmacologically acceptable acid is selected from the inorganic acids hydrochloric acid, hydrobromic acid, nitric acid, sulphuric acid and phosphoric acid or from the organic acids ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid and propionic acid.

5. Medicament formulation according to one of claims 1 to 4, characterised by a pH of 2.5 to 6.5.

6. Medicament formulation according to one of claims 1 to 5, characterised in that they contain benzalkonium chloride as excipient.

7. Medicament formulation according to claim 6, characterised in that the content of benzalkonium chloride is 5 to 15 mg per 100 ml solution.

8. Medicament formulation according to one of claims 1 to 7, characterised in that the content of **1** is about 91 to 500 mg per 100 ml solution.

9. Medicament formulation according to one of claims 1 to 8, characterised in that they contain a complexing agent as a further ingredient.

10. Medicament formulation according to claim 9, characterised in that the content of complexing agent is 5 to 15 mg per 100 ml solution.

11. Use of a medicament formulation according to one of claims 1 to 10 for preparing a pharmaceutical composition for the treatment of respiratory complaints.

12. Inhalation kit consisting of a medicament formulation according to one of claims 1 to 10 and an inhaler suitable for nebulising this medicament formulation.

13. Inhalation kit according to claim 12, wherein the inhaler is a Respimat®.