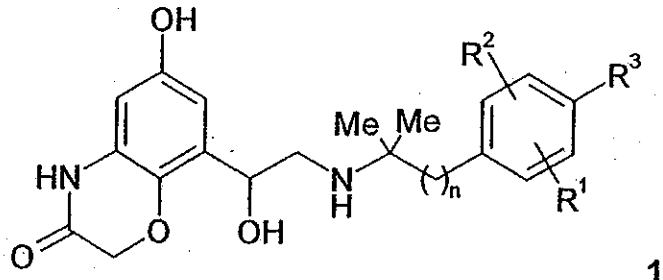
NOVEL MEDICAMENTS FOR THE TREATMENT OF CHRONIC OBSTRUCTIVE PULMONARY DISEASE

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 COPD (chronic obstructive pulmonary disease), as well as new compounds of general formula 1 and processes for preparing them.

Background to the invention

Betamimetics (ß-adrenergic substances) are known from the prior art. Reference may be made, for example, to the disclosures of US 4,460,581, which proposes betamimetics for the treatment of a variety of complaints.

For drug treatment of diseases it is often desirable to prepare medicaments with a longer duration of activity. As a rule, this ensures that the concentration of the active substance in the body needed to achieve the therapeutic effect is guaranteed for a longer period without the need to re-administer the drug at frequent intervals. Moreover, giving an active substance at longer time intervals contributes to the well-being of the patient to a high degree.

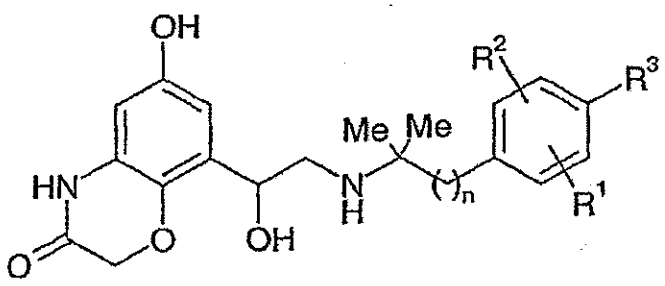
It is particularly desirable to prepare a pharmaceutical composition which can be used therapeutically by administration once a day (single dose). The use of a drug once a day has the advantage that the patient can become accustomed relatively quickly to taking the drug regularly at certain times of the day.

The aim of the present invention is therefore to provide betamimetics which have a therapeutic benefit in the treatment of COPD and are characterised 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 characterised by a high degree of selectivity with respect to the β_2-adreno-receptor.

Summary of Invention

In a first aspect, there is provided a compound of formula 1



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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, 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.

In a second aspect, there is provided a pharmaceutical composition comprising a compound of formula 1 as defined above, or an acid addition salt thereof with a pharmacologically acceptable acid, and a pharmaceutically acceptable excipient or carrier.

In a third aspect, there is provided R-6-Hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

In a fourth aspect, there is provided R-8-{2-[2-(2,4-Difluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

In a fifth aspect, there is provided R-8-{2-[2-(3,5-Difluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

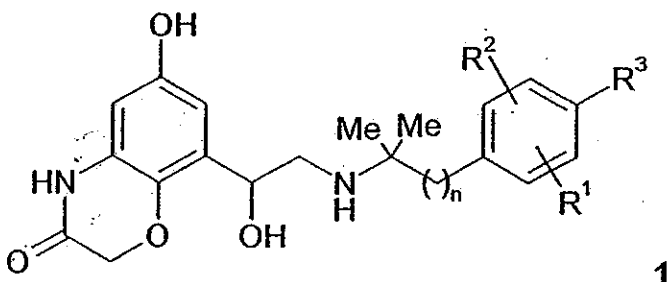
In a sixth aspect, there is provided R-8-{2-[2-(4-Ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

In a seventh aspect, there is providedR-8-{2-[2-(4-Fluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

Detailed description of the invention

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

Accordingly, the present invention relates to compounds of general formula **1**



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wherein

n	denotes 1 or 2,
R^1	denotes hydrogen, C_1-C_4-alkyl, halogen, OH or -O-C_1-C_4-alkyl;
R^2	denotes hydrogen, C_1-C_4-alkyl, halogen, OH or -O-C_1-C_4-alkyl;
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.

It is preferable to use compounds of general formula 1, wherein

n denotes 1 or 2,

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

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

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.

It is preferable to use compounds of general formula 1 wherein

n denotes 1 or 2;

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

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

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, -O-C_1-C_4-alkylene-CO-O-C_1-C_4-alkyl,

for preparing a pharmaceutical composition for the treatment of COPD.

It is particularly preferred to use compounds of general formula 1 wherein

n denotes 1 or 2,

R^1 denotes hydrogen, methyl or ethyl ;

R^2 denotes hydrogen, methyl or ethyl ;

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.

It is particularly preferred to use compounds of general formula 1 wherein

n denotes 1 or 2,

R^1 denotes hydrogen or methyl;

R^2 denotes hydrogen or methyl;

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.

Also of particular importance according to the invention is the use of compounds of general formula 1 wherein

n denotes 1 or 2,

R^1 denotes hydrogen or methyl;

R^2 denotes hydrogen or methyl;

R^3 denotes hydrogen, OH, methoxy or -O-CH_2-COOH;

for preparing a pharmaceutical composition for the treatment of COPD.

A preferred aspect of the present invention further relates to the use of compounds of general formula 1 wherein n = 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.

Another preferred aspect of the present invention relates to the use of compounds of general formula 1 wherein n = 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.

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

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.
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.

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.

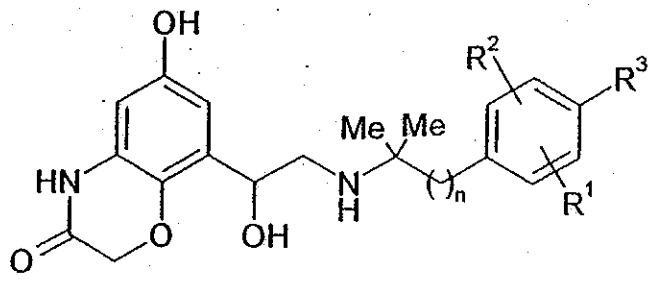
In another aspect the present invention relates to the abovementioned use of the compounds of formula 1 in the form of the acid addition salts with pharmacologically acceptable acids as well as optionally in the form of the solvates and/or hydrates thereof.

