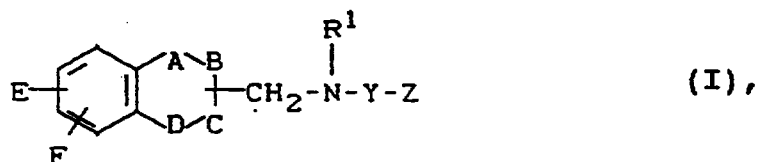


The invention relates to substituted aminomethyltetralins and their heterocyclic analogues, processes for their preparation and their use in medicaments.

It is known that 2-N-dipropyl-amino-8-hydroxy-tetralin binds to central receptors of the 5-HT₁ type with high affinity and selectivity. It is further known that substituted aminomethylbenzodioxanes have a high affinity for receptors of the 5-HT₁ type and show an effect both on the cardiovascular and the central nervous system (EP-A 0,236,930).

In addition, it is known that 3-aminochromans and 3-aminomethylchromans have a stimulating effect on the central nervous system (Ind. J. Chem., Sect. B. 21B (4), 344-347).

Substituted aminomethyltetralins and their heterocyclic analogues of the general formula



in which

Y - denotes a straight-chain alkylene chain having 2-5 carbon atoms,

Z - denotes a group of the formula

$$\begin{array}{c} \text{R}^2 \\ \diagup \\ \text{N} \\ \diagdown \\ \text{R}^3 \end{array}$$

where

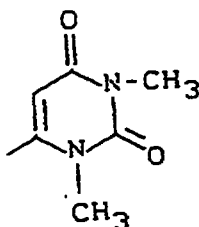
R² and R³ are identical or different and

- represent hydrogen, methyl, ethyl, propyl or

- represent phenyl, benzyl or pyridyl, which is

optionally substituted by fluorine, chlorine, methyl or methoxy

- represent a group of the formula



or

5 - represent a group of the formula $-\text{COR}^9$ or $-\text{SO}_2\text{R}^{10}$,

in which

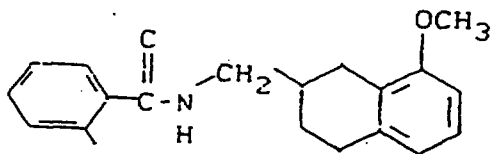
R^9 - represents methyl, ethyl or ethoxy or

- represents phenyl or benzyl, optionally substituted by methyl, methoxy, fluorine or chlorine,

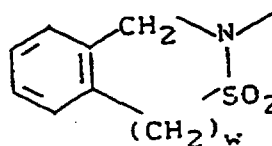
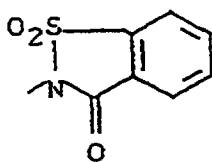
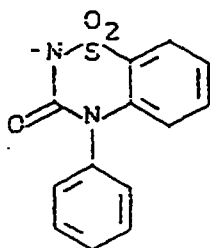
10 R^{10} - represents methyl, ethyl or propyl,

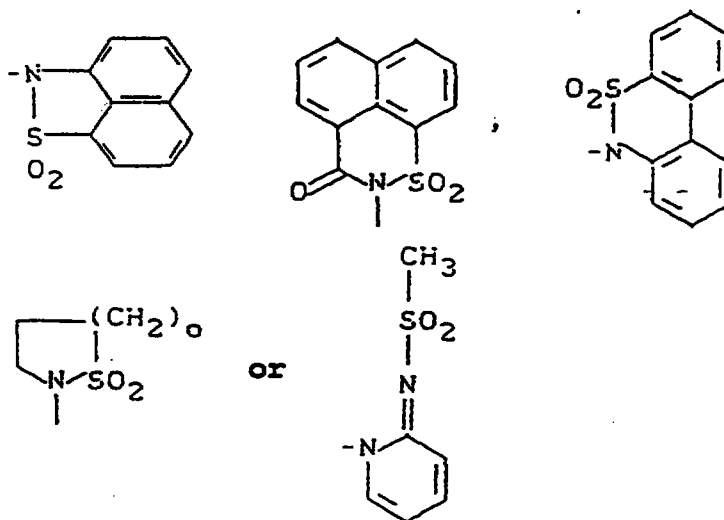
- represents phenyl, naphthyl or benzyl, which is optionally substituted by fluorine or chlorine or

- represents a group of the formula



15 R^2 and R^3 together with the nitrogen atom form a heterocycle from the series comprising





where

w - denotes a number 0, 1 or 2 and

o - denotes a number 1 or 2

5 R¹ - denotes hydrogen, ethyl, methyl, propyl or benzyl
or

- denotes the group -(Y¹-Z¹), where Y¹ and Z¹ may be identical or different to Y and Z and have the abovementioned meaning of Y and Z,

10 A and D represent a group of the formula -CH₂-, oxygen, or the CH or N part of a C=C-C=N double bond, with the proviso that either only A or only D may represent oxygen,

B - represents a group of the formula >CH₂ or >CH or the CH part of a C=C or C=N double bond,

15 C - represents a group of the formula >CH or the C part of a C=C or C=N double bond,

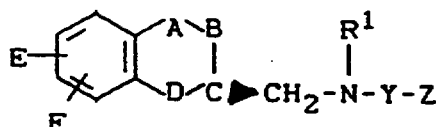
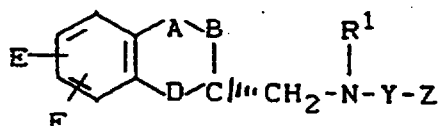
E and F are identical or different and represent hydrogen, ethoxy, methoxy, fluorine, cyano or a group of the formula -CONR²R³, in which R² and R³ denote hydrogen,

20

[lacuna]

E and F together form a phenyl or cyclohexane ring,
and their salts have been found.

In the context of the present invention, the compounds
according to the invention may have several asymmetric
5 carbon atoms and therefore exist in various stereochemic-
al forms. Moreover, compounds having a sulfoxide group
may likewise exist in various stereochemical forms. The
following isomeric forms of the substituted aminomethyl-
tetralins and their heterocyclic analogues may be men-
10 tioned as examples.



The compounds according to the invention may also exist
in the form of their salts. In general, salts with
15 inorganic or organic acids may be mentioned here.

In the context of the present invention physiologically
acceptable salts are preferred.

Physiologically acceptable salts of the substituted
aminomethyltetralins and their heterocyclic analogues may
20 be salts of the substances according to the invention
with mineral acids, carboxylic acids or sulphonic acids.
For example, salts with hydrochloric acid, hydrobromic
acid, sulphuric acid, phosphoric acid, methanesulphonic
acid, ethanesulphonic acid, toluenesulphonic acid,
25 benzenesulphonic acid, naphthalenedisulphonic acid,
acetic acid, propionic acid, lactic acid, oxalic acid,
malonic acid, succinic acid, maleic acid, fumaric acid,
malic acid, tartaric acid, citric acid or benzoic acid
are particularly preferred.

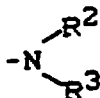
The substances according to the invention surprisingly show an advantageous effect on the central nervous system and may be used for the therapeutic treatment of humans and animals. Compared to the already known structurally related compounds, they are distinguished by a greater selectivity for the 5-HT_{1A} receptor owing to a partly serotonin-antagonistic effect and lower side-effects.

Preferred compounds of the formula I are those

in which

10 Y - denotes a straight-chain alkylene chain having 2-5 carbon atoms,

Z - denotes a group of the formula

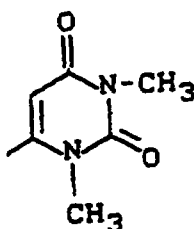


in which

15 R² and R³ are identical or different and

- represent hydrogen, methyl, benzyl or pyridyl

- represent a group of the formula



or

20 - represent a group of the formula -COR⁹ or SO₂R¹⁰,

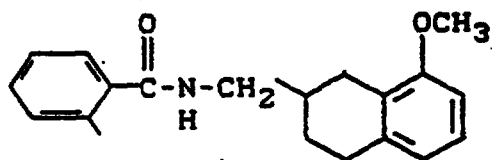
in which

R^9 - represents phenyl or ethoxy

R^{10} - represents phenyl or naphthyl, which may be substituted by fluorine or

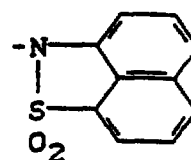
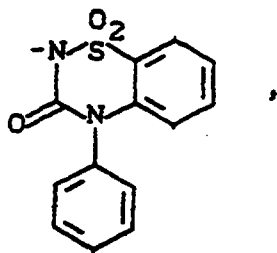
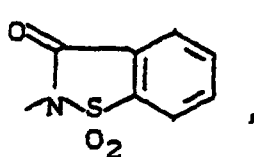
- represents methyl [lacuna]

5 - for a group of the formula

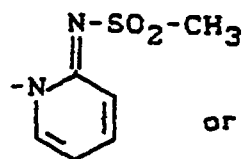
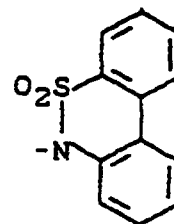
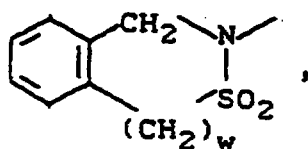
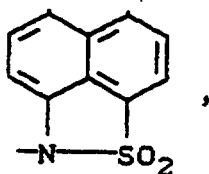


or

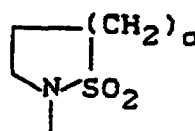
R^2 and R^3 together with the nitrogen atom form a hetero cycle of the formula



10



or



where

w - denotes a number 0, 1 or 2 and

o - denotes a number 1 or 2,

R¹ - denotes hydrogen, methyl, propyl or benzyl or

5 - denotes a group $-(Y^1-Z^1)$, where Y¹ and Z¹ may be identical or different to Y and Z and have the abovementioned meaning of Y and Z

A and D represent a group of the formula $-\text{CH}_2-$, oxygen or the CH or N part of a C=C [lacuna] C=N double bond, with the proviso that either only A or only D may represent oxygen,

10 B - represents a group of the formula

>CH_2 or >CH or the CH part of a C=C or C=N double bond,

C - represents a group of the formula >CH or the C part of a C=C or C=N double bond,

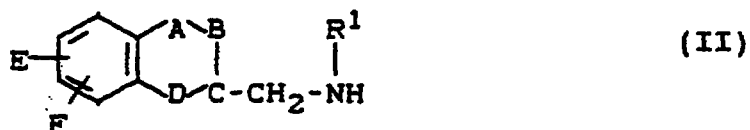
15 E and F are identical or different and represent hydrogen, ethoxy, methoxy, fluorine, cyano or a group of the formula $-\text{CONR}^2\text{R}^3$, in which R² and R³ denote hydrogen,

[lacuna]

20 E and F together form a cyclohexane or phenyl ring, and their salts.

Processes for the preparation of the compounds of the general formula (I) according to the invention have furthermore been found, characterized in that

25 [A] compounds of the general formula (II)



in which

A, B, C, D, E, F and R¹ have the abovementioned meaning,

5 (A1) are reacted with alkylating agents of the formula (III)



in which

Y and Z have the abovementioned meanings,
with the provisos that

10 Z does not represent amino and
R² does not represent hydrogen if
R³ represents alkyl or aryl,

and

L denotes a leaving group for alkylating agents

15 or

(A2) are reductively alkylated using aldehydes of the
formula (IV)



in which

20 Z has the abovementioned meaning and Y² is an alkylene chain Y shortened by one methylene group,

or

(A3) are reacted with reactive acid derivatives of the general formula (V)



in which

- 5 Y^2 and Z have the meanings indicated under process variants (A1) and M denotes a leaving group for acylating agents,

and the corresponding acid amides are reduced using hydrogen in the presence of a catalyst, using boranes or
10 using complex metal hydrides,

or

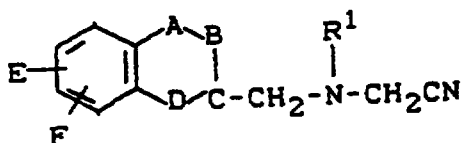
(A4) are alkylated using nitriles of the formula



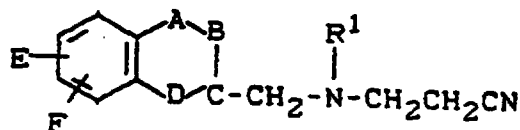
in which

- 15 G represents monochlorinated lower alkyl (C_1 to C_3), vinyl or lower alkyl (C_1 to C_3)- substituted vinyl,

to give compounds of the formula (VI) and (VII)



(VI)

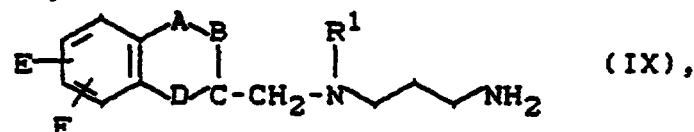
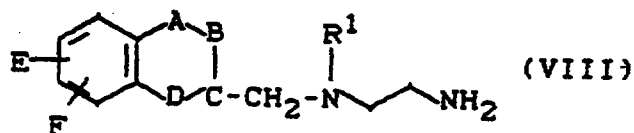


(VII),

in which

A , B , C , D , E , F and R^1 have the abovementioned meaning,

the nitriles obtained are hydrogenated to give the amines (VIII) and (IX)



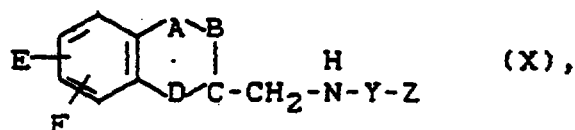
in which

A, B, C, D, E, F and R¹ have the abovementioned meaning,

- 5 and these are reacted in a manner known per se by alkylation, reductive alkylation, acylation, reaction with isocyanates or sulphonylations,

or in that

[B] compounds of the general formula (X)



- 10 in which

A, B, C, D, E, F, Y and Z have the abovementioned meanings,

with the provisos that

Z does not represent amino and

- 15 R² does not represent hydrogen if

R³ represents alkyl or aryl,

(B1) are alkylated using alkylating agents of the formula (XI)



in which

R^1 has the abovementioned meaning and

L denotes a leaving group for alkylating agents,

5 or

(B2) by reductively alkylating using aldehydes of the formula (XII)



10 in which R^{14} denotes a radical R^1 shortened by one methylene group,

or

(B3) are reacted with reactive acid derivatives of the general formula (XIII)



15 in which

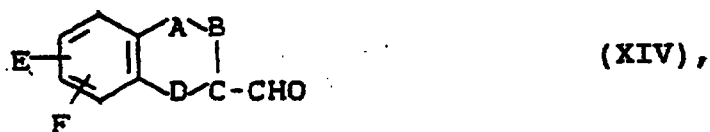
R^{14} has the abovementioned meaning and

M denotes a leaving group for acylating agents,

20 and the corresponding acid amides are reduced using hydrogen in the presence of a catalyst or using complex metal hydrides,

or in that

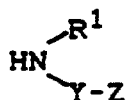
[C] aldehydes of the formula (XIV)



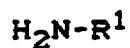
in which

A, B, C, D, E and F have the abovementioned meaning,

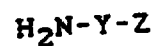
are reductively aminated using amines of the formula
(XV), (XVI) or (XVII)



(XV)



(XVI)



