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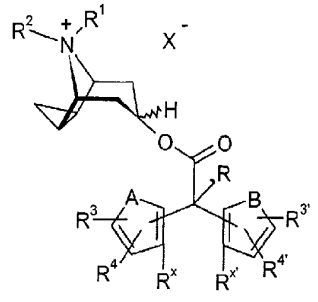
Zur Erklärung der Zweibuchstaben-Codes und der anderen Abkürzungen wird auf die Erklärungen ("Guidance Notes on Codes and Abbreviations") am Anfang jeder regulären Ausgabe der PCT-Gazette verwiesen.

(54) **Title:** ANTICHOLINERGIC AGENTS, METHOD FOR PRODUCING THE SAME AND USE THEREOF AS MEDICAMENTS

(54) **Bezeichnung:** ANTICHOLINERGIKA, VERFAHREN ZU DEREN HERSTELLUNG SOWIE DEREN VERWENDUNG ALS ARZNEIMITTEL



(I)

(57) **Abstract:** The invention relates to novel anticholinergic agents of general formula (1), in which X $^-$ and the groups A, B, R, R^1, R^2, R^3, R$^{3'}$, R^4, R$^{4'}$, R^x and R$^{x'}$ can be defined as per the claims and the description. The invention also relates to a method for producing said agents and to the use thereof as medicaments.

(57) **Zusammenfassung:** Die vorliegende Erfindung betrifft neue Anticholinergika der allgemeinen Formel (1), worin X $^-$ und die Reste A, B, R, R^1, R^2, R^3, R$^{3'}$, R^4, R$^{4'}$, R^x und R$^{x'}$, die in den Ansprüchen und in der Beschreibung genannten Bedeutungen haben können, Verfahren zu deren Herstellung sowie deren Verwendung als Arzneimittel.

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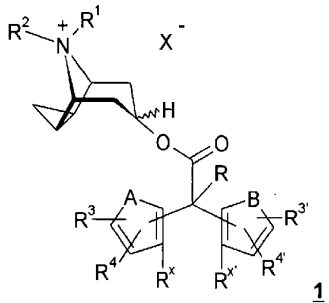
Anticholinergic agents, method of producing the same and use thereof as medicaments

The present invention relates to new anticholinergics of general formula 1



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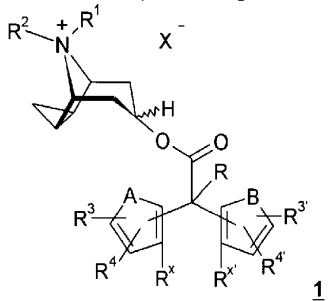
wherein X $^-$ and the groups A, B, R, R^1, R^2, R^3, $R^{3'}$, R^4, $R^{4'}$, R^x and $R^{x'}$, may have the meanings given in the claims and in the specification, processes for preparing them and their use as pharmaceutical compositions.

Description of the invention

The present invention relates to compounds of general formula 1



1

wherein

X $^-$ denotes an anion with a single negative charge, preferably an anion selected from among chloride, bromide, iodide, sulphate, phosphate, methanesulphonate, nitrate, maleate, acetate, citrate, fumarate, tartrate, oxalate, succinate, benzoate and p-toluenesulphonate;

A and B which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$,

-CH=CH, or -N(C_1-C_4-alkyl)-;

R denotes hydrogen, hydroxy, -C_1-C_4-alkyl, -C_1-C_4-alkyloxy, -C_1-C_4-alkylene-Halogen, -O-C_1-C_4-alkylene-halogen, -C_1-C_4-alkylene-OH, -CF_3, CHF_2, -C_1-C_4-alkylene-C_1-C_4-alkyloxy, -O-COC$_1$-C_4-alkyl, -O-COC$_1$-C_4-alkylene-halogen, -C_1-C_4-alkylene-C_3-C_6-cycloalkyl, -O-COCF_3 or halogen;

R^1 and R^2 which may be identical or different, denote -C_1-C_5-alkyl, which may optionally be substituted by -C_3-C_6-cycloalkyl, hydroxy or halogen,
or
R^1 and R^2 together denote a -C_3-C_5-alkylene bridge;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, -CF_3, -CHF_2, CN, NO_2 or halogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, -CF_3, -CHF_2, CN, NO_2 or halogen
or
R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, -CH_2, -CH_2-CH_2-, -N(C_1-C_4-alkyl), -CH(C_1-C_4-alkyl)- and -C(C_1-C_4-alkyl)$_2$.

Preferred compounds of general formula **1** are those wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -O, -S, -NH or -CH=CH-;

R denotes hydrogen, hydroxy, -C_1-C_4-alkyl, -C_1-C_4-alkyloxy, -CF_3, -CHF_2, fluorine, chlorine or bromine;

R^1 and R^2 which may be identical or different, denote C_1-C_4-alkyl, which may optionally be substituted by hydroxy, fluorine, chlorine or bromine,
or
R^1 and R^2 together denote a -C_3-C_4-alkylene-bridge;

R3, R4, R3' and R4', which may be identical or different, denote hydrogen, C1-C4-alkyl, C1-C4-alkyloxy, hydroxy, -CF3, -CHF2, CN, NO2, fluorine, chlorine or bromine;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, -CF_3, -CHF_2, CN, NO_2, fluorine, chlorine or

bromine

or

R^X and $R^{X'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH- and $-CH_2-$.

Particularly preferred compounds of general formula **1** are those wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -S or -CH=CH-;

R denotes hydrogen, hydroxy, methyl, ethyl, methyloxy, ethyloxy, $-CF_3$, or fluorine;

R^1 and R^2 which may be identical or different, denote methyl, ethyl, $-CH_2F$ or $-CH_2-CH_2F$, preferably methyl or ethyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, methyl, methyloxy, $-CF_3$ or fluorine;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, methyl, methyloxy, $-CF_3$ or fluorine

or

R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

Of particular importance according to the invention are compounds of general formula **1**, wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -S or -CH=CH-;

R denotes hydrogen, hydroxy or methyl;

R^1 and R^2 which may be identical or different, denote methyl or ethyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen or

R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

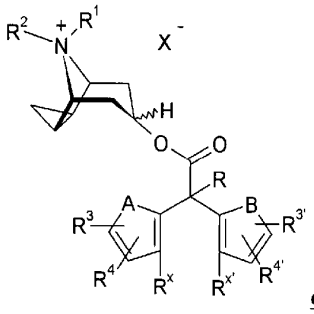
Also preferred according to the invention are compounds of general formula **1**, wherein

X^- denotes bromide;
A and B denote -CH=CH-;
R denotes hydrogen, hydroxy or methyl;
R^1 and R^2 denote methyl;
R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;
R^x and $R^{x'}$ which may be identical or different, denote hydrogen or fluorine, preferably hydrogen or
R^x and $R^{x'}$ together denote a single bond or the bridging group -O-.

The invention relates to the compounds of formula **1** optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates as well as optionally in the form of the pharmacologically acceptable acid addition salts thereof.

