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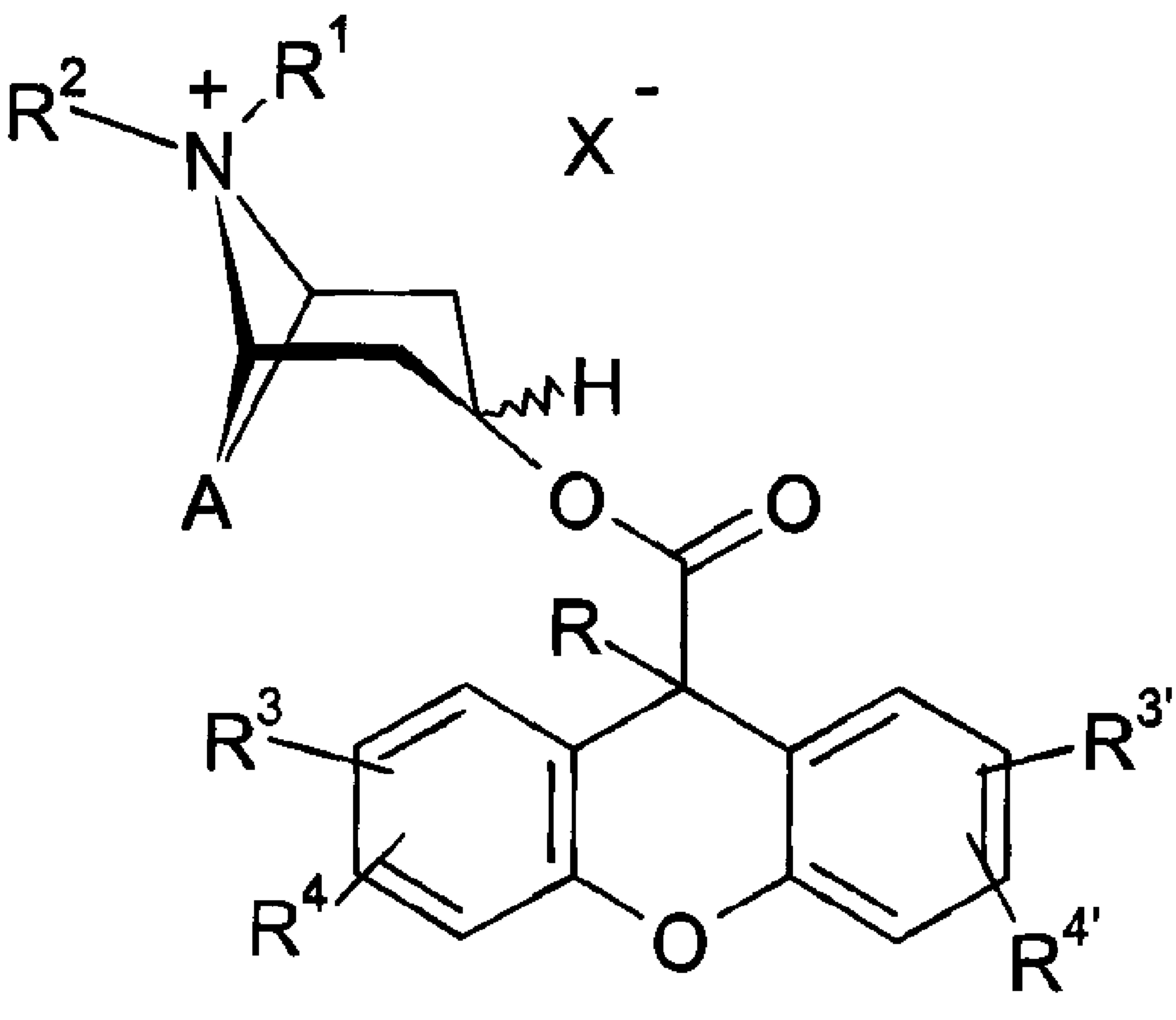
(54) Titre : ESTERS D'ACIDE XANTHENECARBOXYLIQUE DE TROPENOL ET DE SCOPINE SERVANT D'ANTAGONISTES M3, PROCEDES POUR LES PRODUIRE ET LEUR UTILISATION EN TANT QUE MEDICAMENTS

(54) Title: XANTHENE-CARBOXYLIC ACID ESTERS OF TROPENOL AND SCOPINE AS M3 ANTAGONISTS, METHOD FOR PRODUCING THE SAME AND USE THEREOF AS MEDICAMENTS



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(57) Abrégé/Abstract:
The invention relates to novel xanthene-carboxylic acid esters of formula 1: (see formula 1), in which X is an anion with a single negative charge; A is a double-bonded group; R is optionally substituted alkyl, hydroxy or fluorine; R^1 and R^2 are identical or

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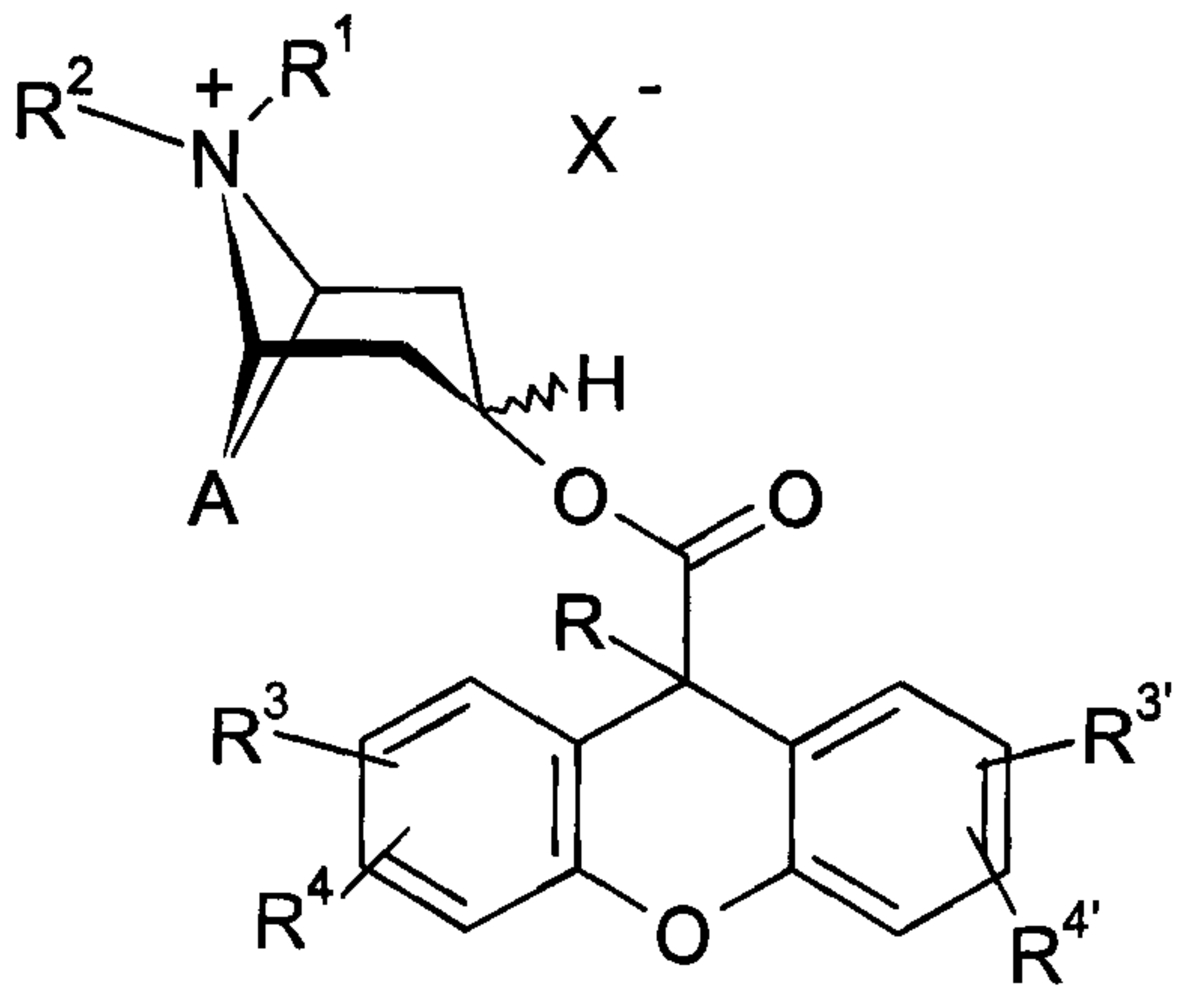
(57) **Abrégé(suite)/Abstract(continued):**
different and are optionally substituted alkyl or together are an alkylene bridge; R^3, R^4, $R^{3'}$, $R^{4'}$ are identical or different and are optionally substituted alkyl, hydrogen, hydroxy, cyano, nitro or halogen. The invention also relates to a method for producing said esters and to the use thereof as medicaments.

ABSTRACT

The invention relates to novel xanthene-carboxylic acid esters of formula **1**:



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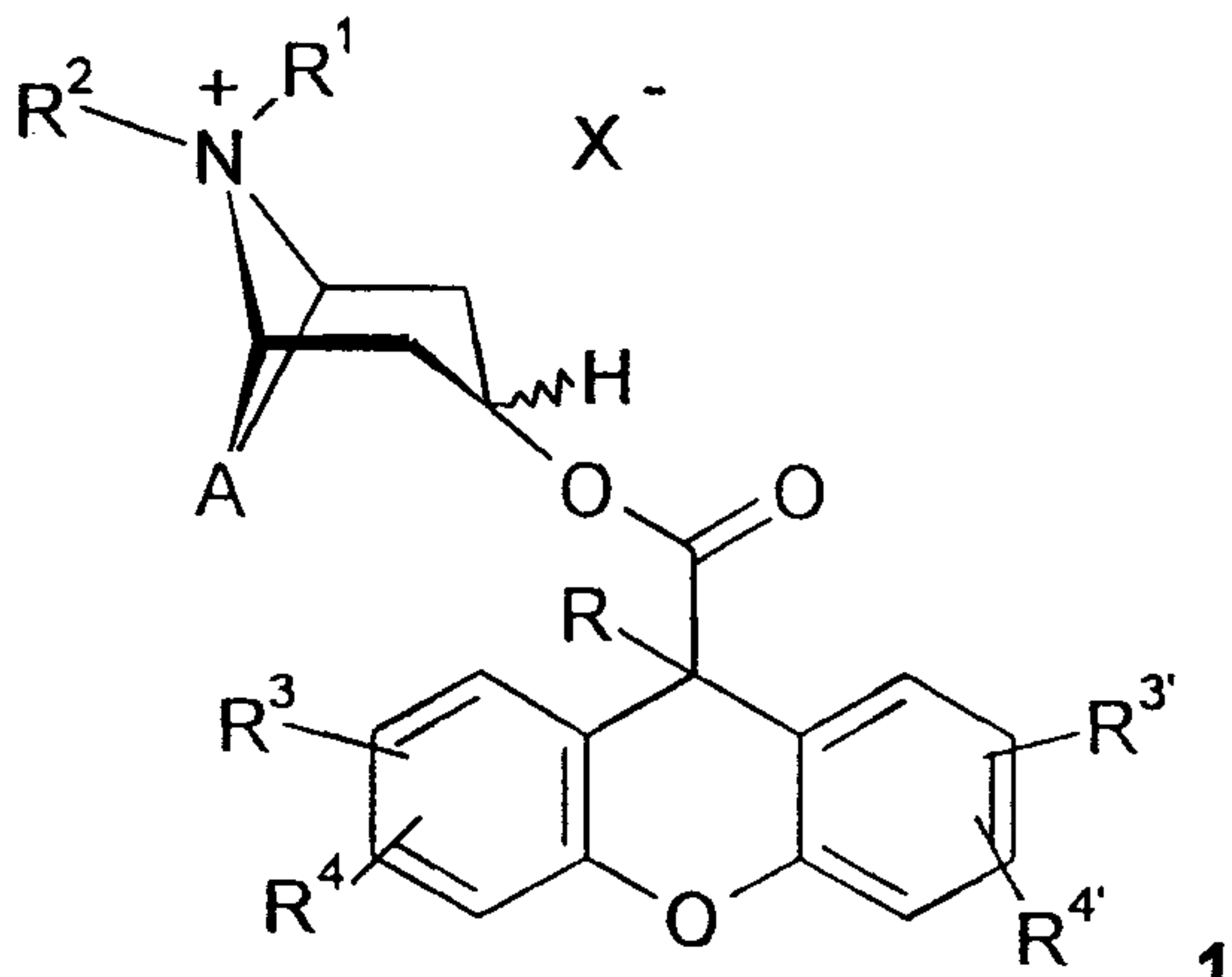
in which X is an anion with a single negative charge; A is a double-bonded group; R is optionally substituted alkyl, hydroxy or fluorine; R^1 and R^2 are identical or different and are optionally substituted alkyl or together are an alkylene bridge; R^3, R^4, $R^{3'}$, $R^{4'}$ are identical or different and are optionally substituted alkyl, hydrogen, hydroxy, cyano, nitro or halogen. The invention also relates to a method for producing said esters and to the use thereof as medicaments.