(XVII)

in which

R¹, Y and Z have the abovementioned meaning

with the provisos that

Z does not represent amino and

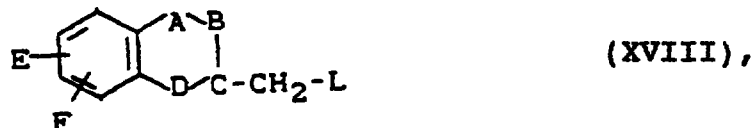
R² does not represent hydrogen if

R³ represents alkyl or aryl,

in a manner known per se,

or in that

[D] compounds of the general formula (XVIII)

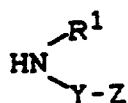


in which

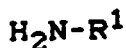
A, B, C, D, E and F and X have the abovementioned meaning and

L denotes a leaving group for alkylating agents,

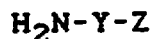
are reacted with amines of the formulae



(XV)



(XVI)



(XVII),

in which

5 R¹, Y and Z have the abovementioned meaning,

with the provisos that

Z does not represent amino and

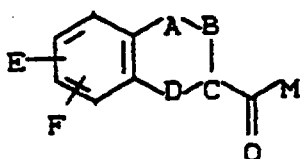
R² does not represent hydrogen if

R³ represents alkyl or aryl,

10 or reacted with an alkali metal azide and the azido function is subsequently reduced to an amino function,

or in that

15 [E] reactive carboxylic acid derivatives of the formula (XIX)



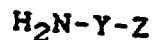
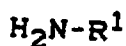
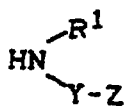
(XIX),

in which

A, B, C, D, E and F have the abovementioned meaning, and

20 M denotes a leaving group for acylating agents,

are reacted with amines of the formulae



(XV)

(XVI)

(XVII),

in which

R^1 , Y and Z have the abovementioned meaning,

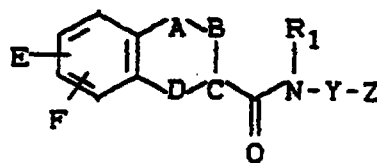
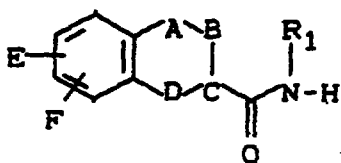
with the provisos that

5 Z does not represent amino and

R^2 does not represent hydrogen if

R^3 represents alkyl or aryl,

and the amides thus obtained of the formulae (XX)
and (XXI)



10

(XX)

(XXI),

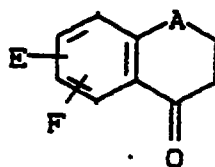
in which

A, B, C, D, E, F, R^1 , Y and Z have the abovementioned meaning,

15 are catalytically reduced using hydrogen, using
complex metal hydrides or using boranes,

or in that

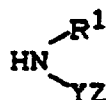
[F] compounds of the general formula (XXII)



(XXII),

in which A, E and F have the abovementioned meaning
are reacted with formaldehyde and amines of the
formula (XV)

5



(XV),

in which

R¹, Y and Z have the abovementioned meaning,

with the provisos that

10

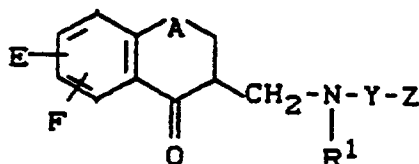
Z does not represent amino and

R² does not represent hydrogen if

R³ represents alkyl or aryl,

and the intermediates obtained of the general
formula (XXIII)

15



(XXIII),

in which

A, E, F, R¹, Y and Z have the abovementioned meaning

are further reacted by reduction of the carbonyl
function or by partial reduction of the carbonyl
function to the alcohol function, subsequent elimi-
nation of water and, if desired, hydrogenation of

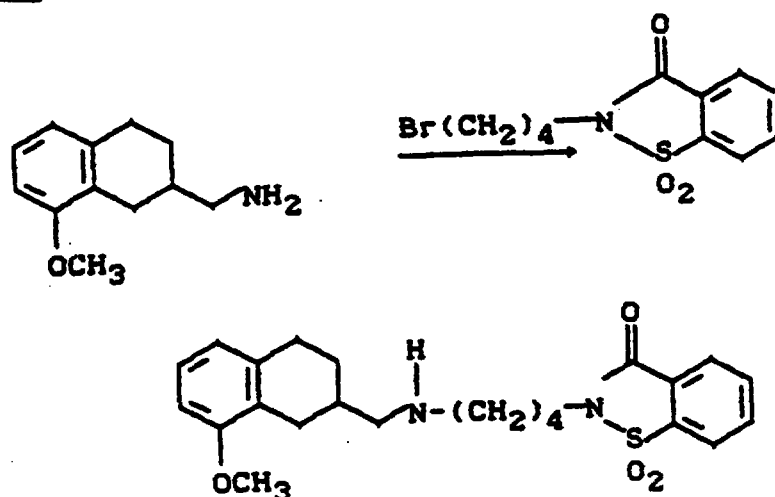
20

the C=C double bond using hydrogen.

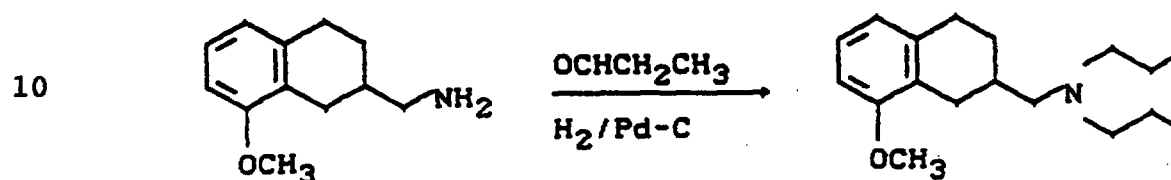
The equations below illustrate the processes for the preparation of the compounds of the general formula I according to the invention:

5 Process A:

Variant A1:



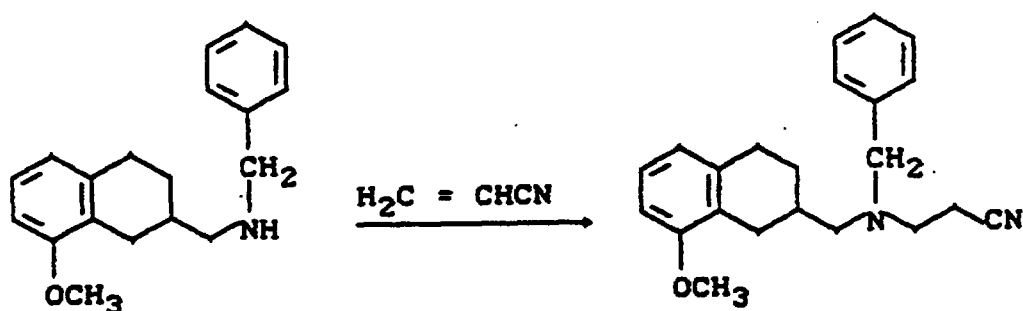
Variant A2:

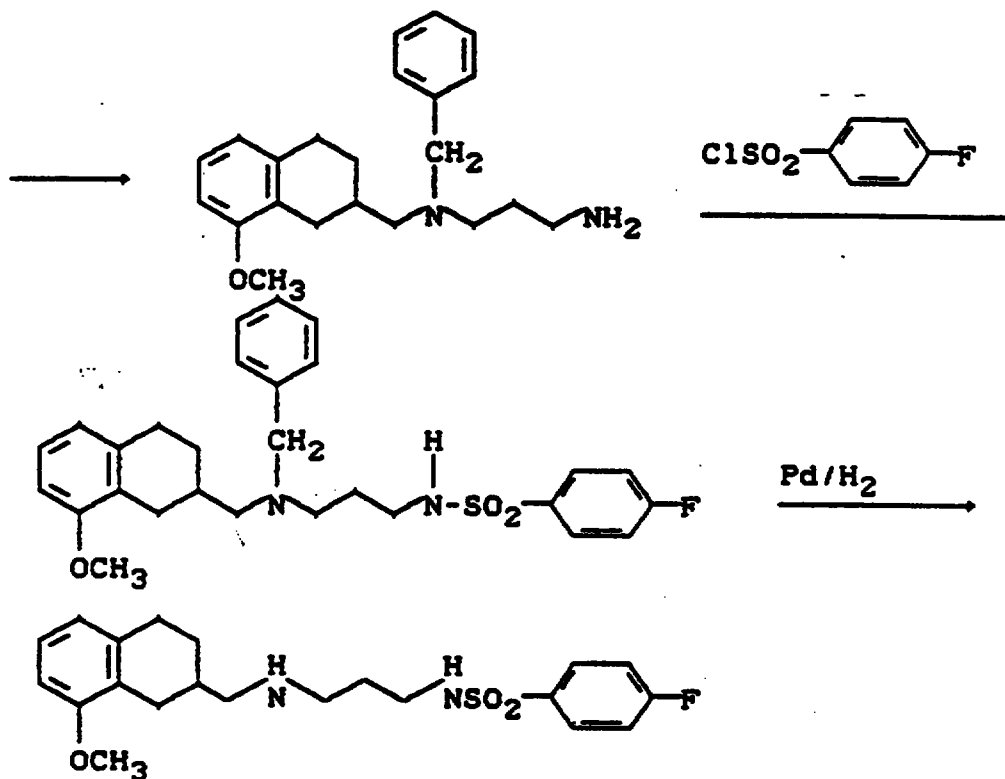


Variant A3:



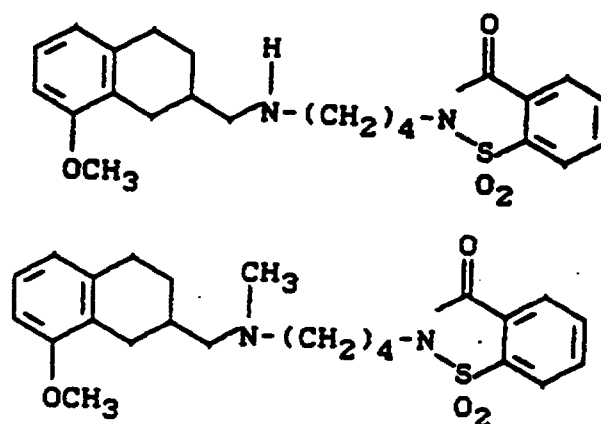
Variant A4:



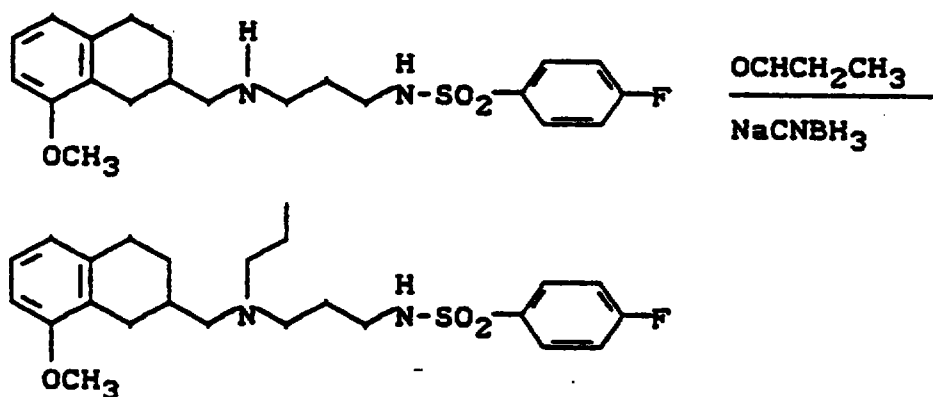


Process B:

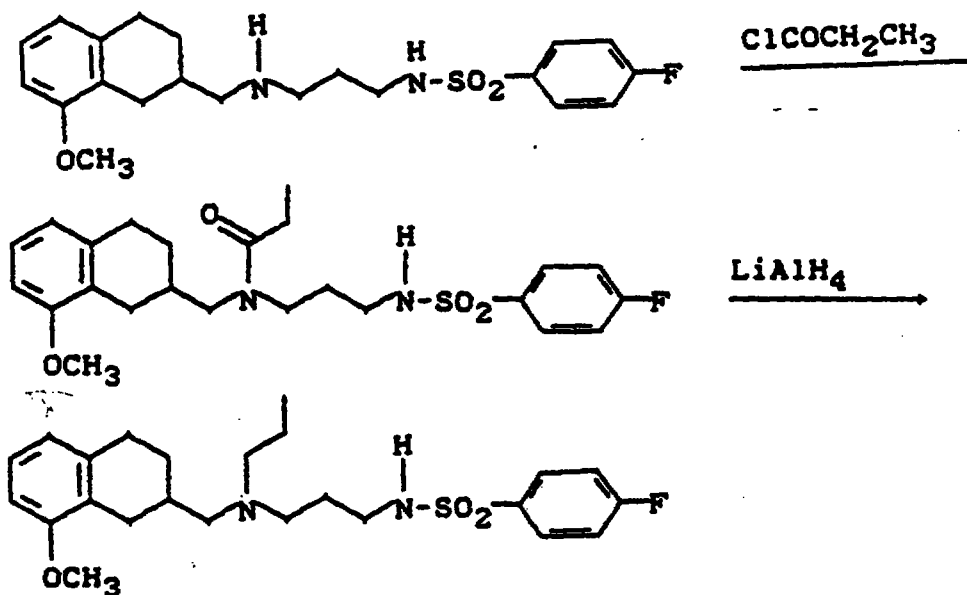
Variant B1:



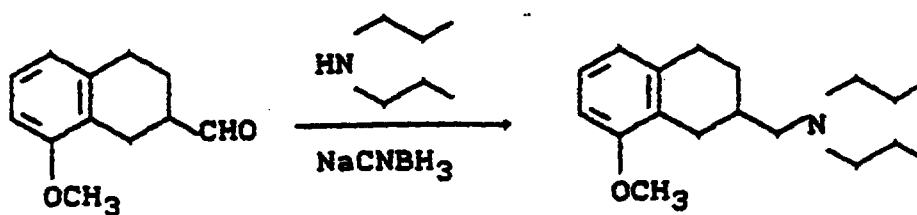
Variant B2:



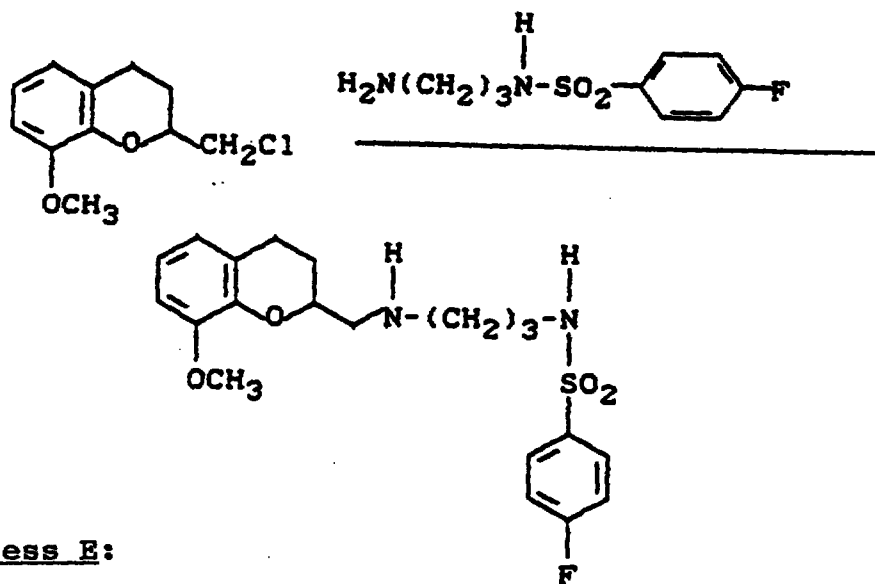
Variant B3:



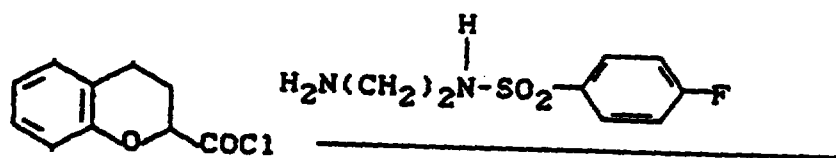
Process C:

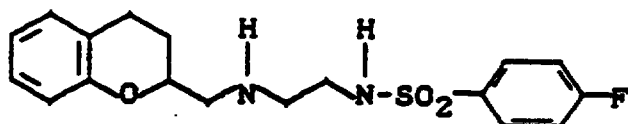
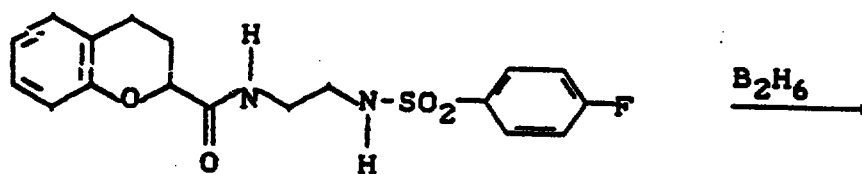


Process D:

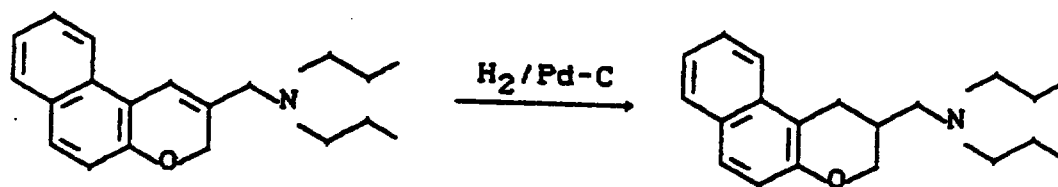
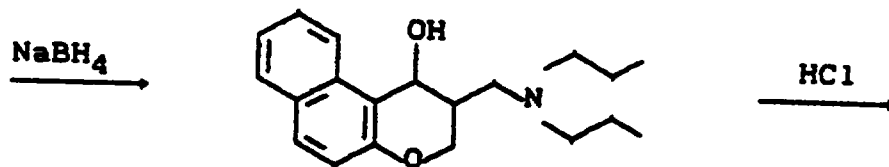
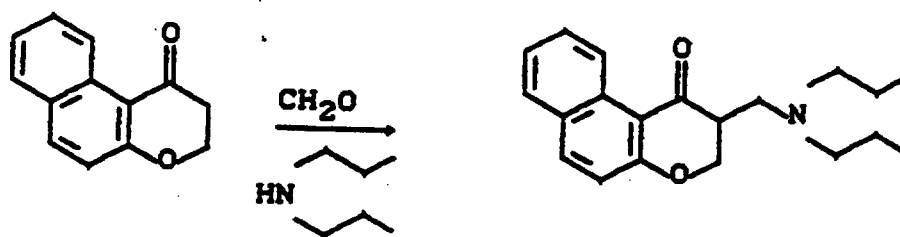


Process E:





Process F:



Diesterweg-Salle 1975). For example, chlorine, bromine, iodine, tosylate, mesylate or the group $-\text{OSO}_2\text{CF}_3$ may be mentioned here.

5 Leaving groups for acylating agents (M) are known per se (Lit. H.R. Christen, Grundlagen der organischen Chemie (Fundamentals of Organic Chemistry), Sauerländer-Diesterweg-Salle 1975). For example, chlorine, bromine, alkoxy(C_1 to C_4), aryloxy, imidazolyl, thiazolyl, methane-sulphonyloxy or alkoxy(C_1 to C_4)carbonyl may be mentioned
10 here.

The reaction is in general carried out in a temperature range from 0°C to $+150^\circ\text{C}$, preferably in a range from room temperature to $+80^\circ\text{C}$.

15 The reaction is in general carried out at atmospheric pressure. However it is also possible to carry out the reaction at elevated or reduced pressure.

Reaction accelerators employed are in general alkali metal iodides, sodium iodide or potassium iodide being preferred.

20 In this connection, the base is employed in an amount from 1 to 5, preferably from 1 to 2, moles relative to 1 mole of the halogen compound. The halogen compound is preferably employed in up to a 10-fold, preferably in up to a 5-fold, excess amount over the compounds of the
25 formula (II) or (X).

The reductive alkylation of the amines (II) and (X) with the aldehydes (IV) and (XII) is in general carried out in one step. If the amine (II) is a primary amine, the reaction can also be carried out in two steps, a Schiff's
30 base or an enamine being obtained first.

The preparation of the Schiff's bases or enamines in the first step is carried out in inert organic solvents, if

appropriate in the presence of a catalyst and if appropriate in the presence of a water-binding agent. The process according to the invention may be carried out in two steps, i.e. with isolation of the intermediates. It is also possible to carry out the reduction as a one-pot process.

In this connection, suitable inert solvents are the customary organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, butyl methyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol diethyl ether, or halogenated hydrocarbons such as, for example, methylene chloride, chloroform or carbon tetrachloride, or hydrocarbons such as benzene, toluene, xylene, or mineral oil fractions, or amides such as dimethylformamide or hexamethylphosphoramide or acetic acid. In addition, it is possible to use mixtures of the solvents mentioned.

Protonic acids are in general used as catalysts. These preferably include inorganic acids such as, for example, hydrochloric acid or sulphuric acid, or organic carboxylic acids having 1-6 C atoms, optionally substituted by fluorine, chlorine and/or bromine, such as, for example, acetic acid, trifluoroacetic acid, trichloroacetic acid or propionic acid, or sulphonic acids having C₁-C₄-alkyl radicals or having aryl radicals such as, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or toluenesulphonic acid.

The water formed in the reaction may optionally be removed during or after the reaction mixed with the solvent used, for example by distillation or by addition of water-binding agents, such as, for example, phosphorus pentoxide or preferably by molecular sieve.

The reaction is in general carried out in a temperature

range from 0°C to 150°C, preferably from +20°C to +100°C.

The reaction can be carried out at normal, elevated and at reduced pressure (for example 0.5-5 bar). In general, the reaction is carried out at atmospheric pressure.

- 5 When carrying out the reaction, the compound (XV) is employed in an amount from 0.1-10, preferably from 0.5-5, moles relative to 1 mole of the compounds (II) or (X).

- 10 The reduction of the Schiff's bases or enamines in the second step is carried out either by means of hydrogen in water or in inert organic solvents such as alcohols, ethers or halogenated hydrocarbons, or their mixtures, using catalysts such as Raney nickel, palladium, palladium on animal charcoal or platinum, or using hydrides in inert solvents, if appropriate in the presence of a catalyst.

- 15 Preferably, the reaction is carried out using hydrides, such as complex borohydrides or aluminium hydrides. Sodium borohydride, lithium aluminium hydride or sodium cyanoborohydride are particularly preferably employed in this connection.

- 20 Suitable solvents in this connection are all inert organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether, or diethylene glycol dimethyl ether or amides such as hexamethylphosphoramide or dimethylformamide, or acetic acid. It is also possible to use mixtures of the solvents mentioned.

- 30 Protonic acids are in general used as catalysts in the reduction with sodium cyanoborohydride. These preferably include inorganic acids such as, for example, hydrochloric acid or sulphuric acid, or organic carboxylic

acids having 1-6 C atoms, optionally substituted by fluorine, chlorine and/or bromine, such as, for example, acetic acid, trifluoroacetic acid, trichloroacetic acid or propionic acid, or sulphonic acids having C_1 - C_4 -alkyl radicals or having aryl radicals such as, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or toluenesulphonic acid.

When carrying out the process according to the invention, it has proved favourable to carry out the reaction of the aldehydes (IV) and (XII) with the amines (II) and (X) in an inert solvent, preferably in acetic acid or alcohols, such as, for example, methanol, ethanol, propanol or isopropanol or their mixtures, in the presence of inorganic or organic acids such as, for example, hydrochloric acid or acetic acid, and in the presence of a reducing agent, preferably of complex hydrides such as, for example, sodium borohydride or sodium cyanoborohydride, if appropriate in the presence of a dehydrating agent, preferably molecular sieve, as a one-pot process.

In this case, the reaction is carried out in a temperature range from 0°C to +150°C, preferably from 0°C to +100°C at atmospheric pressure. It is also possible to carry out the reaction at subatmospheric pressure or at excess pressure (for example in a bomb tube).

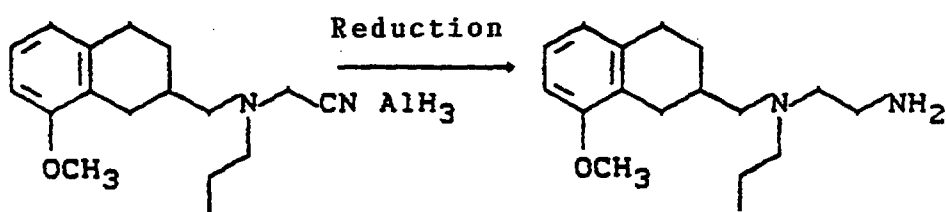
The conversion of functional groups into other functional groups in the abovementioned preparation processes is carried out, depending on the functional groups, by oxidation, reduction, hydrolysis or by reaction with electrophilic reagents and is illustrated in the following.

1. The reduction of the nitrile group to the amino group is in general carried out using metal hydrides, preferably using lithium aluminium hydride, aluminium hydride (prepared, for example, by reaction of lithium aluminium hydride with 100%

strength sulphuric acid or with aluminium chloride) or their mixtures in inert solvents such as ethers or chlorinated hydrocarbons, preferably in ethers such as, for example, tetrahydrofuran, diethyl ether or dioxane in a temperature range from -20°C to +100°C, preferably from 0°C to +50°C, at atmospheric pressure.

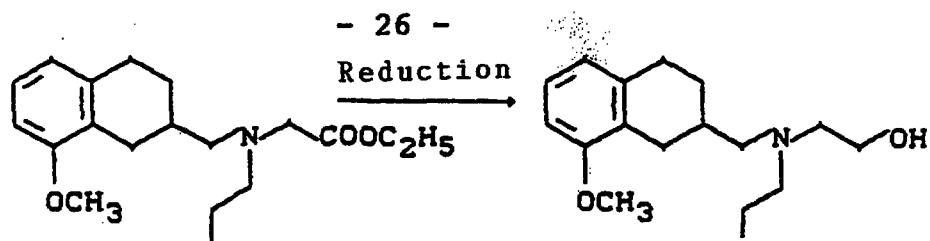
The reduction is additionally possible by hydrogenating the nitriles in inert solvents such as alcohols, for example methanol, ethanol, propanol or isopropanol in the presence of a noble metal catalyst such as platinum, palladium, palladium on animal charcoal or Raney nickel, in a temperature range from 0°C to +150°C, preferably from room temperature to +100°C, at atmospheric pressure or at excess pressure.

The reaction can be illustrated by the following equation:



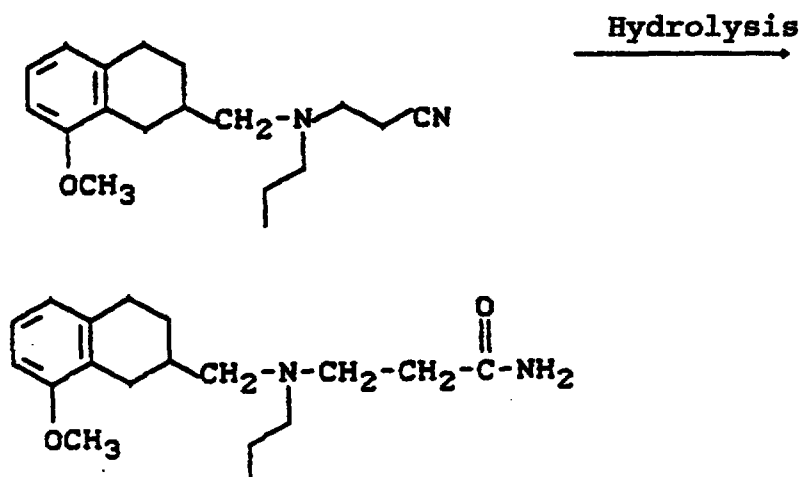
2. The reduction of alkoxy carbonyl groups to alcohol groups is in general carried out using hydrides, preferably using lithium aluminium hydride in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in ethers such as, for example, diethyl ether, tetrahydrofuran or dioxane in a temperature range from 0°C to +150°C, preferably from +20°C to +100°C, at atmospheric pressure.

The reaction can be illustrated by the following equation:



3. The hydrolysis of the nitrile group to the carboxamide group is in general carried out with the aid of strong mineral acids, preferably with hydrogen chloride in inert solvents such as water and/or alcohols such as, for example, methanol, ethanol, propanol or isopropanol in a temperature range from 0°C to +150°C, preferably from +20°C to +100°C, at atmospheric pressure.

The reaction can be illustrated by the following equation:



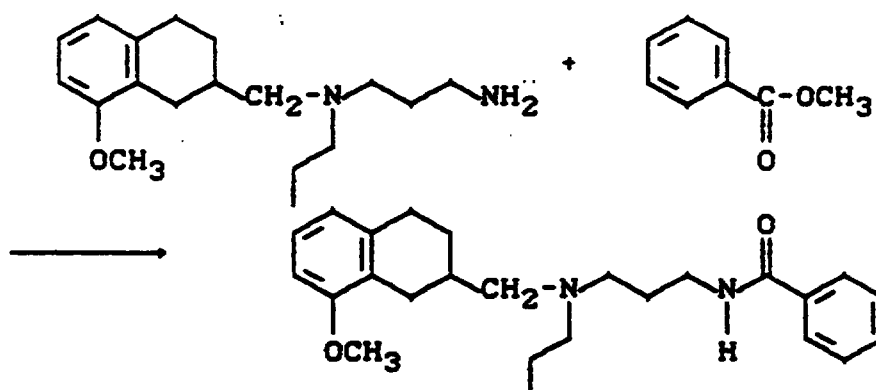
4. A large number of additional compounds according to the invention are obtained by reaction of NH- or OH-acidic compounds (Z in formula (I) is NR^2R^3 , where $\text{R}^2 = \text{H}$ and $\text{R}^3 = \text{H}$, alkyl, aryl or aralkyl), with electrophilic reagents:

- a) The conversion of amines to carboxamides is in general carried out by reaction with carboxylic acid esters in inert solvents such as ethers or their mixtures or hydrocarbons, preferably in

ethers such as, for example, diethyl ether, tetrahydrofuran or dioxane, if appropriate in the presence of bases such as alkali metals, alkali metal hydrides, alkali metal alkoxides or organolithium compounds, preferably in the presence of alkali metals, such as, for example, sodium or alkali metal hydrides such as sodium hydride or potassium hydride in a temperature range from +20°C to +150°C, preferably at the boiling point of the solvent used and at atmospheric pressure.

