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(54) NEW MEDICAMENTS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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(52) **U.S. Cl.** ..... **544/105**; 514/230.5

(57) **ABSTRACT**

A pharmaceutical composition comprising a compound of formula 1

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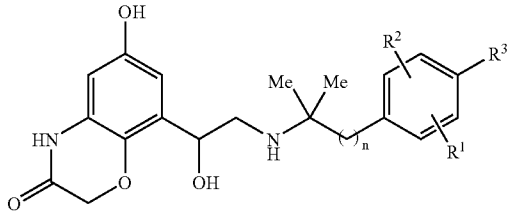


wherein: n is 1 or 2;

$R^1$ is hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl;

$R^2$ is hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl;

$R^3$ is hydrogen, $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof, and a pharmaceutically acceptable excipient or carrier, and methods for using the pharmaceutical formulation in the treatment of chronic obstructive pulmonary disease (COPD).

# NEW MEDICAMENTS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

## RELATED APPLICATIONS

[0001] This application is a Continuation of U.S. Ser. No. 10/705,012, filed Nov. 10, 2003, which claims priority to U.S. Ser. No. 60/434,038, filed Dec. 17, 2002, and German Application No. 102 53 282.6 filed Nov. 15, 2003, each of which is hereby incorporated by reference in its entirety.

## FIELD OF THE INVENTION

[0002] The present invention relates to the use of the compounds of general formula 1

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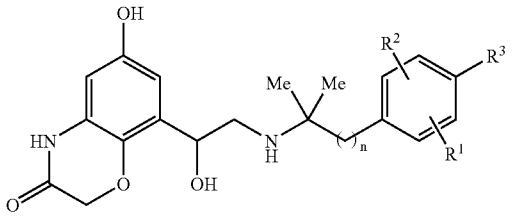


wherein the groups $R^1$, $R^2$, and $R^3$ may have the meanings given in the claims and in the specification, for preparing a pharmaceutical composition for the treatment of chronic obstructive pulmonary disease (COPD), as well as new compounds of general formula 1 and processes for preparing them.

## BACKGROUND OF THE INVENTION

[0003] Betamimetics (β-adrenergic substances) are known from the prior art. Reference may be made, for example, to the disclosures of U.S. Pat. No. 4,460,581, which is hereby incorporated by reference, which proposes betamimetics for the treatment of a variety of complaints.

[0004] 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.

[0005] 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 taking the drug regularly at certain times of the day.

[0006] The aim of the present invention is therefore to provide betamimetics which have a therapeutic benefit in the treatment of COPD and are characterized by a longer duration of activity and can thus be used to prepare pharmaceutical compositions with a longer duration of activity. A particular aim of the invention is to prepare betamimetics which, by virtue of their long-lasting effect, can be used to prepare a drug for administration once a day for treating COPD. In addition to the above objectives, the present invention also sets out to provide betamimetics which are not only exceptionally potent but are also characterized by a high degree of selectivity with respect to the $\beta_2$-adrenoreceptor.

## DETAILED DESCRIPTION OF THE INVENTION

[0007] Surprisingly it has been found that the abovementioned problems are solved by compounds of general formula 1.

[0008] Accordingly, the present invention relates to compounds of general formula 1

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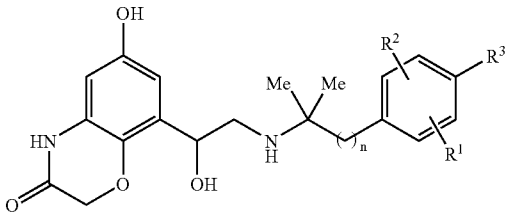


wherein:

[0009] n denotes 1 or 2,

[0010] $R^1$ denotes hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl;

[0011] $R^2$ denotes hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl; and

[0012] $R^3$ denotes hydrogen, $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

for preparing a pharmaceutical composition for the treatment of COPD.

[0013] It is preferable to use compounds of general formula 1, wherein:

[0014] n denotes 1 or 2;

[0015] $R^1$ denotes hydrogen, halogen or $C_1$-$C_4$-alkyl;

[0016] $R^2$ denotes hydrogen, halogen or $C_1$-$C_4$-alkyl; and

[0017] $R^3$ denotes hydrogen, $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

for preparing a pharmaceutical composition for the treatment of COPD.

[0018] It is preferable to use compounds of general formula 1 wherein:

[0019] n denotes 1 or 2;

[0020] $R^1$ denotes hydrogen, fluorine, chlorine or methyl;

[0021] $R^2$ denotes hydrogen, fluorine, chlorine or methyl; and

[0022] $R^3$ denotes hydrogen, $C_1$-$C_4$-alkyl, OH, fluorine, chlorine, bromine, —O—$C_1$-$C_4$-alkyl, —O-$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

for preparing a pharmaceutical composition for the treatment of COPD.

[0023] It is particularly preferred to use compounds of general formula 1 wherein:

[0024] n denotes 1 or 2;

[0025] $R^1$ denotes hydrogen, methyl or ethyl;

[0026] $R^2$ denotes hydrogen, methyl or ethyl; and

[0027] $R^3$ denotes hydrogen, methyl, ethyl, OH, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—CO—O-methyl, or —O—$CH_2$—COOethyl,

for preparing a pharmaceutical composition for the treatment of COPD.

[0028] It is particularly preferred to use compounds of general formula 1 wherein:

[0029] n denotes 1 or 2;

[0030] $R^1$ denotes hydrogen or methyl;

[0031] $R^2$ denotes hydrogen or methyl; and

[0032] $R^3$ denotes hydrogen, methyl, OH, methoxy, —O—$CH_2$—COOH, or —O—$CH_2$—COOethyl,

for preparing a pharmaceutical composition for the treatment of COPD.

[0033] Also of particular importance according to the invention is the use of compounds of general formula 1 wherein:

[0034] n denotes 1 or 2;

[0035] $R^1$ denotes hydrogen or methyl;

[0036] $R^2$ denotes hydrogen or methyl; and

[0037] $R^3$ denotes hydrogen, OH, methoxy, or —O—$CH_2$—COOH,

for preparing a pharmaceutical composition for the treatment of COPD.

[0038] A preferred aspect of the present invention further relates to the use of compounds of general formula 1 wherein n is 1 and the groups $R^1$, $R^2$, and $R^3$ may have the abovementioned meanings, for preparing a pharmaceutical composition for the treatment of COPD.

[0039] Another preferred aspect of the present invention relates to the use of compounds of general formula 1 wherein n is 1 or 2, $R^3$ denotes a group selected from among hydrogen, OH, —O—$C_1$-$C_4$-alkyl, and —O—$C_1$-$C_4$-alkylene-COOH, and wherein the groups $R^1$ and $R^2$ may have the abovementioned meanings, for preparing a pharmaceutical composition for the treatment of COPD.

[0040] Another preferred aspect of the present invention relates to the use of compounds of general formula 1 wherein n is 2, $R^1$ and $R^2$ are each hydrogen, and the group $R^3$ may have the abovementioned meanings, for preparing a pharmaceutical composition for the treatment of COPD.

[0041] In the compounds of formula 1 the groups $R^1$ and $R^2$, if they do not represent hydrogen, may each be arranged in the ortho or meta position relative to the bond to the benzylic "—$CH_2$" group. If neither of the groups $R^1$ and $R^2$ denotes hydrogen, it is preferable according to the invention to use those compounds of formula 1 wherein the two groups $R^1$ and $R^2$ are either in the ortho configuration or both groups $R^1$ and $R^2$ are in the meta configuration, while the use of those compounds wherein both groups $R^1$ and $R^2$ are in the ortho configuration is particularly important.

[0042] In the compounds of formula 1 wherein one of the groups $R^1$ and $R^2$ does not denote hydrogen, it may be in the ortho or meta configuration with respect to the bond to the benzylic "—$CH_2$" group. In this case it is particularly preferred according to the invention to use those compounds of formula 1 wherein the group $R^1$ or $R^2$, which does not denote hydrogen, is in the ortho configuration.

[0043] In another aspect, the present invention relates to the abovementioned use of the compounds of formula 1 in the form of the individual optical isomers, mixtures of the individual enantiomers, or racemates. It is particularly preferable to use the compounds of formula 1 as mentioned above in the form of the enantiomerically pure compounds, while the use of the R enantiomers of the compounds of formula 1 is of particular importance according to the invention.

[0044] In another aspect, the present invention relates to the abovementioned use of the compounds of formula 1 in the form of the acid addition salts with pharmacologically acceptable acids as well as optionally in the form of the solvates and/or hydrates thereof.

[0045] The present invention further relates to the use of the abovementioned compounds of general formula 1 for preparing a pharmaceutical composition for once-a-day treatment of COPD.

[0046] Moreover, the present invention relates to a process for the treatment of COPD, characterized in that one or more of the abovementioned compounds of general formula 1 are administered in therapeutically effective amounts. The present invention also relates to processes for treating COPD, characterized in that one or more of the abovementioned compounds of general formula 1 are administered once a day in therapeutically effective amounts.

[0047] The compounds of general formula 1 are partly known from the prior art. Reference is made here to the disclosure of U.S. Pat. No. 4,460,581. In some cases, however, the compounds of general formula 1 have not yet been disclosed in the prior art. Another aspect of the present invention relates to these new compounds of formula 1 as such.

[0048] Accordingly, the present invention also relates to compounds of general formula 1

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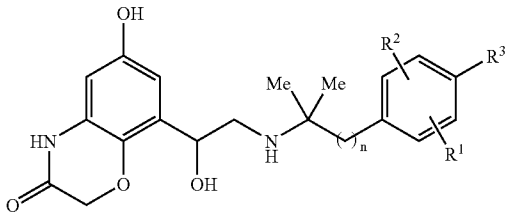



wherein:

[0049] n denotes 1;

[0050] $R^1$ denotes hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

[0051] $R^2$ denotes hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl; and

[0052] $R^3$ denotes $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

with the proviso that, if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH.

[0053] Preferred compounds of general formula 1 are those wherein:

[0054] n denotes 1;

[0055] $R^1$ denotes hydrogen, fluorine, chlorine, methyl, or methoxy;

[0056] $R^2$ denotes hydrogen, fluorine, chlorine, methyl, or methoxy; and

[0057] $R^3$ denotes $C_1$-$C_4$-alkyl, OH, fluorine, chlorine, bromine, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

with the proviso that, if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH.

[0058] Preferred compounds of general formula 1 are those wherein:

[0059] n denotes 1;

[0060] $R^1$ denotes hydrogen or $C_1$-$C_4$-alkyl;

[0061] $R^2$ denotes hydrogen or $C_1$-$C_4$-alkyl; and

[0062] $R^3$ denotes $C_1$-$C_4$-alkyl, OH, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

with the proviso that, if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH.

[0063] Preferred compounds of general formula 1 are those wherein:

[0064] n denotes 1;

[0065] $R^1$ denotes hydrogen, methyl or ethyl;

[0066] $R^2$ denotes hydrogen, methyl or ethyl; and

[0067] $R^3$ denotes methyl, ethyl, OH, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl,

with the proviso that, if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH.

[0068] Also preferred are the compounds of general formula 1 wherein:

[0069] n denotes 1;

[0070] $R^1$ denotes hydrogen or methyl;

[0071] $R^2$ denotes hydrogen or methyl; and

[0072] $R^3$ denotes methyl, OH, methoxy, —O—$CH_2$—COOH, or —O—$CH_2$—COOethyl,

with the proviso that if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH.

[0073] Also preferred according to the invention are compounds of general formula 1 wherein $R^3$ denotes methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl, and $R^1$, $R^2$, and n may have the above meanings.