Xanthene-carboxylic acid esters of tropenol and scopine as M3 antagonists, method for producing the same and use thereof as medicaments

The present invention relates to new xanthenecarboxylates of general formula **1**



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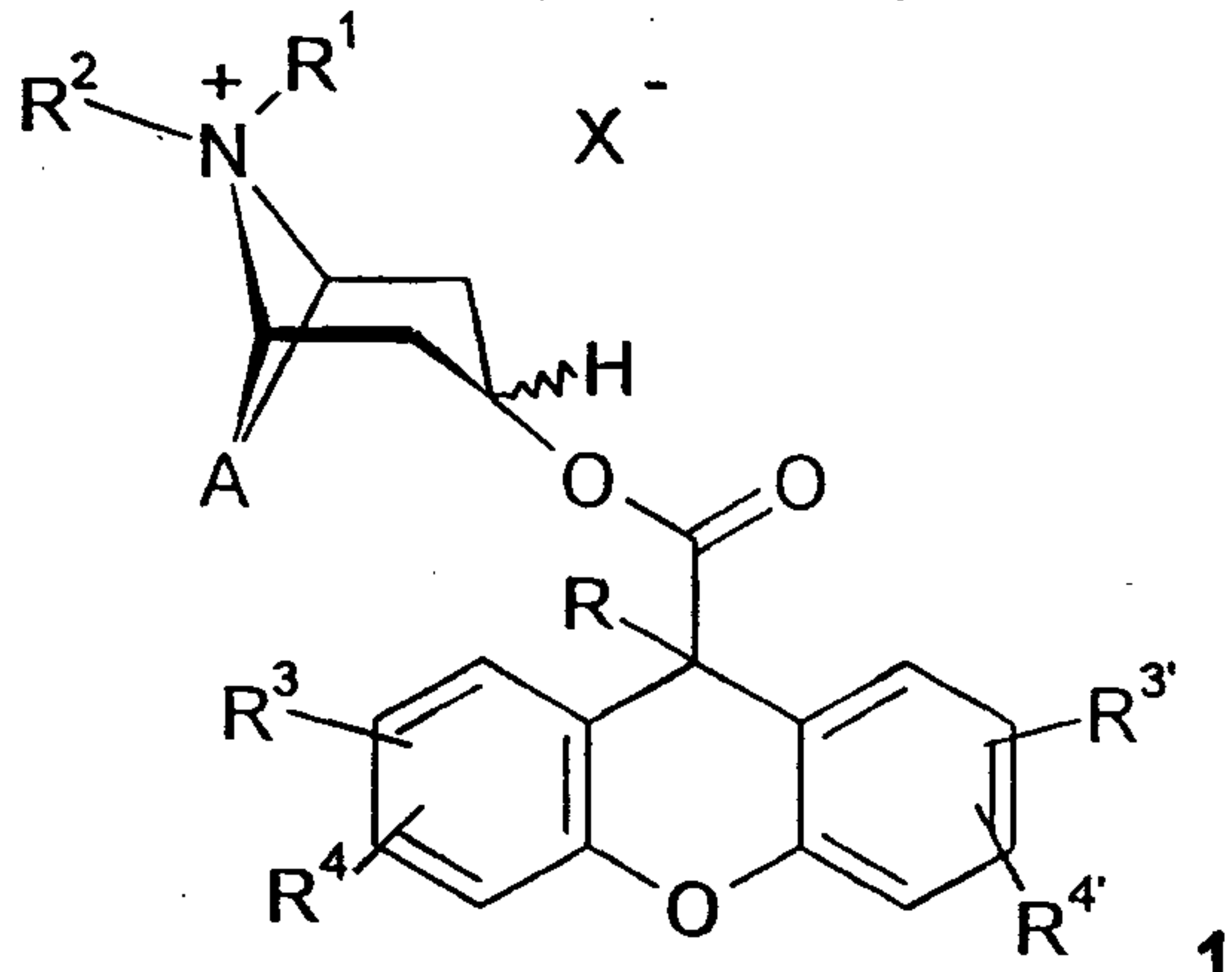
wherein X^- and the groups A, R, R^1, R^2, R^3, $R^{3'}$, R^4 and $R^{4'}$ **are as defined herein, processes for preparing** them and their use as pharmaceutical compositions.

<u>Description of the invention</u>

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



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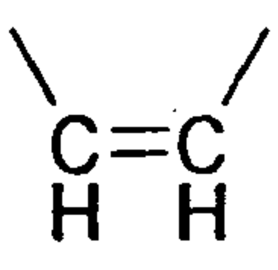
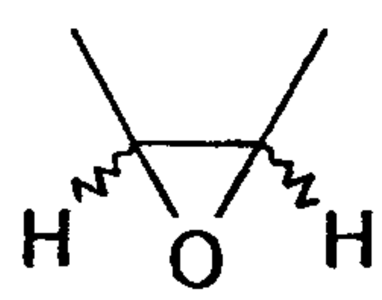
wherein

A denotes a double-bonded group selected from among

 and  ;

X^- 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;

R denotes hydroxy, methyl, hydroxymethyl, ethyl, $-CF_3$, CHF_2 or fluorine;

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,

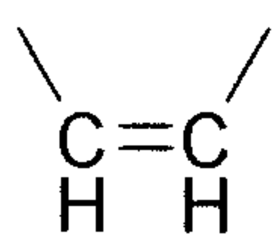
or

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.

Preferred compounds of general formula <u>1</u> are those wherein

A denotes a double-bonded group selected from among



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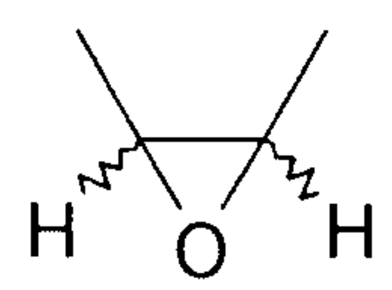


;

X - denotes an anion with a single negative charge selected from among

chloride, bromide, 4-toluenesulphonate and methanesulphonate, preferably bromide;

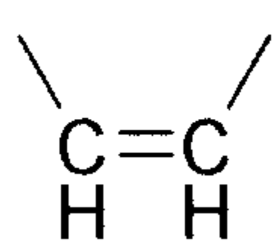
R denotes hydroxy, methyl, hydroxymethyl, ethyl or CHF_2, preferably hydroxy or methyl;

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

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen, methyl, methyloxy, hydroxy, $-CF_3$, $-CHF_2$ or fluorine.

Particularly preferred compounds of general formula <u>1</u> are those wherein

A denotes a double-bonded group selected from among



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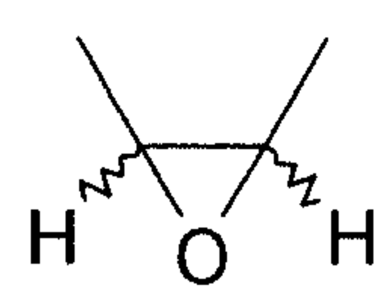

;

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

R denotes hydroxy or methyl;

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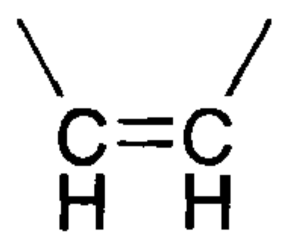
R^1 and R^2 which may be identical or different represent methyl or ethyl, preferably methyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen, $-CF_3$, $-CHF_2$ or fluorine, preferably hydrogen or fluorine.

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

A denotes a double-bonded group selected from among



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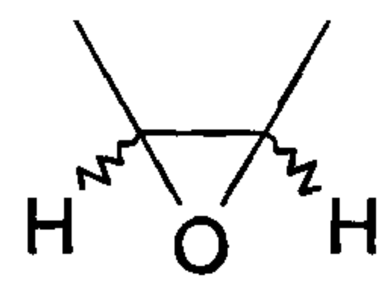


;

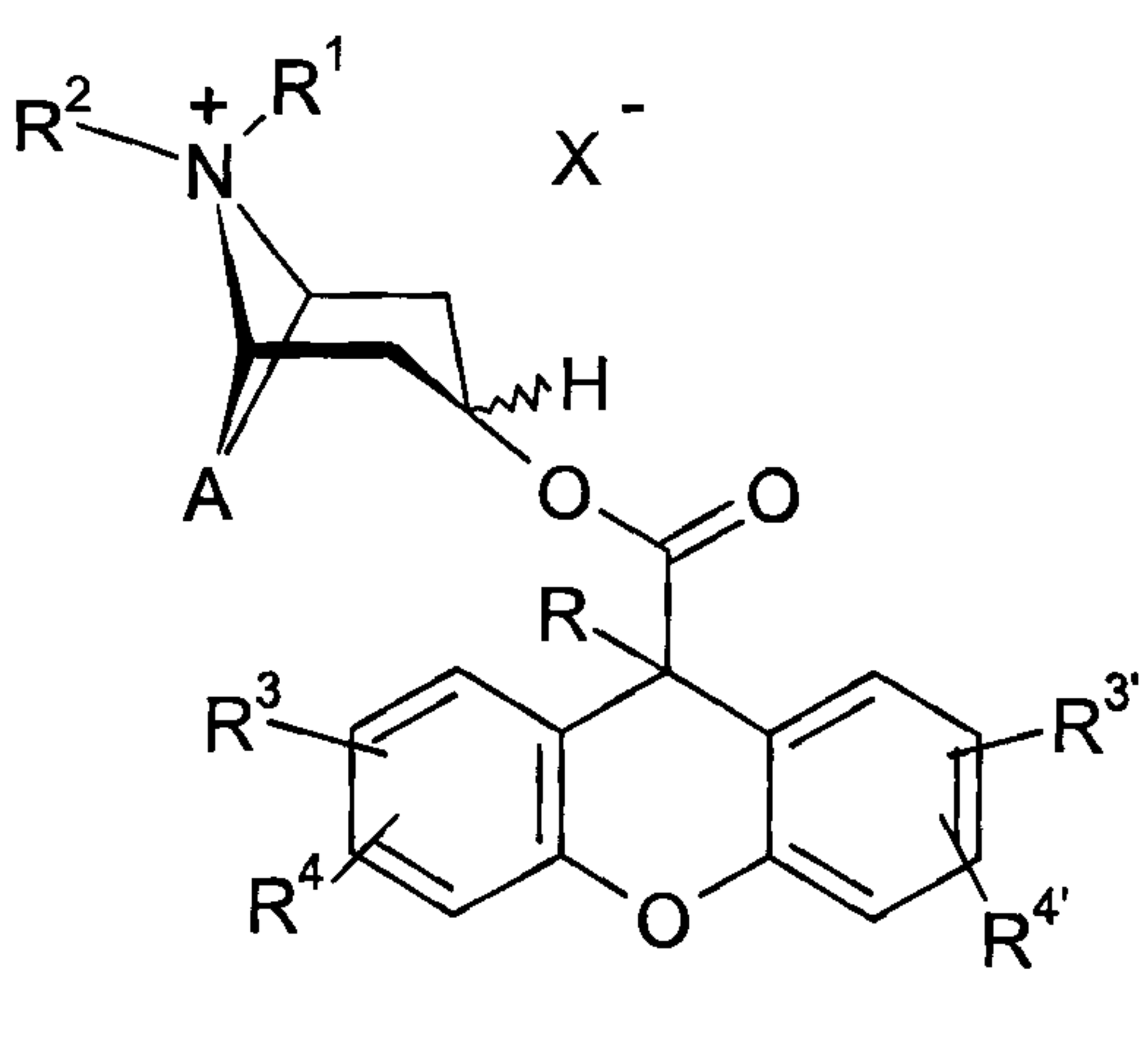
X^- denotes bromide;

R denotes hydroxy or methyl, preferably methyl;

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

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen or fluorine.