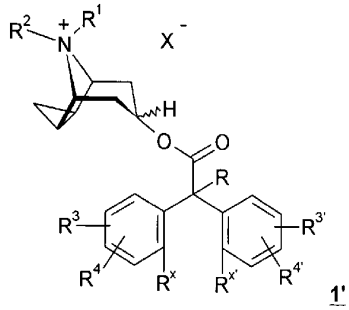
In the compounds of general formula **1** the groups R^3, R^4, $R^{3'}$ and $R^{4'}$, if they do not represent hydrogen, may in each case be arranged in the *ortho*, *meta* or *para* position relative to the bond to the "-C- R" group. If none of the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ denotes hydrogen, R^3 and $R^{3'}$ are preferably linked in the *para* position and R^4 and $R^{4'}$ are preferably linked in the *ortho* or *meta* position, most preferably in the *meta* position. If one of the groups R^3 and R^4 and one of the groups $R^{3'}$ and $R^{4'}$ denotes hydrogen, the other group in each case is preferably bonded in the *meta* or *para* position, most preferably in the *para* position. If none of the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ denotes hydrogen, the compounds of general formula **1** wherein the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ have the same meaning are particularly preferred according to the invention.

Of particular importance according to the invention are the compounds of general formula **1** wherein the two rings which contain A and B are arranged so that A and B are each in the ortho configuration relative to the bond to the "C-R" carbon. This preferred configuration is particularly important when A and B do not represent -CH=CH-. These compounds correspond to the general formula ***ortho*-1**.



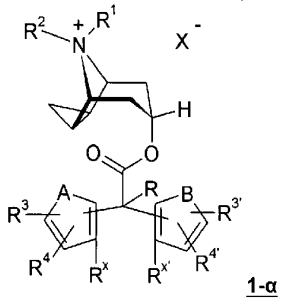
***ortho*-1**

Of particular importance according to the invention are the compounds of general formula **1** wherein A represents -CH=CH- and B represents -CH=CH-. These compounds correspond to general formula **1'**.



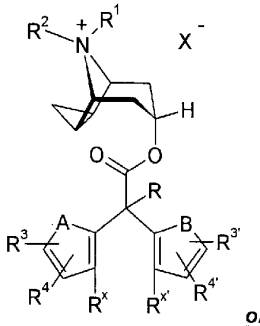
1'

Of particular importance according to the invention are the compounds of general formula **1** wherein the ester substituent at the nitrogen bicyclic group is in the α configuration. These compounds correspond to general formula **1-α**



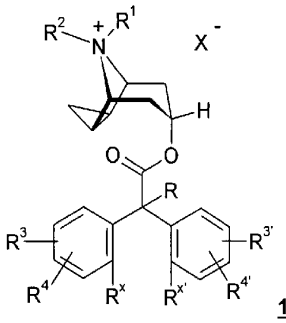
1-α

The compounds of general formula **1** preferred according to the invention wherein the two rings which contain A and B are arranged so that A and B in each case ortho-configured relative to the bond to the "C-R" carbon and wherein moreover the ester substituent at the nitrogen bicyclic group is α-configured correspond to general formula ***ortho*-1-α**



***ortho*-1-α**

The compounds of general formula **1** which are particularly preferred according to the invention wherein A represents -CH=CH- and B represents -CH=CH- and wherein the ester substituent at the nitrogen bicyclic group is α-configured correspond to general formula **1'-α.**



1'-α

The following compounds are particularly important according to the invention:

- cyclopropyltropine benzilate methobromide;
- cyclopropyltropine 2,2-diphenylpropionate methobromide;
- cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide;
- cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide;

- cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide ;
- cyclopropyltropine methyl 4,4'-difluorobenzilate methobromide.

The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 4 carbon atoms. Examples include: methyl, ethyl, propyl or butyl. The groups methyl, ethyl, propyl or butyl may optionally also be referred to by the abbreviations Me, Et, Prop or Bu. Unless otherwise stated, the definitions propyl and butyl also include all 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.

The cycloalkyl groups used, unless otherwise stated, are alicyclic groups with 3 to 6 carbon atoms. These are the cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. According to the invention cyclopropyl is of particular importance within the scope of the present invention.

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

The alkylene-halogen groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably disubstituted, by a halogen. Accordingly, unless otherwise stated, the term alkylene-OH groups denotes branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by a hydroxy.

The alkyloxy groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are linked via an oxygen atom. The following may be mentioned, for example: methyloxy, ethyloxy, propyloxy or butyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to by the abbreviations MeO, EtO, PropO or BuO. Unless otherwise stated, the definitions propyloxy and butyloxy also 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. The word alkoxy may also possibly be used within the scope of the present invention instead of

the word alkyloxy. The groups methyloxy, ethyloxy, propyloxy or butyloxy may optionally also be referred to as methoxy, ethoxy, propoxy or butoxy.

The alkylene-alkyloxy groups used, unless otherwise stated, are branched and unbranched double-bonded alkyl bridges with 1 to 4 carbon atoms which may be mono-, di- or trisubstituted, preferably monosubstituted, by an alkyloxy group.

The -O-CO-alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups with 1 to 4 carbon atoms which are bonded via an ester group. The alkyl groups are bonded directly to the carbonylcarbon of the ester group. The term -O-CO-alkyl-halogen group should be understood analogously. The group -O-CO-CF_3 denotes trifluoroacetate.

Within the scope of the present invention halogen denotes fluorine, chlorine, bromine or iodine. Unless otherwise stated, fluorine and bromine are the preferred halogens. The group CO denotes a carbonyl group.

As explained hereinafter, the compounds according to the invention may be prepared partly analogously to the methods already known in the art (Diagram 1). The carboxylic acid derivatives of formula **3** are known in the art or may be obtained by methods of synthesis known in the art. If only suitably substituted carboxylic acids are known in the art, the compounds of formula **3** may also be obtained directly from them by acid- or base-catalysed esterification with the corresponding alcohols or by halogenation with the corresponding halogenation reagents.

Starting from the compounds of formula **2** the esters of general formula **4** may be obtained by reaction with the carboxylic acid derivatives of formula **3**, wherein R' denotes for example chlorine or a C_1-C_4-alkyloxy group. When R' equals C_1-C_4-alkyloxy this reaction may be carried out for example in a sodium melt at elevated temperature, preferably at about 50-150°C, more preferably at about 90-100°C at low pressure, preferably at below 500 mbar, most preferably at below 75 mbar. Alternatively, instead of the derivatives **3** wherein R' denotes C_1-C_4-alkyloxy, the corresponding acid chlorides (R = Cl) may also be used.

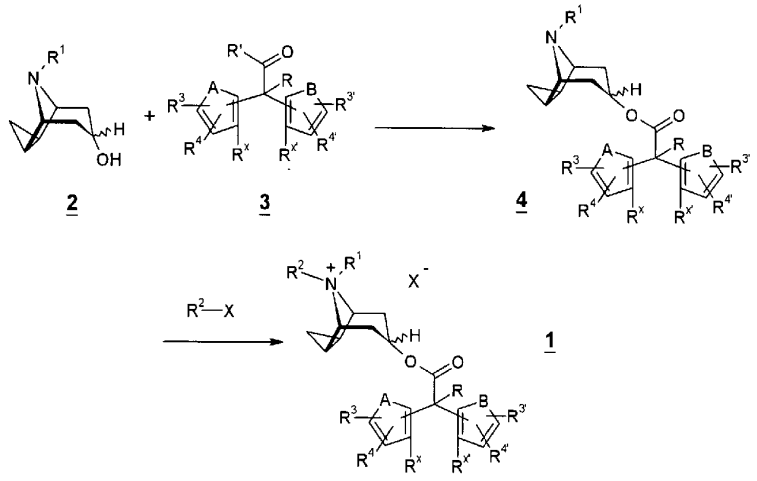
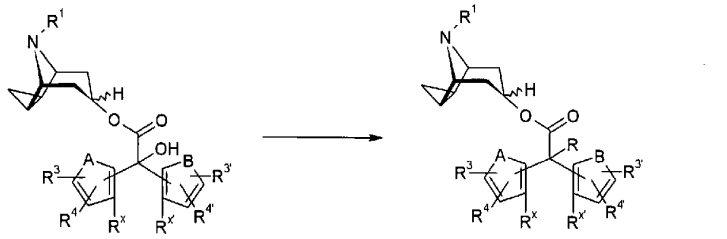