[0074] The present invention also relates to compounds of general formula 1 wherein:

[0075] n denotes 1;

[0076] $R^1$ denotes halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

[0077] $R^2$ denotes halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl; and

[0078] $R^3$ denotes halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl.

[0079] The present invention also relates to compounds of general formula 1 wherein:

[0080] n denotes 1;

[0081] $R^1$ denotes fluorine, chlorine, methyl, or methoxy;

[0082] $R^2$ denotes fluorine, chlorine, methyl, or methoxy; and

[0083] $R^3$ denotes fluorine, chlorine, methyl, or methoxy.

[0084] In another preferred aspect the present invention relates to the compounds of general formula 1 wherein:

[0085] n denotes 1;

[0086] $R^1$ denotes hydrogen;

[0087] $R^2$ denotes hydrogen, fluorine, chlorine, or methyl; and

[0088] $R^3$ denotes methyl, ethyl, isopropyl, tert-butyl, OH, fluorine, chlorine, bromine, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—$CH_2$—COOH, —O—$CH_2$—$CH_2$—$CH_2$—COOH, —O—$CH_2$—COOmethyl, —O—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—COOmethyl, —O—$CH_2$—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—$CH_2$—COOmethyl, or —O—$CH_2$—$CH_2$—$CH_2$—COOethyl.

[0089] Also particularly preferred are compounds of general formula 1 wherein

[0090] n denotes 1;

[0091] $R^1$ denotes hydrogen;

[0092] $R^2$ denotes hydrogen, fluorine, chlorine, or methyl; and

[0093] $R^3$ denotes OH, fluorine, chlorine, methyl, methoxy, ethoxy, or —O—$CH_2$—COOH.

[0094] Other particularly preferred compounds of general formula 1 according to the invention are those wherein

[0095] n denotes 1;

[0096] $R^1$ denotes hydrogen;

[0097] $R^2$ denotes halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl, preferably fluorine, chlorine, methoxy, or methyl; and

[0098] $R^3$ denotes halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl, preferably fluorine, chlorine, methoxy, or methyl.

[0099] Another preferred aspect of the present invention relates to the compounds of general formula 1 wherein n is 1, $R^1$ and $R^2$ denote hydrogen, and the group $R^3$ may have the abovementioned meanings.

[0100] Another preferred aspect of the present invention relates to the compounds of general formula 1 wherein:

[0101] n denotes 1;

[0102] $R^1$ and $R^2$ denote hydrogen; and

[0103] $R^3$ denotes methyl, ethyl, isopropyl, tert-butyl, OH, fluorine, chlorine, bromine, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—$CH_2$—COOH, —O—$CH_2$—$CH_2$—$CH_2$—COOH, —O—$CH_2$—COOmethyl, —O—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—COOmethyl, —O—$CH_2$—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—$CH_2$—COOmethyl, or —O—$CH_2$—$CH_2$—$CH_2$—COOethyl.

[0104] Particularly preferred are compounds of general formula 1 wherein:

[0105] n denotes 1;

[0106] $R^1$ and $R^2$ denote hydrogen; and

[0107] $R^3$ denotes OH, fluorine, chlorine, methoxy, ethoxy, or —O—$CH_2$—COOH, preferably OH, fluorine, chlorine, ethoxy, or methoxy.

[0108] Particularly preferred are compounds of general formula 1 wherein:

[0109] n denotes 1;

[0110] $R^1$ and $R^2$ denote hydrogen; and

[0111] $R^3$ denotes fluorine, chlorine, methoxy, or ethoxy.

[0112] The present invention also relates to compounds of general formula 1 wherein:

[0113] n denotes 1;

[0114] $R^1$ denotes hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

[0115] $R^2$ denotes hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl; and

[0116] $R^3$ denotes hydrogen.

[0117] Also preferred are compounds of general formula 1 wherein:

[0118] n denotes 1;

[0119] $R^1$ denotes hydrogen, fluorine, chlorine, methyl, or methoxy;

[0120] $R^2$ denotes hydrogen, fluorine, chlorine, methyl, or methoxy; and

[0121] $R^3$ denotes hydrogen.

[0122] The present invention also relates to compounds of general formula 1 wherein:

[0123] n denotes 1;

[0124] $R^1$ denotes fluorine, chlorine, methyl, or methoxy;

[0125] $R^2$ denotes fluorine, chlorine, methyl, or methoxy; and

[0126] $R^3$ denotes hydrogen.

[0127] In the compounds of formula 1, the groups $R^1$ and $R^2$, if they do not represent hydrogen, may each be arranged in the ortho or meta position relative to the bond to the benzylic "—$CH_2$" group. If neither of the groups $R^1$ and $R^2$ denotes hydrogen, preferred compounds of formula 1 are those wherein the two groups $R^1$ and $R^2$ are either in the ortho configuration or both groups $R^1$ and $R^2$ are in the meta configuration, while the use of those compounds wherein both groups $R^1$ and $R^2$ are in the ortho configuration is particularly important.

[0128] In the compounds of formula 1 wherein one of the groups $R^1$ and $R^2$ does not denote hydrogen, it may be in the ortho or meta configuration with respect to the bond to the benzylic "—$CH_2$" group. In this case, particularly preferred compounds of formula 1 are those wherein the group $R^1$ or $R^2$, which does not denote hydrogen, is in the ortho configuration.

[0129] Also particularly preferred are compounds of general formula 1 which are selected from among:

[0130] (1) 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxyphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

[0131] (2) 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyethylacetate)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

[0132] (3) 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyacetic acid)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

[0133] (4) 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl-)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0134] (5) 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

[0135] (6) 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

[0136] (7) 8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0137] (8) 8-{2-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0138] (9) 8-{2-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0139] (10) 8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0140] (11) 8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0141] (12) 8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0142] (13) 8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0143] (14) 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methylpropyl}phenoxy)butyric acid;

[0144] (15) 8-{2-[2-(3,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0145] (16) 8-{2-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0146] (17) 8-{2-[2-(4-chlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0147] (18) 8-{2-[2-(4-bromophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0148] (19) 8-{2-[2-(4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0149] (20) 8-{2-[2-(4-fluoro-3-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0150] (21) 8-{2-[2-(4-fluoro-2,6-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0151] (22) 8-{2-[2-(4-chloro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0152] (23) 8-{2-[2-(4-chloro-3-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0153] (24) 8-{2-[2-(4-chloro-2-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0154] (25) 8-{2-[2-(3-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0155] (26) 8-{2-[2-(2,6-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0156] (27) 8-{2-[2-(2,5-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0157] (28) 8-{2-[2-(4-fluoro-3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0158] (29) 8-{2-[2-(3,5-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0159] (30) 8-{2-[2-(4-chloro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0160] (31) 8-{2-[2-(3,4,5-trifluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

[0161] (32) 8-{2-[2-(3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one; and

[0162] (33) 8-{2-[2-(3,4-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one.

[0163] In another aspect, the present invention relates to the abovementioned new compounds of formula 1 in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates. Particularly preferred are compounds of formula 1 in the form of the enantiomerically pure compounds, while the R-enantiomers of the compounds of formula 1 are of exceptional importance according to the invention. Methods of separating racemates into the respective enantiomers are known in the prior art and may be used analogously to prepare the enantiomerically pure R- and S-enantiomers of the compounds of formula 1.

[0164] In another aspect, the present invention relates to the abovementioned compounds of formula 1 in the form of the acid addition salts with pharmacologically acceptable acids as well as optionally in the form of the solvates and/or hydrates thereof.

[0165] In another aspect, the present invention relates to the abovementioned compounds of formula 1 for use as pharmaceutical compositions. The present invention further relates to the use of the abovementioned new compounds of general formula 1 for preparing a pharmaceutical composition for the treatment of COPD. The present invention further relates to the use of the abovementioned new compounds of general formula 1 for preparing a pharmaceutical composition for the once-a-day treatment of COPD.

[0166] Moreover, the present invention relates to a process for the treatment of COPD, characterized in that one or more of the abovementioned compounds of general formula 1 are administered in therapeutically effective amounts. The present invention also relates to processes for treating COPD, characterized in that one or more of the abovementioned new compounds of general formula 1 are administered once a day in therapeutically effective amounts.

[0167] By acid addition salts with pharmacologically acceptable acids are meant, for example, the salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulfate, hydrophosphate, hydromethanesulfonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate, and hydro-p-toluenesulfonate salts, preferably the hydrochloride, hydrobromide, hydrosulfate, hydrophosphate, hydrofumarate, and hydromethanesulfonate salts. Of the abovementioned acid addition salts, the salts of hydrochloric acid, methanesulfonic acid, benzoic acid, and acetic acid are particularly preferred according to the invention.

[0168] For use according to the invention, the compounds of general formula 1 may optionally be used in the form of their individual optical isomers, mixtures of the individual enantiomers or racemates. If the compounds are used in enantiomerically pure form, the R-enantiomers are preferred.

[0169] Unless otherwise stated, the alkyl groups are straight-chained or branched alkyl groups having 1 to 4 carbon atoms. The following are mentioned by way of example: methyl, ethyl, propyl, or butyl. In some cases the abbreviations Me, Et, Prop, or Bu are used to denote the groups methyl, ethyl, propyl, or butyl. Unless otherwise stated, the definitions propyl and butyl include all the possible isomeric forms of the groups in question. Thus, for example, propyl includes n-propyl and isopropyl, butyl includes isobutyl, sec-butyl, and tert-butyl, etc.

[0170] Unless otherwise stated, the alkylene groups are branched and unbranched double-bonded alkyl bridges having 1 to 4 carbon atoms. The following are mentioned by way of example: methylene, ethylene, n-propylene, or n-butylene.

[0171] Unless otherwise stated, the term alkyloxy groups (or —O-alkyl groups) denotes branched and unbranched alkyl groups having 1 to 4 carbon atoms which are linked via an oxygen atom. Examples of these include: methyloxy, ethyloxy, propyloxy, or butyloxy. The abbreviations MeO—, EtO—, PropO—, or BuO— are used in some cases to denote the groups methyloxy, ethyloxy, propyloxy, or butyloxy. Unless otherwise stated, the definitions propyloxy and butyloxy include all possible isomeric forms of the groups in question. Thus, for example, propyloxy includes n-propyloxy and isopropyloxy, butyloxy includes isobutyloxy, 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. Accordingly, the terms methoxy, ethoxy, propoxy, or butoxy may also be used to denote the groups methyloxy, ethyloxy, propyloxy, or butyloxy.

[0172] Halogen within the scope of the present invention denotes fluorine, chlorine, bromine, or iodine. Unless stated otherwise, fluorine, chlorine, and bromine are the preferred halogens.

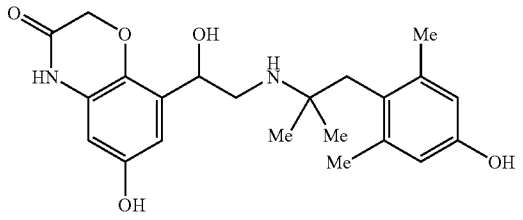
[0173] The compounds according to the invention may be prepared analogously to methods already known from the prior art. Suitable methods of preparation are known for example from U.S. Pat. No. 4,460,581, to the entire contents of which reference is made at this point.

[0174] The examples of synthesis described below serve to illustrate compounds known from the prior art, which may surprisingly be used according to the present invention for the treatment of COPD.

EXAMPLE 1

6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-2,6-dimethylphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one

[0175]

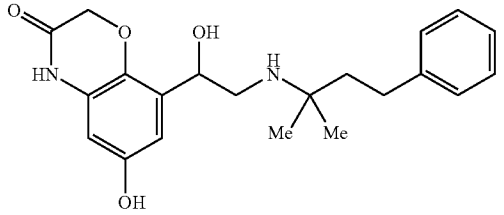



[0176] The compound is known from U.S. Pat. No. 4,460,581.