The invention further relates to a compound of formula 1



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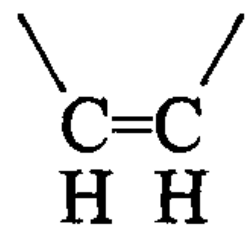
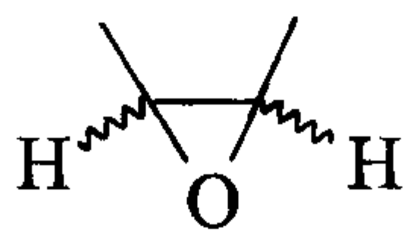
wherein

A denotes a double-bonded group, which is

 or  ;

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

R denotes methyl, ethyl, $-CF_3$, CHF_2;

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;

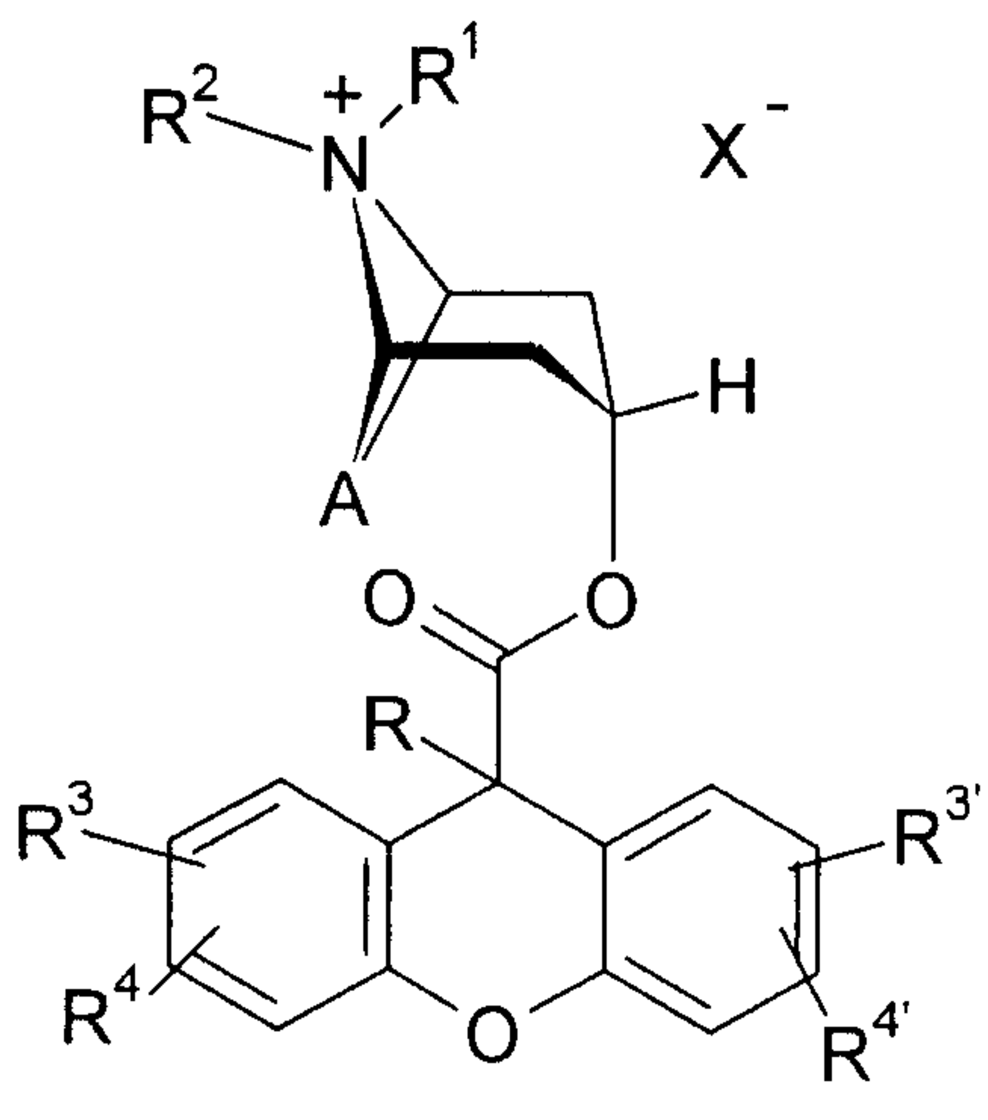
R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different denote hydrogen, $-C_1$-C_4-alkyl, $-C_1$-C_4-alkyloxy, hydroxy, $-CF_3$, $-CHF_2$, CN, NO_2 or halogen,

or a physiologically acceptable salt thereof.

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.

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.

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



1-α̃

The following compounds are of particular importance according to the invention:

- tropenol 9-hydroxy-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxy-xanthene-9-carboxylate methobromide ;
- tropenol 9-methyl-xanthene-9-carboxylate methobromide ;
- scopine 9-methyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-ethyl-xanthene-9-carboxylate methobromide ;
- tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide ;
- scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide .

The alkyl groups used, unless otherwise stated, are branched and unbranched alkyl groups having 1 to 5 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 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.

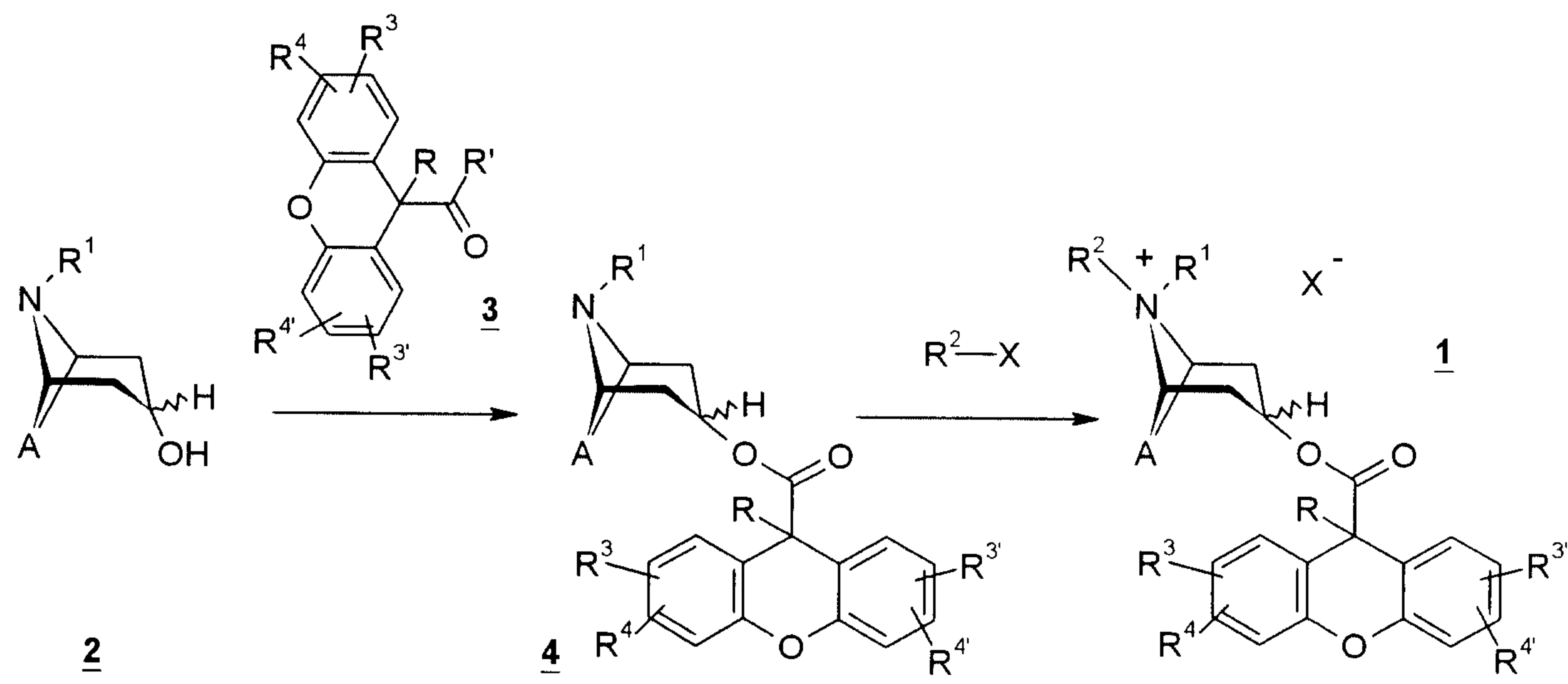


Diagram 1:

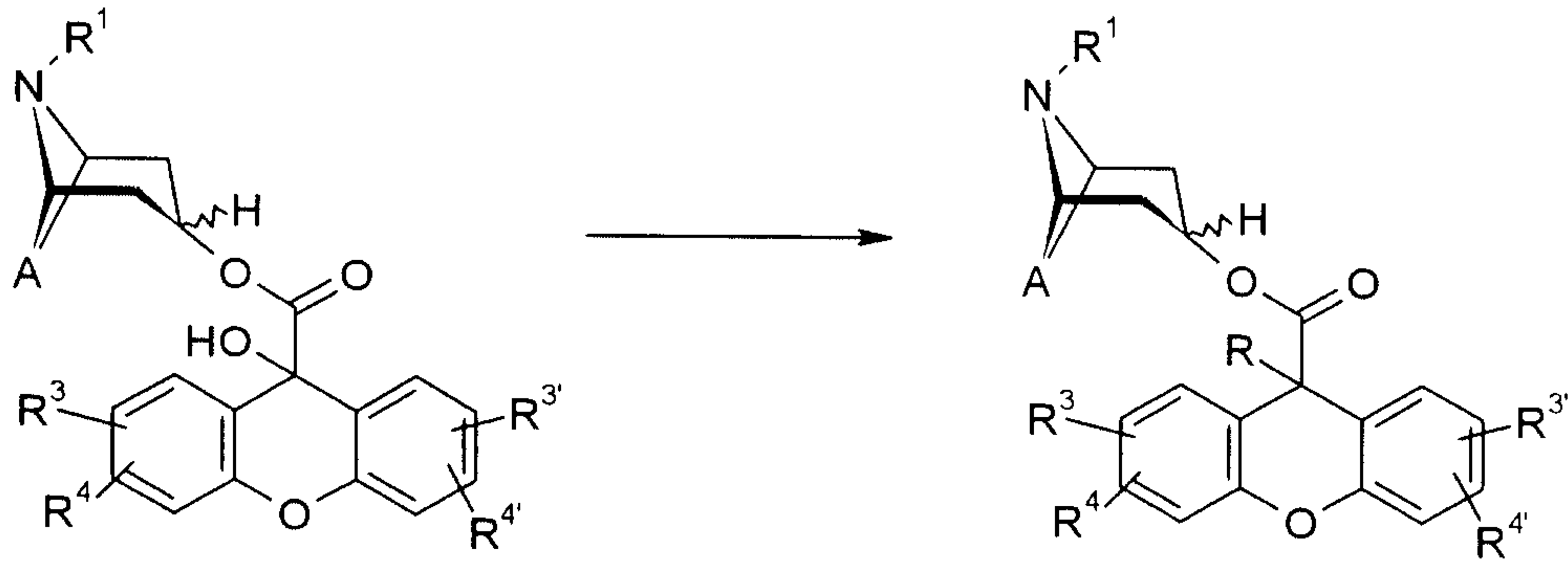
As can be seen from Diagram 1, the compounds of formula 2 may be used as starting products for preparing the compounds of formula 1. These compounds are known in the art.

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 equals Cl) may also be used.

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 to the method of synthesising the compounds of formula 4 shown in Diagram 1 the derivatives 4, wherein the nitrogen bicyclic group denotes a scopine derivative may be obtained by oxidising (epoxidising) compounds of formula 4 wherein the nitrogen bicyclic group is a tropenyl group. According to the invention the following procedure may be used. The compound 4 wherein A denotes -CH=CH- is suspended in a polar organic solvent, preferably in a solvent selected from among N-methyl-2-pyrrolidone (NMP), dimethylacetamide and dimethylformamide, preferably dimethylformamide and then heated to a temperature of about 30-90°C, preferably 40-70°C. Then a suitable oxidising agent is added and the mixture is stirred at constant temperature for 2 to 8 hours, preferably 3 to 6 hours. The oxidising agent is preferably vanadium pentoxide mixed with H_2O_2, most preferably H_2O_2-urea complex combined with vanadium pentoxide. The mixture is worked up in the usual way. The products may be purified by crystallisation or chromatography depending on their tendency to crystallise.