Diagram 1:

The compounds of formula **4** thus obtained may be converted into the target compounds of formula **1** by reacting with the compounds R^2-X, wherein R^2 and X may have the abovementioned meanings. This synthesis step may also be carried out analogously to the examples of synthesis disclosed in WO 92/16528. In the case wherein R^1 and R^2 together form an alkylene bridge there is no need to add the reagent R^2-X, as will be apparent to the skilled man. In this case the compounds of formula **4** contain a suitably substituted group R^1 (for example -C_3-C_5-alkylene-halogen) according to the above definitions and the compounds of formula **1** are prepared by intramolecular quaternisation of the amine.

Alternatively, the compounds of formula **4** wherein R denotes halogen may also be prepared by the method shown in Diagram 2.

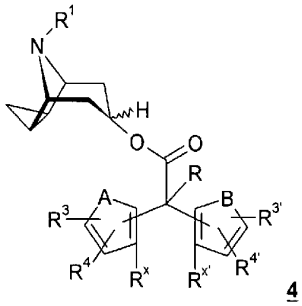
For this, the compounds of formula **4** wherein R denotes hydroxy are converted into the compounds **4** wherein R denotes halogen using suitable halogenation reagents. The method used for the halogenation reactions to be carried out according to Diagram 2 is sufficiently well known in the art.



4 (mit R=OH) 4 (mit R = Halogen)

Diagram 2:

As is apparent from Diagram 1, the intermediate products of general formula 4 have a central importance. Accordingly, in another aspect, the present invention relates to the intermediates of formula 4



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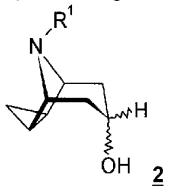
wherein the groups A, B, R, R^1, R^3, $R^{3'}$, R^4, $R^{4'}$, R^x and $R^{x'}$ may be defined as above, optionally in the form of the acid addition salts thereof.
By acid addition salts are meant salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, hydronitrate, hydromaleate, hydroacetate, hydrocitrate, hydrofumarate, hydrotartrate, hydrooxalate, hydrosuccinate, hydrobenzoate and hydro-p-toluenesulphonate, preferably the hydrochloride, hydrobromide, hydrosulphate, hydrophosphate, hydrofumarate and hydromethanesulphonate.

As in the compounds of general formula 1 the groups R^3, R^4, $R^{3'}$ and $R^{4'}$, if they do not represent hydrogen, may in each case be arranged in the *ortho*, *meta* or *para* position relative to the bond to the "-C- R" group in the

compounds of general formula **4** as well. If none of the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ denotes hydrogen, R^3 and $R^{3'}$ are preferably linked in the *para* position and R^4 and $R^{4'}$ are preferably linked in the *ortho* or *meta* position, most preferably in the *meta* position. If one of the groups R^3 and R^4 and one of the groups $R^{3'}$ and $R^{4'}$ denotes hydrogen, the other group in each case is preferably linked in the *meta* or *para* position, most preferably in the *para* position. If none of the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ denotes hydrogen the compounds of general formula **4** which are particularly preferred according to the invention are those wherein the groups R^3, R^4, $R^{3'}$ and $R^{4'}$ have the same meaning.

As is apparent from Diagram 1, the compounds of formula **2** are used as starting products for preparing the compounds of formula **1**. These compounds are not known in the prior art. Accordingly, in another aspect, the present invention relates to compounds of general formula **2**



2

wherein

R^1 denotes hydrogen or -C_1-C_5-alkyl, which may optionally be substituted by -C_3-C_6-cycloalkyl, hydroxy or halogen, optionally in the form of the acid addition salts thereof.

By the acid addition salts are meant salts selected from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate and methanesulphonate.

Preferred compounds of general formula **2** are those wherein

R^1 denotes hydrogen or C_1-C_4-alkyl, which may optionally be substituted by hydroxy, fluorine, chlorine or bromine, optionally in the form of the acid addition salts thereof.

Particularly preferred compounds of general formula **2** are those wherein

R^1 denotes hydrogen, methyl, ethyl, $-CH_2F$ or $-CH_2-CH_2F$, preferably methyl or ethyl, optionally in the form of the acid addition salts thereof.

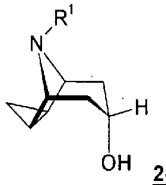
Of particular importance according to the invention are compounds of general formula **2** wherein

R^1 denotes hydrogen, methyl or ethyl, optionally in the form of the acid addition salts thereof.

Also preferred according to the invention are compounds of general formula **2** wherein

R^1 denotes hydrogen or methyl, optionally in the form of the acid addition salts thereof.

Preferably, according to the invention, the compounds of formula **2** are used as starting materials in the α-configured form. These α-configured compounds are therefore of particular importance according to the invention and correspond to general formula **2-α**



2-α

Compounds of general formula 2-α where R^1 = methyl are hereinafter referred to as cyclopropyltropine. It is assumed that the alcohol group will be in the α position and the cyclopropyl group will have the *exo* configuration. (cyclopropyltropine = *exo*-cyclopropyl-α-tropine). The α-configured compound is optionally known as p*seudo*-cyclopropyltropine and the e*ndo* isomer is known as e*ndo*-cyclopropyltropine.

In another aspect the present invention relates to the use of compounds of general formula **2** for preparing the compounds of general formula **4**. Moreover, the present invention relates to the use of the compounds of general formula **2** as starting materials for preparing the compounds of general formula **1**.

The compounds of general formula **2** may be obtained analogously to the methods known from the prior art starting from the corresponding tropenol derivatives. Suitable cyclopropylating reagents include diazomethane, for example.

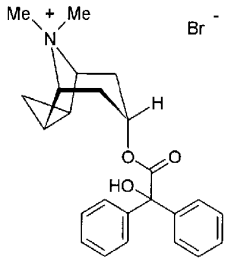
The examples of synthesis described below serve to illustrate the present invention still further. However, they are to be regarded as only examples of the procedure, as further illustration of the invention, without restricting the invention to the object described below by way of example.

Preparation of the compound of formula 2:

Cyclopropyltropine **2a**:
35 ml (0.35 mol) of 40% aqueous potassium hydroxide solution is overlaid with 100 ml of diethyl ether and cooled in the ice bath. For this, 23.64 g (0.101 mol) of N-methyl-N-nitrosourea are added batchwise and then the mixture is stirred for about 10 minutes. The ether phase is decanted off and the solution obtained is used in the following step.