EXAMPLE 2

8-{2-[1,1-dimethyl-3-phenylpropylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0177]



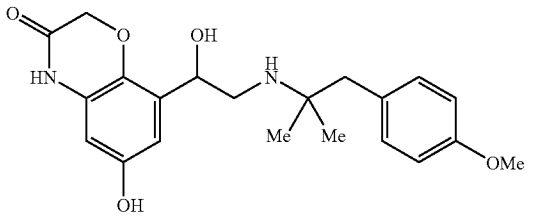

[0178] The compound is known from U.S. Pat. No. 4,460,581.

[0179] The examples of synthesis described below serve to illustrate new compounds according to the invention more fully. They are intended only as examples of procedure to illustrate the invention without restricting it to the subject matter described hereinafter.

EXAMPLE 3

6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxyphenyl)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

[0180]



(a) 8-{2-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-1-hydroxyethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

[0181] 7.5 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)glyoxal hydrate is added at 70° C. to a solution of 3.6 g of 1,1-dimethyl-2-(4-methoxyphenyl)ethylamine in 100 mL ethanol and stirred for 15 minutes. Then 1 g of sodium borohydride is added within 30 minutes at 10° C. to 20° C. The mixture is stirred for one hour, combined with 10 mL acetone, and stirred for a further 30 minutes. The reaction mixture is diluted with 150 mL ethyl acetate, washed with water, dried with sodium sulfate, and evaporated down. The residue is dissolved in 50 mL methanol and 100 mL ethyl acetate and acidified with concentrated hydrochloric acid. After the addition of 100 mL diethyl ether, the product precipitates out. The crystals are filtered off, washed, and recrystallized in 50 mL ethanol. Yield: 7 g (68%; hydrochloride); melting point: 232° C.-234° C.

(b) 8-{2-[1,1-dimethyl-2-(4-methoxyphenyl)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

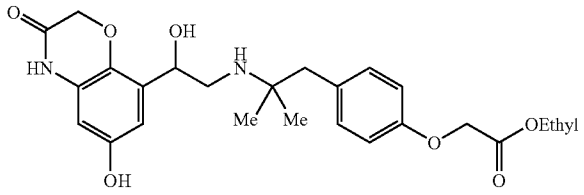
[0182] 6.8 g of the benzyl compound obtained above are hydrogenated in 125 mL methanol with the addition of 1 g palladium on charcoal (5%) at ambient temperature and under normal pressure. The catalyst is filtered off and the filtrate is freed from solvent. After recrystallization of the residue in 50 mL acetone and some water, a solid is obtained, which is filtered off and washed. Yield: 5.0 g (89%; hydrochloride); melting point: 155° C.-160° C.

[0183] The (R)- and (S)-enantiomers of Example 3 may be obtained from the racemate, for example, by chiral HPLC (e.g., column: Chirobiotic T, 250×22.1 mm made by Messrs Astec). The mobile phase may be methanol with 0.05% triethylamine and 0.05% acetic acid. Silica gel with a particle size of 5 μm, to which the glycoprotein Teicoplanin is covalently bound, can be used as the column material. Retention time (R-enantiomer): 40.1 minutes; retention time (S-enantiomer): 45.9 minutes. Both enantiomers are obtained according to this method in the form of their free base. The R-enantiomer of Example 3 is of exceptional importance according to the invention.

EXAMPLE 4

6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyethyl acetate)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one

[0184]



(a) 8-{2-[1,1-dimethyl-2-(4-phenoxyethyl acetate-)ethylamino]-1-hydroxyethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

[0185] The title compound is obtained analogously to the method described in Example 3(a) from 15 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)glyoxal hydrate and 11.8 g of 1,1-dimethyl-2-(4-phenoxyethyl acetate)ethylamine hydrochloride. Yield: 16.5 g (69%, hydrochloride); melting point: 212° C.-214° C.

(b) 8-{2-[1,1-dimethyl-2-(4-phenoxyethyl acetate-)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

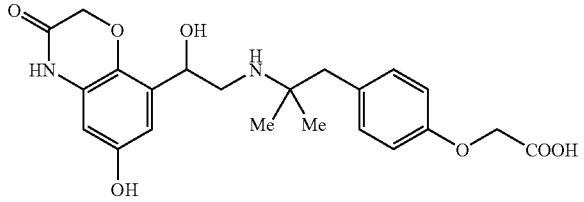
[0186] 8 g of the benzyl alcohol obtained above is dissolved in 100 mL ethanol, 100 mL methanol, and 10 mL water and hydrogenated in the presence of 1 g palladium on charcoal (5%). After the theoretically calculated amount of hydrogen has been taken up, the catalyst is filtered off and the filtrate is evaporated down. The product which crystallizes out when the solvent is distilled off is suction filtered and washed. Yield: 5.5 g (81%; hydrochloride); melting point: 137° C.-140° C.

[0187] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 5

6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyacetic acid)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one

[0188]



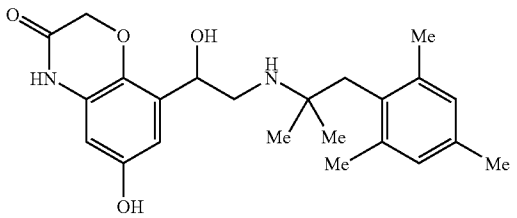
[0189] 11 g of 8-{2-[1,1-dimethyl-2-(4-phenoxyethylacetate)ethylamino]-1-hydroxyethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one hydrochloride (Example 4(a)) is dissolved in 125 mL methanol and hydrogenated in the presence of 1 g palladium on charcoal (5%). After the theoretically calculated amount of hydrogen has been taken up, the catalyst is filtered off. 2.6 g of sodium hydroxide dissolved in 20 mL water is added to the filtrate. The mixture is refluxed for 30 minutes, the methanol is distilled off and combined with 10 mL water, 20 mL n-butanol, and 3.9 mL acetic acid. The solid precipitated is suction filtered and washed with diethyl ether. Yield: 7 g (87%). The hydrochloride is obtained by recrystallization from 0.5 molar hydrochloric acid. Melting point: 152° C.

[0190] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 6

8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0191]




(a) 1-(6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)ethylimino]ethanone

[0192] 7.2 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)glyoxal hydrate and 3.6 g of 1,1-dimethyl-2-(2,4,6-trimethylphenyl)ethylamine are heated to 70° C. for one hour in 100 mL ethanol. After cooling, the crystals precipitated are filtered off and washed with ethanol and diethyl ether. Yield: 8.6 g (94%); melting point: 175° C.

(b) 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl-)ethylamino]-1-hydroxyethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

[0193] 8.6 g of the Schiff base obtained according to Example 6(a) is dissolved in 100 mL ethanol and 20 mL THF, combined with 0.7 g sodium borohydride within 30 minutes at 10° C.-20° C., and stirred for one hour. After the addition of 10 mL acetone, the mixture is stirred for 30 minutes and then diluted with ethyl acetate and water. The product which crystallizes out on acidification with concentrated hydrochloric acid is filtered off and washed. Yield: 7.4 g (80%, hydrochloride); melting point: 235° C. (decomposition).

c) 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

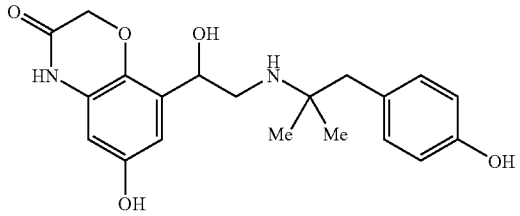
[0194] 7.4 g of the benzyl compound obtained according to Example 6(b) is hydrogenated in 125 mL methanol with the addition of 1 g palladium on charcoal (5%) at ambient temperature under normal pressure. Then the catalyst is filtered off and the filtrate is evaporated down. The product which crystallizes out when acetone is added is suction filtered and washed with acetone and diethyl ether. Yield: 5 g (78%, hydrochloride); melting point 160° C. (decomposition).

[0195] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 7

6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

[0196]




(a) 8-{2-[1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino]-1-hydroxyethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

[0197] The title compound is prepared from 10 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-glyoxal hydrate and 4.6 g of 1,1-dimethyl-2-(4-hydroxyphenyl)ethylamine analogously to the method for Example 3(a). Yield: 9.0 g (64%, hydrochloride); melting point: 255° C.-258° C.

(b) 8-{2-[1,1-dimethyl-2-(4-hydroxyphenyl)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

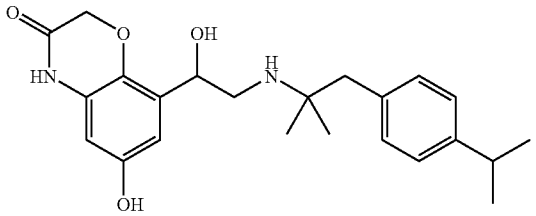
[0198] 5.7 g of the coupling product obtained above are hydrogenated in the presence of 0.6 g palladium on charcoal (5%) in 100 mL methanol. After the theoretically calculated amount of hydrogen has been taken up, the catalyst is filtered off and the filtrate is freed from solvent. The residue is dissolved in ethanol with heating and then combined with diethyl ether. The product precipitated is suction filtered and recrystallized once in water. Yield: 3.6 g (72%, hydrochloride); melting point: 159° C.-162° C.

[0199] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 8

6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

[0200]



(a) 1-(4-isopropylphenyl)-2-methylpropan-2-ol

[0201] The reaction of a Grignard compound, prepared from 20 g (119 mmol) 4-isopropylbenzyl chloride, with 11.4 mL (155 mmol) acetone yields the target compound as a colorless oil. Yield: 13.0 g (57%); mass spectrometry: $[M+H]^+$=193.

(b)
N-[2-(4-isopropylphenyl)-1,1-dimethylethyl]acetamide

[0202] A Ritter reaction is carried out with 10.2 g (53 mmol) of 1-(4-isopropylphenyl)-2-methylpropan-2-ol in the manner described for Example 9(b). The reaction mixture is poured onto ice water and made alkaline with sodium hydroxide solution, whereupon a solid is precipitated. This is suction filtered and dried. Yield: 9.90 g (80%); mass spectrometry: $[M+H]^+$=234.

(c) 2-(4-isopropylphenyl)-1,1-dimethylethylamine

[0203] Reaction of 9.80 g (42 mmol) of N-[2-(4-isopropylphenyl)-1,1-dimethylethyl]acetamide analogously to the method for Example 9(c). Yield: 7.00 g (71%, hydrochloride); melting point 202° C.-206° C.

(d) 6-benzyloxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one

[0204] 2.18 g (6.1 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 1.1 g (5.8 mmol) of 2-(4-isopropylphenyl)-1,1-dimethylethylamine are stirred in 40 mL ethanol at 50° C.-80° C. for one hour. After cooling to ambient temperature, 0.24 g (6.3 mmol) sodium borohydride is added. The mixture is stirred for one hour, diluted with 5 mL acetone, and stirred for a further 30 minutes. The reaction mixture is acidified with hydrochloric acid, combined with 100 mL water and 80 mL ethyl acetate, and made alkaline with ammonia. The organic phase is separated off, dried with sodium sulfate, and freed from solvent. The residue is dissolved in 20 mL ethyl acetate and 10 mL water, acidified with concentrated hydrochloric acid and diluted with diethyl ether. After the addition of a crystallization aid, the solid precipitate is suction filtered and washed. White solid. Yield: 1.7 g (52%, hydrochloride); melting point: 220° C.-222° C.