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

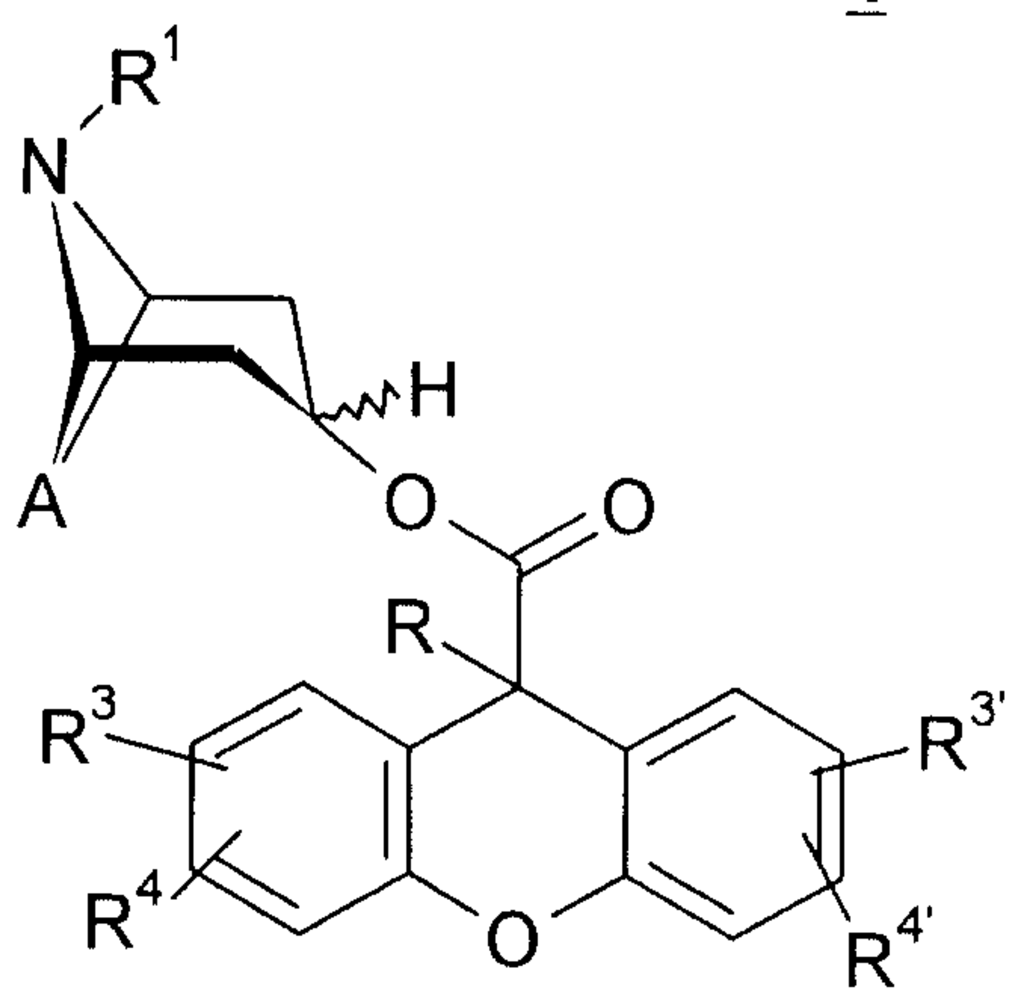


4 (mit R= OH) 4 (mit R= Halogen)

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.

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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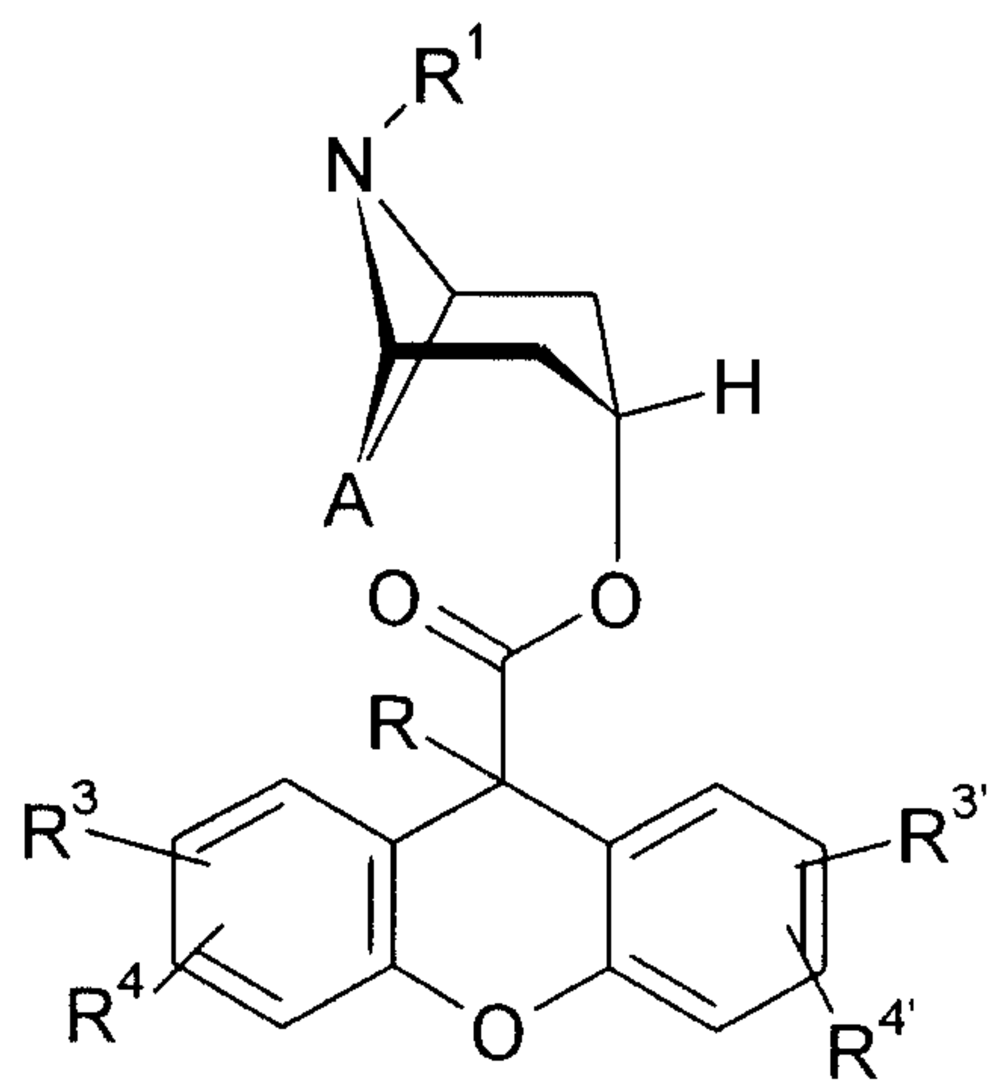
wherein the groups A, R, R^1, R^3, $R^{3'}$, R^4 and $R^{4'}$ may be defined as above, optionally in the form of the acid addition salts thereof.
By acid addition salts are meant salts selected from among the hydrochloride, hydrobromide, hydroiodide, hydrosulphate, hydrophosphate, hydromethanesulphonate, 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.

According to the invention, the compounds of formula **4** in the α-configured form are preferably used as the starting materials. These α-configured compounds are therefore of particularly importance according to the invention and correspond to general formula **4-α**

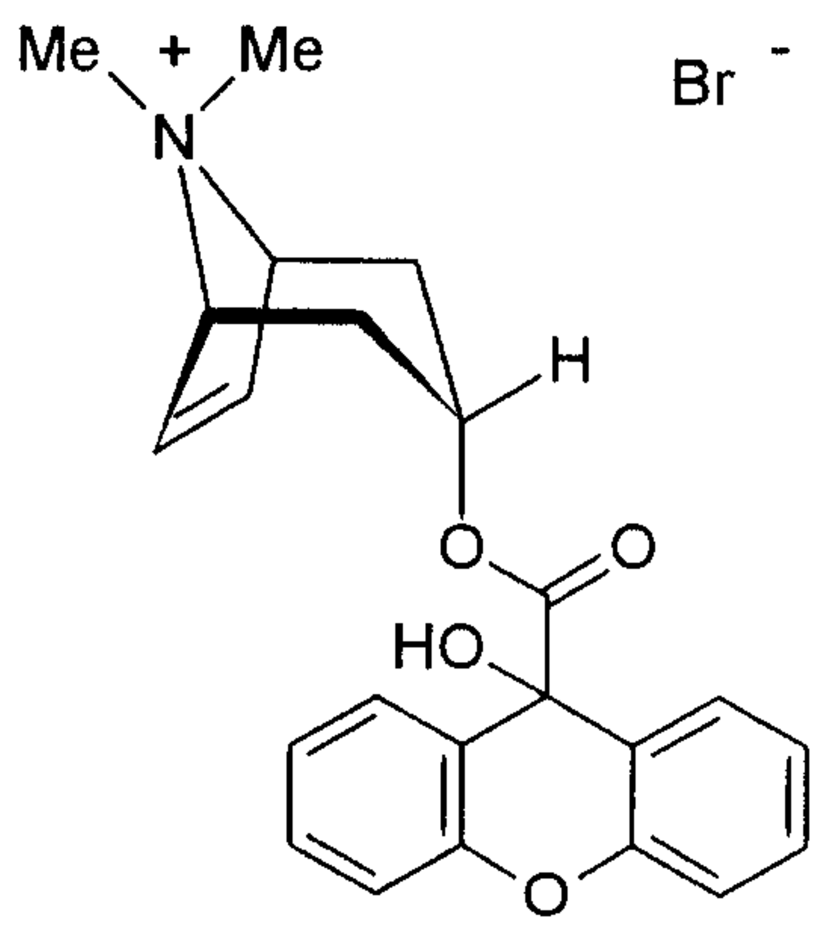


4-α

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**. Moreover the present invention relates to the use of the compounds of general formula **4** as an intermediate product in the preparation of the compounds of general formula **1**.

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

Example 1: tropenol 9-hydroxy-xanthene-9-carboxylate methobromide :



1.1.: methyl 9-hydroxy-xanthene-9-carboxylate **3a:**

a) methyl xanthene-9-carboxylate :

A sodium ethoxide solution is prepared 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 suspension obtained is stirred for 1 hour at ambient temperature. Then the solid is separated off, washed with 1500 ml diethyl ether, the isolated crystals are suspended in 1500 ml of dimethylformamide and combined with 126.73 ml (2.0 mol) of methyl iodide with stirring. The solution formed 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 theory)

Melting point: 82° C.

b) methyl 9-hydroxy-xanthene-9-carboxylate **3a**:

48.05 g (0.2 mol) methyl xanthene-9-carboxylate are dissolved in 1200 ml of tetrahydrofuran and at 0° C combined with 23.63 g (0.2 mol) of potassium tert. butoxide. Oxygen is the piped in for 2 hours at –10° to –5° C, then the mixture is acidified with 2 N aqueous hydrochloric acid and the majority of the solvent is distilled off. 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 and dried and the solvent is distilled off.

The product is purified by crystallisation from diisopropylether and cyclohexane. Yield: 11.10 g white crystals (= 22% of theory)

1.2: tropenol 9-hydroxy-xanthene-9-carboxylate **4a**:

13.65 g (0.053 mol) of methylester **3a**, 8.35 g (0.06 mol) of tropenol and 0.2 g of sodium are heated as a melt at 75 mbar for 4 h over a bath of boiling water with occasional agitation. 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 washed with water, dried over $MgSO_4$ and the solvent is distilled off. The product is purified by recrystallisation from diethyl ether/petroleum ether.

Yield: 5.28 g of white crystals (= 27 % of theory); Melting point: 117°C.