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.

Moreover the present invention relates to a process for the treatment of COPD, characterised 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, characterised in that one or more of the abovementioned compounds of general formula 1 are administered once a day in therapeutically effective amounts.

The compounds of general formula 1 are partly known from the prior art. Reference is made here to the disclosure of US 4460581. 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.

Accordingly the present invention also relates to compounds of general formula 1



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wherein

n	denotes 1;
R^1	denotes hydrogen, halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;
R^2	denotes hydrogen, halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;

R^3 denotes C_1-C_4-alkyl, OH, halogen, -O-C_1-C_4-alkyl, -O-C_1-C_4-alkylene-COOH, -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.

Preferred compounds of general formula **1** are those wherein
n denotes 1;
R^1 denotes hydrogen, fluorine, chlorine, methyl or methoxy;
R^2 denotes hydrogen, fluorine, chlorine, methyl or methoxy;
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, -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.

Preferred compounds of general formula **1** are those wherein
n denotes 1;
R^1 denotes hydrogen or C_1-C_4-alkyl;
R^2 denotes hydrogen or C_1-C_4-alkyl;
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.

Preferred compounds of general formula **1** are those wherein
n denotes 1;
R^1 denotes hydrogen, methyl or ethyl;
R^2 denotes hydrogen, methyl or ethyl;
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.

Also preferred are the compounds of general formula **1** wherein
n denotes 1;
R^1 denotes hydrogen or methyl;
R^2 denotes hydrogen or methyl;
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.

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.

The present invention also relates to compounds of general formula 1 wherein

n denotes 1;
R^1 denotes halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;
R^2 denotes halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;
R^3 denotes halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl.

The present invention also relates to compounds of general formula 1, wherein

n denotes 1;
R^1 denotes fluorine, chlorine, methyl or methoxy;
R^2 denotes fluorine, chlorine, methyl or methoxy ;
R^3 denotes fluorine, chlorine, methyl or methoxy.

In another preferred aspect the present invention relates to the compounds of general formula 1 wherein

n denotes 1;
R^1 denotes hydrogen;
R^2 denotes hydrogen, fluorine, chlorine or methyl;
R^3 denotes methyl, ethyl, iso-propyl, 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 and -O-CH_2-CH_2-CH_2-COOethyl.

Also particularly preferred are compounds of general formula 1 wherein

n denotes 1;
R^1 denotes hydrogen;
R^2 denotes hydrogen, fluorine, chlorine or methyl;

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

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

n denotes 1;

R^1 denotes hydrogen;

R^2 denotes halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl, preferably fluorine, chlorine, methoxy or methyl;

R^3 denotes halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl, preferably fluorine, chlorine, methoxy or methyl.

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

Another preferred aspect of the present invention relates to the compounds of general formula 1 wherein

n denotes 1;

R^1 and R^2 denote hydrogen;

R^3 denotes methyl, ethyl, iso-propyl, 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 and -O-CH_2-CH_2-CH_2-COOethyl.

Particularly preferred are compounds of general formula 1 wherein

n denotes 1;

R^1 and R^2 denote hydrogen;

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

Particularly preferred are compounds of general formula 1, wherein

n denotes 1;

R^1 and R^2 denote hydrogen;

R^3 denotes fluorine, chlorine, methoxy or ethoxy.

The present invention also relates to compounds of general formula 1

wherein

n	denotes 1;
R^1	denotes hydrogen, halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;
R^2	denotes hydrogen, halogen, C_1-C_4-alkyl or -O-C_1-C_4-alkyl;
R^3	denotes hydrogen.

Also preferred are compounds of general formula **1** wherein

n	denotes 1;
R^1	denotes hydrogen, fluorine, chlorine, methyl or methoxy;
R^2	denotes hydrogen, fluorine, chlorine, methyl or methoxy;
R^3	denotes hydrogen.

The present invention also relates to compounds of general formula **1** wherein

n	denotes 1;
R^1	denotes fluorine, chlorine, methyl or methoxy;
R^2	denotes fluorine, chlorine, methyl or methoxy;
R^3	denotes hydrogen.

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. 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.

Also particularly preferred are compounds of general formula **1** which are selected from among

- 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;
- 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-ethyl acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one;

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

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

In 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**.

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.

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.

Moreover the present invention relates to a process for the treatment of COPD, characterised 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, characterised in that one or more of the abovementioned new compounds of general formula **1** are administered once a day in therapeutically effective amounts.

By acid addition salts with pharmacologically acceptable acids are meant, for example, the salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrobenzoate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

Of the abovementioned acid addition salts the salts of hydrochloric acid, methanesulphonic acid, benzoic acid and acetic acid are particularly preferred according to the invention.

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.

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 iso-propyl, butyl includes iso-butyl, sec.butyl and tert.-butyl, etc.

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.

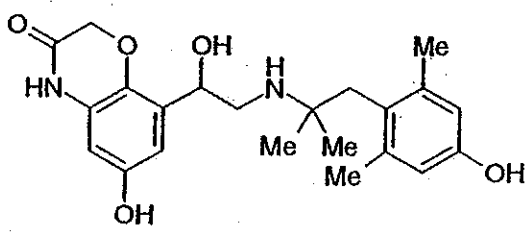
Unless otherwise stated, the term alkyloxy groups (or -O-alkyl groups) denotes branched and unbranched alkyl groups having 1 to 4 carbon atoms which are linked via an oxygen atom. Examples of these include: methyloxy, ethyloxy, propyloxy or butyloxy. The abbreviations MeO-, EtO-, PropO- or BuO- are used 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 iso-propyloxy, butyloxy includes iso-butyloxy, sec.butyloxy and tert.-butyloxy, etc. In some cases, within the scope of the present invention, the term alkoxy is used instead of the term alkyloxy. Accordingly, the terms methoxy, ethoxy, propoxy or butoxy may also be used to denote the groups methyloxy, ethyloxy, propyloxy or butyloxy.