(e) 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1 dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

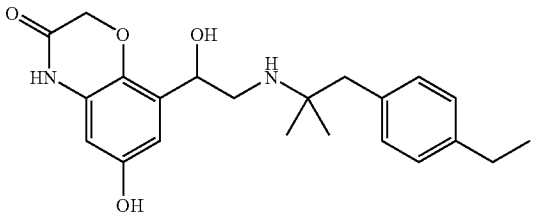
[0205] 1.6 g (3.0 mmol) of 6-benzyloxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one is dissolved in methanol and hydrogenated with palladium on charcoal as catalyst at normal pressure and ambient temperature. The catalyst is suction filtered, the solvent distilled off, and the residue recrystallized from isopropanol. White solid. Yield: 1.1 g (85%, hydrochloride); melting point 248° C.-250° C.; mass spectrometry: $[M+H]^+$=399.

[0206] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 9

8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0207]



(a) 1-(4-ethylphenyl)-2-methylpropan-2-ol

[0208] 14.8 g (90 mmol) of 1-(4-ethylphenyl)propan-2-one dissolved in diethyl ether is added dropwise to 39 mL of a 3 molar solution of methylmagnesium bromide in diethyl ether while being cooled with an ice bath in such a way that the temperature does not exceed 30° C. After the addition has ended, the reaction mixture is refluxed for 1.5 hours and then hydrolyzed with 10% ammonium chloride solution. After the removal of the organic phase, the aqueous phase is extracted with diethyl ether. The combined ether phases are washed with water, dried with sodium sulfate, and evaporated down. The oil thus obtained is further reacted directly. Yield: 15.5 g (90%).

(b)
N-[2-(4-ethylphenyl)-1,1-dimethylethyl]acetamide

[0209] 6.2 mL of concentrated sulfuric acid is added dropwise to 15.5 g (87 mmol) of 1-(4-ethylphenyl)-2-methylpropan-2-ol in 4.8 mL (91 mmol) acetonitrile and 15 mL glacial acetic acid within 15 minutes, during which time the temperature rises to 65° C. It is then stirred for one hour, diluted with ice water, and made alkaline with concentrated sodium hydroxide solution. After another 30 minutes' stirring, the solid precipitated is suction filtered and washed with water. The crude product is dissolved in ethyl acetate, dried with sodium sulfate, and evaporated down. The oil remaining is combined with petroleum ether, whereupon a

solid is precipitated which is filtered off and dried. Yield: 16.3 g (85%); melting point 90° C.-92° C.

(c) 2-(4-ethylphenyl)-1,1-dimethylethylamine

[0210] 16.3 g (74 mmol) of N-[2-(4-ethylphenyl)-1,1-dimethylethyl]acetamide and 8.0 g of potassium hydroxide are refluxed for 15 hours in 60 mL ethylene glycol. The reaction mixture is combined with ice water and extracted three times with diethyl ether. The combined organic phases are washed with water, dried with sodium sulfate, and freed from solvent. To prepare the hydrochloride, the crude product is dissolved in acetonitrile and ethereal hydrochloric acid and diethyl ether are added successively. The solid precipitated is suction filtered and dried. Yield: 11.0 g (69%, hydrochloride); melting point 165° C.-167° C.

(d) 6-benzyloxy-8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0211] The target compound is prepared analogously to the method for Example 8(d) from 2.14 g (6.0 mmol) of 6-benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 1.0 g (5.6 mmol) of 2-(4-ethylphenyl)-1,1-dimethylethylamine. White solid. Yield: 1.7 g (54%, hydrochloride); melting point 210° C.-214° C.

(e) 8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

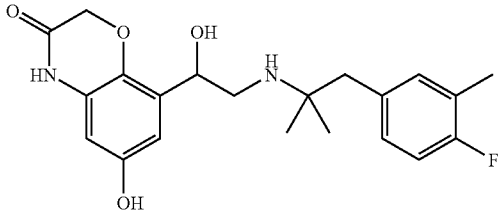
[0212] The hydrogenolysis of 1.45 g (2.75 mmol) of 6-benzyloxy-8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one according to the method for Example 8(e) yields the target compound in the form of a white solid. Yield: 1.07 g (92%; hydrochloride); melting point 266° C.-269° C.; mass spectrometry: $[M+H]^+=385$.

[0213] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 10

8-{2-[2-(4-Fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0214]




(a) 1-fluoro-2-methyl-4-(2-methylpropenyl)benzene

[0215] 100 mL of a 0.5 molar solution of 4-fluoro-3-methylphenylmagnesium bromide in THF are combined with 4.7 mL (50 mmol) isopropylaldehyde within 30 minutes, while the temperature rises to 45° C. The mixture is stirred for 30 minutes, refluxed for 1 hour, and then hydrolyzed with 10% ammonium chloride solution. After separation of the organic phase, extraction is carried out with diethyl ether. The organic phases are combined, dried, and evaporated down. The alcohol thus obtained is dissolved in 100 mL toluene, combined with 1 g of p-toluenesulfonic acid monohydrate, and refluxed for three hours using the water separator. The reaction mixture is poured onto water and made alkaline with concentrated sodium hydroxide solution. After separation of the organic phase, it is washed with water, dried with sodium sulfate, and freed from solvent. Fractional distillation of the residue yields the product in the form of a colorless liquid (boiling point 80° C.-85° C./10 mbar). Yield: 4.1 g (50%).

(b) N-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethyl]formamide

[0216] 4.9 mL concentrated sulfuric acid are added dropwise at 5° C.-15° C. to 1.5 g (31 mmol) sodium cyanide in 5 mL glacial acetic acid. Then the mixture is combined with 3.9 g (24 mmol) of 1-fluoro-2-methyl-4-(2-methylpropenyl-)benzene, dissolved in 10 mL glacial acetic acid, and stirred for 1 hour at 50° C.-60° C. The reaction mixture is diluted with ice water, made alkaline with concentrated sodium hydroxide solution, and extracted with dichloromethane. The organic phase is dried with sodium sulfate and freed from solvents in vacuo. The slightly yellow oil thus obtained is further reacted directly. Yield: 4.3 g (87%).

(c) 2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamine

[0217] 4.3 g (20.6 mmol) of N-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethyl]formamide, 20 mL concentrated hydrochloric acid, and 20 mL water are refluxed for 2 hours. The reaction mixture is diluted with water, made alkaline with concentrated sodium hydroxide solution, and extracted with dichloromethane. The organic phases are dried with sodium sulfate and evaporated down. The residue is dissolved in ethyl acetate, combined with ethereal hydrochloric acid, and cooled. The crystals precipitated are suction filtered and washed with diethyl ether and dried. White solid. Yield: 3.9 g (87%, hydrochloride); melting point 196° C.-198° C.

(d) 6-benzyloxy-8-{2-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0218] 1.10 g (3.1 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.50 g (2.8 mmol) of 2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamine are reacted and worked up analogously to the method for Example 8(d). White solid. Yield: 0.75 g (47%, hydrochloride); melting point 228° C.-230° C.

(e) 8-{2-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0219] The hydrogenation of 0.70 g (1.4 mmol) of 6-benzyloxy-8-{2-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

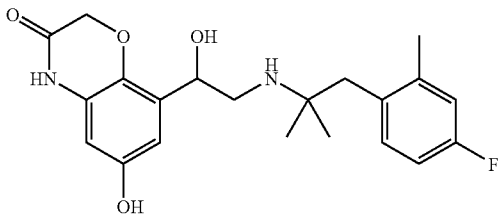
yields the target compound as a white solid. Yield: 0.50 g (87%, hydrochloride); melting point 278° C.-280° C.; mass spectroscopy: $[M+H]^+$=389.

[0220] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 11

8-{2-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0221]



(a) 1-(4-fluoro-2-methylphenyl)-2-methylpropyl acetate

[0222] 500 mL of a 0.5 molar solution of 4-fluoro-6-methylphenylmagnesium bromide and 23.2 mL (260 mmol) isopropylaldehyde are reacted analogously to Example 10(a). After hydrolysis with 10% ammonium chloride solution, the aqueous phase is separated off and extracted with diethyl ether. The combined organic phases are dried with sodium sulfate and evaporated down. The alcohol thus obtained is then dissolved in 50 mL acetic anhydride, combined with 1 mL concentrated sulfuric acid, and refluxed for three hours. Then the reaction mixture is poured onto water, stirred for a further hour, and made alkaline. It is extracted with dichloromethane, the organic phases are dried with sodium sulfate, and the solvents are distilled off. Fractional distillation of the residue yields the product in the form of a colorless liquid (boiling point: 105° C.-110° C./8 mbar). Yield 29.0 g (52%).

(b) N-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethyl]formamide

[0223] 29.0 g (130 mmol) of 1-(4-fluoro-2-methylphenyl)-2-methylpropyl acetate is reacted and worked up analogously to the method for Example 10(b). Yellow oil. Yield: 27.0 g (99%).

(c) 2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamine

[0224] In order to prepare the amine, 27.0 g (130 mmol) of N-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethyl]formamide is reacted as described in the method for Example 10(c). White solid. Yield: 15.5 g (55%, hydrochloride); melting point: 277° C.-280° C.

(d) 6-benzyloxy-8-{2-[2-[4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0225] Prepared analogously to the method for Example 8(d) from 0.95 g (2.66 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.43 g (2.37 mmol) of 2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamine. Yield: 0.75 g (55%, hydrochloride); melting point 233° C.-236° C.

(e) 8-{2-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[14]oxazin-3-one

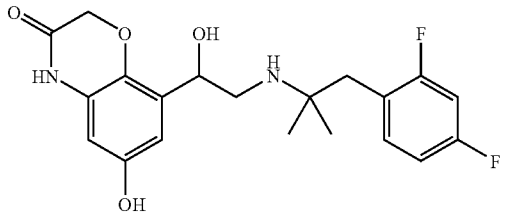
[0226] The debenzylation of 0.70 g (1.36 mmol) of 6-benzyloxy-8-{2-[2-[4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one yields the target compound in the form of a white solid. Yield: 0.50 g (87%, hydrochloride); melting point 278° C.-280° C.; mass spectroscopy: $[M+H]^+$=389.

[0227] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 12

8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0228]



(a) 1-(2,4-difluorophenyl)-2-methylpropan-2-ol

[0229] 11.0 mL acetone, diluted with 50 mL diethyl ether, is added dropwise to a solution of 500 mL of 0.25 molar 2,4-difluorobenzylmagnesium bromide in diethyl ether within 20 minutes. Then the mixture is refluxed for 1.5 hours and then hydrolyzed with 10% ammonium chloride solution. The ether phase is separated off, washed with water, dried with sodium sulfate, and evaporated down. The fractional distillation of the residue yields the alcohol as a colorless liquid (boiling point: 70° C.-73° C./2 mmbar). Yield: 20.0 g (86%).

(b) N-[2-(2,4-difluorophenyl]-1,1-dimethylethyl]formamide

[0230] Ritter reaction with 20 g (110 mmol) of 1-(2,4-difluorophenyl)-2-methylpropan-2-ol according to the method described for Example 10(b). Yellow oil. Yield: 22.0 g (94%).

(c) 2-(2,4-difluorophenyl)-1,1-dimethylethylamine

[0231] Reaction of 22.0 g (100 mmol) of N-[2-(2,4-difluorophenyl]-1,1-dimethylethyl]formamide analogously to the method for Example 10(c). Yield: 16.0 g (72%, hydrochloride); melting point: 201° C.-203° C.