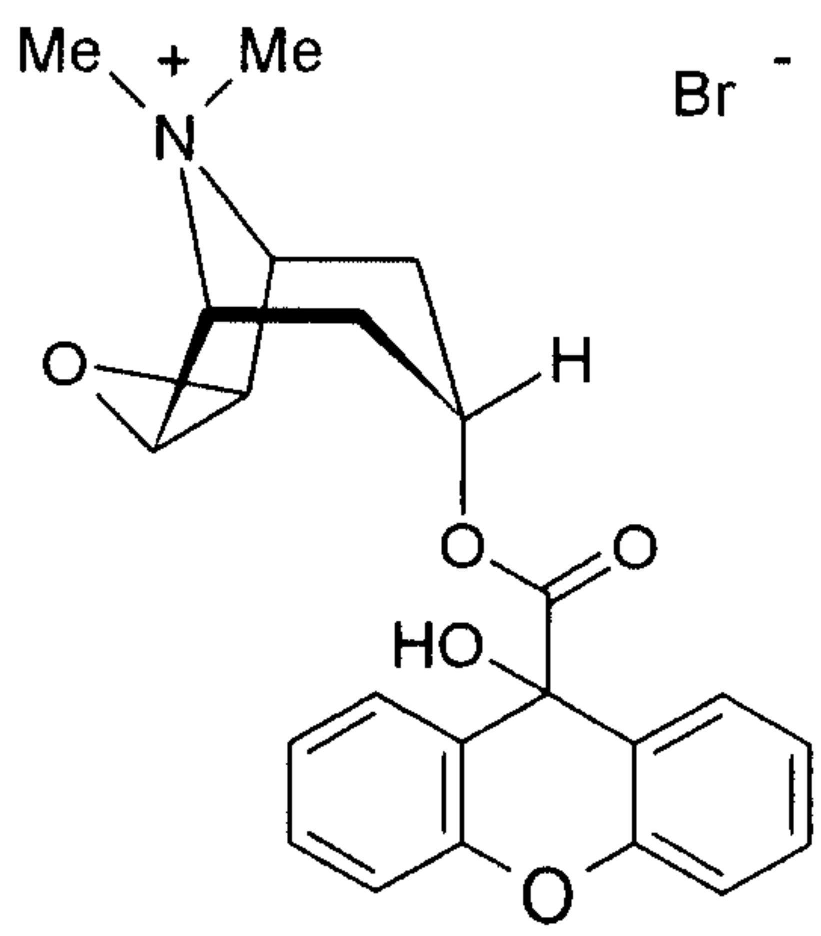
1.3: tropenol 9-hydroxy-xanthene-9-carboxylate -methobromide :

0.8 g (0.002 mol) of **4a** are taken up in 20 ml dichloromethane and 20 ml acetonitrile and combined with 1.14 g (0.006 mol) of 50% methylbromide solution in acetonitrile. The reaction mixture is left to stand for 3 days at ambient temperature, during which time the product crystallises. The crystals precipitated are separated off and recrystallised from acetone to purify them.

Yield: 0.94 g of white crystals (= 93 % of theory); Melting point: 249-250°C.

Elemental analysis:				
	calculated:	C (60.27)	H (5.28)	N (3.06)
	found:	C (60.04)	H (5.34)	N (2.98).

Example 2: scopine 9-hydroxy-xanthene-9-carboxylate methobromide :



2.1: scopine 9-hydroxy-xanthene-9-carboxylate **4b**:

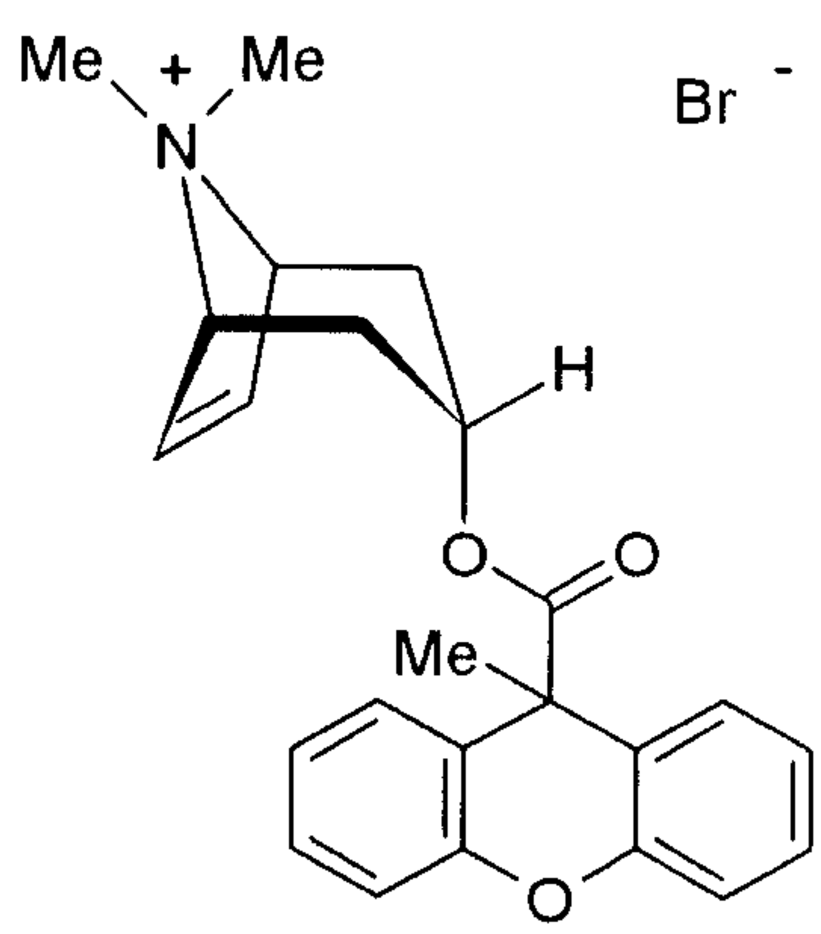
6.8 g (0.019 mol) tropenolester **4a** are suspended in 75 ml of dimethylformamide and combined with 0.36 g (0.002 mol) of vanadium-(V)-oxide. At 60°C a solution of 3.52 g (0.037 mol) of H_2O_2-urea in 15 ml of water is added dropwise and the mixture is stirred for 6 hours at 60°C. After cooling to 20°C the mixture is adjusted to pH 2 with 4 N hydrochloric acid and combined with $Na_2S_2O_5$ dissolved in water. The resulting solution is evaporated to dryness, the residue is extracted with dichloromethane/water.

The acidic aqueous phase obtained is made basic with Na_2CO_3, extracted with dichloromethane and the organic phase is dried over Na_2SO_4 and concentrated.
Then 1 ml of acetylchloride are added at ambient temperature and the mixture is stirred for 1 hour. After extraction with 1 N hydrochloric acid the aqueous phase is made basic, extracted with dichloromethane, the organic phase is washed with water and dried over $MgSO_4$. Finally, the solvent is distilled off. The crude product is purified by recrystallisation from diethyl ether. Yield: 5.7 g of yellow oil (= 79 % of theory).

2.2: scopine 9-hydroxy-xanthene-9-carboxylate methobromide :
4.0 g (0.011 mol) of **4b** are taken up in 60 ml acetonitrile and reacted with 6.27 g (0.033 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3. Yield: 3.6 g of white crystals (= 69 % of theory); Melting point:226-227°C.

Elemental analysis:	calculated:	C (58.24)	H (5.10)	N (2.95)
	found:	C (58.33)	H (4.98)	N (3.05).

Example 3: tropenol 9-methyl-xanthene-9-carboxylate methobromide :



3.1.: 9-methyl-xanthene-9-carboxylic acid **3b**:
a) methyl 9-methyl-xanthene-9-carboxylate :
9.61 g (0.04 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 1.1.a) are dissolved in 150 ml of tetrahydrofuran, combined with a solution of 5.0 g (0.042 mol) potassium tert. butoxide in THF and stirred for 10 minutes. 5 ml (0.08 mol) of methyl iodide are then added dropwise with gentle cooling and after all has been added the mixture is stirred for 1 hour at ambient temperature. The reaction mixture is diluted with water to a total volume of 800 ml, extracted with diethyl ether, the organic phase is extracted with saturated, aqueous Na_2CO_3 solution, washed with water, dried over

$MgSO_4$ and the solvent is distilled off. The product is purified by recrystallisation from methanol.
Yield: 6.05 g of white crystals (= 70% of theory); Melting point:91°-92°C.

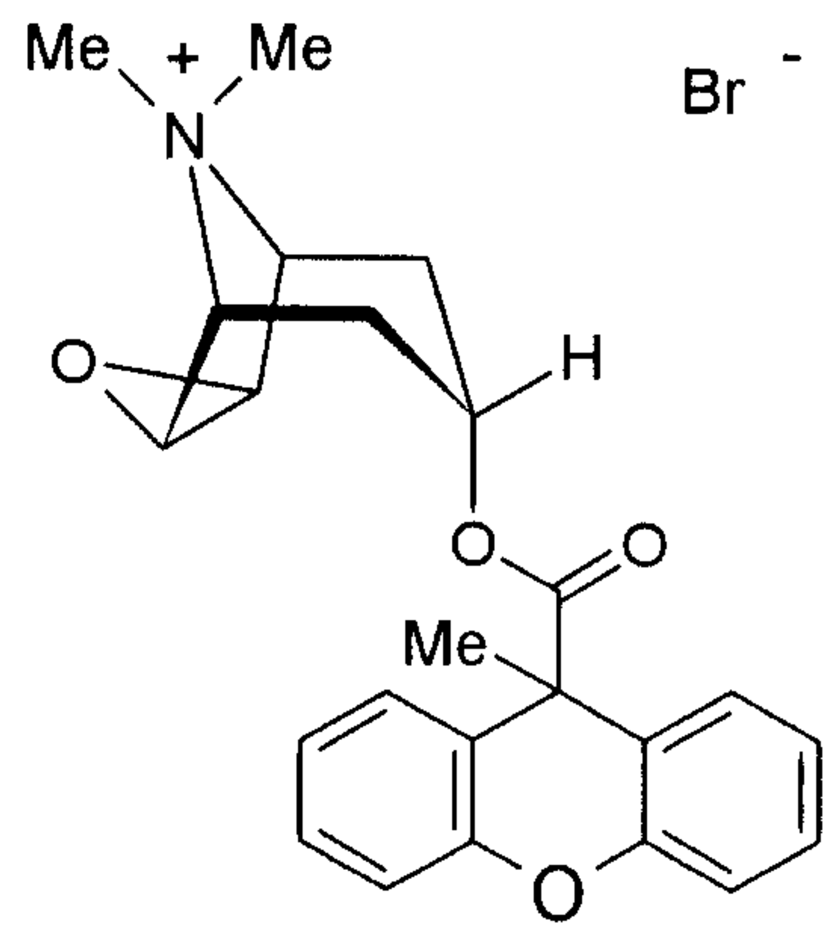
b) 9-methyl-xanthene-9-carboxylic acid **3b**:
20.34 g (0.08 mol) of the methyl ester described above and 80 ml of 2 molar aqueous sodium hydroxide solution are stirred in 200 ml dioxane for 24 hours at ambient temperature, then the dioxane is distilled off, the mixture is made up to a total volume of 600 ml with water, extracted with diethyl ether and the aqueous phase is acidified with 4 N hydrochloric acid. The product crystallises, is suction filtered and washed with water. It is purified by recrystallisation from acetonitrile. Yield: 14.15 g of white crystals (= 74% of theory);
Melting point:207-208°C.

3.2: tropenol 9-methyl-xanthene-9-carboxylate **4c**:
From 7.76 g (0.03 mol) of **3b**, 0.06 mol of oxalyl chloride and 4 drops of dimethylformamide the acid chloride is prepared in 100 ml dichloromethane. It is added dropwise as a solution in dichloromethane to 8.77 g (0.063 mol) of tropenol in 140 ml of dichloromethane, then stirred for 24 hours at 40°C and cooled. The reaction mixture is extracted with water, dried over $MgSO_4$, and filtered off. The filtrate obtained is acidified to pH2 with ethereal hydrochloric acid, extracted with diethyl ether and the aqueous phase is made basic. After extraction with dichloromethane the organic phase is washed neutral with water, dried over $MgSO_4$ and evaporated to dryness. The residue is dissolved in diethyl ether, insoluble matter is filtered off and the solvent is removed by distillation. Yield: 3.65 g of yellow oil (= 34% of theory).

3.3: tropenol 9-methyl-xanthene-9-carboxylate methobromide :
1.65 g (0.005 mol) of **4c** are taken up in 20 ml acetonitrile and reacted with 2.85 g (0.015 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3. Yield: 1.5 g of white crystals (= 65 % of theory); Melting point:212-213°C.

Elemental analysis:	calculated:	C (63.16)	H (5.74)	N (3.07)
	found:	C (62.50)	H (5.94)	N (3.11).