25 ml of the diazomethane solution prepared above are added to a solution of 4.01 g (0.028 mol) of tropenol in 25 ml of diethyl ether and 5 ml of methanol while cooling with an ice bath. Then 53.4 mg (0.000139 mol) of bis(benzonitrile)dichloro-palladium(II) are added. A further 28 ml of the diazomethane solution are then added batchwise. After about 1.5 hours the solvent is distilled off *in vacuo*, the residue remaining is extracted, this solution is filtered and the solvent is removed by distillation.
Yield: 4.25 g of slightly yellowish crystals of **2a** (= 96% of theoretical)

Example 1: Cyclopropyltropine benzilate methobromide:



1.1.: methyl benzilate **3a:**.

90 g (0.394 mol) of benzilic acid are dissolved in 900 ml acetonitrile and at 5°C 109.6 g (0.72 mol) of DBU are added dropwise. After the addition of 204.4 g (1.44 mol) of methyl iodide the mixture is stirred for 24 hours at ambient temperature (about 20-23°C). The solution is evaporated down to the residue, the residue is taken up in diethyl ether and extracted with water. The organic phase is washed with 5% aqueous sodium carbonate solution and water, dried and the solvent is distilled off. The product is purified by recrystallisation from cyclohexane. Yield: 77.19 g of white crystals (= 81% of theoretical)

Melting point: 74°-76°C.

1.2.: cyclopropyltropine benzilate **4a**:

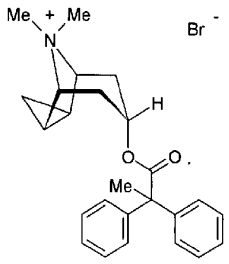
5.34 g (0.022 mol) methyl benzilate **3a**, 1.53 g (0.01 mol) of **2a** and 0.25 g (0.01 mol) of sodium are heated as a melt over a bath of boiling water at 75 mbar for 1 h with occasional shaking. After cooling, the sodium residues are dissolved with acetonitrile, the solution is evaporated to dryness and the residue is extracted with dichloromethane/water. The organic phase is extracted with 10% potassium hydrogen sulphate solution, the resulting aqueous phase is made basic and extracted with dichloromethane. The organic phase is separated off, dried and evaporated to dryness. The product is purified by recrystallisation from acetonitrile. Yield: 2.41 g of white crystals (= 66 % of theoretical).

1.3: cyclopropyltropine benzilate methobromide :

0.46 g (0.0013 mol) of **4a** are taken up in 5 ml acetonitrile and stirred with 1.53 g (0.0082 mol) of 50% methyl bromide solution in acetonitrile in a pressurised reaction vessel at 80°C. After 2 days the solution is evaporated to

dryness, the residue is taken up in acetonitrile and filtered while hot. After cooling the precipitated crystals are separated off, dried and recrystallised from acetonitrile.
Yield: 0.066 g of white crystals (= 11 % of theoretical); melting point: 208-209°C.
Elemental analysis: calculated: C (62.89) H (6.16) N (3.06)
found: C (62.98) H (6.20) N (3.03).

Example 2: Cyclopropyltropine 2,2-diphenylpropionate methobromide:



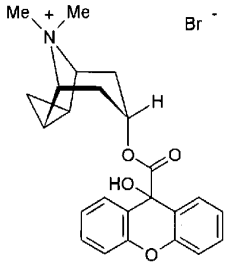
2.1.: 2,2-Diphenylpropionic acid chloride **3b:**.
52.08g (0.33 mol) oxalyl chloride are slowly added dropwise at 20°C to a suspension of 25.0 g (0.11 mol) of 2,2-diphenylpropionic acid, 100 ml of dichloromethane and 4 drops of dimethylformamide. It is stirred for 1 h at 20°C and 0.5 h at 50°C. The solvent is distilled off and the residue remaining is used in the next step without any further purification.

2.2: cyclopropyltropine 2,2-diphenylpropionate **4b**:
2.3 g (0.015 mol) of **2a** and 2.13 g (0.016 mol) of diisopropylethylamine are placed in 30 ml of dichloromethane and within 15 minutes combined with a solution of acid chloride **3b** in dichloromethane prepared as in step 2.1. Then the mixture is stirred for 2 hours at ambient temperature and 72 hours at 40°C. For working up it is washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is converted into its hydrochloride with a solution of HCl in diethyl ether. To purify it the precipitated hydrochloride is taken up in water and extracted with diethyl ether. The aqueous phase is made basic with 10% aq. sodium carbonate solution and extracted with dichloromethane. The organic phase is dried over $MgSO_4$ and the solvent is distilled off.

Yield: 2.15 g of yellow oil (= 36% of theoretical)

2.3: Cyclopropyltropine 2,2-diphenylpropionate methobromide :
1.8 g (0.005 mol) of the free base **4b** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from acetonitrile/diethyl ether.
Yield: 1.53 g of white crystals (= 67 % of theoretical); melting point: 208-209°C;
Elemental analysis: calculated: C (65.79) H (6,63) N (3.07)
found: C (65.47) H (6.77) N (3.03).

Example 3: Cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide :



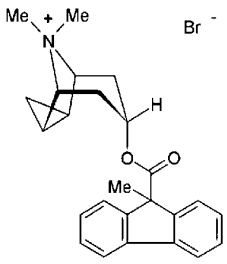
3.1.: methyl 9-hydroxy-xanthene-9-carboxylate **3c:**.
a) methyl xanthene-9-carboxylate:
A sodium ethoxide solution is generated from 21.75 g (0.95 mol) of sodium and 1500 ml of ethanol. 214 g (0.95 mol) of xanthene-9-carboxylic acid is added batchwise to this solution and the resulting suspension is stirred for 1 hour at ambient temperature. Then the solid is separated off, washed with 1500 ml of diethyl ether, the isolated crystals are suspended in 1500 ml of dimethylformamide and 126.73 ml (2.0 mol) of methyl iodide are added with stirring. The solution obtained is left to stand for 24 hours at ambient temperature, then diluted with water to a total volume of 6 l, crystallised, suction filtered, washed with water and dried.
Yield: 167 g of white crystals 7 (= 74% of theoretical)
Melting point: 82°C.

b) methyl 9-hydroxy-xanthene-9-carboxylate **3c**:
48.05 g (0.2 mol) of methyl xanthene-9-carboxylate are dissolved in 1200 ml of tetrahydrofuran and combined with 23.63 g (0.2 mol) of potassium tert. butoxide at 0°C. Oxygen is then piped in for 2 hours at –10° to –5°C, then the mixture is acidified with 2 N aqueous hydrochloric acid and most of the solvent is removed by distillation. The residue remaining is extracted with ethyl acetate and water, the organic phase is extracted with aqueous $Na_2S_2O_5$ solution, washed with water, dried and the solvent is distilled off. The product is purified by crystallisation from diisopropylether and cyclohexane. Yield: 11.10 g of white crystals (= 22% of theoretical)

3.2: cyclopropyltropine [9-hydroxy-xanthene-9-carboxylate **4c**:
6.0 g (0.023 mol) **3c**, 3.065 g (0.02 mol) **2a** and 0.02 g sodium are reacted analogously to step 1.2 to obtain **4c**. Yield: 2.2 g of white crystals(= 25 % of theoretical);
Melting point: 115-116°C.

3.3: cyclopropyltropine 9-hydroxy-xanthene-9-carboxylate methobromide :
2.1 g (0.006 mol) of the free base **4c** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from isopropanol.
Yield: 1.05 g of beige crystals (= 37 % of theoretical); melting point: 218°C;
Elemental analysis: calculated: C (61.02) H (5.55) N (2.97)
found: C (60.40) H (5.72) N (2.96).