(d) 6-benzyloxy-8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0232] Reaction of 0.89 g (2.49 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.40 g (2.16 mmol) of 2-(2,4-difluorophenyl)-1,1-dimethylethylamine in the manner described for Example 8(d). Yield: 0.80 g (62%, hydrochloride); melting point 245° C.-247° C.

(e) 8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

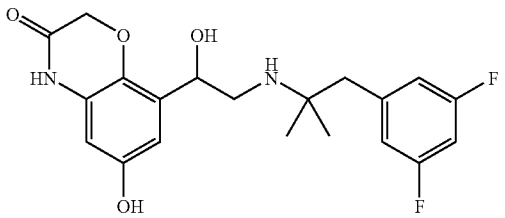
[0233] The hydrogenolysis of 0.70 g (1.35 mmol) of 6-benzyloxy-8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one yields the target compound as a white solid. Yield: 0.48 g (83%, hydrochloride); melting point 279° C.-280° C.; mass spectroscopy: $[M+H]^+$=393.

[0234] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 13

8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0235]




(a) 1-(3,5-difluorophenyl)-2-methylpropan-2-ol

[0236] The target compound is obtained by reacting a Grignard compound, prepared from 25.0 g (121 mmol) of 3,5-difluorobenzyl bromide, with 12.6 mL (171 mmol) of acetone. Yellow oil. Yield: 13.5 g (60%).

(b) 2-(3,5-difluorophenyl)-1,1-dimethylethylamine

[0237] The Ritter reaction of 5.5 g (29.5 mmol) of 1-(3,5-difluorophenyl)-2-methylpropan-2-ol and 1.8 g of sodium cyanide yields 7.0 g of formamide, which is treated with hydrochloric acid to cleave the formyl group. Slightly yellow oil. Yield: 4.6 g (75%).

(c) 6-benzyloxy-8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0238] Prepared from 1.73 g (4.84 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.80 g (4.32 mmol) of 2-(3,5-difluorophenyl)-1,1-dimethylethylamine in the usual way. Yield: 1.50 g (58%, hydrochloride); melting point: 240° C.-244° C.

(d) 8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

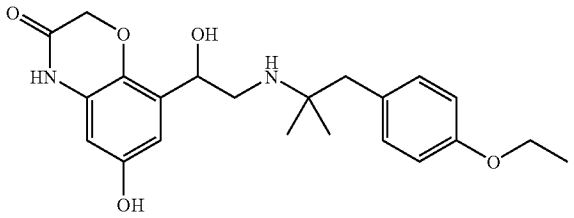
[0239] Hydrogenolysis of 1.30 g (2.43 mmol) of 6-benzyloxy-8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one yields the target compound as a white solid. Yield: 0.90 g (86%, hydrochloride); melting point 150° C.-158° C.; mass spectroscopy: $[M+H]^+$=393.

[0240] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 14

8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0241]




(a) benzyl[2-(4-ethoxyphenyl)-1,1-dimethylethyl]carbaminate

[0242] 15.0 g (50 mmol) of benzyl[2-(4-hydroxyphenyl)-1,1-dimethylethyl]carbaminate is stirred with 7.5 mL (92 mmol) ethyl iodide and 21 g (150 mmol) potassium carbonate for 10 hours at 90° C.-100° C. The reaction mixture is combined with ethyl acetate, washed twice with water, and dried with sodium sulfate. After the solvents have been distilled off, a yellow oil remains (15.0 g, 92%), which is further reacted directly.

(b) 2-(4-ethoxyphenyl)-1,1-dimethylethylamine

[0243] A solution of 15.0 g (49 mmol) benzyl[2-(4-ethoxyphenyl)-1,1-dimethylethyl]-carbaminate in 100 mL glacial acetic acid is combined with 2 g palladium on charcoal (10%) and then hydrogenated at 5 bar and 40° C. to 50° C. The catalyst is filtered off and the filtrate is freed from solvent. The residue is dissolved in a little water, made alkaline with concentrated sodium hydroxide solution, and extracted with ethyl acetate. The organic phase is washed with water, dried with sodium sulfate, and evaporated down. The crude product is dissolved in acetonitrile and acidified with ethereal hydrochloric acid. The solid precipitated after the addition of diethyl ether is suction filtered and dried. Yield: 8.8 g (hydrochloride, 84%); melting point 198° C.-200° C.

(c) 6-benzyloxy-8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

[0244] 2.14 g (6.0 mmol) of 6-benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 1.0 g (5.2

mmol) of 2-(4-ethoxyphenyl)-1,1-dimethylethylamine are stirred in 40 mL ethanol for one hour at 50° C.-80° C. After cooling to ambient temperature, 0.23 g (6.0 mmol) of sodium borohydride are added and the mixture is stirred for a further hour. The reaction mixture is combined with 5 mL acetone, stirred for 30 minutes, acidified with glacial acetic acid, and evaporated down. The residue is combined with water and ethyl acetate and made alkaline. The organic phase is separated off, washed with water, dried with sodium sulfate, and freed from solvent in vacuo. The residue is dissolved again in ethyl acetate and water, combined with concentrated hydrochloric acid, and diluted with diethyl ether. The solid precipitated is suction filtered and washed with diethyl ether. White solid. Yield: 2.0 g (61%, hydrochloride); melting point: 214° C.-216° C.

(d) 8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

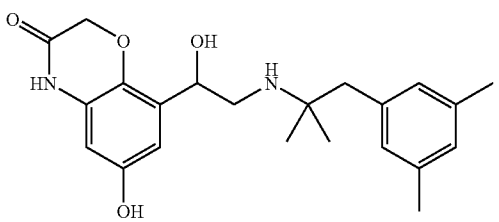
**[0245]** 1.5 g (2.8 mmol) of 6-benzyloxy-8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one in 80 mL methanol are hydrogenated with 250 mg palladium on charcoal (10%) as catalyst at ambient temperature and normal pressure. The catalyst is suction filtered and the filtrate is evaporated down. The residue is dissolved in 5 mL ethanol by heating, seeded, and diluted with ethyl acetate. The solid precipitated is filtered off and washed. White solid. Yield 1.0 g (83%, hydrochloride); melting point: 232° C.-235° C.; mass spectrometry: $[M+H]^+$=401.

**[0246]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 15

8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

**[0247]**




(a) 1-(3,5-dimethylphenyl)-2-methylpropanol-2-ol

**[0248]** Obtained by reacting ethyl (3,5-dimethylphenyl)acetate with methylmagnesium bromide.

(b) 2-(3,5-dimethylphenyl)-1,1-dimethylethylamine

**[0249]** By reacting 6.00 g (34 mmol) of 1-(3,5-dimethylphenyl)-2-methylpropanol-2-ol and 2.00 g (41 mmol) of sodium cyanide in a Ritter reaction, 2.40 g of 2-(3,5-dimethylphenyl)-1,1-dimethylethylformamide (35% yield) is obtained. To liberate the amine, the formamide (2.40 g, 11.7 mmol) is treated with hydrochloric acid. The method and working up are analogous to the method for Example 10(c). Oil. Yield: 1.70 g (82%); mass spectroscopy: $[M+H]^+$=178.

(c) 6-benzyloxy-8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one

**[0250]** Prepared analogously to the method for Example 8(d) from 1.47 g (4.1 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.65 g (3.7 mmol) of 2-(3,5-dimethylphenyl)-1,1-dimethylethylamine. Yield: 1.1 g (51%, hydrochloride); melting point: 220° C.-222° C.

(d) 8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

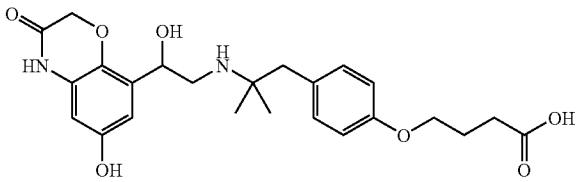
**[0251]** The target compound was obtained after hydrogenolysis of 0.90 g (1.71 mmol) of 6-benzyloxy-8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-4H-benzo[1,4]oxazin-3-one and recrystallization of the crude product from isopropanol. White solid. Yield: 0.50 g (69%, hydrochloride); melting point: 235° C.-238° C.; mass spectroscopy: $[M+H]^+$=385.

**[0252]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 16

4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)ethylamino]-2-methylpropyl}phenoxy)butyric acid

**[0253]**




(a) ethyl 4-[4-(2-amino-2-methylpropyl)-phenoxy]-butyrate

**[0254]** 4.5 g (15.0 mmol) of benzyl[2-(4-hydroxyphenyl)-1,1-dimethylethyl]carbaminate, 2.3 mL (16.0 mmol) of ethyl 4-bromobutyrate, 2.3 g (16.6 mmol) of potassium carbonate, and 0.3 g (1.8 mmol) of potassium iodide in 20 mL dimethylformamide are heated to 120° C. for 13 hours. The reaction mixture is diluted with ethyl acetate and washed successively with water, sodium hydroxide solution, and water. The organic phase is dried with sodium sulfate and evaporated down. The residue is purified by chromatogra-

phy (eluent: cyclohexane-ethyl acetate (9:1)). 5.0 g of a yellow oil is isolated which is dissolved in 50 mL acetic acid and hydrogenated with 1.0 g palladium on charcoal as catalyst at 40° C. and 3 bar. The catalyst is filtered off and the filtrate is freed from solvent. The residue is dissolved in diethyl ether and combined with ethereal hydrochloric acid. The solid precipitated is suction filtered and dried. Yield: 2.9 g (66% in two stages, hydrochloride); melting point: 103° C.-105° C.

(b) ethyl 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxyethylamino]-2-methylpropyl}phenoxy)butyrate

**[0255]** 1.20 g (3.36 mmol) of benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 0.90 g (3.22 mmol) of ethyl 4-[4-(2-amino-2-methylpropyl)phenoxy]butyrate are reacted in the manner described for Example 8(d). The crude product is dissolved in 10 mL ethyl acetate and 10 mL water and combined with oxalic acid with stirring. The solution is diluted with diethyl ether and the solid precipitated is suction filtered and washed with diethyl ether. Yield: 1.20 g (54%, oxalate); melting point 223° C.-227° C.

(c) 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxyethylamino]-2-methylpropyl}phenoxy)butyric acid

**[0256]** A solution of 1.00 g (1.73 mmol) of ethyl 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxyethylamino]-2-methylpropyl}phenoxy)butyrate in 25 mL methanol is combined with 2.5 mL of 1 N sodium hydroxide solution, refluxed for 30 minutes, and then neutralized with 1 N hydrochloric acid. The solution is evaporated down and the residual oil is dissolved by heating in 5 mL of n-butanol. After the addition of a crystallization aid, a solid is precipitated out which is suction filtered and washed with acetone and diethyl ether. Yield: 0.75 g (79%); melting point: 216° C.-218° C.

(d) 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methylpropyl}phenoxy)butyric acid

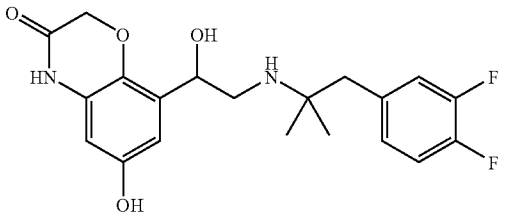
**[0257]** 0.70 g (1.28 mmol) of 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxyethylamino]-2-methylpropyl}phenoxy)butyric acid is dissolved in 25 mL methanol and 2 mL acetic acid and hydrogenated in the presence of 150 mg palladium on charcoal (10%) at ambient temperature and normal pressure. The catalyst is filtered off and the filtrate is freed from solvent. The product is obtained by crystallization from a methanol-acetone mixture. Yield: 0.40 g (68%); melting point: 201° C.-204° C.; mass spectroscopy: $[M+H]^+$=459.