Example 4: scopine 9-methyl-xanthene-9-carboxylate methobromide



4.1: scopine 9-methyl-xanthene-9-carboxylate **4d**:

1.9 g (0.005 mol) of tropenol ester **4c** are suspended in 30 ml of dimethylformamide and reacted with 0.12 g (0.001 mol) of vanadium-(V)-oxide and 0.01 mol of H_2O_2-urea in water analogously to the method according to step 2.1.

Yield: 1.4 g of white crystals (= 74 % of theory).

4.2: scopine 9-methyl-xanthene-9-carboxylate methobromide :

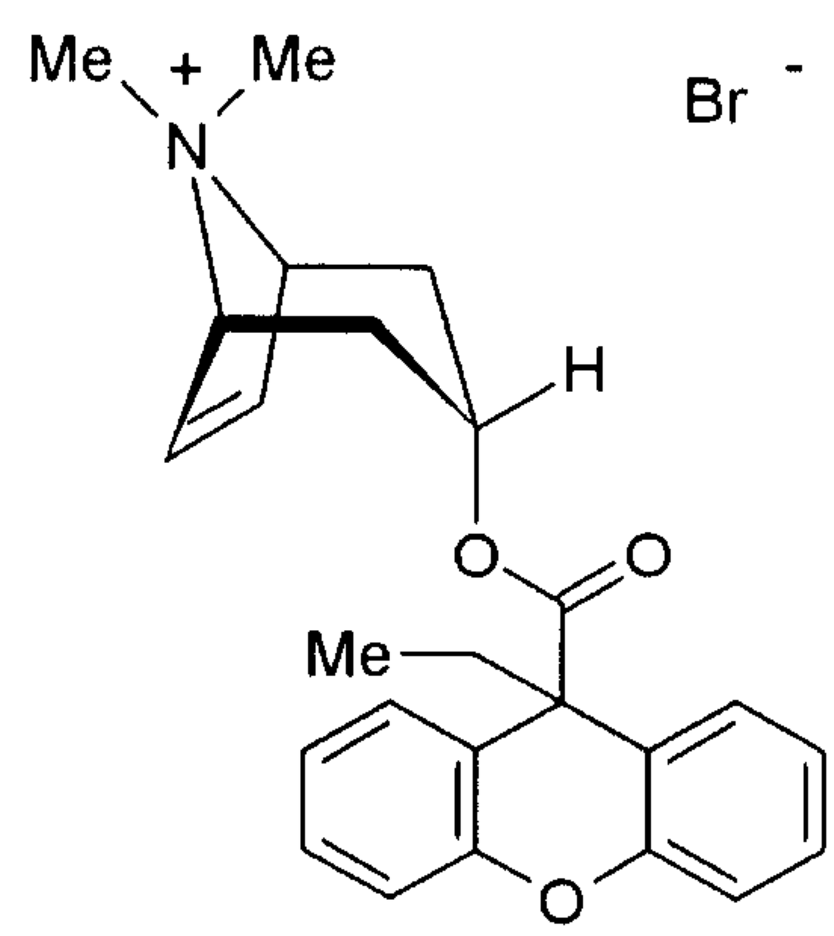
1.35 g (0.004 mol) of **4d** are taken up in 10 ml of dichloromethane and 20 ml of acetonitrile and reacted with 2.28 g (0.012 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3.

Yield: 1.35 g of white crystals (= 71 % of theory); Melting point:208-209°C.

Elemental analysis: calculated: C (61.02) H (5.55) N (2.97)

found: C (59.78) H (5.70) N (2.96).

Example 5: tropenol 9-ethyl-xanthene-9-carboxylate methobromide :



5.1.: 9-ethyl-xanthene-9-carboxylic acid **3c:**.

a) methyl 9-ethyl-xanthene-9-carboxylate:

10.0 g (0.042 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 1.1.a) are dissolved in 100 ml of tetrahydrofuran and combined batchwise with 5.16 g (0.044 mol) of potassium tert. butoxide while cooling. Then at about 18-22°C 6.296 ml (0.083 mol) of bromoethane are added dropwise and after it has all been added the mixture is stirred for about 1.5 hours at ambient temperature. The precipitate formed is suction filtered and the solvent is removed by distillation. The residue remaining is taken up in diethyl ether and extracted with water. The organic phase is dried over $MgSO_4$ and the solvent is removed by distillation. The crude product obtained is used in the next step without any further purification.

Yield: 7.92 g of yellow oil. (= 70% of theory).

b) 9-ethyl-xanthene-9-carboxylic acid **3c**:

7.92 g (0.03 mol) of the ethyl ester described above and 29.5 ml of 2 molar aqueous sodium hydroxide solution are refluxed in 80 ml dioxane for 2.5 hours. The mixture is worked up as in step 3.1.b).

Yield: 4.46 g of white crystals (= 58% of theory); Melting point:175-176°C.

5.2: tropenol 9-ethyl-xanthene-9-carboxylate **4e**:

From 4.46 g (0.03 mol) of **3c**, 4.45 g (0.035 mol) of oxalyl chloride and 3 drops of dimethylformamide the acid chloride is prepared in 40 ml of dichloromethane. It is added as a solution in dichloromethane to 4.87 g (0.035 mol) of tropenol in 60 ml of dichloromethane and reacted analogously to the procedure according to step 3.2 and worked up.

Yield: 0.97 g of oil (= 15% of theory).

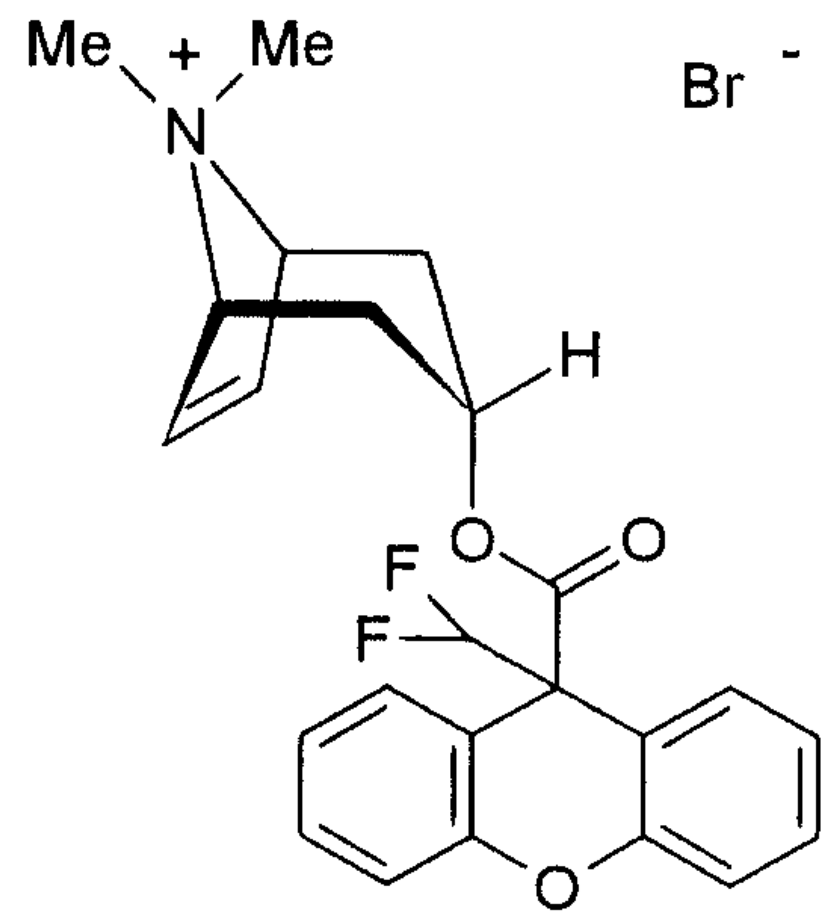
5.3: tropenol 9-ethyl-xanthene-9-carboxylate methobromide :

0.97 g (0.003 mol) of **4e** are taken up in 70 ml acetonitrile and reacted with 1.77 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to Step 1.3. To purify it the product is recrystallised from acetonitrile.

Yield: 0.65 g white crystals (= 46 % of theory); Melting point:217-218°C.

Elemental analysis: calculated: C (63.83) H (6.00) N (2.98)
found: C (61.76) H (6.32) N (2.92).

Example 6: tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide :



6.1.: 9-difluoromethyl-xanthene-9-carboxylic acid **3d**:

a) methyl 9-difluoromethyl-xanthene-9-carboxylate :

16.8 g (0.07 mol) of methyl 9-xanthenecarboxylate (obtainable according to step 1.1.a) are dissolved in 300 ml of tetrahydrofuran and 9.1 g (0.077 mol) of potassium tert. butoxide are added batchwise while cooling. Then difluorochloromethane is piped in at 0°C over a period of 1.5 hours. After all the gas has been piped in the reaction mixture is left to stand for 72 hours at ambient temperature. The reaction mixture is then diluted with water to a total volume of about 2000 ml, extracted with ethyl acetate, the organic phase is separated off and washed with 5% aqueous sodium carbonate solution. After being extracted again with water the organic phase is dried over $MgSO_4$ and the solvent is removed by distillation. The crude product is purified by chromatography on silica gel (eluant: cyclohexane/ethyl acetate 98:2) or by recrystallisation from cyclohexane.

Yield: 5.35 g of white crystals (= 26% of theory); Melting point: 101°C.

b) 9-difluoromethyl-xanthene-9-carboxylic acid **3d**:

5.38 g (0.019 mol) of the ester described above and 18.5 ml of 2 molar aqueous sodium hydroxide solution are reacted in 60 ml of dioxane and worked up analogously to the reaction in Step 3.1.b).

Yield: 2.77 g white crystals (= 53% of theory); Melting point: 181-182°C.

6.2: 9-difluoromethyl-xanthene-9-carboxylate tropenol **4f**:

From 2.77 g (0.01 mol) of **3d**, 1 ml of oxalyl chloride and 1 drop of dimethylformamide the acid chloride is prepared. It is added to 2.78 g (0.02 mol) of tropenol in 50 ml of 1,2-dichloroethane and reacted and worked up analogously to step 3.2. Yield: 0.6 g of oil (= 15% of theory).

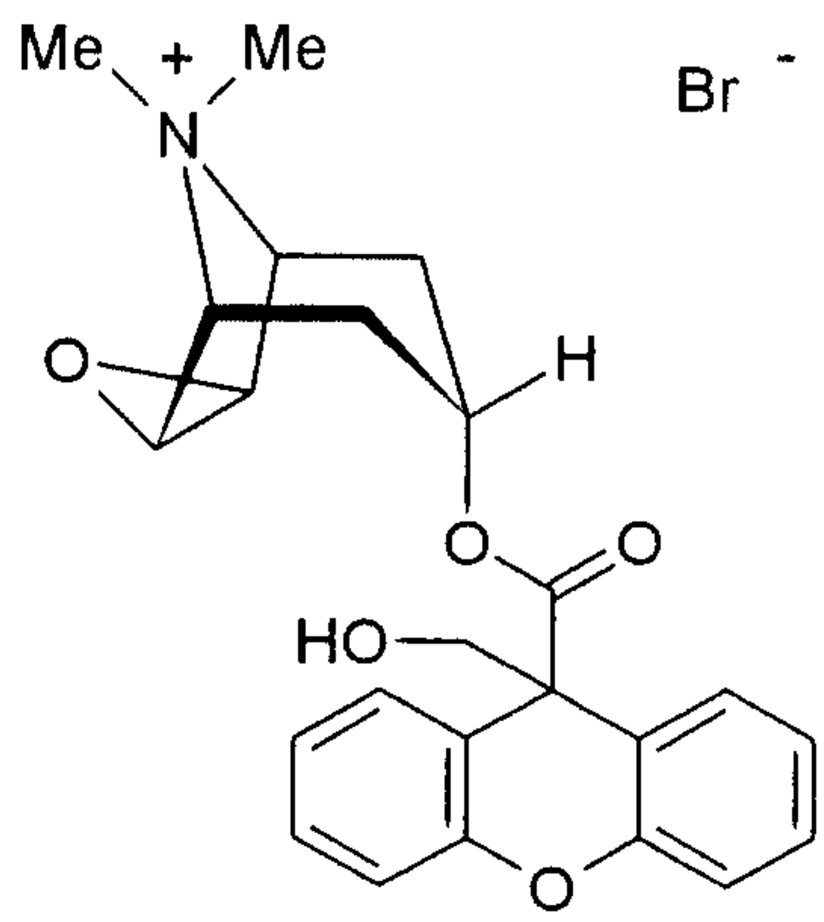
6.3: tropenol 9-difluoromethyl-xanthene-9-carboxylate methobromide :

0.6 g (0.002 mol) **4f** are taken up in 20 ml acetonitrile and reacted with 1.14 g (0.006 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3.