Example 4: cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide :



4.1.: 9-methyl-fluorene-9-carboxylic acid **3d:**

a) methyl 9-methyl-fluorene-9-carboxylate:

A sodium ethoxide solution is prepared from 7.6 g (0.33 mol) sodium and 300 ml of ethanol, and 69.6 g (0.33 mol) of 9-fluorenecarboxylic acid are added batchwise thereto. After the addition has ended it is stirred for 2.5 hours at ambient temperature. Then it is evaporated to dryness, the residue is suspended in 600 ml of dimethylformamide and 93.96 g (0.662 mol) of methyl iodide is added dropwise. The mixture is stirred for 3 hours at constant temperature. The cloudy solution is stirred into 500 ml of water and 300 ml diethyl ether with cooling, and extracted, the organic phase is washed with water and 10% sodium carbonate solution, dried and evaporated to dryness. The residue is purified by column chromatography, eluant: cyclohexane / ethyl acetate 96:4.

Yield: 12.61 g of white crystals (= 16% of theoretical); melting point: 108°-109°C.

b) 9-methyl-fluorene-9-carboxylic acid **3d**:

12.6 g (0.053 mol) of methyl 9-methyl-fluorene-9-carboxylate and 53 ml of 2 molar aqueous sodium hydroxide solution are stirred in 120 ml of 1,4-dioxane for 24 hours at ambient temperature. The dioxane is distilled off, water is added to give a total volume of 300 ml and the mixture is extracted with diethyl ether. The aqueous phase is acidified with 3 molar aqueous HCl, crystallised and filtered.

Yield: 11.25 g of white crystals (= 95% of theoretical); melting point: 168°-169°C.

4.2: cyclopropyltropine 9-methyl-fluorene-9-carboxylate **4d**:

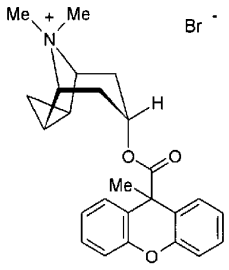
The acid chloride is prepared from 4.0 g (0.018 mol) of **3d**, 4.53 g (0.036 mol) of oxalyl chloride and 4 drops of dimethylformamide in 40 ml dichloromethane. 2.48 g (0.016 mol) of **2a** and 1.91 g (0.019 mol) of triethylamine are suspended in 30 ml of dichloroethane, the acid chloride is added dropwise to 30 ml of dichloroethane at 30°C within 15 minutes and then stirred for 24 hours at 40°C. The suspension is extracted with dichloromethane and water, the organic phase is washed with aqueous acetic acid, dried and the solvent is removed by distillation.

The product is converted into its hydrochloride. To purify it the precipitated hydrochloride is taken up in water and extracted with diethyl ether. The aqueous phase is made basic and extracted with dichloromethane. The

organic phase is dried over $MgSO_4$ and the solvent is distilled off. The crude product is purified by recrystallisation from acetonitrile. Yield: 1.81 g of slightly beige crystals (= 30% of theoretical); melting point: 138°-139°C.

4.3: cyclopropyltropine 9-methyl-fluorene-9-carboxylate methobromide :
1.81 g (0.005 mol) of the free base **4d** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from acetonitrile. Yield: 1.26 g of white crystals (= 56 % of theoretical); melting point: 228-229°C;
Elemental analysis: calculated: C (66.09) H (6.21) N (3.08)
found: C (66.26) H (6.26) N (3.11).

Example 5: Cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide:



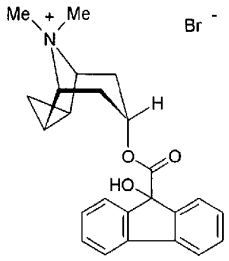
5.1.: 9-methyl-xanthene-9-carboxylic acid **3e:**.
a) methyl 9-methyl-xanthene-9-carboxylate:
Starting from 9.61 g (0.04 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 3.1.a) the reaction to obtain the title compound is carried out analogously to the method in step 4.1.a.
Yield: 6.05 g of white crystals (= 60% of theoretical); melting point: 91-92°C.

b) 9-methyl-xanthene-9-carboxylic acid **3e**:
Starting from 20.34 g (0.08 mol) of methyl 9-methyl-xanthene-9-carboxylate the reaction to obtain the title compound is carried out analogously to the method in step 4.1.b.
Yield: 14.15 g of white crystals (= 74% of theoretical); melting point: 207-208°C.

5.2 Cyclopropyltropine 9-methyl-xanthene-9-carboxylate **4e**:
The acid chloride is prepared from 5.0 g (0.021 mol) of **3e**, 5.53 g (0.042 mol) of oxalyl chloride and 4 drops of dimethylformamide in 50 ml of dichloromethane. 3.06 g (0.02 mol) of **2a** and the acid chloride produced above are reacted analogously to the method in step 4.2 to obtain the title compound.
Yield: 1.95 g of slightly beige crystals (= 26 % of theoretical); melting point: 87-88°C.

5.3: cyclopropyltropine 9-methyl-xanthene-9-carboxylate methobromide :
1.95 g (0.005 mol) of the free base **4e** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from acetonitrile.
Yield: 0.54 g of white crystals (= 23 % of theoretical); melting point: 193-194°C;
Elemental analysis: calculated: C (63.83) H (6.00) N (2.98)
found: C (61.42) H (6.24) N (2.97).

Example 6: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide :

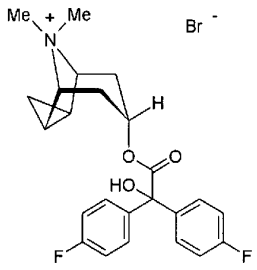


6.1: methyl 9-hydroxy-fluorene-9-carboxylate **3f:**.
50.4 g (0.223 mol) of 9-hydroxy-9-fluorenecarboxylic acid are dissolved in 500 ml of methanol, combined with 5 ml (0.089 mol) of conc. sulphuric acid and refluxed for 1 hour. After cooling 100 ml of sodium hydrogen carbonate solution (approx. pH 8) are added and the methanol is largely evaporated down. It is extracted with dichloromethane and water, the organic phase is dried and evaporated to dryness. The purification is carried out by recrystallisation from ethyl acetate.
Yield: 50.0g of white crystals (= 93% of theoretical).

6.2: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate **4f**:
6.0 g (0.025 mol) of **3f**, 3.45 g (0.023 mol) of **2a** and 0.03 g of sodium are reacted analogously to step 1.2 to obtain **4f**. The purification is carried out by recrystallisation from acetonitrile. Yield: 3.46 g of white crystals (= 38 % of theoretical); melting point: 131-132°C.

6.3: Cyclopropyltropine 9-hydroxy-fluorene-9-carboxylate methobromide :
3.36 g (0.009 mol) of the free base **4f** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from isopropanol. Yield: 3.32 g of white crystals (= 79 % of theoretical); melting point: 219-220°C;
Elemental analysis: calculated: C (63.16) H (5.74) N (3.07)
found: C (62.93) H (5.93) N (3.10).