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.

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 US 4460581, to the entire contents of which reference is made at this point.

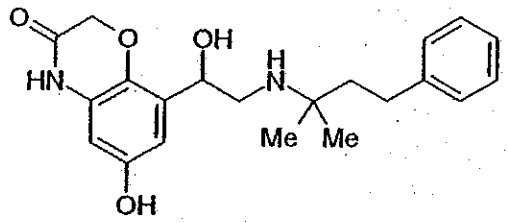
The examples of synthesis described below serve to illustrate compounds known from the prior art, which may surprisingly be used according to the present invention for the treatment of COPD.

Example 1: 6-hydroxy-8-{1-hydroxy-2-[2-(4-hydroxy-2,6-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



The compound is known from US 4460581.

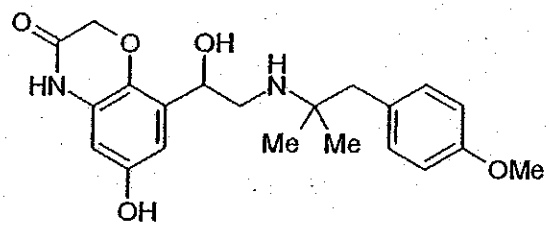
Example 2: 8-{2-[1,1-dimethyl-3-phenyl-propylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



The compound is known from US 4460581.

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-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



a) 8-{2-[1,1-dimethyl-2-(4-methoxy-phenyl)-ethylamino]-1-hydroxy-ethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

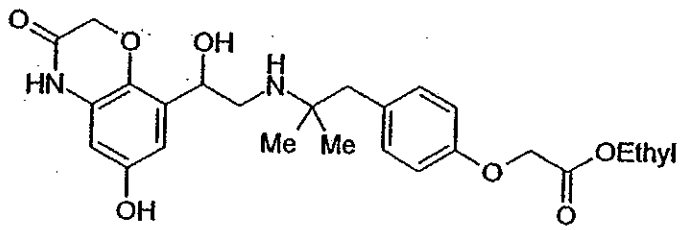
7.5 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-glyoxal hydrate are added at 70°C to a solution of 3.6 g of 1,1-dimethyl-2-(4-methoxyphenyl)-ethylamine in 100 mL ethanol and stirred for 15 minutes. Then 1 g of sodium borohydride is added within 30 minutes at 10 to 20°C. The mixture is stirred for one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

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

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 recrystallisation 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 = 155-160°C.

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 x 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 min, retention time (S-enantiomer) = 45.9 min. 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-phenoxy- ethyl acetate)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



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

The title compound is obtained analogously to the method described in Example 3a) from 15 g of (6-benzyloxy-4H-benzo[1,4]oxazin-3-on)-glyoxal hydrate and 11.8 g 1,1-dimethyl-2-(4-phenoxy-ethyl acetate)-ethylamine hydrochloride.

Yield: 16.5 g (69%, hydrochloride); melting point = 212-214°C.

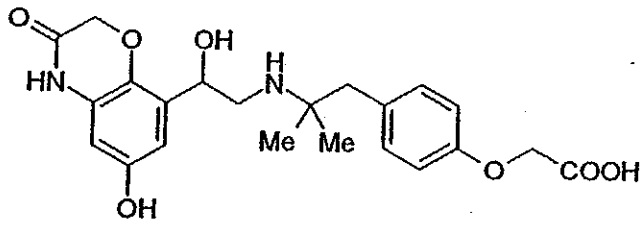
b) 8-{2-[1,1-dimethyl-2-(4-phenoxy-ethyl-acetate)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

8 g of the benzyl alcohol obtained above are 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 crystallises out when the solvent is distilled off is suction filtered and washed.

Yield: 5.5 g (81%; hydrochloride); melting point = 137-140°C.

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.

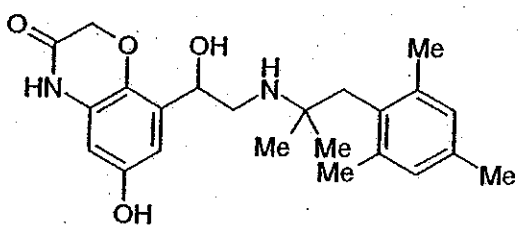
Example 5: 6-hydroxy-8-{1-hydroxy-2-[2-(4-phenoxy-acetic acid)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



11 g of 8-{2-[1,1-dimethyl-2-(4-phenoxy-ethyl-acetate)-ethylamino]-1-hydroxy-ethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one hydrochloride (Example 4a) are 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 sodium hydroxide dissolved in 20 mL water are 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 recrystallisation from 0.5 molar hydrochloric acid. Melting point = 152°C.

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-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-2-[1,1-dimethyl-2-(2,4,6-trimethylphenyl)-ethylimino]-ethanone
7.2 g (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-glyoxal hydrate and 3.6 g 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-hydroxy-ethyl}-6-benzyloxy-4H-benzo[1,4]oxazin-3-one

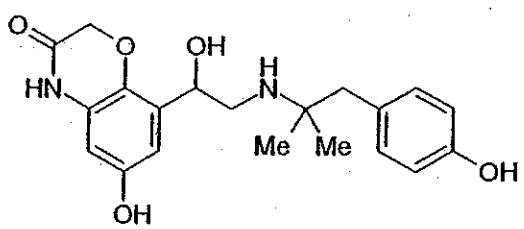
8.6 g of the Schiff base obtained according to method 6a) are dissolved in 100 mL ethanol and 20 mL THF, combined with 0.7 g sodium borohydride within 30 min at 10-20°C and stirred for one hour. After the addition of 10 mL acetone the mixture is stirred for 30 minutes and then diluted with ethyl acetate and water. The product which crystallises out on acidification with conc. 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-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

7.4 g of the benzyl compound obtained in Step b) are 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 crystallises 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).

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-hydroxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



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

The title compound is prepared from 10 g (6-benzyloxy-4H-benzo[1,4]oxazin-3-one)-glyoxal hydrate and 4.6 g 1,1-dimethyl-2-(4-hydroxy-phenyl)-ethylamine analogously to the method for Example 3a).