**[0258]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 17

8-{2-[2-(3,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

**[0259]**




(a) 1-(3,4-difluorophenyl)-2-methylpropan-2-ol

**[0260]** From 23.0 g (111 mmol) of 3,4-difluorobenzyl bromide a Grignard is prepared, which is then reacted with 11.6 mL (158 mmol) of acetone. Slightly yellow oil. Yield: 9.7 g (47%); $R_f$ value: 0.55 (ethyl acetate-petroleum ether (1:3)).

(b) N-[2-(3,4-difluorophenyl)-1,1-dimethylethyl]formamide

**[0261]** The target compound is obtained by a Ritter reaction with 4.0 g (21.5 mmol) of 1-(3,4-difluorophenyl)-2-methylpropan-2-ol. Slightly yellow oil. Yield: 4.0 g (87%); mass spectrometry: $[M+H]^+$=214.

(c) 2-(3,4-difluorophenyl)-1,1-dimethylethylamine

**[0262]** 4.00 g (18.5 mmol) of N-[2-(3,4-difluorophenyl)-1,1-dimethylethyl]formamide is dissolved in ethanol, combined with concentrated hydrochloric acid, and refluxed overnight. The reaction solution is poured onto ice water, made alkaline with sodium hydroxide, and extracted with tert-butylmethyl ether. The organic phases are washed with water, dried with sodium sulfate, and evaporated down. Yellow oil. Yield: 3.2 g (92%); mass spectrometry: $[M+H]^+$=186.

(d) 8-{2-[2-(3,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

**[0263]** 357 mg (1 mmol) of 6-benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 185 mg (1 mmol) of 2-(3,4-difluorophenyl)-1,1-dimethylethylamine are stirred for 30 minutes in 5 mL tetrahydrofuran at ambient temperature. It is cooled to 0° C. and, under an argon atmosphere, 1.5 mL of a 2 molar solution of lithium borohydride in tetrahydrofuran is added dropwise. The mixture is stirred for 30 minutes at ambient temperature, combined with 10 mL dichloromethane, and 3 mL water, stirred for a further hour and then filtered through an EXTRELUT®

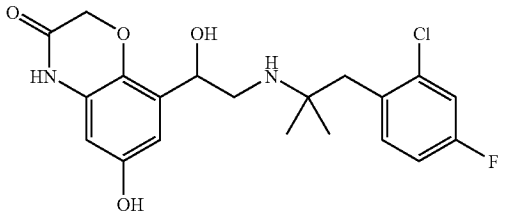
column. The eluate containing the ethanol amine is freed from solvent. The residue is dissolved in methanol and hydrogenated with palladium on charcoal (10%) as catalyst at 2.5 bar and ambient temperature. Then the catalyst is separated off and the crude product is purified by chromatography. White solid. Yield: 31 mg (6%, trifluoroethyl acetate); mass spectroscopy: $[M+H]^+$=393.

**[0264]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 18

8-{2-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

**[0265]**



(a) 1-(2-chloro-4-fluorophenyl)-2-methylpropan-2-ol

**[0266]** Prepared from 20 g (97 mmol) of methyl (2-chloro-4-fluorophenyl)acetate and 98 mL of a 3 molar solution of methylmagnesium bromide analogously to the method for Example 8(a).

(b) N-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethyl]formamide

**[0267]** 7.5 g (37 mmol) of 1-(2-chloro-4-fluorophenyl)-2-methylpropan-2-ol was reacted and worked up according to the method described for Example 10(b). The oil thus obtained was chromatographed for further purification on a short silica gel column (petroleum ether-ethyl acetate (9:1)). Oil. Yield 7.4 g (87%); mass spectrometry: $[M+H]^+$=230/232.

(c)
2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamine

**[0268]** Reaction of 7.4 g (32 mmol) of N-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethyl]-formamide as described in the method for Example 17(c). Brown oil. Yield: 5.14 g (79%); mass spectrometry: $[M+H]^+$=202/204.

(d) 8-{2-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

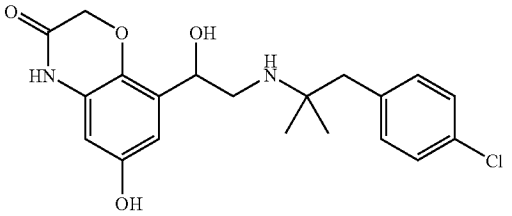
**[0269]** 357 mg (1 mmol) of 6-benzyloxy-8-(2-ethoxy-2-hydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 202 mg (1 mmol) of 2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamine are reacted with lithium borohydride analogously to the method for Example 10(d). To debenzylate the ethanolamine thus obtained, it is dissolved in 3 mL of dichloromethane and cooled to −78° C. At this temperature, 2 mL of a 1 molar solution of boron tribromide in dichloromethane is added and the mixture is slowly allowed to come up to ambient temperature. The reaction mixture is combined with 10 mL dichloromethane and 3 mL water and filtered through an EXTRELUT® column. The eluate is freed from solvent and the residue is purified by chromatography. White solid. Yield: 70 mg (13%, trifluoroethyl acetate); mass spectroscopy: $[M+H]^+$=409/11.

**[0270]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 19

8-{2-[2-(4-chlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

**[0271]**



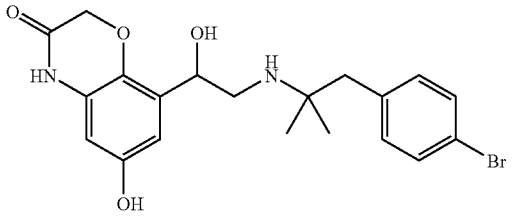
**[0272]** A solution of 300 mg (0.91 mmol) of 6-benzyloxy-8-(2,2-dihydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 200 mg (1.09 mmol) of 2-(4-chlorophenyl)-1,1-dimethylethylamine in 3 mL ethanol was combined with molecular sieve and stirred for 90 minutes at 80° C. It was allowed to cool to ambient temperature, 35 mg (0.91 mmol) of sodium borohydride was added, and the mixture was stirred for 1 hour. Then the reaction mixture was combined with sodium hydrogen carbonate solution and extracted with ethyl acetate. The combined organic phases were freed from solvent and the residue was chromatographed (eluent: hexane-ethyl acetate-methanol), yielding 305 mg of ethanolamine. This was dissolved in 3 mL dichloromethane and cooled to −78° C. under an argon atmosphere. 3 mL of a 1 molar solution of boron tribromide in dichloromethane were added dropwise and the mixture was stirred for one hour at −78° C. and for 20 minutes at ambient temperature. Then at −78° C., 3 mL of concentrated ammonia solution was added dropwise and the mixture was stirred for 5 minutes. The reaction mixture was combined with ammonium chloride solution and extracted with ethyl acetate. The combined organic phases were evaporated down and the residue was further purified by chromatography (silica gel; eluent: dichloromethane-methanol+1% ammonia). Beige-colored solid: 93 mg (26%); mass spectrometry: $[M+H]^+$=391.

**[0273]** The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 20

8-{2-[2-(4-bromophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0274]



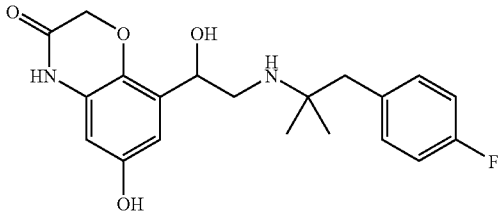
[0275] The preparation of the ethanolamine and debenzylation were carried out as described in Example 19 from 300 mg (0.91 mmol) of 6-benzyloxy-8-(2,2-dihydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 250 mg (1.09 mmol) of 2-(4-bromophenyl)-1,1-dimethylethylamine. Beige solid. Yield: 54 mg (14%); mass spectrometry: $[M+H]^+$=435, 437.

[0276] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

EXAMPLE 21

8-{2-[2-(4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0277]



[0278] 300 mg (0.91 mmol) of 6-benzyloxy-8-(2,2-dihydroxyacetyl)-4H-benzo[1,4]oxazin-3-one and 183 mg (1.09 mmol) of 2-(4-fluorophenyl)-1,1-dimethylethylamine were dissolved in 3 mL of ethanol. Molecular sieve was added and the mixture was heated to 80° C. for 30 minutes. After cooling to ambient temperature, 35 mg (0.91 mmol) of sodium borohydride was added. The mixture was stirred for 1 hour at ambient temperature, then sodium hydrogen carbonate solution was added to the reaction mixture and it was extracted with ethyl acetate. The organic phases were evaporated down and the residue was chromatographed (eluent: hexane-ethyl acetate-methanol). The ethanolamine thus obtained (223 mg) was dissolved in methanol to cleave the benzyl protecting group and hydrogenated with 150 mg palladium hydroxide as catalyst at ambient temperature and normal pressure. The catalyst was separated off by filtering through CELITE® filter agent, the filtrate was freed from solvent and the residue was chromatographed (silica gel; eluent: dichloromethane-methanol). Beige solid. Yield: 76 mg (22%); mass spectrometry: $[M+H]^+$=375.

[0279] The (R)- and (S)-enantiomers of this example can be obtained by separating the racemate analogously to current methods of racemate cleaving known in the prior art.

[0280] The following compounds of Formula 1 according to the invention may be obtained analogously to the synthesis examples described above:

EXAMPLE 22

8-{2-[2-(4-fluoro-3-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 23

8-{2-[2-(4-fluoro-2,6-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 24

8-{2-[2-(4-chloro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 25

8-{2-[2-(4-chloro-3-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 26

8-{2-[2-(4-chloro-2-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 27

8-{2-[2-(3-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 28

8-{2-[2-(2,6-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 29

8-{2-[2-(2,5-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 30

8-{2-[2-(4-fluoro-3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 31

8-{2-[2-(3,5-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 32

8-{2-[2-(4-chloro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 33

8-{2-[2-(3,4,5-trifluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

EXAMPLE 34

8-{2-[2-(3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one; and

EXAMPLE 35

8-{2-[2-(3,4-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

[0281] The compounds of general formula 1 may be used on their own or combined with other active substances of formula 1 according to the invention. The compounds of general formula 1 may optionally also be combined with other pharmacologically active substances. These include, in particular, anticholinergics, optionally other betamimetics, antiallergic agents, PDE-IV inhibitors, PAF-antagonists, leukotriene-antagonists, and corticosteroids and combinations of these active substances.

[0282] Examples of preferred anticholinergics which may be mentioned include ipratropium, oxitropium, and tiotropium salts. Pharmaceutical combinations which contain the abovementioned salts, in addition to the compounds of formula 1 according to the invention, preferably contain those salts of ipratropium, oxitropium, or tiotropium wherein the anion is selected from among the chloride, bromide, iodide, sulfate, phosphate, methanesulfonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate, and p-toluenesulfonate, optionally in the form of one of the solvates or hydrates thereof.

[0283] Within the scope of the present invention, the corticosteroids which may optionally be used in conjunction with the compounds of formula 1 may be compounds selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide, rofleponide, and dexamethasone. In some cases, within the scope of the present patent application, the term steroids is used on its own instead of the word corticosteroids. Any reference to steroids within the scope of the present invention includes a reference to salts or derivatives which may be formed from the steroids. Examples of possible salts or derivatives include: sodium salts, sulfobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates, or furoates. In some cases, the corticosteroids may also occur in the form of their hydrates.

[0284] Within the scope of the present invention, the term dopamine agonists, which may optionally be used in conjunction with the compounds of formula 1, denotes compounds selected from among bromocriptine, cabergoline, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindole, ropinirole, talipexole, terguride, and viozan. Any reference to the abovementioned dopamine agonists also includes, within the scope of the present invention, a reference to any pharmacologically acceptable acid addition salts and hydrates thereof which may exist. By the physiologically acceptable acid addition salts thereof which may be formed by the abovementioned dopamine agonists are meant, for example, pharmaceutically acceptable salts selected from 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, and maleic acid.