Moreover, it is possible to prepare the amides using carboxylic acid halides or anhydrides, preferably using carboxylic acid chlorides in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in ethers such as, for example, diethyl ether, tetrahydrofuran, or halogenated hydrocarbons such as methylene chloride or chloroform, if appropriate in the presence of bases such as alkali metal carbonates, for example sodium carbonate or potassium carbonate, or organic amines such as, for example, triethylamine or pyridine, in a temperature range from -20°C to +100°C, preferably from 0°C to +60°C, at atmospheric pressure.

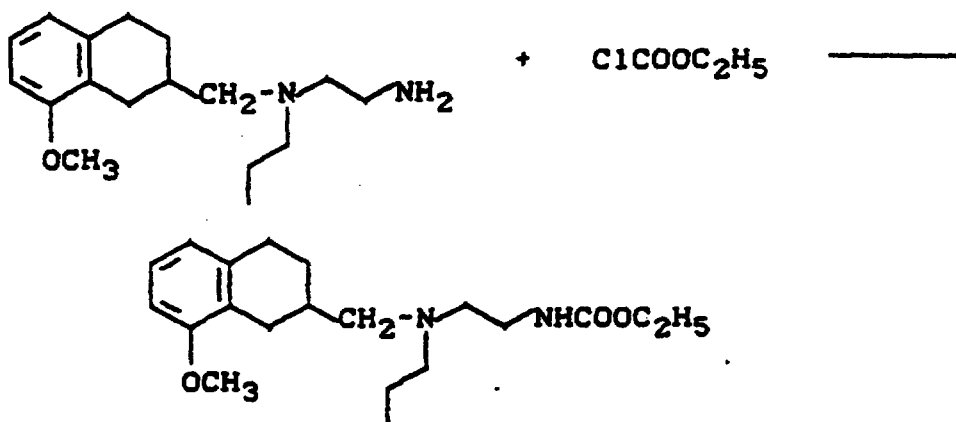
The reaction can be illustrated by the following equation:



b) The conversion of amines to carbamates is in

general carried out using carbonic acid esters, preferably using carbonic acid esters which carry a phenyl ester radical or using chlorocarbonic acid esters, in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in ethers such as, for example, diethyl ether, tetrahydrofuran or dioxane, in a temperature range from +20°C to +150°C, preferably from +20°C to +100°C, at atmospheric pressure. The reaction can also be carried out in a two-phase system, the aqueous phase containing an auxiliary base such as sodium carbonate or potassium carbonate or sodium hydrogen carbonate or potassium hydrogen carbonate.

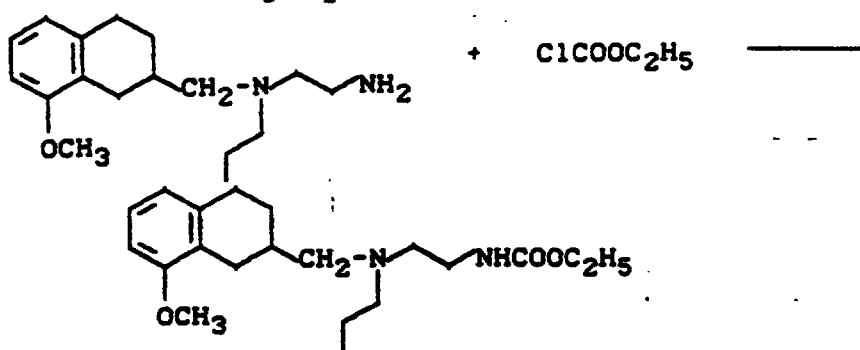
The reaction can be illustrated by the following equation:



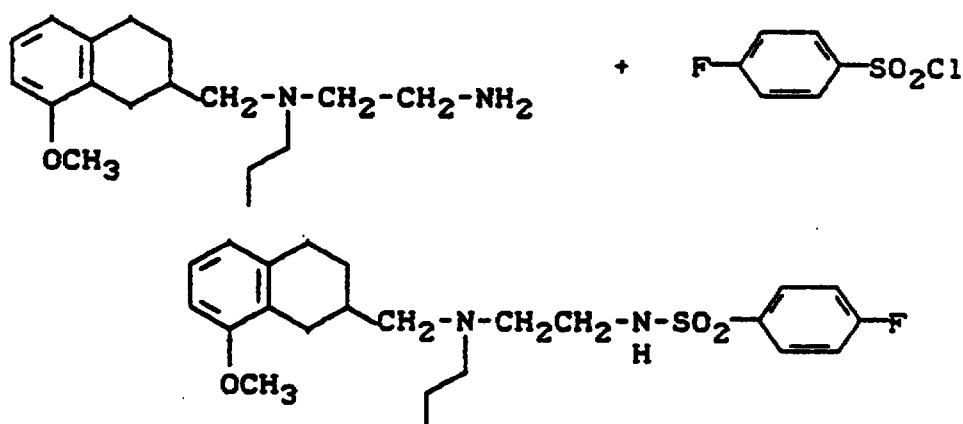
c) The conversion of amines into ureas is in general carried out by reaction with isocyanates in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in ethers such as, for example, diethyl ether or tetrahydrofuran, or in halogenated hydrocarbons such as, for example, methylene chloride or chloroform, in a temperature range from -20°C to +150°C, preferably from 0°C to +100°C, at atmospheric pressure.

The reaction can be illustrated by the

following equation:

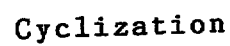


- 5 d) The conversion of amines to sulphonamides or aminosulphamoyl derivatives is in general carried out using sulphonyl halides or using amidosulphonyl halides, preferably using the corresponding chlorides in inert solvents such as ethers, hydrocarbons or halogenated hydrocarbons or their mixtures, preferably in halogenated hydrocarbons such as, for example, methylene chloride or chloroform, if appropriate in the presence of bases such as alkali metal hydroxides, alkali metal carbonates, alkali metal alkoxides or organic amines, preferably using alkali metal hydroxides such as sodium hydroxide or potassium hydroxide, alkali metal carbonates such as, for example, sodium carbonate or potassium carbonate, or organic amines such as triethylamine or pyridine, in a temperature range from -20°C to $+100^{\circ}\text{C}$, preferably from 0°C to $+50^{\circ}\text{C}$ at atmospheric pressure.



- e) Cyclic sulphonamides are in general prepared by

15



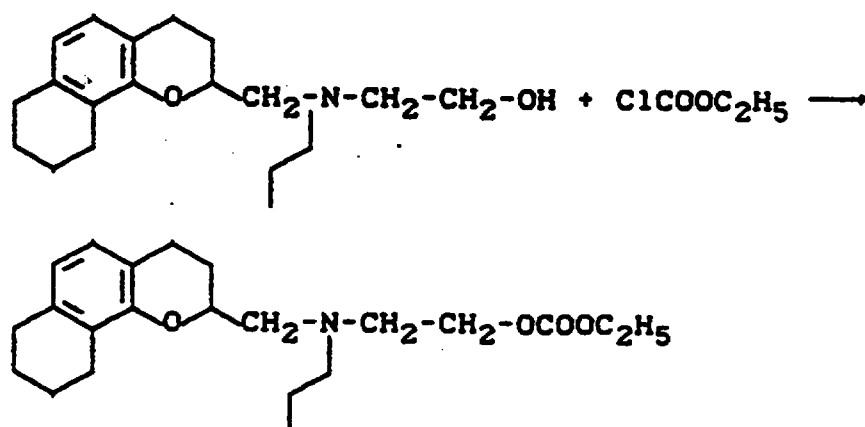
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tetrahydrofuran, if appropriate in the presence of bases such as alkali metal hydroxides, alkali metal carbonates or organic amines, preferably in the presence of organic amines such as triethylamine, pyridine, picoline or dimethylaminopyridines in a temperature range from -20°C to $+100^{\circ}\text{C}$, preferably from 0°C to room temperature at atmospheric pressure.

10

The reaction can be illustrated by the following equation:

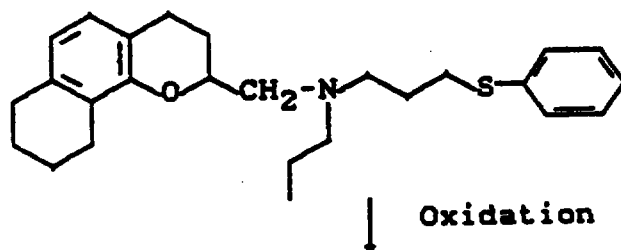


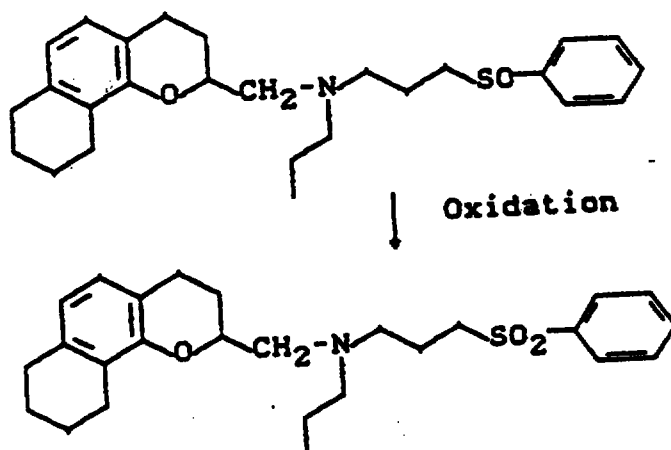
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5. The oxidation of the thioether group to sulfoxides or sulphones is in general carried out using oxidizing agents such as peroxo compounds or hydrogen peroxide itself, preferably using hydrogen peroxide, in inert solvents such as carboxylic acids and carboxylic acid anhydrides, preferably in acetic acid, in a temperature range from -20°C to $+100^{\circ}\text{C}$, preferably from 0°C to $+50^{\circ}\text{C}$.

20

The reaction can be illustrated by the following equation:





The amines of the general formula (XV), (XVI) and (XVII) employed as starting materials are known or can be prepared by known methods [Houben-Weyl's "Methoden der organischen Chemie" ("Methods of Organic Chemistry") volume XI/1 and XI/2).

Amines which can be used, for example, according to the invention are:

ammonia, methylamine, ethylamine, propylamine, isopropylamine, butylamine, 4-dimethylaminobutylamine, 4-diethylaminobutylamine, 3-dimethylaminopropylamine, 3-diethylaminopropylamine, 2-dimethylaminoethylamine, 2-diethylaminoethylamine, 2-amino-1-ethoxycarbonylamidoethane, 3-amino-1-ethoxycarbonylamidopropane, 4-amino-1-ethoxycarbonylamidobutane, 3-aminoquinuclidine, 2-[(phenylaminocarbonyl)amino]ethylamine, 2-[(phenylaminocarbonyl)amino]propylamine, 4-aminomethylpiperidine, 4-(ethoxycarbonyl)aminoethylpiperidine, N-methylpiperazine, 4-amino-1-carboxyethylpiperidine, N,N-dimethylpropylidenediamine, N,N-diethylpropylidenediamine, N,N-diethylethylidenediamine, N,N-dimethylethylenediamine, N-(2-aminoethyl)ethyl carbamate or N-(2-aminoethyl)propyl carbamate.

The reactions of the compounds of the general formula (XIX), (XXII) and (XIV) are carried out using amines of the general formula (XV), (XVI) and (XVII) in inert

organic solvents, if appropriate in the presence of a catalyst and if appropriate in the presence of water-binding agents.

5 Suitable inert solvents in this connection are the customary organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, butyl methyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or
10 diethylene glycol dimethyl ether, or halogenated hydrocarbons such as, for example, methylene chloride, chloroform or carbon tetrachloride, or hydrocarbons such as benzene, toluene, xylene, or mineral oil fractions, or amides such as dimethylformamide or hexamethylphosphoramide, or acetic acid. In addition it is possible to use
15 mixtures of the solvents mentioned.

Acids are in general used as catalysts. These preferably include inorganic acids such as, for example, hydrochloric acid or sulphuric acid, or organic sulphonic or
20 carboxylic acids such as, for example, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid, toluenesulphonic acid, acetic acid or propionic acid.

The water formed in the reaction can optionally be removed during or after the reaction mixed with the
25 solvent used, for example by distillation or by addition of water-binding agents, such as, for example, phosphorus pentoxide or preferably by molecular sieve.

The reactions are in general carried out in a temperature range from 0°C to +150°C, preferably from +20°C to +100°C.

30 The reaction can be carried out at atmospheric, elevated or at reduced pressure (for example 0.5-5 bar). In general, the reaction is carried out at atmospheric pressure.

The reductions of the compounds of the formulae (XX), (XXI) and (XXIII) are carried out either by means of hydrogen in water or inert organic solvents such as alcohols, ethers or halogenated hydrocarbons, or their mixtures, using catalysts such as Raney nickel, palladium, palladium on animal charcoal or platinum, or else using hydrides in inert solvents, if appropriate in the presence of a catalyst.

The reactions are preferably carried out using hydrides, such as complex borohydrides or aluminium hydrides. Sodium borohydride, lithium aluminium hydride, sodium cyanoborohydride or hydroboric acid are particularly preferably employed in this connection.

Suitable solvents in this connection are all inert organic solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or diethylene glycol dimethyl ether, or amides such as hexamethylphosphoramide, or dimethylformamide or acetic acid. It is also possible to use mixtures of the solvents mentioned.

Acids are in general used as catalysts in the reduction with sodium cyanoborohydride. These preferably include inorganic acids such as, for example, hydrochloric acid or sulphuric acid or organic carboxylic acids or sulphonic acids, such as, for example, acetic acid, trifluoroacetic acid, trichloroacetic acid, methanesulphonic acid, ethanesulphonic acid, benzenesulphonic acid or toluenesulphonic acid.

The reduction of the acid amides is carried out either by means of hydrogen in water or inert organic solvents in alcohols, ethers or halogenated hydrocarbons or their mixtures, using catalysts such as Raney nickel, palladium, palladium on animal charcoal or platinum, or

else using hydrides in inert solvents, if appropriate in the presence of a catalyst, or using boranes, diboranes or their complex compounds.

5 The reactions are preferably carried out using hydrides, such as complex borohydrides or aluminium hydrides. Sodium borohydride, lithium aluminium hydride, sodium cyanoborohydride or hydroboric acid are particularly preferably employed in this connection.

10 The compounds of the general formula (XIX) are known per se or can be prepared by customary methods (J. Med. Chem. 1972, 15, 8650, J. Gen. Chem. (USSR) 36, 3856 (1960)).

15 The compounds of the formula (XXII) are known or can be prepared by customary methods (J. Med. Chem., 1972, 15, No. 8, Publs. Soc. Chim. Tr. 1958, 325, J. Am. Chem. Soc. (9, 2341, 1947)).

20 The halogen compounds of the general formulae (III) and (XI) are known or can be prepared by known methods [Beilstein's Handbuch der organischen Chemie (Beilstein's Handbook of Organic Chemistry) 2, 197, 201, 250, 278; 3, 9, 10; 21, 461, 462, 463].

Halogen compounds which can be used, for example, according to the invention are:
chloroacetonitrile, 2-chloropropionitrile, 3-chlorobutyronitrile, 3-bromopropylphthalimide, 3-chloropropylphthalimide, 2-bromoethylphthalimide, 4-bromobutylphthalimide, 4-chlorobutylphthalimide, N,N-diethylchloroacetamide, N,N-dimethylchloroacetamide, methyl chloroacetate, ethyl chloroacetate, ethyl bromoacetate, methyl bromoacetate, 2- δ -bromobutyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide or 2- γ -bromopropyl-1,2-benzisothiazol-3(2H)-one-1,1-dioxide.