Yield: 0.44 g beige crystals (= 45 % of theory); Melting point:227-228°C.

Elemental analysis: calculated: C (58.55) H (4.91) N (2.84)
found: C (57.19) H (5.11) N (2.86).

Example 7: scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide



7.1.: scopine 9-hydroxymethyl-xanthene-9-carboxylate **4g**:

3.63 g (0.010 mol) of scopine xanthene-9-carboxylate, which may be obtained as described in WO 92/16528, are dissolved in 20 ml of dimethylformamide and combined with 0.36 g (0.012 mol) of paraformaldehyde. After the addition of 0.168 g (0.002 mol) of potassium tert. butoxide at 20°C the mixture is stirred for 2 hours at ambient temperature. The mixture is acidified to pH 2 with 4 N hydrochloric acid with cooling and the solvent is distilled off *in vacuo*. The residue remaining is extracted with diethyl ether and water, the aqueous phase is made basic with 10% sodium carbonate solution and extracted with dichloromethane. The organic phase is separated off and washed with water, dried and the solvent is distilled off *in vacuo*. To purify it the product is recrystallised from acetonitrile.

Yield: 1.55 g white crystals (= 36% of theory); Melting point:232°C.

7.2: scopine 9-hydroxymethyl-xanthene-9-carboxylate methobromide :

1.15 g (0.003 mol) of **4g** are taken up in 20 ml acetonitrile and reacted with 1.71 g (0.009 mol) of 50% methyl bromide solution in acetonitrile analogously to step 1.3.

Yield: 1.28 g of white crystals (= 87 % of theory); Melting point:234°C.

Elemental analysis: calculated: C (59.02) H (5.37) N (2.87) found: C (59.30) H (5.41) N (3.03).

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 MgCl2, 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.

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 thereof, 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 thereof, 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 for combining with the compounds of general 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.

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 and
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.

Especially preferred examples of EGFR-kinase inhibitors which may be used according to the invention as a combination with the compounds of formula **1** 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, 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 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.

Particularly preferred examples of p38 kinase inhibitors which may be used according to the invention as a combination with the compounds of formula 1 include, in particular, 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, 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.

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.

When the compounds of formula **1** are used for the treatment of asthma or COPD they are preferably administered as preparations or pharmaceutical formulations for inhalation. For inhalation the compounds may be in the form of 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 detail in the next part of the specification.

The inhalable powders which may be used according to the invention may contain the compounds **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. dextrane), polyalcohols (e.g. sorbitol, mannitol, xylitol), salts (e.g. sodium chloride, calcium carbonate) or mixtures of these excipients with one another. 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 excipients 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 by 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 which may be used according to the invention may contain the compounds **1** dissolved in the propellant gas or in dispersed form. The compounds **1** may be present in separate preparations or in a combined preparation, while the compounds **1** may either both be dissolved, both dispersed or only one component is dissolved and the other may be 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 propellant gases mentioned above may be used on their own or in mixtures thereof. Particularly preferred propellant gases are fluorinated 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 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 already form an acid addition salt. 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.

In these formulations it may be possible to do without the addition of editic acid (EDTA) or one of the known salts thereof, sodium edetate, as stabiliser or complexing agent. Other embodiments contain(s) this compound (these compounds. In a preferred embodiment the content, based on sodium edetate, is less than 100 mg/100 ml, preferably less than 50 mg/100 ml, most preferably less than 20 mg/100ml. Generally, inhalable solutions in which the content of sodium edetate is from 0 to 10 mg/100 ml are preferred. Cosolvents and/or other excipients may be added to the propellent-free inhalable solutions. Preferred cosolvents are thus those which contain hydroxyl groups or other polar groups, such as alcohols - particularly isopropylalcohol, glycols - particularly propyleneglycol, polyethyleneglycol,

polypropyleneglycol, glycolether, glycerol, polyoxyethylene alcohols and polyoxyethylene fatty acid esters. By excipients and additives are meant, in this context, any pharmacologically acceptable substance which is not an active substance, but can be formulated together with the active substance(s) in the pharmacologically suitable solvent to improve the qualitative properties of the active substance formulation. Preferably, these substances have no noticeable or at least no unwanted pharmacological activity in the context of the desired therapy. The excipients and additives include e.g. surfactants such as soya lecithin, oleic acid, sorbitan esters such as polysorbates, polyvinylpyrrolidone, other stabilisers, complexing agents, antioxidants and/or preservatives which guarantee or extend 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 for example sodium chloride as isotonic agents.
The preferred excipients include antioxidants, such as for example ascorbic acid, unless already used to adjust the pH, vitamin A, vitamin E, tocopherols and similar vitamins or provitamins which occur in the human body.

Preservatives may be used to protect the formulation from contamination with pathogens. Suitable preservatives are those known in the art, particularly cetylpyridinium chloride, benzalkonium chloride or benzoic acid or benzoates such as sodium benzoate in the concentration known from the prior art. The abovementioned preservatives are preferably present in concentrations of up to 50mg/100ml, most preferably between 5 and 20 mg/100ml.
Preferred formulations contain only benzalkonium chloride and sodium edetate, in addition to the solvent water and the active substance **1**.
In another preferred embodiment, no sodium edetate is used.

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.
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**

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**

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.

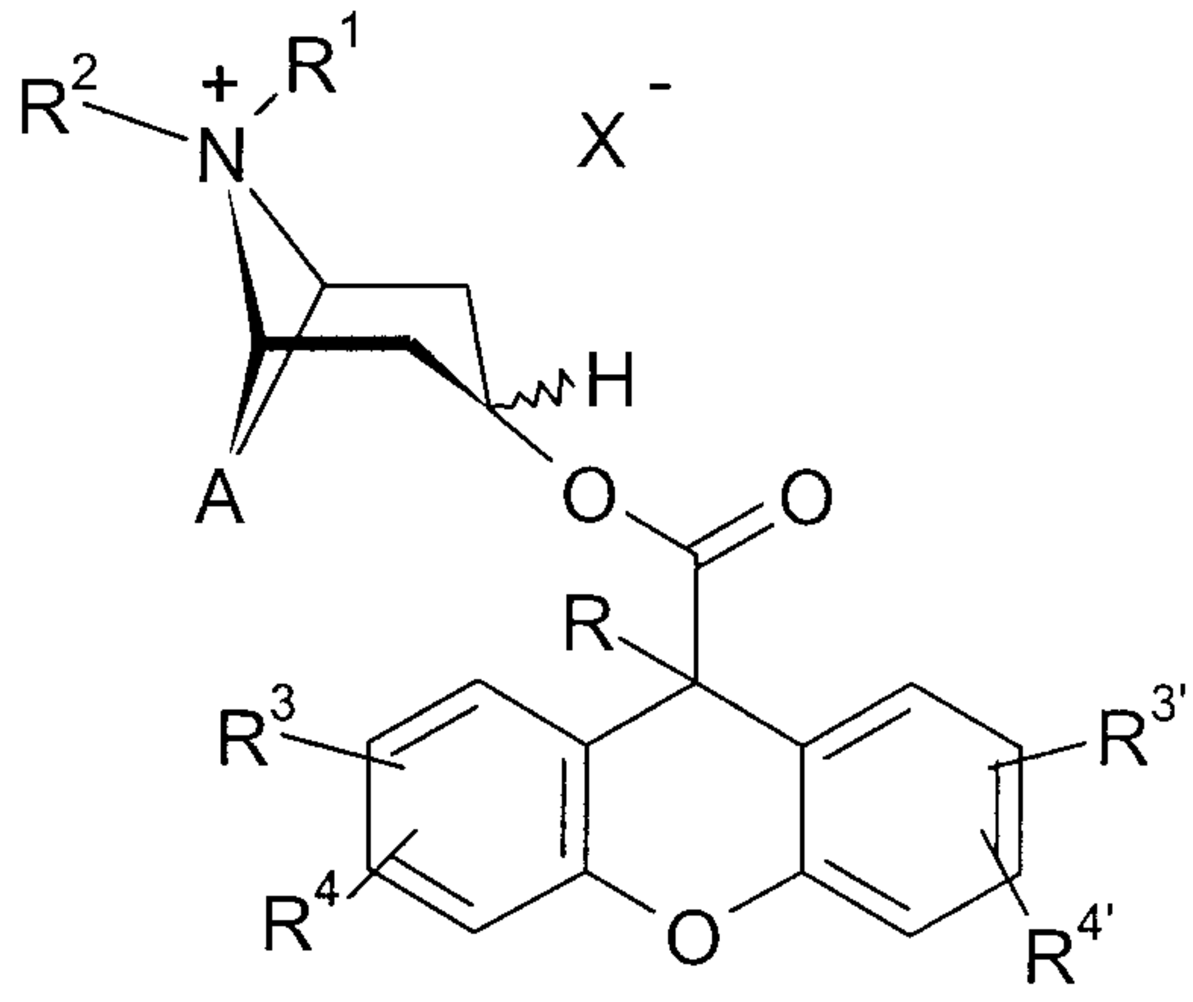
G) Inhalable powder

active substance **1**	10 µg
lactose monohydrate	ad 5 mg

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

CLAIMS:

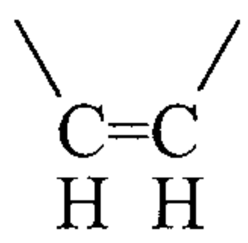
1. Compound of formula **1**



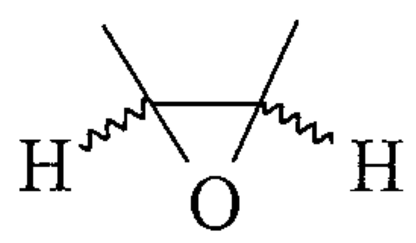
1

wherein

A denotes a double-bonded group, which is



or



;

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

R denotes methyl, ethyl, $-CF_3$ or CHF_2;

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,

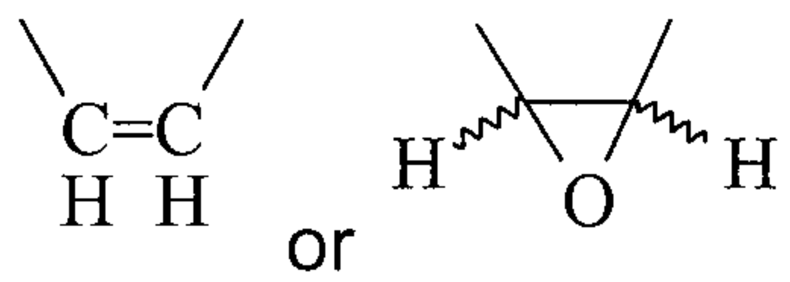
or

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.

2. Compound of formula **1** according to claim 1, wherein

A denotes a double-bonded group, which is


;

X^- denotes an anion with a single negative charge, which is chloride, bromide, 4-toluenesulphonate or methanesulphonate;

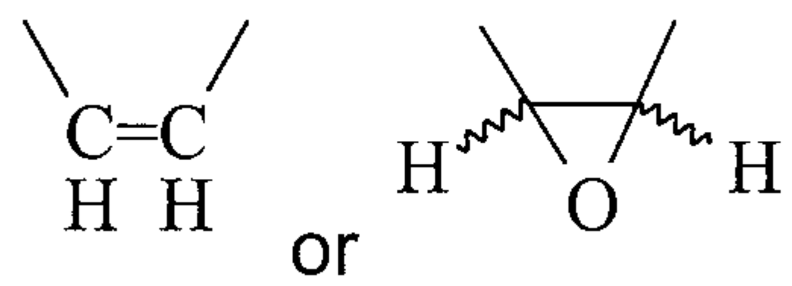
R denotes methyl, ethyl or CHF_2;

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

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen, methyl, methyloxy, hydroxy, $-CF_3$, $-CHF_2$ or fluorine.