[0285] Examples of antiallergic agents which may be used according to the invention as a combination with the compound of formula 1 include epinastine, cetirizine, azelastine, fexofenadine, levocabastine, loratadine, mizolastine, ketotifene, emedastine, dimetindene, clemastine, bamipine, hexachlorophenirامine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastine, desloratadine, and meclizine. Any reference to the abovementioned antiallergic agents also includes, within the scope of the present invention, a reference to any pharmacologically acceptable acid addition salts thereof which may exist.

[0286] Examples of PDE-IV inhibitors which may be used according to the invention as a combination with the compound of formula 1 include compounds selected from among enprofylline, roflumilast, ariflo, Bay-198004, CP-325,366, BY343, D-4396 (Sch-351591), V-11294A, and AWD-12-281. Any reference to the abovementioned PDE-IV inhibitors also includes, within the scope of the present invention, a reference to any pharmacologically acceptable acid addition salts thereof which may exist. By the physiologically acceptable acid addition salts which may be formed by the abovementioned PDE-IV inhibitors are meant, for example, pharmaceutically acceptable salts selected from 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, and maleic acid. According to the invention, the salts selected from among the acetate, hydrochloride, hydrobromide, sulfate, phosphate, and methanesulfonate are preferred in this context.

[0287] Suitable preparations for administering the compounds of formula 1 include, for example, tablets, capsules, suppositories, solutions, powders, etc. The content of the pharmaceutically active compound(s) should be in the range from 0.05 to 90 wt.-%, preferably 0.1 to 50 wt.-% of the composition as a whole. Suitable tablets may be obtained, for example, by mixing the active substance(s) with known excipients, for example inert diluents such as calcium carbonate, calcium phosphate, or lactose, disintegrants such as corn starch or alginic acid, binders such as starch or gelatine, lubricants such as magnesium stearate or talc and/or agents for delaying release, such as carboxymethyl cellulose, cellulose acetate phthalate, or polyvinyl acetate. The tablets may also comprise several layers.

[0288] Coated tablets may be prepared accordingly by coating cores produced analogously to the tablets with substances normally used for tablet coatings, for example, collidone or shellac, gum arabic, talc, titanium dioxide, or sugar. To achieve delayed release or prevent incompatibilities the core may also consist of a number of layers. Similarly the tablet coating may consist of a number or layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

[0289] Syrups or elixirs containing the active substances or combinations thereof according to the invention may additionally contain a sweetener such as saccharine, cyclamate, glycerol or sugar and a flavor enhancer, e.g., a flavoring such as vanillin or orange extract. They may also contain suspension adjuvants or thickeners such as sodium carboxymethyl cellulose, wetting agents such as, for example, condensation products of fatty alcohols with ethylene oxide, or preservatives such as p-hydroxybenzoates.

[0290] Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates or stabilizers such as alkali metal salts of ethylenediaminetetraacetic acid, optionally using emulsifiers and/or dispersants, while if water is used as diluent, for example, organic solvents may optionally be used as solubilizers or dissolving aids, and the solutions may be transferred into injection vials or ampoules or infusion bottles.

[0291] Capsules containing one or more active substances or combinations of active substances may, for example, be prepared by mixing the active substances with inert carriers such as lactose or sorbitol and packing them into gelatine capsules.

[0292] Suitable suppositories may be made for example by mixing with carriers provided for this purpose, such as neutral fats or polyethyleneglycol or the derivatives thereof.

[0293] Excipients which may be used include, for example, water, pharmaceutically acceptable organic solvents such as paraffins (e.g., petroleum fractions), vegetable oils (e.g., groundnut or sesame oil), mono- or polyfunctional alcohols (e.g., ethanol or glycerol), carriers such as, e.g., natural mineral powders (e.g., kaolins, clays, talc, chalk), synthetic mineral powders (e.g., highly dispersed silicic acid and silicates), sugars (e.g., cane sugar, lactose and glucose), emulsifiers (e.g., lignin, spent sulfite liquors, methylcellulose, starch, and polyvinylpyrrolidone) and lubricants (e.g., magnesium stearate, talc, stearic acid, and sodium lauryl sulfate).

[0294] For oral use, the tablets may obviously contain, in addition to the carriers specified, additives such as sodium citrate, calcium carbonate, and dicalcium phosphate together with various additional substances such as starch, preferably potato starch, gelatin, and the like. Lubricants such as magnesium stearate, sodium lauryl sulfate, and talc may also be used to produce the tablets. In the case of aqueous suspensions, the active substances may be combined with various flavor enhancers or colorings in addition to the abovementioned excipients.

[0295] For administering the compounds of formula 1 for the treatment of COPD, it is particularly preferred according to the invention to use preparations or pharmaceutical formulations which are suitable for inhalation. Inhalable preparations include inhalable powders, propellant-containing metered-dose aerosols, or propellant-free inhalable solutions. Within the scope of the present invention, the term propellant-free inhalable solutions also includes concentrates or sterile inhalable solutions ready for use. The formulations which may be used within the scope of the present invention are described in more detail in the next part of the specification.

[0296] The inhalable powders which may be used according to the invention may contain 1 either on its own or in admixture with suitable physiologically acceptable excipients.

[0297] If the active substances 1 are present in admixture with physiologically acceptable excipients, the following physiologically acceptable excipients may be used to prepare these inhalable powders according to the invention: monosaccharides (e.g., glucose or arabinose), disaccharides (e.g., lactose, saccharose, or maltose), oligo- and polysaccharides (e.g., dextrans), polyalcohols (e.g., sorbitol, mannitol, or xylitol), salts (e.g., sodium chloride or calcium carbonate) or mixtures of these excipients. Preferably, mono- or disaccharides are used, while the use of lactose or glucose is preferred, particularly, but not exclusively, in the form of their hydrates. For the purposes of the invention, lactose is the particularly preferred excipient, while lactose monohydrate is most particularly preferred.

[0298] Within the scope of the inhalable powders according to the invention the excipients have a maximum average particle size of up to 250 μm, preferably between 10 μm and 150 μm, most preferably between 15 μm and 80 μm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 μm to 9 μm to the excipient mentioned above. These finer excipients are also selected from the group of possible excipients listed hereinbefore. Finally, in order to prepare the inhalable powders according to the invention, micronised active substance 1, preferably with an average particle size of 0.5 μm to 10 μm, more preferably from 1 μm to 5 μm, is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronizing and finally mixing the ingredients together are known from the prior art.

[0299] The inhalable powders according to the invention may be administered using inhalers known from the prior art.

[0300] The inhalation aerosols containing propellant gas according to the invention may contain the compounds 1 dissolved in the propellant gas or in dispersed form. The compounds 1 may be contained in separate formulations or in a common formulation, in which the compounds 1 are either both dissolved, both dispersed or in each case only one component is dissolved and the other is dispersed. The propellant gases which may be used to prepare the inhalation aerosols are known from the prior art. Suitable propellant gases are selected from among hydrocarbons such as n-propane, n-butane, or isobutane and halohydrocarbons such as fluorinated derivatives of methane, ethane, propane, butane, cyclopropane, or cyclobutane. The abovementioned propellant gases may be used on their own or mixed together. Particularly preferred propellant gases are halogenated alkane derivatives selected from TG134a and TG227 and mixtures thereof.

[0301] The propellant-driven inhalation aerosols may also contain other ingredients such as co-solvents, stabilizers,

surfactants, antioxidants, lubricants, and pH adjusters. All these ingredients are known in the art.

[0302] The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art, such as metered dose inhalers (MDIs).

[0303] Moreover, the active substances 1 according to the invention may be administered in the form of propellant-free inhalable solutions and suspensions. The solvent used may be an aqueous or alcoholic, preferably an ethanolic solution. The solvent may be water on its own or a mixture of water and ethanol. The relative proportion of ethanol compared with water is not limited but the maximum is preferably up to 70 percent by volume, more particularly up to 60 percent by volume and most preferably up to 30 percent by volume. The remainder of the volume is made up of water. The solutions or suspensions containing 1 are adjusted to a pH of 2 to 7, preferably 2 to 5, using suitable acids. The pH may be adjusted using acids selected from inorganic or organic acids. Examples of particularly suitable inorganic acids include hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, and/or phosphoric acid. Examples of particularly suitable organic acids include ascorbic acid, citric acid, malic acid, tartaric acid, maleic acid, succinic acid, fumaric acid, acetic acid, formic acid, and/or propionic acid etc. Preferred inorganic acids are hydrochloric and sulfuric acids. It is also possible to use the acids which have already formed an acid addition salt with one of the active substances. Of the organic acids, ascorbic acid, fumaric acid and citric acid are preferred. If desired, mixtures of the above acids may be used, particularly in the case of acids which have other properties in addition to their acidifying qualities, e.g., as flavorings, antioxidants or complexing agents, such as citric acid or ascorbic acid, for example. According to the invention, it is particularly preferred to use hydrochloric acid to adjust the pH.

[0304] If desired, the addition of edetic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabilizer or complexing agent may be omitted in these formulations. Other embodiments may contain this compound or these compounds. In a preferred embodiment the content based on sodium edetate is less than 100 mg/100 mL, preferably less than 50 mg/100 mL, more preferably less than 20 mg/100 mL. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10 mg/100 mL are preferred.

[0305] Co-solvents and/or other excipients may be added to the propellant-free inhalable solutions. Preferred co-solvents are those which contain hydroxyl groups or other polar groups, e.g., alcohols, particularly isopropyl alcohol, glycols, particularly propyleneglycol, polyethyleneglycol, polypropyleneglycol, glycol ether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. The terms excipients and additives in this context denote any pharmacologically acceptable substance which is not an active substance but which can be formulated with the active substance or substances in the physiologically suitable solvent in order to improve the qualitative properties of the active substance formulation. Preferably, these substances have no pharmacological effect or, in connection with the desired therapy, no appreciable or at least no undesirable pharmacological effect. The excipients and additives include, for example, surfactants such as soya lecithin, oleic acid, sorbitan esters, such as polysorbates, polyvinylpyrrolidone, other stabilizers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavorings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

[0306] 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 and provitamins occurring in the human body.

[0307] Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those which are known in the art, particularly cetyl pyridinium chloride, benzalkonium chloride, or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The preservatives mentioned above are preferably present in concentrations of up to 50 mg/100 mL, more preferably between 5 and 20 mg/100 mL.

[0308] Preferred formulations contain, in addition to the solvent water and the active substance 1, only benzalkonium chloride and sodium edetate. In another preferred embodiment, no sodium edetate is present.

[0309] The dosage of the compounds according to the invention is naturally highly dependent on the method of administration and the complaint which is being treated. When administered by inhalation, the compounds of formula 1 are characterized by a high potency even at doses in the μg range. The compounds of formula 1 may also be used effectively above the μg range. The dosage may then be in the gram range, for example.

[0310] In another aspect, the present invention relates to the above-mentioned pharmaceutical formulations as such which are characterized in that they contain a compound of formula 1, particularly the above-mentioned pharmaceutical formulations which can be administered by inhalation.