25
30

The aldehydes of the general formulae (IV) and (XII) employed as starting materials are known or can be

prepared by known methods [Beilstein's Handbuch der organischen Chemie (Beilstein's Handbook of Organic Chemistry) 1, 594, 629, 662].

5 Aldehydes which can be used, for example, according to the invention are:
acetaldehyde, propionaldehyde, butyraldehyde or benzaldehyde.

The compounds according to the invention can be used as active compounds in medicaments.

10 The substances according to the invention have a particularly high affinity for cerebral 5-hydroxytryptamine receptors of the 5-HT₁ type.

15 They have agonistic, partially agonistic or antagonistic effects on the serotonin receptor. In comparison to the structurally related known compounds, they surprisingly exhibit a greater therapeutic breadth.

20 The high-affinity ligands for the serotonin-1 receptor described in the present invention thus represent active compounds for controlling diseases which are characterized by disturbances of the serotonergic system, in particular with involvement of receptors which have a high affinity for 5-hydroxytryptamine (5-HT₁ type). They are therefore suitable for the treatment of disorders of the central nervous system such as anxiety, tension and
25 depression states, sexual dysfunctions caused by the central nervous system and disturbances in sleep and the absorption of food. Furthermore, they are suitable for eliminating cognitive deficiencies, for improving powers of learning and memory and for treating Alzheimer's
30 disease.

Furthermore, these active compounds are also suitable for the modulation of the cardiovascular system. They also intervene in the regulation of the cerebral circulation

and thus represent effective agents for controlling migraine.

They are also suitable for the prophylaxis and control of the effects of occurrences of cerebral infarct (Apoplexia cerebri) such as stroke or cerebral ischaemia. The compounds according to the invention can also be employed for the control of pain states. They are also suitable for the control of disorders of the intestinal tract which are characterized by disturbances of the serotoninergic system and also by disturbances of the carbohydrate metabolism.

The new active compounds may be converted in a known manner into the customary formulations, such as tablets, coated tablets, pills, granules, aerosols, syrups, emulsions, suspensions and solutions, using inert, non-toxic, pharmaceutically suitable excipients or solvents. In this connection, the therapeutically active compound should in each case be present in a concentration from about 0.5 to 90% by weight of the total mixture, i.e. in amounts which are sufficient in order to achieve the dosage range indicated.

The formulations are prepared, for example, by extending the active compounds using solvents and/or excipients, if appropriate using emulsifiers and/or dispersants, where, for example, in the case of the use of water as a diluent if appropriate organic solvents may be used as auxiliary solvents.

Auxiliaries which may be mentioned, for example, are: water, non-toxic organic solvents, such as paraffins (for example mineral oil fractions), vegetable oils (for example groundnut/sesame oil), alcohols (for example: ethyl alcohol, glycerol), excipients, such as, for example, ground natural minerals (for example kaolins, aluminas, talc, chalk), ground synthetic minerals (for example highly disperse silica, silicates), sugar (for

example sucrose, lactose and dextrose), emulsifiers (for example polyoxyethylene fatty acid esters, polyoxyethylene fatty alcohol ethers), dispersants (for example lignin, sulphite waste liquors, methylcellulose, starch and polyvinyl-pyrrolidone) and lubricants (for example magnesium stearate, talc, stearic acid and sodium sulphate).

Administration takes place in a customary manner, preferably orally or parenterally, in particular perlingually or intravenously. In the case of oral administration, tablets may, of course, also contain additions, such as sodium citrate, calcium carbonate and dicalcium phosphate together with various additives, such as starch, preferably potato starch, gelatin and the like in addition to the excipients mentioned. Furthermore, lubricants, such as magnesium stearate, sodium lauryl sulphate and talc may additionally be used for tableting. In the case of aqueous suspensions, various flavour enhancers or colourants may be added to the active compounds in addition to the abovementioned auxiliaries.

In the case of parenteral administration, solutions of the active compounds may be employed using suitable liquid excipients.

In general, it has proved advantageous on intravenous administration to administer amounts of about 0.001 to 1 mg/kg, preferably about 0.01 to 0.5 mg/kg, of body weight to obtain effective results, and on oral administration the dosage is about 0.01 to 20 mg/kg, preferably 0.1 to 10 mg/kg, of body weight.

In spite of this, it may sometimes be necessary to depart from the amounts mentioned, depending on the body weight or the type of application route, on individual behaviour towards the medicament, the manner of its formulation and the point in time or interval at which administration takes place. Thus, in some cases it may be sufficient to

manage with less than the minimum amount previously mentioned, whereas in other cases the upper limit mentioned must be exceeded. In the case of the administration of larger amounts, it may be advisable to divide
5 these into a number of individual doses over the day.

Preparation examples

The R_f values were in each case determined - unless stated otherwise - by thin layer chromatography on silica gel (aluminium foil, silica gel 60 F 254, E. Merck).
10 Visualization of the substance streaks was carried out by examining under UV light and/or by spraying with 1% strength potassium permanganate solution.

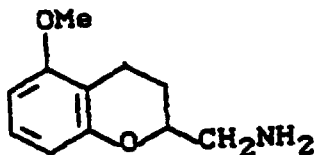
Flash chromatography was carried out on silica gel 60, 0.040-0.064 mm, E. Merck (see Still et al., J. Org. Chem. 43, 2923, 1978; for relatively simple separation problems see Aldrichimica Acta 18, 25, 1985).
15 Elution using solvent gradients means: beginning with the pure, non-polar solvent mixture component, the polar eluent component is admixed to an increasing extent until
20 the desired product is eluted (TLC checking).

In all products, the solvent was finally distilled off at 13.3 Pa (0.1 torr). Salts were stored at this pressure overnight over potassium hydroxide and/or phosphorus pentoxide.

25 Starting compounds and preparation examples

Example 1

2-Aminomethyl-5-methoxy-chroman



0.85 g (4.1 mmol) of 2-carboxamido-5-methoxy-chroman in

5 ml of THF was added dropwise to a boiling suspension of 0.30 g (8.2 mmol) of lithium aluminium hydride in 5 ml of THF. After heating to reflux for 3 h, the mixture was cooled and 0.3 ml of water and 0.5 ml of 20% sodium hydroxide solution were successively added. Filtration over kieselguhr and concentration gave 0.62 g of crude product which was purified by flash chromatography (toluene-ethyl acetate, then ethanol gradients).

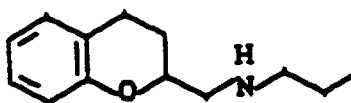
Yield: 0.52 g (66%)

10 R_f : (toluene/methanol 4:1) = 0.16

IR (CHCl_3): 3389, 3009, 2947, 1607, 1593, 1470.

Example 2

2-(N-Propyl)aminomethyl-chroman

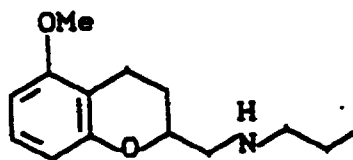


15 The compound was prepared analogously to the directions of Example 1.

IR (CHCl_3): 3320 (broad), 3010, 2965, 2879, 1607, 1584, 1490, 1457, 1235.

Example 3

20 2-(N-Propyl)aminomethyl-5-methoxy-chroman



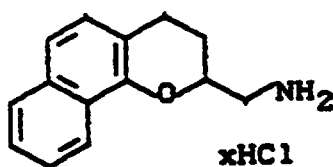
The compound was prepared analogously to the directions of Example 1.

25 $^1\text{H-NMR}$ (CDCl_3): 0.85 (t; 3H), 1.55 (quint.; 3H), 1.7 (m; 1H), 2.0 (m;

1H), 2.5-3.0 (m; 6H), 3.7
(s; 3H), 4.1 (m, 1H), 6.4
(d; 1H), 6.5 (d; 1H), 7.0
(t, 1H).

5 Example 4

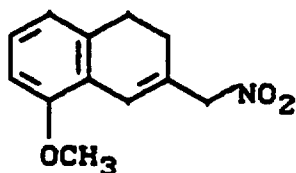
2-Aminomethyl-benzo(h)chroman hydrochloride



The compound was prepared analogously to Example 24 from 2-carboxamido-benzo(h)chroman.

10 Example 5

1-Methoxy-5,6-dihydro-7-nitromethyl-naphthalene



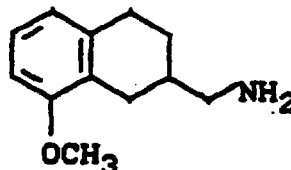
44.1 g of 8-methoxy-2-tetralone (0.25 mol) were stirred at 70°C under argon for 3 h in 402 ml of nitromethane (7.50 mol) and 2.5 ml of ethylenediamine. After the mixture has cooled to room temperature, a yellow crystallate is filtered off with suction. The nitromethane is distilled off from the solution in vacuo. The residue is dissolved in 500 ml of toluene. The solvent is again distilled off in vacuo in order to remove nitromethane residues. The residue is then dissolved in 200 ml of toluene again. An insoluble component is filtered off and the solution is concentrated to 50 ml. The concentrated solution is then chromatographed on 500 g of silica gel using toluene. After concentrating the main fraction, the final product is obtained as a yellow oil.

Yield: 40.4 g = 73% of theory

R_f = 0.45

Example 6

2-Aminomethyl-8-methoxytetralin



5

14.9 g of the compound from Example 5 (68 mmol) are hydrogenated in 300 ml of methanol using elemental hydrogen. 3.4 g of palladium/active charcoal are employed as a catalyst. The temperature is limited to 25-30°C by slight cooling.

10

The catalyst is then filtered off with suction and the reaction solution is substantially concentrated in vacuo. 300 ml of toluene are then added and distilled off again in vacuo in order to remove methanol residues. The residue is again dissolved in 300 ml of toluene, and the solution is washed with 5% strength potassium carbonate solution and water. The organic phase is dried over sodium sulphate. The solvent is then again distilled off in vacuo.

15

The crude product is dissolved in 25 ml of toluene and the solution is applied to 60 g of silica gel 60 (Merck). The silica gel is first washed with toluene and the final product is then eluted using methanol/triethylamine 95:5. A pale yellow oil is obtained after concentrating the methanolic solution.

20

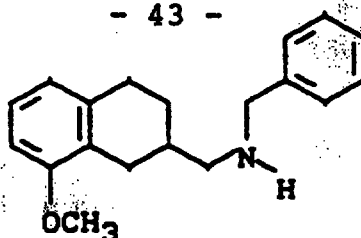
25

Yield: 9.5 g = 73% of theory

R_f : 0.28 (silica gel; methanol/triethylamine 95:5)

Example 7

2-(N-Benzyl)-aminomethyl-8-methoxytetralin



- 13.4 g of 2-aminoethyl-8-methoxytetralin (70 mmol) are dissolved in 420 ml of methanol. 3.0 ml of acetic acid (52.5 mmol) are then added dropwise. A further 5.3 g of sodium cyanoborohydride (84 mmol) are added after 5 min. The reaction solution is warmed to 60°C and a solution of 7.4 g of benzaldehyde (70 mmol) in 74 ml of methanol is then added dropwise in the course of 30 min. The mixture is then boiled under reflux for 3 h.
- 10 After cooling, the solvent is distilled off in vacuo and the residue is dissolved in 420 ml of dichloromethane and 210 ml of water. The organic phase is again washed with water and dried over sodium sulphate. The solvent is again distilled off in vacuo and the residue is stirred
- 15 with 700 ml of diethyl ether and 140 ml of 5N sodium hydroxide solution. The organic phase is washed with water until neutral and dried over sodium sulphate. The solvent is distilled off in vacuo.

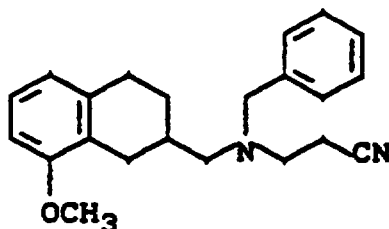
The residue is chromatographed on 200 g of silica gel 60 (Merck). Diisopropyl ether is used as the eluent. The final product in this case is obtained as a colourless viscous oil.

Yield: 11.7 g = 59% of theory

$R_f = 0.25$ (silica gel; toluene/methanol 95:5)

25 Example 8

2-[N-Benzyl-N-2'-cyanoethyl]-aminomethyl-8-methoxy-tetralin



11.7 g of the compound from Example 7 (41.6 mmol) and 0.15 g of copper acetate in 13.7 ml of acrylonitrile (208 mmol) were boiled under reflux for 2 h under argon. The mixture was then diluted using 7 ml of acrylonitrile.

- 5 After the mixture had slowly cooled to room temperature, it was cooled to 10°C after 2 h. The crystallisate was filtered off with suction and dried at 40°C in vacuo.

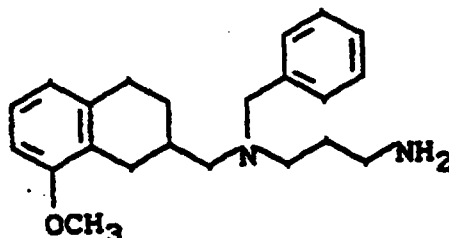
Yield: 10.6 g = 76% of theory

R_f = 0.77 (silica gel; toluene/methanol 95:5)

- 10 M.p.: = 111-112°C

Example 9

2-[N-Benzyl-N-3'-aminopropyl]-aminomethyl-8-methoxy-tetralin



- 15 4.8 g of lithium aluminium hydride (125.6 mmol) are suspended under argon in 315 ml of absolute diethyl ether. 10.5 g of the compound from Example 8 (31.4 mmol) are then introduced in portions in the course of 20 min. The temperature is in this case limited to 20-25°C by slight cooling. The mixture is then stirred at room temperature for a further 3 h.
- 20

A mixture of 260 ml of tetrahydrofuran and 15 ml of water is then added dropwise. The mixture is stirred for 30 min and the precipitate is then filtered off with suction.

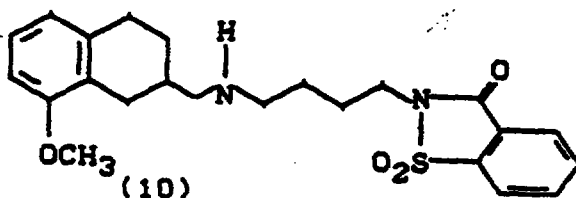
- 25 The solution is concentrated to 250 ml and stirred into 2.5 l of water. The mixture is extracted using toluene and the organic phase is washed until neutral and dried over sodium sulphate. After the solvent has been distilled off in vacuo, the final product remains as a pale yellow oil.
- 30

Yield: 10.1 g = 95% of theory

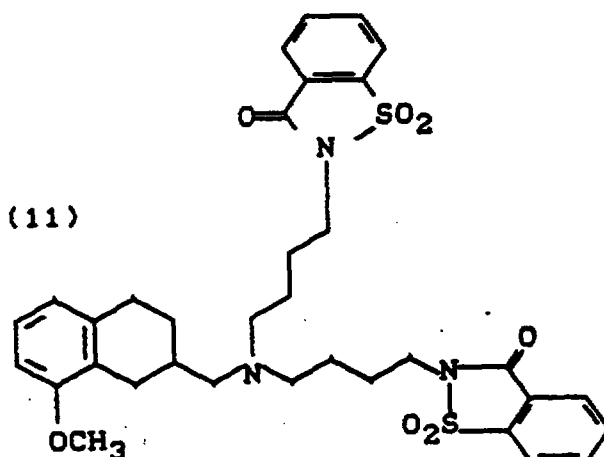
R_f = 0.32 (silica gel; methanol/toluene 95:5)

Example 10 and Example 11

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-8-methoxytetralin



2-{N-Di[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-8-methoxytetralin



- 0.95 g of 2-aminomethyl-8-methoxytetralin (5 mmol), 0.70 ml of triethylamine (5 mmol) and 1.59 g of 2-(4-bromo-butyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (5 mmol) are stirred at 40°C for 24 h in 19 ml of dimethylformamide. The reaction solution is then stirred into a mixture of 190 ml of 5% strength sodium chloride solution, 60 ml of toluene and 5 ml of 1N hydrochloric acid. After the organic phase has been separated off, the aqueous phase containing the final product precipitated as the resinous hydrochloride is stirred with 60 ml of toluene and 7 ml of triethylamine (50 mmol). The organic

phase is separated off again, washed until neutral with water and dried over sodium sulphate. The solvent is distilled off in vacuo. The residue is chromatographed on silica gel 60 (Merck). Toluene/methanol 85:15 is in this case used as the eluent. The main fractions contain the two final products as yellow, viscous oils.