Example 7: Cyclopropyltropine 4,4'-difluoromethyl benzilate methobromide :



7.1.: 4,4'-difluoromethyl benzilate **3g:**.
a) 4,4'-difluorobenzilic acid:
A solution of 24.62 g (0.1 mol) of 4,4'-difluorobenzil in 250 ml dioxane is added dropwise to a solution of 49.99 g (1.25 mol) of NaOH flakes in 300 ml of water at about 100°C and stirred for 2 h. The dioxane is largely distilled off and the aqueous solution remaining is extracted with dichloromethane. When the aqueous solution is acidified with sulphuric acid a precipitate is deposited, which is suction filtered, washed and dried. The filtrate is extracted with dichloromethane, the organic phase is dried over Na_2SO_4 and evaporated to dryness.
Yield: 25.01 g (= 95 % of theoretical); melting point: 133°-136°C

b) 4,4'-difluoromethyl benzilate **3g**:
25.0 g (0.095 mol) of 4,4'-difluorobenzilic acid are added to freshly prepared sodium ethoxide solution from 2.17 g (0.095 mol) of sodium and 200 ml of ethanol at 20°C and stirred for 3 h. The solution is evaporated to dryness, the residue is dissolved in DMF, 22.57 g (0.16 mol) of methyl iodide are added dropwise at 20°C and the mixture is stirred for 24 h. 300 ml of water are added dropwise to the suspension formed, while cooling with ice, the mixture is extracted with diethyl ether, the organic phase is washed with water, dried over Na_2SO_4 and evaporated to dryness.
Yield: 21.06 g (= 80 % of theoretical).

7.2: cyclopropyltropine 4,4'-difluoromethyl benzilate **4g**:
6.2 g (0.022 mol) of **3g**, 3.37 g (0.022 mol) of **2a** and 0.051 g sodium are reacted analogously to step 1.2 to obtain **4g**. The purification is carried out by recrystallisation from acetonitrile.
Yield: 4.15 g of white crystals (= 47 % of theoretical); melting point: 120-121°C.

7.3: cyclopropyltropine 4,4'-difluoromethyl benzilate methobromide :
2.0 g (0.005 mol) of the free base **4g** are reacted analogously to the method in step 1.3. The purification is carried out by recrystallisation from ethanol/diethyl ether.
Yield: 1.8 g of white crystals (= 73 % of theoretical); melting point: 206-207°C;
Elemental analysis: calculated: C (58.31) H (5.30) N (2.83)
found: C (58.15) H (5.42) N (2.84).

It was found that the compounds according to the invention of formula **1** are antagonists of the M3 receptor (Muscarinic Receptor subtype 3). The compounds according to the invention have Ki values of less than 10nM in terms of their affinity for the M3 receptor. These values were determined by the method described below.

Chemicals
3H-NMS was obtained from Messrs Amersham of Braunschweig, with a specific radioactivity of 3071 GBq/mmol (83 Ci/mmol). All the other reagents were obtained from Serva of Heidelberg and Merck of Darmstadt.

Cell membranes:
We used cell membranes from CHO (Chinese hamster ovary) cells which were transfected with the corresponding genes of the human muscarinic receptor subtypes hm1 to hm5 (BONNER). The cell membranes of the desired subtype were thawed, resuspended by hand with a glass homogeniser and diluted with HEPES buffer to a final concentration of 20-30 mg of protein/ml.

Receptor binding studies:
The binding assay was carried out in a final volume of 1 ml and consisted of 100 µl of unlabelled substance in various concentrations, 100 µl of radioligand (3H-N-methylscopolamine 2 nmol/L (3H-NMS), 200 µl of membrane preparation and 600 µl of HEPES buffer (20 mmol/L HEPES, 10 mmol/L $MgCl_2$, 100 mmol/L NaCl, adjusted with 1 mol/L NaOH to pH 7.4).
The nonspecific binding was determined using 10 µmol/l of atropine.
The preparation was incubated for 45 min. at 37°C in 96-well microtitre plates (Beckman, polystyrene, No. 267001) as a double measurement. The incubation was ended by filtering using an Inotech Cell Harvester (type IH 110) through Whatman G-7 filters. The filters were washed with 3 ml of ice-cooled HEPES buffer and dried before measuring.

Determining the radioactivity:
The radioactivity of the filter mats was measured simultaneously using a two-dimensional digital autoradiograph (Berthold, Wildbad, type 3052).

Evaluation:
The Ki values were calculated using implicit equations which were derived directly from the mass-action law, with the model for the 1 receptor 2 ligand reaction (SysFit software, SCHITTKOWSKI).

Literature:
BONNER TI, New subtypes of muscarinic acetylcholine receptors Trends Pharmacol. Sci. 10, Suppl.: 11-15 (1989); SCHITTKOWSKI K Parameter estimation in systems of nonlinear equations Numer Math. 68: 129-142 (1994).

The compounds of formula **1** according to the invention are characterised by their range of uses in the therapeutic field. Particular mention should be made of those applications for which the compounds of formula **1** according to the invention may preferably be used on the basis of their pharmaceutical activity as anticholinergics.

These are for example the treatment of asthma or COPD (chronic obstructive pulmonary disease). The compounds of general formula **1** may also be used to treat vagally induced sinus bradycardia and to treat heart rhythm disorders. Generally, the compounds according to the invention may also be used therapeutically to treat spasms, for example, in the gastrointestinal tract . They may also be used to treat spasms in the urinary tract and also to treat menstrual pain, for example. Of the ranges of indications mentioned above, the treatment of asthma and COPD with the compounds of formula **1** according to the invention is of particular importance.

The compounds of general formula **1** may be used on their own or in conjunction with other active substances of formula **1**. The compounds of general formula **1** may also be used in combination with other pharmacologically active substances. These may be, in particular, betamimetics, antiallergics, PAF antagonists, PDE-IV inhibitors, leukotriene antagonists, p38 kinase inhibitors, EGFR kinase inhibitors and corticosteroids as well as combinations of active substances thereof.

Examples of betamimetics which may be used according to the invention in conjunction with the compounds of formula **1** include compounds selected from among bambuterol, bitolterol, carbuterol, clenbuterol, fenoterol, formoterol, hexoprenaline, ibuterol, pirbuterol, procaterol, reproterol, salmeterol, sulphonterol, terbutaline, tolubuterol, 4-hydroxy-7-[2-{[2-{[3-(2-phenylethoxy)propyl]sulphonyl}ethyl]-amino}ethyl]-2(3H)-benzothiazolone, 1-(2-fluoro-4-hydroxyphenyl)-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-

(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, 5-hydroxy-8-(1-hydroxy-2-isopropylaminobutyl)-2H-1,4-benzoxazin-3-(4H)-one, 1-(4-amino-3-chloro-5-trifluormethylphenyl)-2-tert.-butylamino)ethanol and 1-(4-ethoxycarbonylamino-3-cyano-5-fluorophenyl)-2-(tert.-butylamino)ethanol, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts, the solvates and/or the hydrates thereof. Most preferably, the betamimetics used as active substances in conjunction with the compounds of formula **1** according to the invention are selected from among fenoterol, formoterol, salmeterol, 1-[3-(4-methoxybenzyl-amino)-4-hydroxyphenyl]-2-[4-(1-benzimidazolyl)-2-methyl-2-butylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-N,N-dimethylaminophenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-methoxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-[3-(4-n-butyloxyphenyl)-2-methyl-2-propylamino]ethanol, 1-[2H-5-hydroxy-3-oxo-4H-1,4-benzoxazin-8-yl]-2-{4-[3-(4-methoxyphenyl)-1,2,4-triazol-3-yl]-2-methyl-2-butylamino}ethanol, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts and the hydrates thereof. Of the betamimetics mentioned above the compounds formoterol and salmeterol are particularly preferred, optionally in the form of the racemates, the enantiomers, the diastereomers and optionally the pharmacologically acceptable acid addition salts thereof, and the hydrates thereof. According to the invention, the acid addition salts of the betamimetics selected, for example, from among the hydrochloride, hydrobromide, sulphate, phosphate, fumarate, methanesulphonate and xinafoate are preferred. Particularly preferred in the case of salmeterol are the salts selected from among the hydrochloride, sulphate and xinafoate, of which the xinafoate is particularly preferred. Particularly preferred in the case of formoterol are the salts selected from among the hydrochloride, sulphate and fumarate, of which the hydrochloride and fumarate are particularly preferred. According to the invention, formoterol fumarate is of exceptional importance.