[0311] The following examples of formulations illustrate the present invention without restricting its scope:

EXAMPLES OF PHARMACEUTICAL FORMULATIONS

[0312]

| A. Tablets | per tablet |
|---|---|
| active substance 1 | 100 mg |
| lactose | 140 mg |
| maize starch | 240 mg |
| polyvinylpyrrolidone | 15 mg |
| magnesium stearate | 5 mg |
| | 500 mg |

[0313] The finely ground active substance, lactose, and some of the maize starch are mixed together. The mixture is screened, then moistened with a solution of polyvinylpyrrolidone in water, kneaded, wet granulated, and dried. The granules, the remaining maize starch and the magnesium stearate are screened and mixed together. The mixture is pressed into tablets of suitable shape and size.

| B. Tablets | per tablet |
|---|---|
| active substance 1 | 80 mg |
| lactose | 55 mg |
| maize starch | 190 mg |
| microcrystalline cellulose | 35 mg |
| polyvinylpyrrolidone | 15 mg |
| sodium carboxymethyl starch | 23 mg |
| magnesium stearate | 2 mg |
| | 400 mg |

[0314] The finely ground active substance, some of the corn starch, lactose, microcrystalline cellulose, and polyvinylpyrrolidone are mixed together, the mixture is screened and worked with the remaining corn starch and water to form a granulate which is dried and screened. The sodium carboxymethyl starch and the magnesium stearate are added and mixed in and the mixture is compressed to form tablets of a suitable size.

| C. Ampoule Solution | |
|---|---|
| active substance 1 | 50 mg |
| sodium chloride | 50 mg |
| water for inj. | 5 mL |

[0315] The active substance is dissolved in water at its own pH or optionally at pH 5.5 to 6.5 and sodium chloride is added to make the solution isotonic. The resulting solution is filtered to remove pyrogens and the filtrate is transferred under aseptic conditions into ampoules which are then sterilized and heat-sealed. The ampoules contain 5 mg, 25 mg, and 50 mg of active substance.

| D. Metering Aerosol | |
|---|---|
| active substance 1 | 0.005 |
| sorbitan trioleate | 0.1 |
| monofluorotrichloromethane and TG134a:TG227 (2:1) | to 100 |

[0316] The suspension is transferred into a conventional aerosol container with metering valve. Preferably 50 μl suspension are released on each actuation. The active substance may also be released in higher doses if desired (e.g., 0.02 wt.-%).

| E. Solutions (in mg/100 mL) | |
|---|---|
| active substance 1 | 333.3 mg |
| benzalkonium chloride | 10.0 mg |
| EDTA | 50.0 mg |
| HCl (1 N) | to pH 3.4 |

[0317] This solution can be prepared in the usual way.

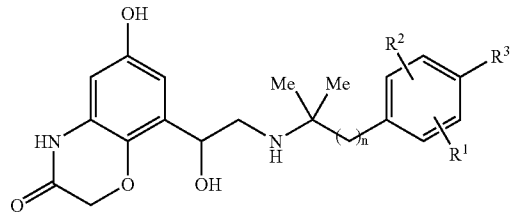
| F. Inhalable Powder | |
|---|---|
| active substance 1 | 12 μg |
| lactose monohydrate | to 25 mg |

[0318] The inhalable powder is prepared in the usual way by mixing the individual ingredients.

We claim:

**1**. A pharmaceutical composition comprising a compound of formula 1

1




wherein:

n is 1 or 2;

$R^1$ is hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl;

$R^2$ is hydrogen, $C_1$-$C_4$-alkyl, halogen, OH, or —O—$C_1$-$C_4$-alkyl;

$R^3$ is hydrogen, $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl, or

an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof; and

a pharmaceutically acceptable excipient or carrier.

**2**. The pharmaceutical composition according to claim 1, wherein:

$R^1$ is hydrogen, halogen or $C_1$-$C_4$-alkyl;

$R^2$ is hydrogen, halogen, or $C_1$-$C_4$-alkyl; and

$R^3$ is hydrogen, $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl.

**3**. The pharmaceutical composition according to claim 1, wherein:

$R^1$ is hydrogen, fluorine, chlorine, or methyl;

$R^2$ is hydrogen, fluorine, chlorine, or methyl; and

$R^3$ is hydrogen, $C_1$-$C_4$-alkyl, OH, fluorine, chlorine, bromine, —O—$C_1$-$C_4$-alkyl, —O-$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl.

**4**. The pharmaceutical composition according to claim 1, wherein:

$R^1$ is hydrogen, methyl, or ethyl;

$R^2$ is hydrogen, methyl, or ethyl; and

$R^3$ is hydrogen, methyl, ethyl, OH, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—CO—O-methyl, or —O—$CH_2$—COOethyl.

**5**. The pharmaceutical composition according to claim 1, wherein:

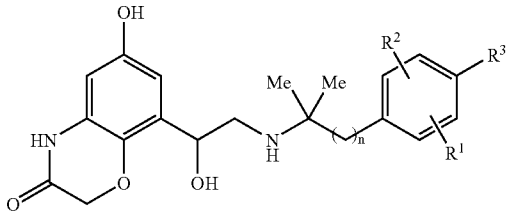
$R^1$ is hydrogen or methyl;

$R^2$ is hydrogen or methyl; and

$R^3$ is hydrogen, methyl, OH, methoxy, —O—$CH_2$—COOH, or —O—$CH_2$—COOethyl.

**6**. A compound of formula 1

1




wherein:

n is 1;

$R^1$ is hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

$R^2$ is hydrogen, halogen, $C_1$-$C_4$-alkyl or —O—$C_1$-$C_4$-alkyl;

$R^3$ is $C_1$-$C_4$-alkyl, OH, halogen, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

with the proviso that if $R^1$ and $R^2$ each represent ortho-methyl, $R^3$ cannot simultaneously be OH,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**7**. The compound of formula 1 according to claim 6, wherein $R^3$ is methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**8**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is hydrogen, fluorine, chlorine, methyl, or methoxy;

$R^2$ is hydrogen, fluorine, chlorine, methyl, or methoxy;

$R^3$ is $C_1$-$C_4$-alkyl, OH, fluorine, chlorine, bromine, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**9**. The compound of formula 1 according to claim 8, wherein $R^3$ is methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**10**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is hydrogen or $C_1$-$C_4$-alkyl;

$R^2$ is hydrogen or $C_1$-$C_4$-alkyl; and

$R^3$ is $C_1$-$C_4$-alkyl, OH, —O—$C_1$-$C_4$-alkyl, —O—$C_1$-$C_4$-alkylene-COOH, or —O—$C_1$-$C_4$-alkylene-CO—O—$C_1$-$C_4$-alkyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**11**. The compound of formula 1 according to claim 10, wherein $R^3$ is methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**12**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is hydrogen, methyl, or ethyl;

$R^2$ is hydrogen, methyl, or ethyl;

$R^3$ is methyl, ethyl, OH, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl or —O—$CH_2$—COOethyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**13**. The compound of formula 1 according to claim 12, wherein $R^3$ is methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—COOmethyl, or —O—$CH_2$—COOethyl, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**14**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

$R^2$ is halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl; and

$R^3$ is halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**15**. The compound of formula 1 according to claim 14, wherein:

$R^1$ is fluorine, chlorine, methyl, or methoxy;

$R^2$ is fluorine, chlorine, methyl, or methoxy; and

$R^3$ is fluorine, chlorine, methyl, or methoxy,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**16**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is hydrogen;

$R^2$ is hydrogen, fluorine, chlorine, or methyl; and

$R^3$ is methyl, ethyl, isopropyl, tert-butyl, OH, fluorine, chlorine, bromine, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—$CH_2$—COOH, —O—$CH_2$—$CH_2$—$CH_2$—COOH, —O—$CH_2$—COOmethyl, —O—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—COOmethyl, —O—$CH_2$—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—$CH_2$—COOmethyl, or —O—$CH_2$—$CH_2$—$CH_2$—COOethyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**17**. The compound of formula 1 according to claim 16, wherein:

$R^1$ is hydrogen;

$R^2$ is hydrogen, fluorine, chlorine, or methyl; and

$R^3$ is OH, fluorine, chlorine, methyl, methoxy, ethoxy, or —O—$CH_2$—COOH,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**18**. The compound of formula 1 according to claim 6, wherein:

$R^1$ and $R^2$ are each hydrogen; and

$R^3$ is methyl, ethyl, isopropyl, tert-butyl, OH, fluorine, chlorine, bromine, methoxy, ethoxy, —O—$CH_2$—COOH, —O—$CH_2$—$CH_2$—COOH, —O—$CH_2$—$CH_2$—$CH_2$—COOH, —O—$CH_2$—COOmethyl, —O—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—COOmethyl, —O—$CH_2$—$CH_2$—COOethyl, —O—$CH_2$—$CH_2$—$CH_2$—COOmethyl, or —O—$CH_2$—$CH_2$—$CH_2$—COOethyl,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**19**. The compound of formula 1 according to claim 18, wherein $R^3$ is OH, fluorine, chlorine, methoxy, ethoxy, —O—$CH_2$—COOH, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**20**. The compound of formula 1 according to claim 19, wherein $R^3$ is OH, fluorine, chlorine, methoxy, or ethoxy, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**21**. The compound of formula 1 according to claim 6, wherein:

$R^1$ is hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl;

$R^2$ is hydrogen, halogen, $C_1$-$C_4$-alkyl, or —O—$C_1$-$C_4$-alkyl; and

$R^3$ is hydrogen,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**22**. The compound of formula 1 according to claim 21, wherein:

$R^1$ is hydrogen, fluorine, chlorine, methyl or methoxy; and

$R^2$ is hydrogen, fluorine, chlorine, methyl or methoxy,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**23**. A compound of formula 1 selected from:

(1) 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxyphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

(2) 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyethylacetate)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

(3) 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxyacetic acid)-1,1-dimethylethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

(4) 8-{2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)ethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(5) 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxyphenyl)-1,1-dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

(6) 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropylphenyl)-1,1dimethylethylamino]ethyl}-4H-benzo[1,4]oxazin-3-one;

(7) 8-{2-[2-(4-ethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(8) 8-{2-[2-(4-fluoro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(9) 8-{2-[2-(4-fluoro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(10) 8-{2-[2-(2,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(11) 8-{2-[2-(3,5-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(12) 8-{2-[2-(4-ethoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(13) 8-{2-[2-(3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(14) 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methylpropyl}phenoxy)butyric acid;

(15) 8-{2-[2-(3,4-difluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(16) 8-{2-[2-(2-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(17) 8-{2-[2-(4-chlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(18) 8-{2-[2-(4-bromophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(19) 8-{2-[2-(4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(20) 8-{2-[2-(4-fluoro-3-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(21) 8-{2-[2-(4-fluoro-2,6-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(22) 8-{2-[2-(4-chloro-2-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(23) 8-{2-[2-(4-chloro-3-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(24) 8-{2-[2-(4-chloro-2-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(25) 8-{2-[2-(3-chloro-4-fluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(26) 8-{2-[2-(2,6-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(27) 8-{2-[2-(2,5-difluoro-4-methoxyphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(28) 8-{2-[2-(4-fluoro-3,5-dimethylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(29) 8-{2-[2-(3,5-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(30) 8-{2-[2-(4-chloro-3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(31) 8-{2-[2-(3,4,5-trifluorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

(32) 8-{2-[2-(3-methylphenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one; and

(33) 8-{2-[2-(3,4-dichlorophenyl)-1,1-dimethylethylamino]-1-hydroxyethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one,

or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof.

**24**. A pharmaceutical composition comprising a compound of formula 1 according to one of claims 6 to 23, or an acid addition salt thereof with a pharmacologically acceptable acid, or a solvate or hydrate thereof, and a pharmaceutically acceptable excipient or carrier.

**25**. The pharmaceutical composition according to claim 24, wherein the pharmaceutical composition is an inhalable powder, propellant-containing metered-dose aerosol, or propellant-free inhalable solution.

* * * * *