Both bases can be precipitated as the hydrochloride from toluene solution using ethereal hydrogen chloride solution.

10 Example 10

Yield: 0.59 g = 28% of theory

R_f: 0.30 silica gel; (toluene/methanol 85:15)

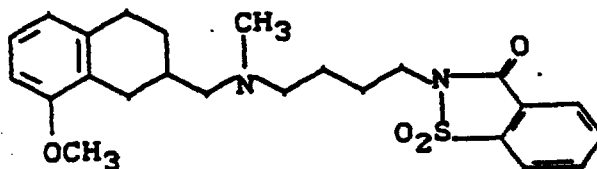
Example 11

Yield: 0.50 g = 15% of theory

15 R_f: 0.73 silica gel; (toluene/methanol 85:15)

Example 12

2-{N-Methyl-N[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-8-methoxytetralin



20 2.9 g of 2-aminomethyl-8-methoxytetralin (15 mmol) 2.1 ml of triethylamine (15 mmol) and 4.8 g of 2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide (15 mmol) are stirred at 40°C for 50 h in 58 ml of dimethylformamide. A solution of 1.4 g of methyl iodide (10 mmol) and 3.2 ml of dimethylformamide is then added dropwise and the mixture is stirred at 40°C for a further 18 h.

The reaction solution is then stirred into a mixture of 600 ml of water, 3.8 g of potassium carbonate (27.5 mmol) and 300 ml of toluene. The organic phase is washed with water until neutral and dried over sodium sulphate. The solvent is distilled off in vacuo.

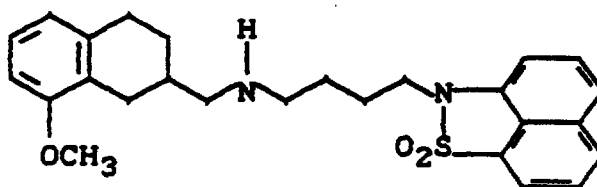
The residue is dissolved in a diisopropyl ether-toluene mixture (80:20) and prepurified by filtration through 20 g of silica gel. The final product is isolated from the residue obtained by distilling off the solvent by means of column chromatography on silica gel 60 (Merck). Ethyl acetate is in this case used as the eluent.

The hydrochloride can be precipitated from the toluene solution as a solid by using ethereal hydrogen chloride solution.

Yield: 0.85 = 12.9% of theory
 R_f = 0.25 (silica gel; ethyl acetate or toluene/methanol 95:5)

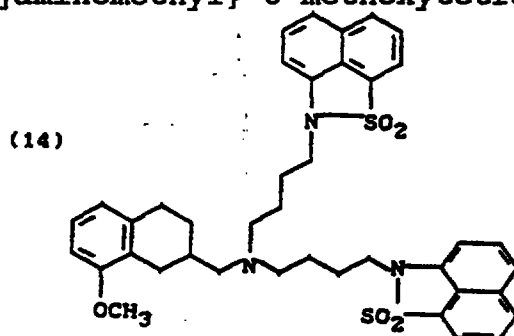
Example 13 and Example 14

2-{N-[4-(1,1-Dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)-butyl]aminomethyl}-8-methoxytetralin



(13)

2-{N-Di[4-(1,1-dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)butyl]aminomethyl}-8-methoxytetralin



(14)

1.6 g of 2-amino-8-methoxytetralin (8.4 mmol), 1.16 ml of triethylamine (8.4 mmol) and 1.59 g of 2-(4-bromobutyl)-2H-naphth[1,8-cd]isothiazole 1,1-dioxide are stirred for 48 h at 40°C in 32 ml of dimethylformamide. The reaction solution is then stirred into a mixture of 320 ml of 5% strength sodium chloride solution, 100 ml of toluene, 8.4 ml of 1N hydrochloric acid and kieselguhr. The kieselguhr containing the hydrochloride of the final product attached thereto is filtered off with suction - and introduced into a mixture of 300 ml of water and 100 ml of toluene. The final product is transferred to the organic phase by dropwise addition of 9 ml of 1N sodium hydroxide solution.

After filtration, the organic phase is separated off, washed with water until neutral and dried over sodium sulphate. After the solvent has been distilled off in vacuo, the residue is separated into the two final products by column chromatography on silica gel 60 (Merck). Ethyl acetate is in this case used as the eluent.

Both bases can be precipitated as the hydrochloride from ethereal solution using ethereal hydrogen chloride solution.

Example 13

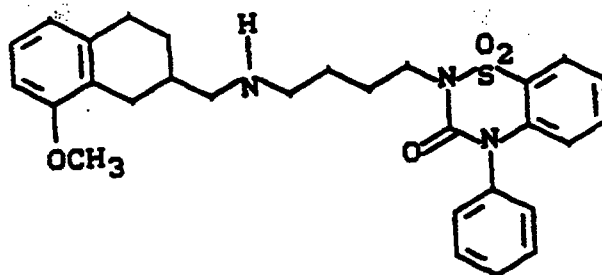
Yield: 1.51 g = 39.8% of theory
 $R_f = 0.28$

Example 14

Yield: 0.63 g = 10.6% of theory
 $R_f = 0.60$

Example 15

2-{N-[4-(1,1-Dioxido-3-oxo-4-phenyl-3,4-dihydro-2H-1,2,4-benzothiadin-2-yl)butyl]aminomethyl}-8-methoxytetralin



0.95 g of 2-aminomethyl-8-methoxytetralin (5 mmol), 0.70 ml of triethylamine (5 mmol) and 2.05 g of 2-(4-bromobutyl)-3-oxo-4-phenyl-3,4-dihydro-2H-1,2,4-benzothiadiazine 1,1-dioxide are stirred for 24 h at 40°C in 19 ml of dimethylformamide. The reaction solution is then stirred into a mixture of 190 ml of 5% strength sodium chloride solution, 60 ml of toluene and 5 ml of 1N hydrochloric acid. After the organic phase has been separated off, the aqueous phase containing the final product precipitated as the resinous hydrochloride is stirred with 60 ml of toluene and 7 ml of triethylamine (50 mmol). The organic phase is separated off again, washed until neutral with water and dried over sodium sulphate. The solvent is distilled off in vacuo. The residue is chromatographed on silica gel 60 (Merck). Toluene/methanol 85:15 is used as the eluent in this case.

The hydrochloride can be precipitated as a solid from the toluene solution using ethereal hydrogen chloride solution.

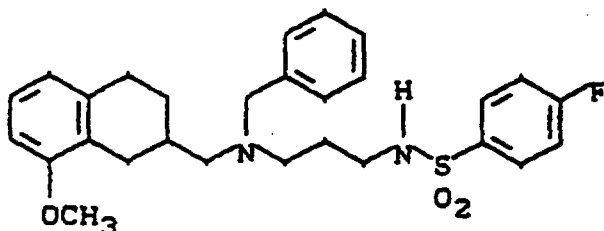
Yield: 0.83 g = 31.9% of theory

$R_f = 0.28$ (silica gel; toluene/methanol 85:15),

M.p.: -148°C

Example 16

2-{N-Benzyl-N-[3-(4-fluorophenylsulphonylamido)propyl]-aminomethyl}8-methoxytetralin



0.95 g (2.8 mmol) of the compound from Example 9 is dissolved in 19 ml of dichloromethane. After addition of 0.39 g (2.8 mmol) of finely ground potassium carbonate, a solution of 0.60 g of 4-fluorobenzenesulphonyl chloride and 9.5 ml of dichloromethane is added dropwise at 15-20°C. The reaction solution is then stirred at room temperature for a further 18 h.

15 ml of water are then added. The organic phase is washed until neutral with water, dried over sodium sulphate and concentrated in vacuo. The residue is dissolved in 50 ml of diisopropyl ether, and the solution is filtered. The solution is then again concentrated to about 10 ml and chromatographed on 25 g of silica gel. Diisopropyl ether is used as the eluent. The final product is obtained as a pale brown viscous oil.

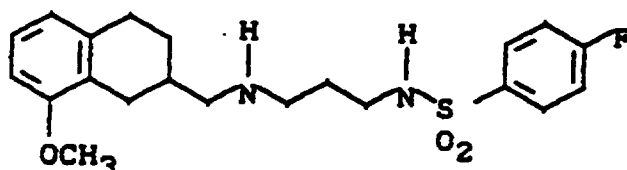
Yield: 1.08 g = 78% of theory

R_f = 0.58 (silica gel; toluene/methanol 95:5)

R_f = 0.23 (silica gel; diisopropyl ether)

Example 17

20 2-{N-[3-(4-Fluorophenylsulphonylamido)propyl]amino-methyl}8-methoxytetralin



1.0 g of the compound from Example 16 (2 mmol) is hydrogenated in 50 ml of methanol and 2.4 ml of methanolic hydrogen chloride solution (0.9 mmol/ml) using elemental hydrogen. 0.1 g of palladium/activated charcoal is employed as the catalyst.

The catalyst is then filtered off and the solution is concentrated to 10 ml in vacuo. The solution is then

5

10

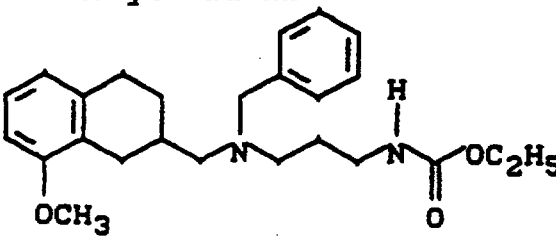
Yield: 0.47 g = 58% of theory

$R_f = 0.25$ (silica gel; toluene/methanol 85:15)

15

Example 18

2-{N-Benzyl-N-[3-(ethoxycarbonylamido)propyl]amino-
methyl}8-methoxytetralin



20

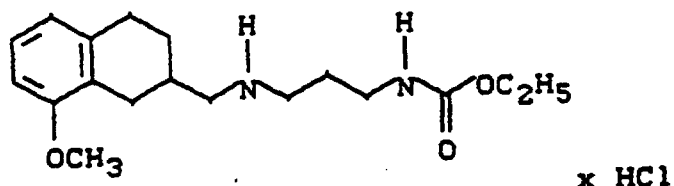
Yield: 2.00 g = 92% of theory

25

$R_f = 0.30$ (silica gel; diisopropyl ether)

Example 19

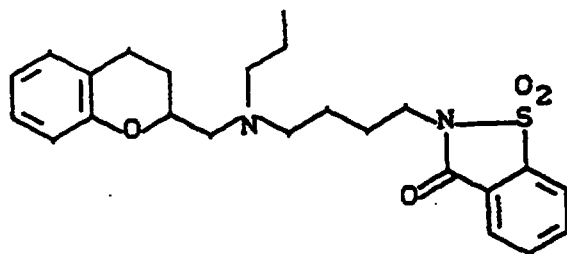
2-{N-[3-(Ethoxycarbonylamido)propyl]aminomethyl}-8-methoxytetralin



- 5 The compound is obtained as a viscous oil after hydrogenation from 1.80 g of the compound from Example 18, 90 ml of methanol, 7.3 ml of methanolic hydrogen chloride solution and 0.22 g of palladium/activated carbon analogously to the working directions for compound 17.
- 10 The base was dissolved in ether and an insoluble component was filtered off. The hydrochloride is precipitated from the solution using ethereal hydrogen chloride solution. The white solid is filtered off with suction and dried in vacuo at 40°C.
- 15 Yield: 0.60 g = 38% of theory
 R_f = 0.40 (silica gel; toluene/methanol 70:30)
 R_f = 0.20 (base)
M.p.: 188°/191-193°C

Example 20

- 20 2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl-N-propyl]aminomethyl}-chroman



The mixture of 4.90 g (24 mmol) of 3,4-dihydro-2-(N-propyl)aminomethyl-2H-chromene, 8.60 g (27 mmol) of 2-(4-

bromobutyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide, 6.6 g (48 mmol) of powdered potassium carbonate and 0.1 g of sodium iodide in 100 ml of anhydrous dimethylformamide was stirred at 60-70°C for 12 h.

- 5 After filtering and concentrating at about 2 torr, the mixture was purified by flash chromatography (toluene/ethyl acetate gradient; silica gel). In this manner, 4.5 g (44%) of product were obtained as a viscous oil.

R_f: (toluene/methanol 4:1) 0.47

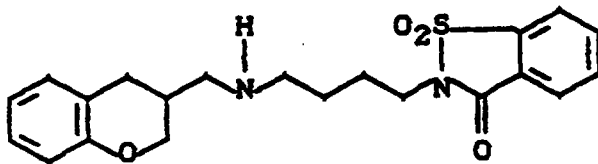
- 10 IR (CHCl₃): 3011, 2958, 2874, 1733, 1598, 1584, 1489.

The hydrochloride was obtained as a colourless, amorphous solid by treatment with ethereal hydrochloric acid in ether.

- 15 ¹H-NMR (CD₃OD): 1.0 (t; 3H), 1.6-2.2 (m; 8H), 2.7-3.0 (m; 2H), 5.2-3.6 (m; solvent signal underneath, CHD₂OD), 3.9 (m; 2H), 4.5 (m; 1H), 6.75-7.1 (m; 4H), 7.8-8.2 (m; 4H), 7.9 (s; -OH, -NH-)
- 20

Example 21

3-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]amiomethyl}-chroman



- 25 Preparation was carried out from 3-aminomethylchroman analogously to the directions of Example 20.

R_f: (toluene/methanol 4:1): 0.33.

The hydrochloride is obtained by precipitation with ethereal hydrochloric acid.

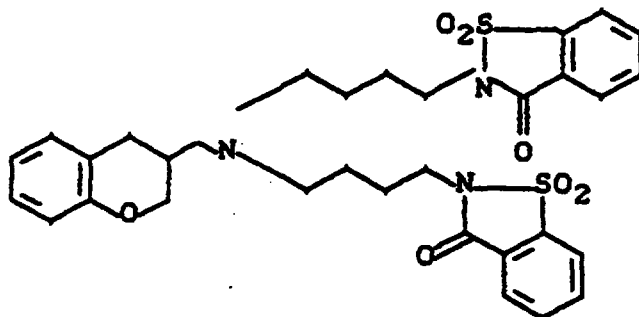
Amorphous, hygroscopic solid.