Yield: 9.0 g (64%, hydrochloride); melting point = 255-258°C.

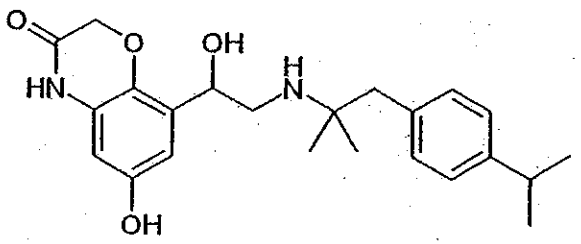
b) 8-{2-[1,1-dimethyl-2-(4-hydroxy-phenyl)-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

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 recrystallised once in water.

Yield: 3.6 g (72%, hydrochloride); melting point = 159-162°C.

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-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one



a) 1-(4-isopropyl-phenyl)-2-methyl-propan-2-ol

The reaction of a Grignard compound, prepared from 20 g (119 mmol) 4-isopropylbenzylchloride, with 11.4 ml (155 mmol) acetone yields the target compound as a colourless oil.

Yield: 13.0 g (57%); mass spectrometry: $[M+H]^+$ = 193.

b) N-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethyl]-acetamide

A Ritter reaction is carried out with 10.2 g (53 mmol) 1-(4-isopropyl-phenyl)-2-methyl-propan-2-ol in the manner described for Example 9b). 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-isopropyl-phenyl)-1,1-dimethyl-ethylamine

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

d) 6-benzyloxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

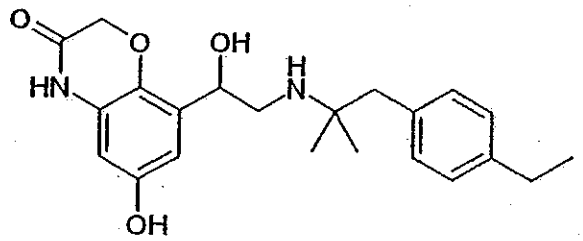
2.18 g (6.1 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 1.1 g (5.8 mmol) 2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamine are stirred in 40 mL ethanol at 50-80°C for one hour. After cooling to ambient temperature 0.24 g (6.3 mmol) sodium borohydride are added. The mixture 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 sulphate and freed from solvent. The residue is dissolved in 20 mL ethyl acetate and 10 mL water, acidified with conc. hydrochloric acid and diluted with diethyl ether. After the addition of a crystallisation aid the solid precipitate is suction filtered and washed. White solid.
Yield: 1.7 g (52 %, hydrochloride); melting point 220-222°C.

e) 6-hydroxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

1.6 g (3.0 mmol) 6-benzyloxy-8-{1-hydroxy-2-[2-(4-isopropyl-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one are 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 recrystallised from isopropanol. White solid.
Yield: 1.1 g (85%, hydrochloride); melting point 248-250°C; mass spectrometry: $[M+H]^+$ = 399.

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-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(4-ethyl-phenyl)-2-methyl-propan-2-ol

14.8 g (90 mmol) of 1-(4-ethyl-phenyl)-propan-2-one, dissolved in diethyl ether, are 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 hydrolysed 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 sulphate and evaporated down. The oil thus obtained is further reacted directly. Yield: 15.5 g (90%).

b) N-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethyl]-acetamide

6.2 mL conc. sulphuric acid are added dropwise to 15.5 g (87 mmol) 1-(4-ethyl-phenyl)-2-methyl-propan-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 conc. 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 sulphate 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 90-92°C.

c) 2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamine

16.3 g (74 mmol) of N-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethyl]-acetamide and 8.0 g of potassium hydroxide are refluxed for 15 hours in 60 mL ethyleneglycol. 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 sulphate 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 165-167°C.

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

The target compound is prepared analogously to the method for Example 8d) from 2.14 g (6.0 mmol) 6-benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 1.0 g (5.6 mmol) 2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamine. White solid.

Yield: 1.7 g (54%, hydrochloride); melting point 210-214°C.

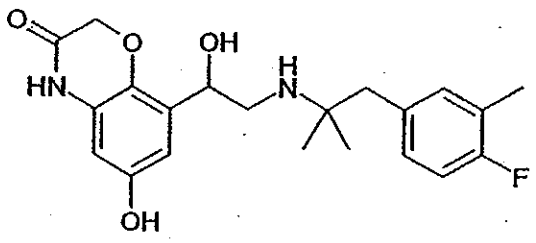
e) 8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

The hydrogenolysis of 1.45 g (2.75 mmol) 6-benzyloxy-8-{2-[2-(4-ethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one according to the method for Example 8e) yields the target compound in the form of a white solid.

Yield: 1.07 g (92%; hydrochloride); melting point 266-269°C; mass spectrometry: $[M+H]^+ = 385$.

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-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



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

100 mL of a 0.5 molar solution of 4-fluoro-3-methyl-phenylmagnesium 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 hydrolysed 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-toluenesulphonic acid monohydrate and refluxed for three hours using the water separator. The reaction mixture is poured onto water and made alkaline with conc. sodium hydroxide solution. After separation of the organic phase it is washed with water, dried with sodium sulphate and freed from solvent. Fractional distillation of the residue yields the product in the form of a colourless liquid (boiling point 80-85°C/10 mbar). Yield: 4.1 g (50%).

b) N-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethyl]-formamide

4.9 mL conc. sulphuric acid are added dropwise at 5-15°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) 1-fluoro-2-methyl-4-(2-methyl-propenyl)-benzene, dissolved in 10 mL glacial acetic acid, and stirred for 1 hour at 50-60°C. The reaction mixture is diluted with ice water, made alkaline with conc. sodium hydroxide solution and extracted with dichloromethane. The organic phase is dried with sodium sulphate 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-methyl-phenyl)-1,1-dimethyl-ethylamine

4.3 g (20.6 mmol) N-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethyl]-formamide, 20 mL conc. hydrochloric acid and 20 mL water are refluxed for 2 hours. The reaction mixture is diluted with water, made alkaline with conc. sodium hydroxide solution and extracted with dichloromethane. The organic phases are dried with sodium sulphate 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 196-198°C.

d) 6-benzyloxy-8-{2-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one

1.10 g (3.1 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.50 g (2.8 mmol) 2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamine are reacted and worked up analogously to the method for Example 8d). White solid.