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, GW 215864, KSR 592, ST-126 and dexamethasone. Preferably, within the scope of the

present invention, the corticosteroids are selected from among flunisolide, beclomethasone, triamcinolone, budesonide, fluticasone, mometasone, ciclesonide and dexamethasone, while budesonide, fluticasone, mometasone and ciclesonide are important and budesonide and fluticasone are particularly important. 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.

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. Preferred PDE-IV inhibitors are selected from among enprofylline, roflumilast, ariflo and AWD-12-281, while AWD-12-281 is particularly preferred as the combination partner with the compound of formula **1** according to the invention. 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.

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. It is preferable within the scope of the present invention to use, as combination partners with the compounds of formula **1**,

dopamine agonists selected from among pramipexol, talipexol and viozan, pramipexol being of particular importance. 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. Preferred antiallergic agents which may be used within the scope of the present invention in combination with the compounds of formula **1** according to the invention are selected from among epinastin, cetirizin, azelastin, fexofenadin, levocabastin, loratadine, ebastin, desloratidine and mizolastin, epinastin and desloratidine being particularly preferred. 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 PAF antagonists which may be used according to the invention as a combination with the compounds of formula **1** include 4-(2-chlorophenyl)-9-methyl-2-[3-(4-morpholinyl)-3-propanon-1-yl]-6H-thieno-[3,2-f] [1,2,4]triazolo[4.3-a][1,4]diazepine, 6-(2-chlorophenyl)-8,9-dihydro-1-methyl-8-[(4-morpholinyl)carbonyl]-4H,7H-cyclo-penta-[4.5]thieno-[3,2-f][1,2,4]triazolo[4,3-a][1,4]diazepine.

Examples of EGFR kinase inhibitors which may be used as a combination with the compounds of formula **1** according to the invention include, in particular, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[4-((R)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(3-chloro-4-

fluoro-phenyl)amino]-7-[4-((S)-6-methyl-2-oxo-morpholin-4-yl)-butyloxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-(2-{4-[(S)-(2-oxo-tetrahydrofuran-5-yl)carbonyl]-piperazin-1-yl}-ethoxy)-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(3-chloro-4-fluoro-phenyl)amino]-7-[2-((S)-6-methyl-2-oxo-morpholin-4-yl)-ethoxy]-6-[(vinylcarbonyl)amino]-quinazoline, 4-[(3-chloro-4-fluorophenyl)amino]-6-[(4-{N-[2-(ethoxycarbonyl)-ethyl]-N-[(ethoxycarbonyl)methyl]amino}-1-oxo-2-buten-1-yl)amino]-7-cyclopropylmethoxy-quinazoline, 4-[(R)-(1-phenyl-ethyl)amino]-6-{[4-(morpholin-4-yl)-1-oxo-2-buten-1-yl]amino}-7-cyclopropylmethoxy-quinazoline and 4-[(3-chloro-4-fluorophenyl)amino]-6-[3-(morpholin-4-yl)-propyloxy]-7-methoxy-quinazoline. Any reference to the abovementioned EGFR kinase 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 or pharmacologically acceptable acid addition salts thereof which may be formed by the EGFR kinase inhibitors are meant, according to the invention, 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. The salts of the EGFR kinase inhibitors selected from among the salts of acetic acid, hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid and methanesulphonic acid are preferred according to the invention.

Particularly preferred examples of p38 kinase inhibitors which may be used as a combination with the compounds of formula **1** according to the invention include 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalin-1-yl]-urea; 1-[5-*tert*-butyl-2-*p*-tolyl-2H-pyrazol-3-yl]-3-[4-(2-(1-oxothiomorpholin-4-yl)ethoxy)naphthalin-1-yl]-urea; 1-[5-*tert*-butyl-2-(2-methylpyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-pyridine-4-yl-ethoxy)naphthalin-1-yl]-urea; 1-[5-*tert*-butyl-2-(2-methoxypyridin-5-yl)-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalin-1-yl]-urea or 1-[5-*tert*-butyl-2-methyl-2H-pyrazol-3-yl]-3-[4-(2-morpholin-4-yl-ethoxy)naphthalen-1-yl]-urea. Any reference to the abovementioned p38 kinase 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 or pharmacologically acceptable acid addition salts thereof which may be formed by the p38 kinase inhibitors are meant, according to the invention, 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.

If the compounds of formula **1** are used in conjunction with other active substances, the combination with steroids, PDE IV inhibitors or betamimetics is particularly preferred, of the categories of compounds mentioned above. The combination with betamimetics, particularly with long-acting betamimetics, is of particular importance. The combination of the compounds of formula **1** according to the invention with salmeterol or formoterol is particularly preferred.

Suitable preparations for administering the salts of formula **1** include for example tablets, capsules, suppositories and solutions, etc. Administration of the compounds according to the invention by inhalation is of particular importance according to the invention (particularly for treating asthma or COPD). 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 or 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 asthma or 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 metering 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 their 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 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 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.

According to the invention, the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser or complexing agent is unnecessary 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 according to the invention. 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.
Particularly when administered by routes other than by inhalation the compounds according to the invention may be administered in higher doses (for example, but not restrictively, in the range from 1 to 1000 mg).

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
corn starch	240 mg
polyvinylpyrrolidone	15 mg
magnesium stearate	5 mg
	500 mg

The finely ground active substance, lactose and some of the corn 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 corn starch and the magnesium stearate are screened and mixed together. The mixture is compressed to produce tablets of suitable shape and size.

B)

Tablets	per tablet
active substance **1**	80 mg
lactose	55 mg
corn 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 Difluorodichloromethane 2 : 3	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
formoterol fumarate	333.3 mg
benzalkonium chloride	10.0 mg
EDTA	50.0 mg
HCl (1n)	ad pH 3.4

This solution may be prepared in the usual way.

F) Inhalable powder

active substance 1	6 µg
formoterol fumarate	6 µg
lactose monohydrate	ad 25 mg

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

G) Inhalable powder

active substance 1	10 µg
lactose monohydrate	ad 5 mg

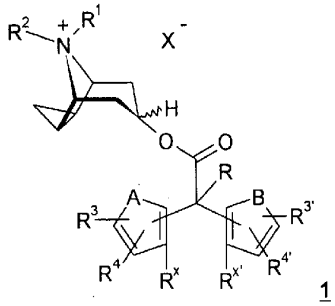
The inhalable powder is prepared in the usual way by mixing the individual ingredients.

Throughout this specification and the claims which follow, unless the context requires otherwise, the word "comprise", and variations such as "comprises" and "comprising", will be understood to imply the inclusion of a stated integer or step or group of integers or steps but not the exclusion of any other integer or step or group of integers or steps.