¹H-NMR (hydrochloride; CD₃OD):

- 5 1.8-2.0 (m; NH), 2.4 (m; 1H), 2.65 ("dd"; 1H)
 2.9-3.2 (m; 5H), 3.75 (t; 2H), 4.0 (m; 1H), 4.25
 (m; 1H), 6.7-7.1 (m; 4H), 7.9-8.1 (m; 4H)

Example 22

- 3-{N,N-Di[1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-chroman
10



In addition to Example 21, the compound 22 is formed in the reaction of 3-aminomethyl-chroman with 4-bromobutyl-saccharin.

- 15 R_f: (toluene/ethyl acetate 1:1): 0.58

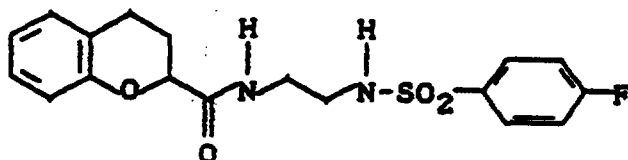
The hydrochloride was obtained as an amorphous solid by treating with ethereal hydrochloric acid:

¹H-NMR (hydrochloride, CD₃OD):

- 20 1.8-2.0 (m; 8H), 2.5-2.8 (m; 2H), 2.9-3.4 (m;
 contains solvent signals), 3.75 (m; 4H), 4.0 (m;
 1H), 4.25 (m; 1H), 6.7-7.1 (m; 4H), 7.9-8.1 (m;
 8H) and also signals from about 8% diethyl ether.

Example 23

2-[N-2-(4-Fluorophenylsulphonamido)ethyl]carboxamido-2H-chroman

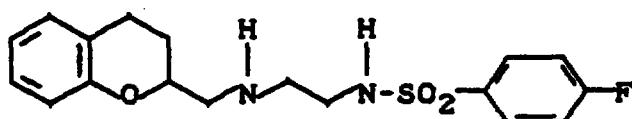


- 5 The reaction of 2-chromancarbonyl chloride and 2-(4-fluorophenylsulphonamido)ethylamine in the presence of sodium hydrogen carbonate in ether/dioxane gives Example 23.

R_f: (toluene/ethyl acetate 1:1): 0.35

10 Example 24

2-[N-(4-Fluorophenylsulphonylamido)ethyl]aminomethyl-chroman hydrochloride



x HCl

- 15 The solution of 4.50 g (11.9 mmol) of the compound from Example 23 in 100 ml of absolute THF were added at 0°C to 16.6 ml (16.6 mmol) of a 1M solution of BH₃ in THF.

50 ml of THF were then added dropwise. After stirring for 2 hours at room temperature the mixture was cooled to 0° and 2 ml of concentrated hydrochloric acid were added.

- 20 The precipitate was filtered off with suction after 30 min and washed with THF and n-hexane. In this manner, 3.35 g (70%) of product were obtained as colourless crystals.

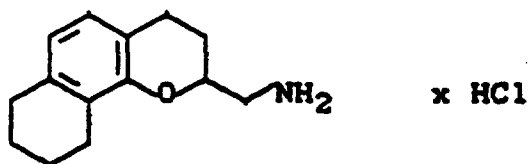
Melting point: 212-214°C

MS: 364, 231, 176 (100%), 95

1H-NMR (CD₃OD): 1.75 (m; 1H), 2.1 (m; 1H),
2.7-3.0 (m; 2H), 3.1-3.5 (m;
contains solvent signal).
4.4 (m; 1H), 6.8 (m; 2H),
7.1 (m; 2H), 7.2-7.4 (m;
2H), 8.0 (m; 2H).

Example 25

2-Aminomethyl-7,8,9,10-tetrahydro-benzo(h)-chroman
hydrochloride



The preparation is carried out from the corresponding carboxamide using borane-THF complexes analogously to the working directions of Example 24.

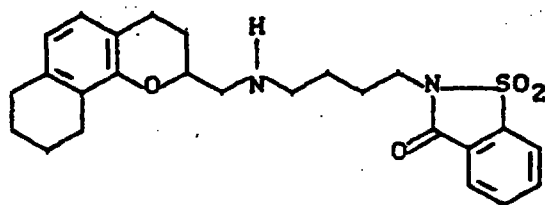
¹H-NMR (CD₃OD): 1.4-1.9 (m; 5H), 2.0-2.1 (m;
1H), 2.6-3.0 (m; 6H), 3.1-
3.4 (m; several H; also
CD₂HOD), 4.2-4.3 (m; 1H),
4.9 (s; H₂O, -NH₂), 6.6 (d;
1H), 6.8 (d; 1H).

The free base was obtained using sodium hydrogen carbonate/ethyl acetate extraction.

Rf: (dichloromethane/methanol 10:1): 0.27

Example 26

2-{N-[4-(1,1-Dioxido-3-oxo-2,4-dihydro-benzisothiazol-2-yl)-butyl]aminomethyl}-7,8,9,10-tetrahydro-benzo(H)chroman



The compound from Example 25 was prepared analogously according to the working procedure of Example 20.

MS: 454, 424, 267, 200

5 R_f : ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1), 0.58

The corresponding hydrochloride is amorphous.

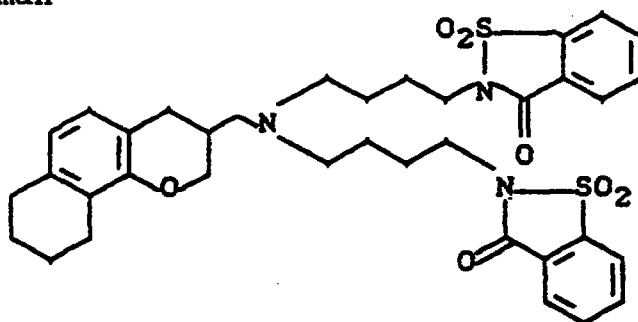
$^1\text{H-NMR}$ (CD_3OD):

10

1.6-2.1 (m; 10H), 2.5-3.0 (m; 5H), 3.1-3.4 (m; several H, underneath CD_2HOD), 3.9 (t; 2H), 4.3 (m; 1H), 4.9 (s; H_2O , NH), 6.6 (d; 1H), 6.75 (d; 1H), 7.9-8.1 (m; 4H).

Example 27

15 2-(N,N-{Di[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-7,8,9,10-tetrahydro-benzo(h)chroman



The compound is formed in the preparation of Example 26.

20 R_f : ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1) 0.86

The amorphous hydrochloride of the compound was precipitated using ethereal hydrochloric acid in ether.

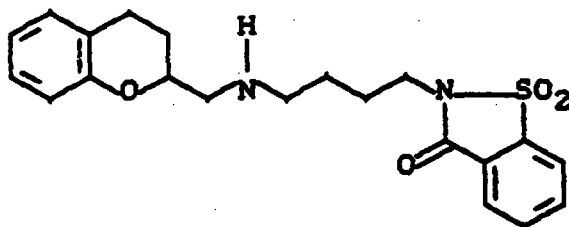
¹H-NMR (CD₃OD): 1.4-2.1 (m; 14H), 2.5-3.0 (m; 7H), 3.2-3.6 (m; several H; underneath CD₂HOD), 3.9 (m; 4H), 4.5 (m; 1H), 4.9 (s; H₂O, NH), 6.5 (d; 1H), 6.75 (d; 1H), 7.9-8.1 (m; 8H).

5

Example 28

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}chroman

10



The compound is prepared from 2-aminomethyl-3,4-dihydro-2H-chromene analogously to the working directions of Example 20.

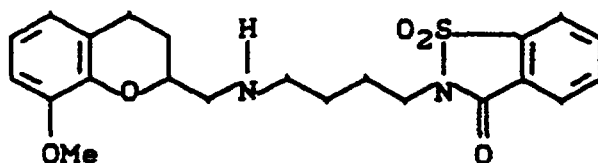
15 The corresponding hydrochloride has a melting point of 188°C-195°C.

R_f: (toluene/ethyl acetate 1:1) = 0.37

Example 29

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}-8-methoxy-chroman

20

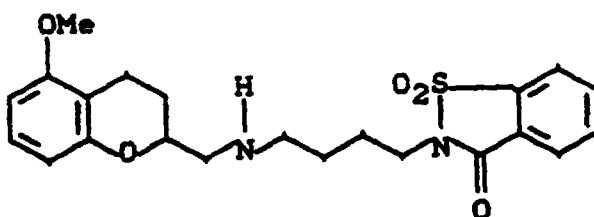


The compound is prepared from 2-aminomethyl-3,4-dihydro-8-methoxy-2H-chromene analogously to the working directions of Example 20.

25 R_f: (toluene/methanol 4:1): 0.33

Example 30

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-
5-yl)butyl]aminomethyl}-5-methoxy-chroman



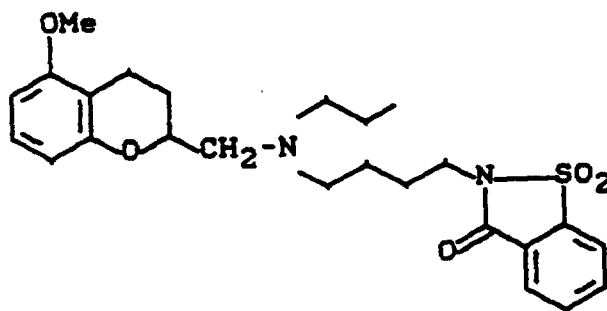
The compound is prepared from 2-aminomethyl-3,4-dihydro-5-methoxy-2H-chromene analogously to the working directions of Example 20.

10 R_f: (toluene/methanol 4:1) 0.3

The hydrochloride has a melting point of 253-257°C.

Example 31

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl-N-propyl]aminomethyl}-5-methoxy-chroman



The compound is prepared from 3,4-dihydro-2-(n-propyl)aminomethyl-5-methoxy-2H-chromene analogously to the working directions of Example 20.

R_f: (toluene/methanol 4:1), 0.33

20 MS: 472, 309, 196

The corresponding hydrochloride exhibits the following shifts:

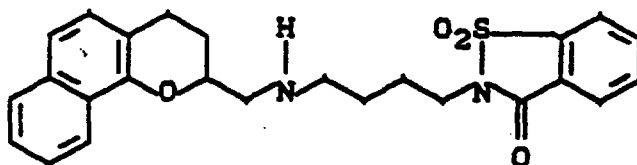
¹H-NMR (CD₃OD): 1.0 (t; 3H), 1.6-2.2 (m; 8H), 2.5-2.9 (m; 2H), 3.1-3.5 (m; contains signal from CD₂HOD), 3.7 (s; 3H), 3.9 (t; 2H), 4.4 (m; 1H), 4.9 (s; H₂O, -NH), 6.5 (m; 2H), 7.0 (m; 1H), 7.8-8.1 (m; 4H)

5

Example 32

2-{N-[4(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}benzo(h)chroman

10

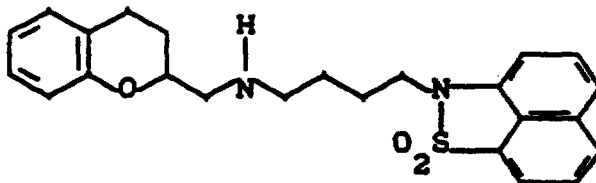


The compound is prepared from 2-aminomethyl-3,4-dihydro-2H-benzo(h)chromene hydrochloride analogously to the working directions of Example 20.

15 M.p. : 97 - 102°C

Example 33

2-{N-[4-(1,1-Dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)-butyl]aminomethyl}-chroman



20 The compound is prepared from 2-aminomethyl-3,4-dihydro-2H-chromene and 2-(4-bromobutyl)-2H-naphth[1,8-cd]isothiazole 1,1-dioxide (accessible from 2H-naphth-[1,8-cd]isothiazole 1,1-dioxide and 1,4-dibromobutane using a base) according to the working directions of Example 20.

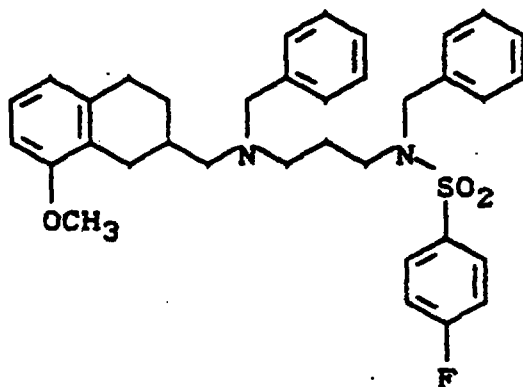
25 R_f: (toluene/ethyl acetate 1:1) = 0.41
The corresponding hydrochloride is amorphous.

$^1\text{H-NMR}$ (CD_3OD) :

1.7 (m; 1H), 2.0 (m; 5H), 2.6-2.9 (m; 2H), 3.2-3.5 (m; underneath signals from the solvent), 3.9 (m; 2H), 4.5 (m; 1H), 6.65 (dd; 1H), 6.75 (ddd; 1H), 6.9-7.1 (m; 2H), 7.5-7.6 (m; 2H), 7.8 (dd; 1H), 8.05 (d; 1H), 8.2 (d; 1H).

Example 34

2-{N-Benzyl-N-[3-(N-benzyl-4-fluorophenyl-sulphonamido)-propyl]aminomethyl}8-methoxytetralin



79 mg of sodium hydride (3.3 mmol) are suspended under argon in 15 ml of dry dimethylformamide. A solution of 1.49 g of the compound from Example 16 (3 mmol) in 15 ml of dry dimethylformamide is then added dropwise at 20-25°C in the course of 30 min. The mixture is then warmed to 30°C for a further 1 h. A solution of 0.56 g of benzyl bromide (3 mmol) in 15 ml of dry dimethylformamide is then added dropwise in the course of 15 min. The mixture is stirred at room temperature for a further 18 h in order to complete the reaction.

25 For working up, the mixture is stirred into a mixture of 450 ml of 5% strength sodium chloride solution and 150 ml of toluene. The organic phase is washed with water until neutral and dried over sodium sulphate, and the solvent is distilled off.

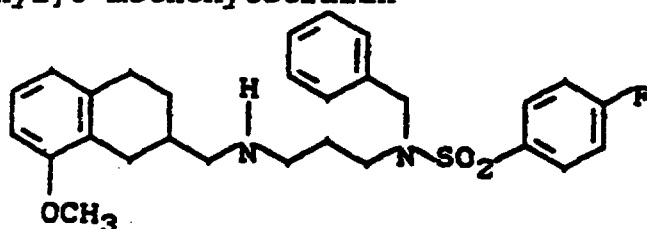
The crude product is chromatographed on 90 g of silica gel 60 using diisopropyl ether. A colourless resin is obtained.

Yield: 1.26 g = 76% of theory

5 $R_f = 0.52$ (silica gel, diisopropyl ether)

Example 35

2-{N-[3-(N-Benzyl-4-fluorophenylsulphonamido)propyl]-aminomethyl}8-methoxytetralin



10 The compound is obtained as a viscous oil after hydrogenation from 1.15 g of the compound from Example 34 (2.1 mmol), 55 ml of methanol, 5.9 ml of methanolic hydrogen chloride solution (3.2 mmol) and 0.11 g of palladium/activated carbon analogously to the working
15 directions for Example 17.

The base does not crystallize from diisopropyl ether in this case and was therefore precipitated as the hydrochloride by adding ethereal hydrogen chloride solution dropwise. The precipitate was filtered off with suction
20 and dried at 50°C/0.1 mb. A white solid is obtained.