Yield: 0.75 g (47%, hydrochloride); melting point 228-230°C.

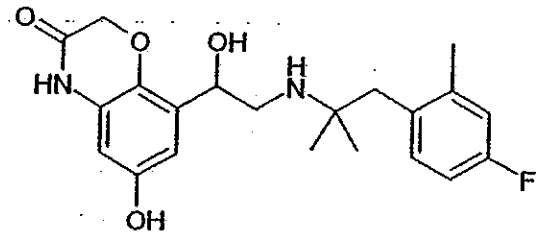
e) 8-{2-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

The hydrogenation of 0.70 g (1.4 mmol) 6-benzyloxy-8-{2-[2-(4-fluoro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one yields the target compound as a white solid.

Yield: 0.50 g (87%, hydrochloride); melting point 278-280°C; mass spectroscopy: $[M+H]^+ = 389$.

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-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(4-fluoro-2-methyl-phenyl)-2-methyl-propyl acetate

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 10a). 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 sulphate and evaporated down. The alcohol thus obtained is then dissolved in 50 mL acetic anhydride, combined with 1 mL conc. sulphuric 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 sulphate and the solvents are distilled off. Fractional distillation of the residue yields the product in the form of a colourless liquid (boiling point 105-110°C/8 mbar). Yield 29.0 g (52%).

b) N-[2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethyl]-formamide

29.0 g (130 mmol) 1-(4-fluoro-2-methyl-phenyl)-2-methyl-propyl acetate are reacted and worked up analogously to the method for Example 10b). Yellow oil. Yield: 27.0 g (99%).

c) 2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamine

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

d) 6-benzyloxy-8-{2-[2-[4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one

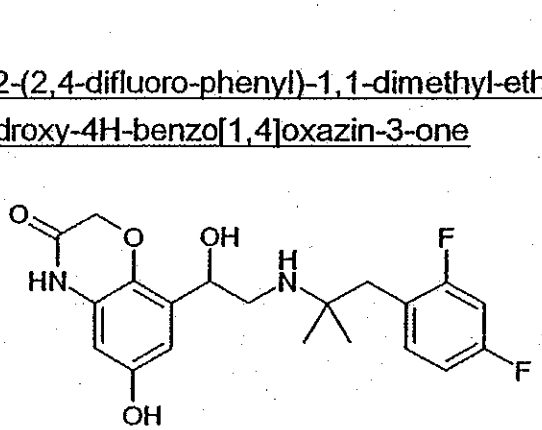
Prepared analogously to the method for Example 8d) from 0.95 g (2.66 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.43 g (2.37 mmol) 2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamine.
Yield: 0.75 g (55%, hydrochloride); melting point 233-236°C.

e) 8-{2-[2-(4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

The debenzylation of 0.70 g (1.36 mmol) 6-benzyloxy-8-{2-[2-[4-fluoro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-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 278-280°C; mass spectroscopy: $[M+H]^+ = 389$.

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-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(2,4-difluoro-phenyl)-2-methyl-propan-2-ol

11.0 mL acetone, diluted with 50 mL diethyl ether, are 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 hydrolysed with 10% ammonium chloride solution. The ether phase is separated off, washed with water, dried with sodium sulphate and evaporated down. The fractional distillation of the residue yields the alcohol as a colourless liquid (boiling point 70-73°C/ 2 mmbar). Yield: 20.0 g (86%).

b) N-[2-(2,4-difluoro-phenyl]-1,1-dimethyl-ethyl]-formamide
Ritter reaction with 20 g (110 mmol) 1-(2,4-difluoro-phenyl)-2-methyl-propan-2-ol according to the method described for Example 10b). Yellow oil. Yield: 22.0 g (94%).

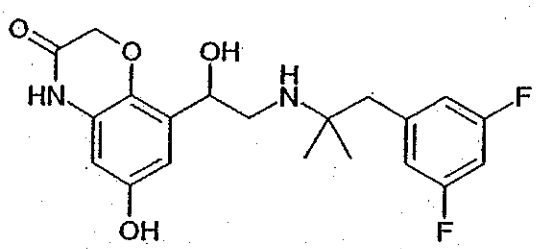
c) 2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamine
Reaction of 22.0 g (100 mmol) N-[2-(2,4-difluoro-phenyl]-1,1-dimethyl-ethyl]-formamide analogously to the method for Example 10c).
Yield: 16.0 g (72%, hydrochloride); melting point 201-203°C.

d) 6-benzyloxy-8-{2-[2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one
Reaction of 0.89 g (2.49 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.40 g (2.16 mmol) 2-(2,4-difluoro-phenyl)-1,1-dimethyl-ethylamine in the manner described for Example 8d).
Yield: 0.80 g (62%, hydrochloride); melting point 245-247°C.

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

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-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(3,5-difluoro-phenyl)-2-methyl-propan-2-ol

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

b) 2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamine

The Ritter reaction of 5.5 g (29.5 mmol) 1-(3,5-difluoro-phenyl)-2-methyl-propan-2-ol and 1.8 g 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-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one

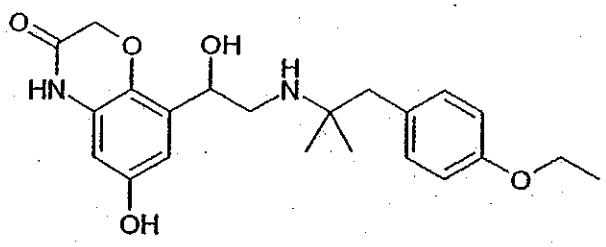
Prepared from 1.73 g (4.84 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.80 g (4.32 mmol) 2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamine in the usual way.
Yield: 1.50 g (58 %, hydrochloride); melting point 240-244°C.

d) 8-{2-[2-(3,5-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

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

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-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) benzyl [2-(4-ethoxy-phenyl)-1,1-dimethyl-ethyl]-carbaminate

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

b) 2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamine

A solution of 15.0 g (49 mmol) benzyl [2-(4-ethoxy-phenyl)-1,1-dimethyl-ethyl]-carbaminate in 100 mL glacial acetic acid is combined with 2 g palladium on charcoal (10%) and then hydrogenated at 5 bar and 40 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 conc. sodium hydroxide solution and extracted with ethyl acetate. The organic phase is washed with water, dried with sodium sulphate 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 198-200°C.

c) 6-benzyloxy-8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one

2.14 g (6.0 mmol) 6-benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 1.0 g (5.2 mmol) 2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamine are stirred in 40 mL ethanol for one hour at 50-80°C. After cooling to ambient temperature 0.23 g (6.0 mmol) 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 sulphate and freed from solvent in vacuo. The residue is dissolved again in ethyl acetate and water, combined with conc. 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 214-216°C.