The reference to any prior art in this specification is not, and should not be taken as, an acknowledgment or any form of suggestion that that prior art forms part of the common general knowledge in Australia.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1) Compounds of general formula **1**



1

wherein

X^- denotes an anion with a single negative charge,

A and B which may be identical or different, preferably identical, denote -O, -S, -NH, $-CH_2$, -CH=CH, or $-N(C_1-C_4\text{-alkyl})$-;

R denotes hydrogen, hydroxy, $-C_1-C_4$-alkyl, $-C_1-C_4$-alkyloxy, $-C_1-C_4$-alkylene-halogen, $-O-C_1-C_4$-alkylene-halogen, $-C_1-C_4$-alkylene-OH, $-CF_3$, CHF_2, $-C_1-C_4$-alkylene-C_1-C_4-alkyloxy, $-O-COC_1-C_4$-alkyl, $-O-COC_1-C_4$-alkylene-halogen, $-C_1-C_4$-alkylene-C_3-C_6-cycloalkyl, $-O-COCF_3$ or halogen;

R^1 and R^2 which may be identical or different, denote $-C_1-C_5$-alkyl, which may optionally be substituted by $-C_3-C_6$-cycloalkyl, hydroxy or halogen,

or

R^1 and R^2 together denote a $-C_3-C_5$-alkylene bridge;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen;

R^x and $R^{x'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen

or

R^x and $R^{x'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH, $-CH_2$, $-CH_2-CH_2$-, $-N(C_1-C_4\text{-alkyl})$, $-CH(C_1-C_4\text{-alkyl})$- and $-C(C_1-C_4\text{-alkyl})_2$.

2) Compounds of general formula 1 according to claim 1, wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -O, -S, -NH or -CH=CH-;

R denotes hydrogen, hydroxy, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, $-CF_3$, $-CHF_2$, fluorine, chlorine or bromine;

R^1 and R^2 which may be identical or different, denote C_1-C_4-alkyl, which may optionally be substituted by hydroxy, fluorine, chlorine or bromine,

or

R^1 and R^2 together denote a $-C_3$-C_4-alkylene-bridge;

R3, R4, R3' and R4', which may be identical or different, denote hydrogen, C1-C4-alkyl, C1-C4-alkyloxy, hydroxy, -CF3, -CHF2, CN, NO2, fluorine, chlorine or bromine;

R^x and $R^{x'}$ which may be identical or different, denote hydrogen, C_1-C_4-alkyl, C_1-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2, fluorine, chlorine or bromine

or

R^x and $R^{x'}$ together denote a single bond or a bridging group selected from among the bridges -O, -S, -NH- and $-CH_2-$.

3) Compounds of general formula 1 according to one of claims 1 or 2, wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -S or -CH=CH-;

R denotes hydrogen, hydroxy, methyl, ethyl, methyloxy, ethyloxy, $-CF_3$, or fluorine;

R^1 and R^2 which may be identical or different, denote methyl, ethyl, $-CH_2F$ or $-CH_2$-CH_2F, preferably methyl or ethyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, methyl, methyloxy, $-CF_3$ or fluorine;

R^x and $R^{x'}$ which may be identical or different, denote hydrogen, methyl, methyloxy, $-CF_3$ or fluorine

or

R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

4) Compounds of general formula **1** according to one of claims 1 to 3, wherein

X^- denotes an anion with a single negative charge selected from among the chloride, bromide and methanesulphonate, preferably bromide;

A and B which may be identical or different, preferably identical, denote -S or -CH=CH-;

R denotes hydrogen, hydroxy or methyl;

R^1 and R^2 which may be identical or different, denote methyl or ethyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen, $-CF_3$ or fluorine, preferably hydrogen or
R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

5) Compounds of general formula **1** according to one of claims 1 to 4, wherein

X^- denotes bromide;

A and B denote -CH=CH-;

R denotes hydrogen, hydroxy or methyl;

R^1 and R^2 denote methyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$, which may be identical or different, denote hydrogen or fluorine, preferably hydrogen;

R^X and $R^{X'}$ which may be identical or different, denote hydrogen or fluorine, preferably hydrogen or
R^X and $R^{X'}$ together denote a single bond or the bridging group -O-.

6) Compounds of general formula **1** according to one of claims 1 to 5, optionally in the form of the individual optical isomers, mixtures of the individual enantiomers or racemates as well as optionally in the form of the pharmacologically acceptable acid addition salts thereof.

7) A compound of general formula **1** according to one of claims 1 to 6 for use in therapy.

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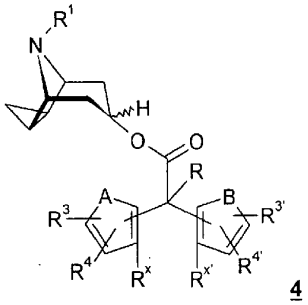
8) Use of a compound of general formula **1** according to one of claims 1 to 6 for preparing a medicament for the treatment of diseases in which anticholinergics can develop a therapeutic benefit.

9) Use of a compound of general formula **1** according to one of claims 1 to 6 for preparing a medicament for the treatment of asthma, COPD, vagally induced sinus bradycardia, heart rhythm disorders, spasms in the gastrointestinal tract, spasms in the urinary tract and menstrual pain.

10) Pharmaceutical preparations, containing as active substance one or more compounds of general formula **1** according to one of claims 1 to 6 or the physiologically acceptable salts thereof optionally in combination with conventional excipients and/or carriers.

11) Pharmaceutical preparations according to claim 10, characterised in that they contain, in addition to one or more of the compounds of formula **1**, at least one other active substance which is selected from among the betamimetics, antiallergics, PAF antagonists, PDE IV inhibitors, leukotriene antagonists, p38 kinase inhibitors, EGFR kinase inhibitors and corticosteroids.

12) Intermediate products of general formula **4**



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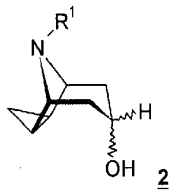
wherein the groups A, B, R, R^1, R^3, $R^{3'}$, R^4, $R^{4'}$, R^x and $R^{x'}$ may have the meanings given in claims 1 to 5, optionally in the form of the acid addition salts thereof.

13) Compounds of general formula **2**



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wherein R^1 may have the meanings given in claims 1 to 5, optionally in the form of the acid addition salts thereof.

14) A method of treating diseases in which anticholinergics can bring about a therapeutic benefit comprising administering a therapeutically effective amount of a compound of general formula **1** according to any one of claims 1 to 6.

15) A compound of general formula **1** according to any one of claims 1 to 6 substantially as hereinbefore described and with reference to the Examples.

16) A compound as defined in claim 7 substantially as hereinbefore described and with reference to the Examples.

17) Use of a compound as defined in claims 8 or 9 substantially as hereinbefore described and with reference to the Examples.

18) A pharmaceutical composition according to claim 10 or 11 substantially as hereinbefore described and with reference to the Examples.

19) Intermediate products according to claim 12 substantially as hereinbefore described and with reference to the Examples.

20) A method of treatment according to claim 14 substantially as hereinbefore described and with reference to the Examples.

21) Compounds of general formula **2** according to claim 13 substantially as hereinbefore described and with reference to the Examples.

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Boehringer Ingelheim Pharma GmbH & Co KG

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