3. Compound of formula <u>1</u> according to claim 1 or 2, wherein

A denotes a double-bonded group, which is


;

X^- denotes an anion with a single negative charge, which is chloride, bromide or methanesulphonate;

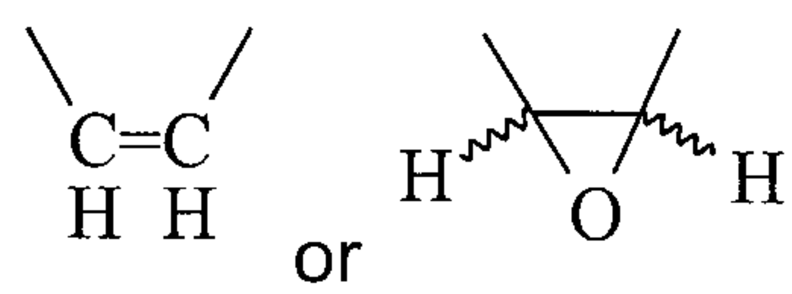
R denotes methyl;

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 represent hydrogen, $-CF_3$, $-CHF_2$ or fluorine.

4. Compound of formula <u>1</u> according to claim 1, 2 or 3, wherein

A denotes a double-bonded group, which is:


;

X^- denotes bromide;

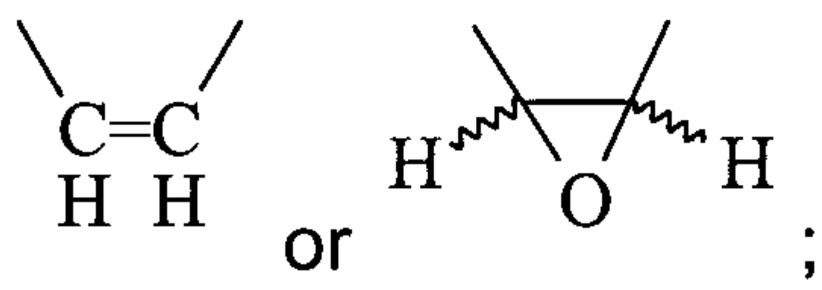
R denotes methyl;

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 represent hydrogen or fluorine.

5. Compound of formula <u>1</u> according to claim 1, 2, 3 or 4, wherein

A denotes a double-bonded group, which is:



X⁻ denotes bromide;

R denotes methyl;

R^1 and R^2 each denote methyl;

R^3, R^4, $R^{3'}$ and $R^{4'}$ which may be identical or different represent hydrogen or fluorine.

6. Compound of formula 1 according to claim 1, 2, 3, 4 or 5 in the form of the individual optical isomers thereof, a mixture of the individual enantiomers thereof or a racemate thereof.

7. Use of a compound of formula 1 as defined in claim 1, 2, 3, 4 or 5 for preparing a pharmaceutical composition for the treatment of a disease in which an anticholinergic can develop a therapeutic benefit.

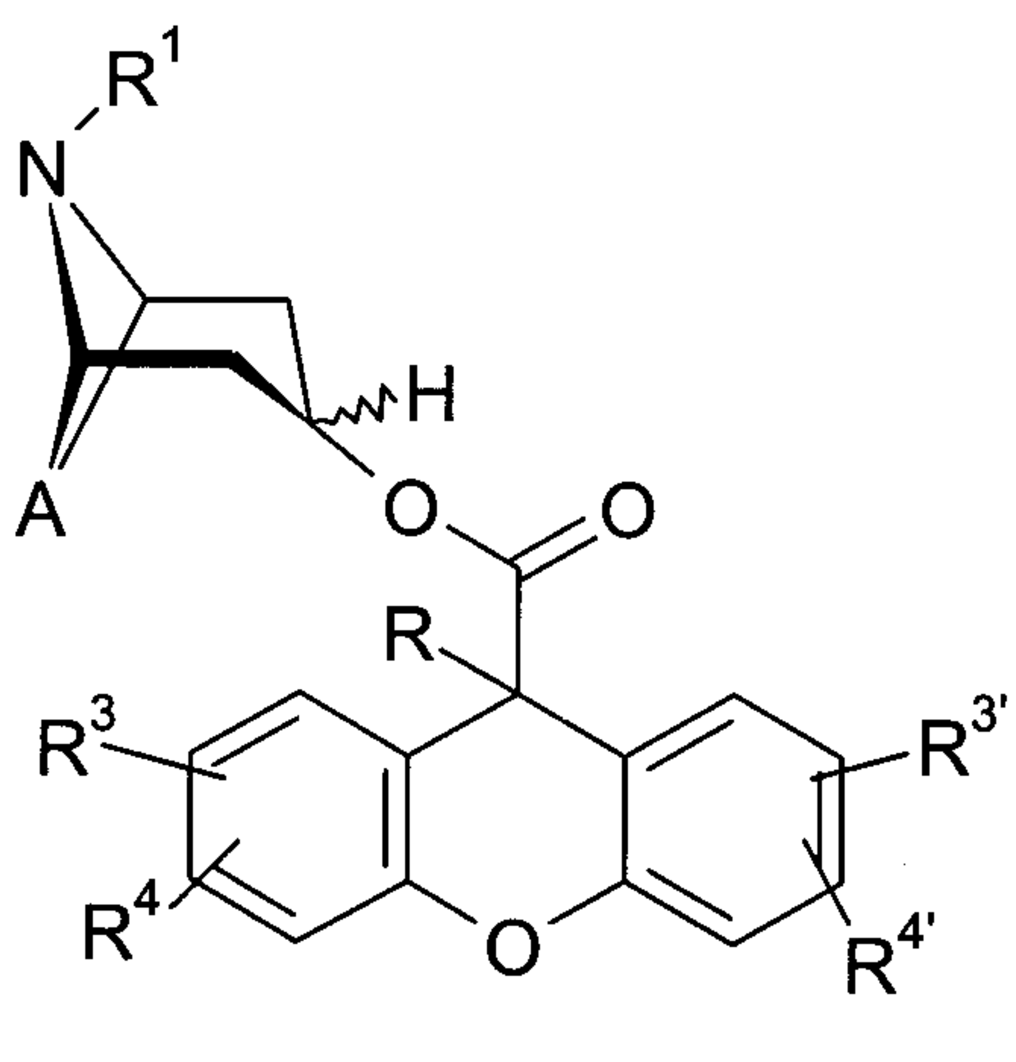
8. Use of a compound of formula 1 as defined in claim 1, 2, 3, 4 or 5 for preparing a pharmaceutical composition for the treatment of asthma, COPD, vagally induced sinus bradycardia, a heart rhythm disorder, a spasm in the gastrointestinal tract, a spasm in the urinary tract or menstrual pain.

9. Pharmaceutical preparation, containing one or more compounds of formula **1** as defined in claim 1, 2, 3, 4 or 5 in combination with conventional excipients and/or carriers.

10. Pharmaceutical preparation according to claim 9, which contains, in addition to one or more of the compounds of formula **1** , at least one other active substance which is selected from the group consisting of betamimetics, antiallergics, PAF antagonists, PDE IV inhibitors, leukotriene antagonists, p38 kinase inhibitors, EGFR-kinase inhibitors and corticosteroids.

11. A pharmaceutical preparation according to claim 9 for treatment of asthma, COPD, vagally induced sinus bradycardia, a heart rhythm disorder, a spasm in the gastrointestinal tract, a spasm in the urinary tract or menstrual pain.

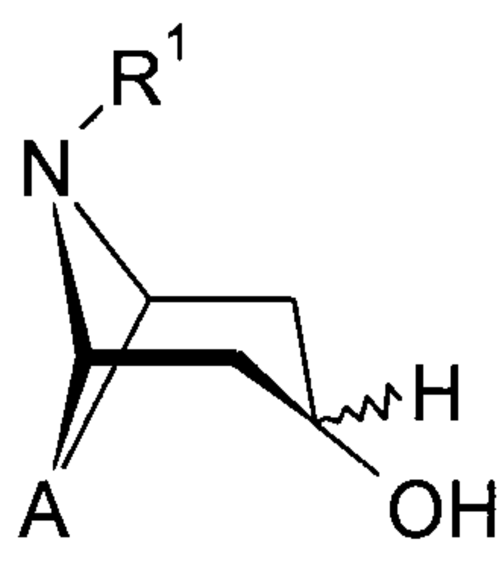
12. Compound of formula **4**



4

wherein the groups A, R, R^1, R^3, $R^{3'}$, R^4 and $R^{4'}$ are as defined in claim 1, 2, 3, 4 or 5, optionally in the form of an acid addition salt thereof.

13. Use of a compound of formula **2**



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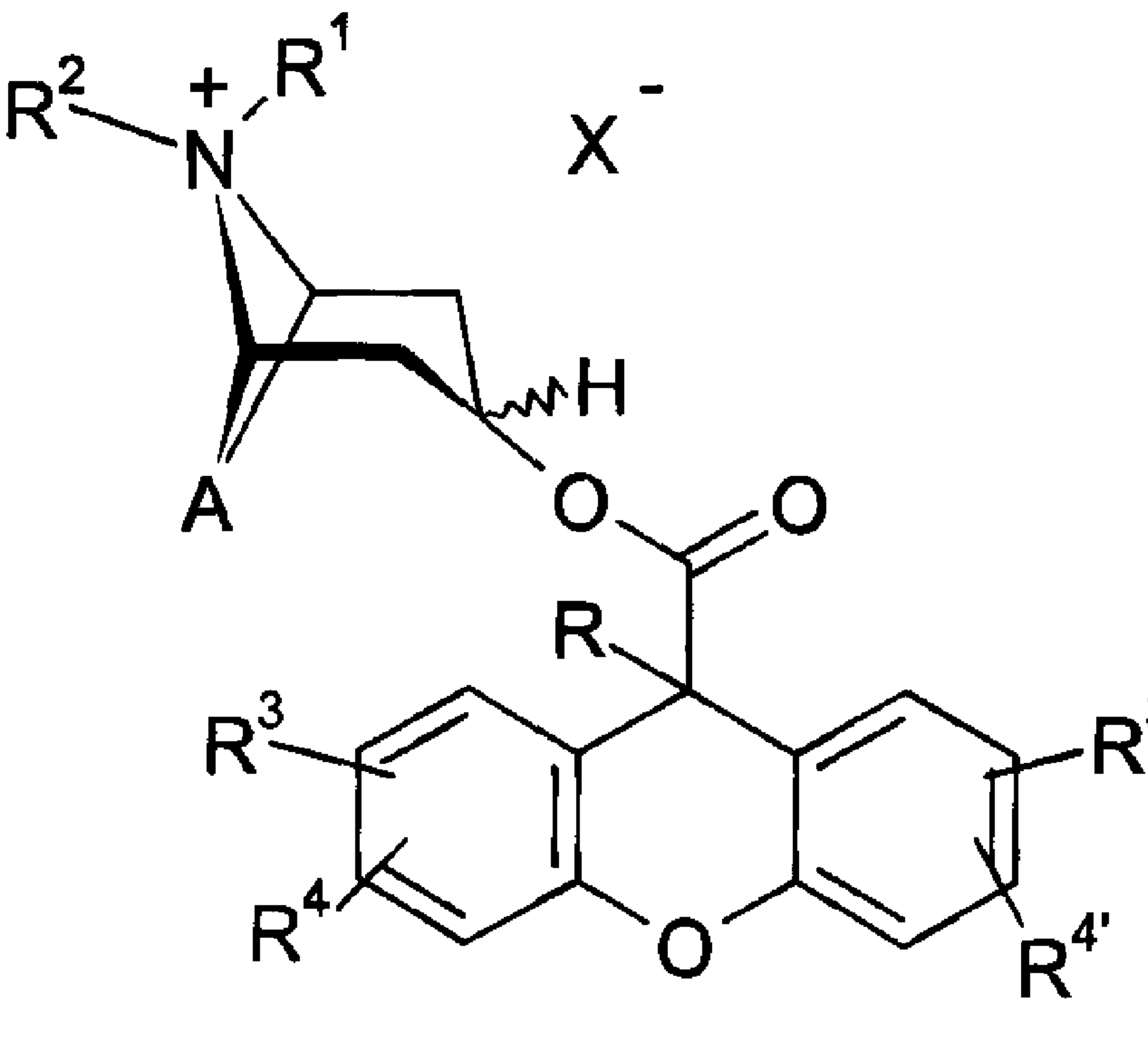
wherein the groups A and R^1 are as defined in claim 1, 2, 3, 4 or 5, optionally in the form of an acid addition salt thereof, for preparing a compound of formula **1** as defined in claim 1, 2, 3, 4, 5 or 6.



1