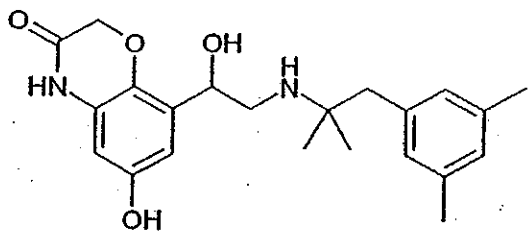
d) 8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

1.5 g (2.8 mmol) 6-benzyloxy-8-{2-[2-(4-ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-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 232-235°C; mass spectrometry: $[M+H]^+ = 401$.

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-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(3,5-dimethyl-phenyl)-2-methyl-propanol-2-ol

Obtained by reacting ethyl (3,5-dimethyl-phenyl)-acetate with methylmagnesium bromide.

b) 2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamine

By reacting 6.00 g (34 mmol) 1-(3,5-dimethyl-phenyl)-2-methyl-propanol-2-ol and 2.00 g (41 mmol) sodium cyanide in a Ritter reaction 2.40 g of 2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylformamide (35% yield) are 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 10c). Oil. Yield: 1.70 g (82%); mass spectroscopy: $[M+H]^+ = 178$.

c) 6-benzyloxy-8-{2-[2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-4H-benzo[1,4]oxazin-3-one

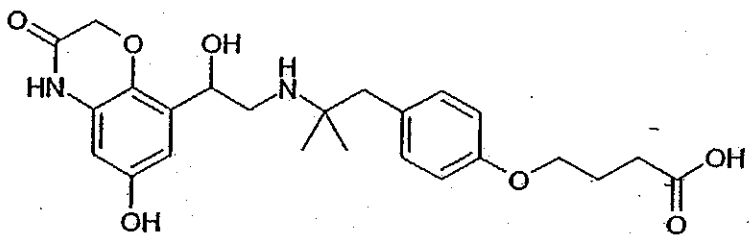
Prepared analogously to the method for Example 8d) from 1.47 g (4.1 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.65 g (3.7 mmol) 2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamine.
Yield: 1.1 g (51 %, hydrochloride); melting point 220-222°C.

d) 8-{2-[2-(3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

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

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-methyl-propyl}-phenoxy)-butyric acid



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

4.5 g (15.0 mmol) benzyl [2-(4-hydroxy-phenyl)-1,1-dimethyl-ethyl]-carbaminate, 2.3 mL (16.0 mmol) ethyl 4-bromo-butyrate, 2.3 g (16.6 mmol) potassium carbonate and 0.3 g (1.8 mmol) potassium iodide in 20 mL dimethylformamide are heated to 120°C for 13 h. 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 sulphate and evaporated down. The residue is purified by chromatography (eluant: cyclohexane/ethyl acetate = 9:1). 5.0 g of a yellow oil are 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 = 103-105°C.

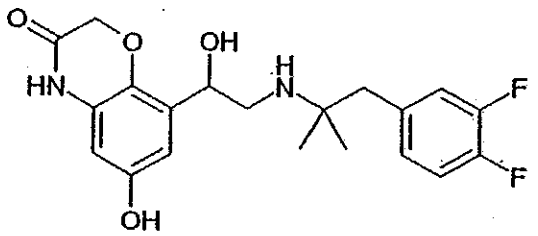
b) ethyl 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenoxy)-butyrate
1.20 g (3.36 mmol) benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 0.90 g (3.22 mmol) ethyl 4-[4-(2-amino-2-methyl-propyl)-phenoxy]-butyrate are reacted in the manner described for Example 8d). 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 223-227°C.

c) 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid
A solution of 1.00 g (1.73 mmol) ethyl 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenoxy)-butyrate in 25 mL methanol is combined with 2.5 mL 1 N sodium hydroxide solution, refluxed for 30 minutes and then neutralised 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 crystallisation aid a solid is precipitated out which is suction filtered and washed with acetone and diethyl ether.
Yield: 0.75 g (79%); melting point 216-218°C.

d) 4-(4-{2-[2-hydroxy-2-(6-hydroxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid
0.70 g (1.28 mmol) 4-(4-{2-[2-(6-benzyloxy-3-oxo-3,4-dihydro-2H-benzo[1,4]oxazin-8-yl)-2-hydroxy-ethylamino]-2-methyl-propyl}-phenoxy)-butyric acid are 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 crystallisation from a methanol/acetone mixture. Yield: 0.40 g (68%); melting point 201-204°C; mass spectroscopy: $[M+H]^+ = 459$.

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-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(3,4-difluoro-phenyl)-2-methyl-propan-2-ol

From 23.0 g (111 mmol) 3,4-difluorobenzyl bromide a Grignard is prepared, which is then reacted with 11.6 mL (158 mmol) 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-difluoro-phenyl)-1,1-dimethyl-ethyl]-formamide

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

c) 2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamine

4.00 g (18.5 mmol) N-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethyl]-formamide are dissolved in ethanol, combined with conc. 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 sulphate and evaporated down. Yellow oil. Yield: 3.2 g (92%); mass spectrometry: $[M+H]^+$ = 186.

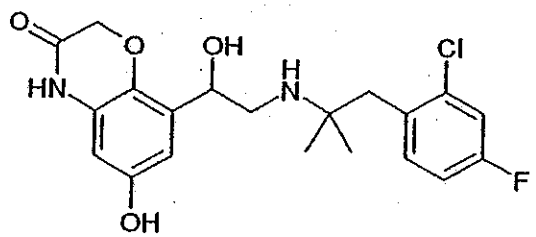
d) 8-{2-[2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

357 mg (1 mmol) 6-benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 185 mg (1 mmol) 2-(3,4-difluoro-phenyl)-1,1-dimethyl-ethylamine 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 min at ambient temperature, combined with 10 mL dichloromethane and 3 mL water, stirred for a further hour and then filtered through Extrelut ®. The eluate containing the ethanolamine 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.

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-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



a) 1-(2-chloro-4-fluoro-phenyl)-2-methyl-propan-2-ol

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

b) N-[2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethyl]-formamide

7.5 g (37 mmol) 1-(2-chloro-4-fluoro-phenyl)-2-methyl-propan-2-ol were reacted and worked up according to the method described for Example 10b). 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-fluoro-phenyl)-1,1-dimethyl-ethylamine

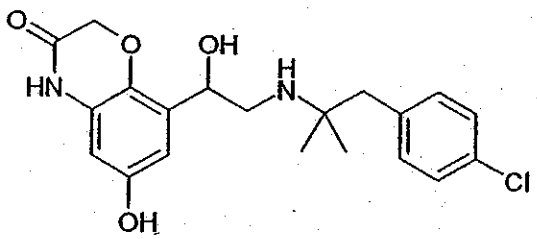
Reaction of 7.4 g (32 mmol) N-[2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethyl]-formamide as described in the method for Example 17c). Brown oil.
Yield: 5.14 g (79%); mass spectrometry: $[M+H]^+$ = 202/204.

d) 8-{2-[2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

357 mg (1 mmol) of 6-benzyloxy-8-(2-ethoxy-2-hydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 202 mg (1 mmol) 2-(2-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamine are reacted with lithium borohydride analogously to the method for Example 10d). 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 Extrelut®. 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.

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-chloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

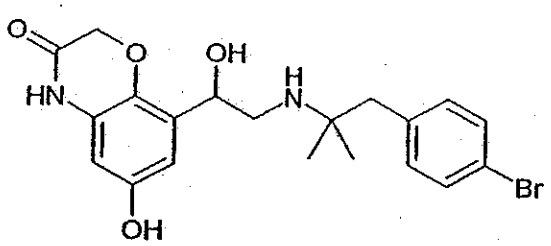


A solution of 300 mg (0.91 mmol) 6-benzyloxy-8-(2,2-dihydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 200 mg (1.09 mmol) 2-(4-chloro-phenyl)-1,1-dimethyl-ethylamine in 3 mL ethanol was combined with molecular sieve and stirred for 90 minutes at 80°C. It was allowed to cool to ambient temperature, 35 mg (0.91 mmol) of sodium borohydride were 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 (eluant: 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 conc. ammonia solution were 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; eluant: dichloromethane/methanol + 1% ammonia). Beige-coloured solid: 93 mg (26%); mass spectrometry: $[M+H]^+$ = 391.

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.

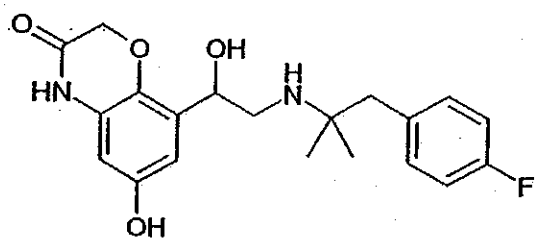
Example 20: 8-{2-[2-(4-bromo-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



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

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-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one



300 mg (0.91 mmol) of 6-benzyloxy-8-(2,2-dihydroxy-acetyl)-4H-benzo[1,4]oxazin-3-one and 183 mg (1.09 mmol) 2-(4-fluoro-phenyl)-1,1-dimethyl-ethylamine 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) sodium borohydride were 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 (eluant: 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®, the filtrate was freed from solvent and the residue was chromatographed (silica gel; eluant: dichloromethane/methanol). Beige solid. Yield: 76 mg (22%); mass spectrometry: $[M+H]^+ = 375$.

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.

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-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 23: 8-{2-[2-(4-fluoro-2,6-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 24: 8-{2-[2-(4-chloro-2-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 25: 8-{2-[2-(4-chloro-3-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 26: 8-{2-[2-(4-chloro-2-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 27: 8-{2-[2-(3-chloro-4-fluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 28: 8-{2-[2-(2,6-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 29: 8-{2-[2-(2,5-difluoro-4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 30: 8-{2-[2-(4-fluoro-3,5-dimethyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 31: 8-{2-[2-(3,5-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 32: 8-{2-[2-(4-chloro-3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 33: 8-{2-[2-(3,4,5-trifluoro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 34: 8-{2-[2-(3-methyl-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one;

Example 35: 8-{2-[2-(3,4-dichloro-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one.

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.

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, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate, optionally in the form of one of the solvates or hydrates thereof.

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, sulphobenzoates, phosphates, isonicotinates, acetates, propionates, dihydrogen phosphates, palmitates, pivalates or furoates. In some cases the corticosteroids may also occur in the form of their hydrates.

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, cabergolin, alpha-dihydroergocryptine, lisuride, pergolide, pramipexol, roxindol, ropinirol, talipexol, tergurid 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, sulphuric acid, phosphoric acid, methanesulphonic acid, acetic acid, fumaric acid, succinic acid, lactic acid, citric acid, tartaric acid and maleic acid.

Examples of antiallergic agents which may be used according to the invention as a combination with the compound of formula 1 include epinastin, cetirizin, azelastin, fexofenadin, levocabastin, loratadine, mizolastin, ketotifen, emedastin, dimetinden, clemastine, bamipin, cexchloropheniramine, pheniramine, doxylamine, chlorophenoxamine, dimenhydrinate, diphenhydramine, promethazine, ebastin, desloratidine 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.

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, sulphuric acid, phosphoric acid, methanesulphonic 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, sulphate, phosphate and methanesulphonate are preferred in this context.

Suitable preparations for administering the compounds of formula 1 include for example tablets, capsules, suppositories, solutions and 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.

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 of layers to achieve delayed release, possibly using the excipients mentioned above for the tablets.

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 flavour enhancer, e.g. a flavouring 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.

Solutions are prepared in the usual way, e.g. with the addition of isotonic agents, preservatives such as p-hydroxybenzoates or stabilisers 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 solubilisers or dissolving aids, and the solutions may be transferred into injection vials or ampoules or infusion bottles.

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.

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.

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 sulphite liquors, methylcellulose, starch and polyvinylpyrrolidone) and lubricants (e.g. magnesium stearate, talc, stearic acid and sodium lauryl sulphate).

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 laurylsulphate and talc may also be used to produce the tablets. In the case of aqueous suspensions the active substances may be combined with various flavour enhancers or colourings in addition to the abovementioned excipients.

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.

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.

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, maltose), oligo- and polysaccharides (e.g. dextrans), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, 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.

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 and 150 µm, most preferably between 15 and 80 µm. It may sometimes seem appropriate to add finer excipient fractions with an average particle size of 1 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 to 10 µm, more preferably from 1 to 5 µm, is added to the excipient mixture. Processes for producing the inhalable powders according to the invention by grinding and micronising and finally mixing the ingredients together are known from the prior art.

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

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.

The propellant-driven inhalation aerosols may also contain other ingredients such as co-solvents, stabilisers, surfactants, antioxidants, lubricants and pH adjusters. All these ingredients are known in the art.

The propellant-driven inhalation aerosols according to the invention mentioned above may be administered using inhalers known in the art (MDIs = metered dose inhalers).

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, sulphuric 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 sulphuric 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 flavourings, 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.

If desired, the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser 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/100ml, preferably less than 50mg/100ml, more preferably less than 20mg/100ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10mg/100ml are preferred.

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, glycolether, 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 stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or prolong the shelf life of the finished pharmaceutical formulation, flavourings, vitamins and/or other additives known in the art. The additives also include pharmacologically acceptable salts such as sodium chloride as isotonic agents.

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.

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.

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.

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 characterised 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.

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

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

Examples of pharmaceutical formulations

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

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

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

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 sterilised 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	ad 100

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/100ml)

active substance **1**	333.3 mg
benzalkonium chloride	10.0 mg
EDTA	50.0 mg
HCl (1N)	ad pH 3.4

This solution can be prepared in the usual way.

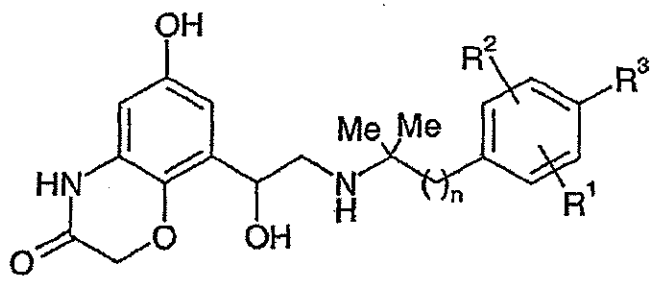
F) Inhalable powder

active substance **1**	12 µg
lactose monohydrate	ad 25 mg

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

Claims:

1. 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, 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.

2. The compound of formula 1 according to claim 1, 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.

3. The compound of formula 1 according to claim 1, 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, 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.

4. The compound of formula 1 according to claim 3, 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.

5. The compound of formula 1 according to claim 1, 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, -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.

6. The compound of formula 1 according to claim 5, 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.

7. The compound of formula 1 according to claim 1, wherein:

R^1 is hydrogen, methyl, or ethyl;

R^2 is hydrogen, methyl, or ethyl;

R^3 is methyl, ethyl, 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.

8. The compound of formula 1 according to claim 7, 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.

9. The compound of formula 1 according to claim 1, 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.

10. The compound of formula 1 according to claim 9, 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.

11. The compound of formula 1 according to claim 1, wherein:

R^1 is hydrogen;

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

R^3 is methyl, ethyl, isopropyl, tert-butyl, 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.

12. The compound of formula 1 according to claim 11, wherein:

R^1 is hydrogen;

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

R^3 is fluorine, chlorine, methyl, methoxy, ethoxy, or -O-CH_2-COOH,

or an acid addition salt thereof with a pharmacologically acceptable acid.

13. The compound of formula 1 according to claim 1, wherein:

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

R^3 is methyl, ethyl, isopropyl, tert-butyl, 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.

14. The compound of formula 1 according to claim 13, wherein R^3 is OH, fluorine, chlorine, methoxy, ethoxy, or -O-CH_2-COOH, or an acid addition salt thereof with a pharmacologically acceptable acid.

15. The compound of formula 1 according to claim 14, wherein R^3 is fluorine, chlorine, methoxy, or ethoxy, or an acid addition salt thereof with a pharmacologically acceptable acid.

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

R^1 is hydrogen, halogen, C_1-C_4-alkyl, or -OC_1-C_4-alkyl; and

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

or an acid addition salt thereof with a pharmacologically acceptable acid.

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

18. A compound of formula 1 according to claim 6 selected from:

(1) 6-hydroxy-8-{1-hydroxy-2-[2-(4-methoxyphenyl)-1,1-dimethylethylamino]ethy- l}-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)-1,1 dimethylethylamino]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.

19. A pharmaceutical composition comprising a compound of formula 1 according to one of claims 1 to 18, or an acid addition salt thereof with a pharmacologically acceptable acid, and a pharmaceutically acceptable excipient or carrier.

20. The pharmaceutical composition according to claim 19, wherein the pharmaceutical composition is an inhalable powder, propellant-containing metered-dose aerosol, or propellant-free inhalable solution.

21. R-6-Hydroxy-8-{1-hydroxy-2-[2-(4-methoxy-phenyl)-1,1-dimethyl-ethylamino]-ethyl}-4H-benzo[1,4]oxazin-3-one

22. R-8-{2-[2-(2,4-Difluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

23. R-8-{2-[2-(3,5-Difluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

24. R-8-{2-[2-(4-Ethoxy-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one

25. R-8-{2-[2-(4-Fluor-phenyl)-1,1-dimethyl-ethylamino]-1-hydroxy-ethyl}-6-hydroxy-4H-benzo[1,4]oxazin-3-one