Yield: 0.70 g = 70% of theory

M.p.: 130°C/157-158°C

$R_f = 0.40$ (silica gel; toluene/methanol 85:15)

Example 36

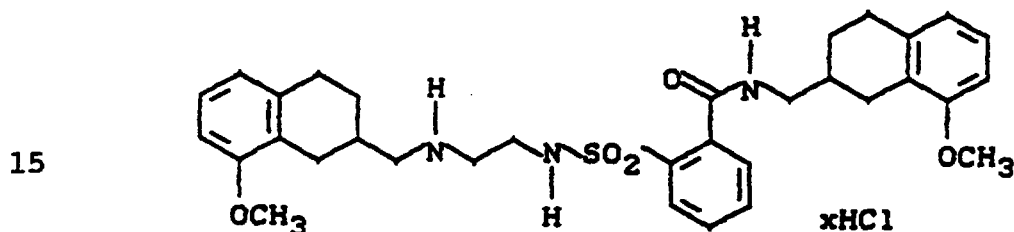
25 2-{N-Benzyl-N-[3-(N-methyl-4-fluorophenylsulphonamido)propyl]aminomethyl}8-methoxytetralin

5

10

$R_f = 0.47$ (silica gel, diisopropyl ether)

2-{N-[2-(2-Carboxamido-N-(8-methoxytetralin-2-yl-methyl)-phenylsulphonamido)ethyl]aminomethyl}8-methoxytetralin-



20

25

being kept at a maximum of 11. The organic phase is then washed with water until neutral and dried over sodium sulphate. The solvent is then distilled off at 30°C and 40 mb.

- 5 The crude product obtained is chromatographed on 90 g of silica gel 60 using ethyl acetate. A yellow resin is obtained.

The base can be precipitated as the hydrochloride from toluene solution by adding ethereal hydrogen chloride solution dropwise.

10

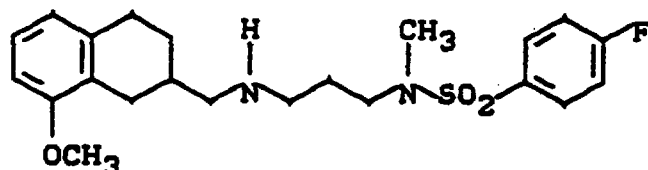
Yield: 1.51 g = 51% of theory

R_f = 0.32 (silica gel; toluene/methanol 85:15)

R_f = 0.15 (ethyl acetate)

Example 38

- 15 2-{N-[3-(N-Methyl-4-fluorophenylsulphonamido)propyl]-aminomethyl}8-methoxytetralin



The compound is obtained as a viscous oil after hydrogenation from 3.90 g of the compound from Example 36 (7.6 mmol), 195 ml of methanol, 21 ml of methanolic hydrogen chloride solution (11.4 mmol) and 0.38 g of palladium/activated carbon analogously to the working directions for Example 17.

20

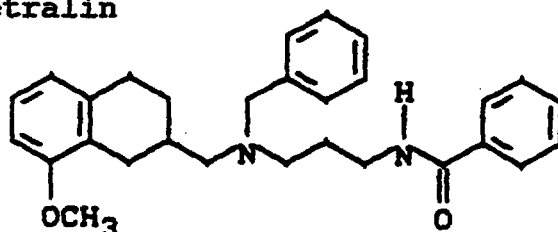
The base crystallizes from diisopropyl ether. A white solid is obtained.

25

Yield: 2.15 g = 67% of theory; M.p.: 66-67°C

R_f = 0.23 (silica gel; toluene/methanol 85:15)

2-{N-Benzyl-N-[3-(phenylcarboxamido)propyl]aminomethyl}-
8-methoxytetralin



- 5 The compound was prepared from 3.39 g of the compound from Example 9 g (10 mmol), 1.38 g of potassium carbonate (10 mmol) and 1.41 g of benzoyl chloride (10 mmol) in dichloromethane analogously to the working directions for Example 16.
- 10 The crude product was chromatographed on 90 g of silica gel 60 using diisopropyl ether (dissolved in a little toluene for application). The pure product then crystallizes out from the main fraction. The crystallisate was filtered off with suction and dried at 50°C/1 mb. A white
- 15 crystallisate is obtained.

Yield: 3.6 g = 82% of theory

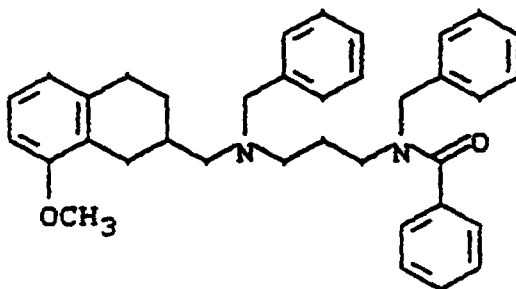
M.p.: 95.5–96.5°C

$R_f = 0.10$ (silica gel; toluene/methanol 85:15)

$R_f = 0.10$ (diisopropyl ether)

20 Example 40

2-{N-Benzyl-N-[3-(N-benzyl-phenylcarboxamido)propyl]-aminomethyl}8-methoxytetralin



The compound is prepared from 1.77 g of the compound from

Example 39 (4 mmol), 106 mg of sodium hydride (4.4 mmol) and 0.68 g of benzyl bromide (4 mmol) in dry dimethylformamide analogously to the working directions for Example 34.

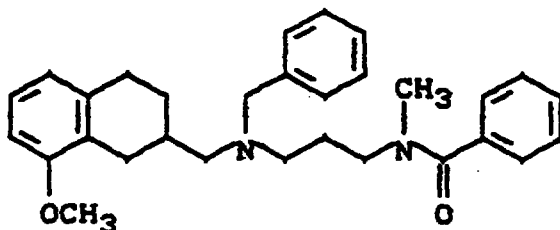
- 5 The crude product is chromatographed on 90 g of silica gel 60 using diisopropyl ether. A colourless resin is obtained.

Yield: 1.73 g = 81% of theory

R_f = 0.28 (silica gel; diisopropyl ether)

10 Example 41

2-{N-Benzyl-N-[3-(N-methyl-phenylcarboxamido)propyl]-aminomethyl}8-methoxytetralin



- The compound is prepared from 1.77 g of the compound from
15 Example 39 (4 mmol), 106 ml of sodium hydride (4.4 mmol)
and 0.57 g of methyl iodide (4 mmol) in dry dimethylform-
amide analogously to the working directions for Example
34.

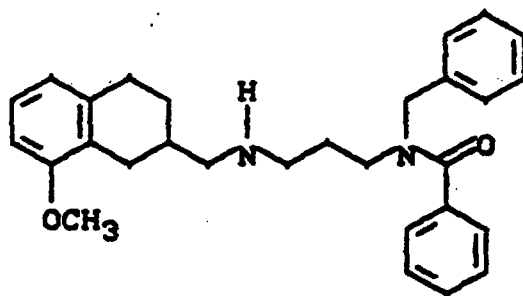
- The crude product is chromatographed on 250 g of silica gel 60 using diisopropyl ether/methanol 95:5. A colourless resin is obtained.

Yield: 1.62 g = 89% of theory

$R_f = 0.52$ (silica gel; toluene/methanol 90:10)

Example 42

- 25 2-{N-[3-(N-Benzyl-phenylcarboxamido)propyl]aminomethyl}-
8-methoxytetralin



The compound is obtained as a viscous oil after hydrogenation from 1.68 g of the compound from Example 40 (3.2 mmol), 84 ml of methanol, 8.9 ml of methanolic hydrogen chloride solution (4.8 mmol) and 0.16 g of palladium/activated charcoal analogously to the working directions for Example 17.

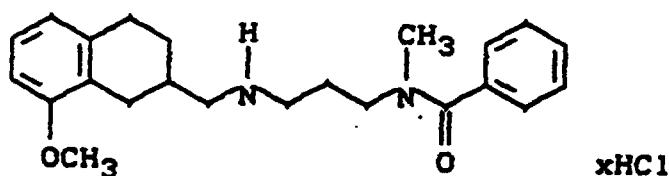
The base was converted into the hydrochloride.

A white solid is obtained.

Yield: 1.18 g = 76% of theory
 $R_f = 0.32$ (silica gel; toluene/methanol 85:15)

Example 43

2-{N-[3-(N-Methyl-phenylcarboxamido)propyl]aminomethyl}-8-methoxytetralin



15

The compound is obtained as a viscous oil after hydrogenation from 1.46 g of the compound from Example 41 (3.2 mmol), 73 ml of methanol, 8.9 ml of methanolic hydrogen chloride solution (4.8 mmol) and 0.16 g of palladium/activated charcoal analogously to the working directions for Example 17.

20

The base was converted into the hydrochloride analogously to the working directions of Example 19.

A white solid is obtained.

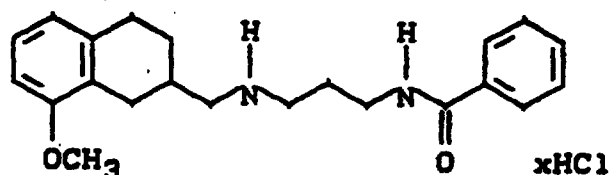
M.p.: 128-130°C

R_f = 0.38 (silica gel; toluene/methanol 70:30)

R_f = 0.28 (base)

5 Example 44

2-{N-[3-(Phenylcarboxamido)propyl]aminomethyl}-8-methoxy-tetralin



10 The compound is obtained as a viscous oil after hydrogenation from 1.20 g of the compound from Example 39 (2.7 mmol), 60 ml of methanol, 7.6 ml of methanolic hydrogen chloride solution (4.1 mmol) and 0.14 g of palladium/activated charcoal analogously to the working directions for Example 17.

15 The base was converted into the hydrochloride analogously to the working directions of Example 19.

A white solid is obtained.

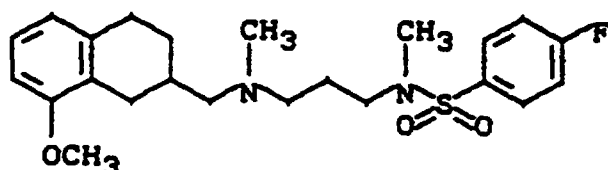
M.p.: 134.5-137°C

R_f = 0.35 (silica gel; toluene/methanol 70:30)

20 R_f = 0.22 (base)

Example 45

2-{N-Methyl-N-[3-(N-methyl-4-fluorophenylsulphonamido)propyl]aminomethyl}-8-methoxytetralin.



The compound is prepared from 1.05 g of the compound from Example 38 (2.5 mmol), 0.12 g of acetic acid (1.88 mmol), 0.19 g of sodium cyanoborohydride (3.0 mmol), 33 ml of methanol and a solution of 0.21 g of 37% strength aqueous formaldehyde solution (2.5 mmol) in 5 ml of methanol analogously to the working directions for Example 7.

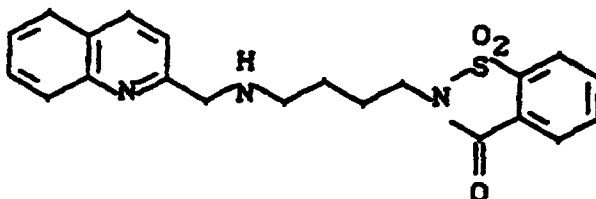
The base is obtained as a colourless viscous oil.

Yield: 1.03 g = 95% of theory

R_f = 0.47 (silica gel, toluene/methanol 85:15).

10 Example 46

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl}quinoline



The solution of 8.91 g (28 mmol) of 2-(4-bromobutyl)-1,2-benzisothiazol-3(2H)-one 1,1-dioxide in 30 ml of anhydrous dimethylformamide is added dropwise to a mixture of 4.9 g (31 mmol) of 2-aminomethylquinoline and 2.8 g (28 mmol) of triethylamine in 100 ml of anhydrous dimethylformamide and the mixture is stirred at 40°C for 14 h. The mixture is then poured into 600 ml of water and extracted using ethyl acetate, and the organic phase is washed with water and dried over sodium sulphate. After filtering and evaporating off the solvent, 8 g of a brown, viscous oil which is purified by column chromatography on silica gel (eluent: methylene chloride/methanol/conc. ammonia solution (10:0.1:0.1)) are obtained.

Yield: 1.75 g = 16% of theory, yellow oil.

R_f = 0.32 (silica gel; methylene chloride/methanol 100:5).

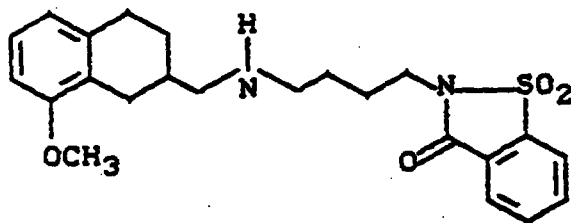
¹H-NMR (CD₂Cl₂):

1.65-1.72 (m; -CH₂-CH₂-; 2H),
 1.9-2.0 (m; -CH₂-; 2H),
 2.3-2.6 (m; NH), 2.8 (t;
 5 NH-CH₂-; 2H), 3.82 (t;
 -CON-CH₂; 2H), 4.09 (s;
 NH-CH₂-ar; 2H), 7.45-8.15
 (m; Ar; 10H).

The base can be precipitated from methanolic solution as the naphthalene-1,5-disulphonic acid salt by adding
 10 equimolar amounts of methanolic naphthalene-1,5-disulphonic acid solution dropwise. M.p.: 224°C.

Example 47:

2-{N-[4(1,1-Dioxido-2,3-dihydro-benzisothiazol-2-yl)-butyl] aminomethyl}-8-methoxy-tetralin



15 2 g of 2-aminomethyl-8-methoxytetralin (10.5 mmol), 3.2 g
 of 2-(4-bromobutyl)-1,2-(2H)benziosothiazole 1,1-dioxide
 (10.5 mmol) and 1.46 ml of triethylamine (10.5 mmol) are
 stirred at 40°C for 24 h in 40 ml of dimethyl-formamide.
 The reaction solution is then stirred into a mixture of
 20 440 ml of water and 140 ml toluene. The organic phase is
 washed with water and dried over sodium sulphate. The
 solvent is distilled off in vacuo. The residue is
 purified by column chromatography on silica gel 60
 (Merck) using toluene/methanol 70:30. The residue
 25 obtained after distilling off the solvent from the main
 fraction crystallizes after tritulating with ether.

Yield: 900 mg = .21% of theory

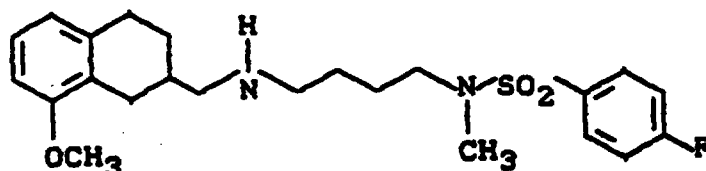
M.p.: 94-95°C

TLC: $R_f = 0.3$

Silica gel/toluene-methanol 70:30

Example 48

2-{N-[4-(N-Methyl-4-fluorophenylsulphonamido)butyl]-aminomethyl}-8-methoxy-tetralin



The compound is prepared from 1 g of 2-aminomethyl-8-methoxytetralin (5.2 mmol), 1.7 g of N-methyl-N-(4-bromobutyl)-4-fluorophenylsulphonamide (5.2 mmol) and 0.73 ml of triethylamine (5.2 mmol) in 20 ml of dimethylformamide analogously to the working directions of Example 47.

The final product is precipitated from ethereal solution as the hydrochloride using ethereal hydrogen chloride solution.

Yield: 400 mg = 16% of theory

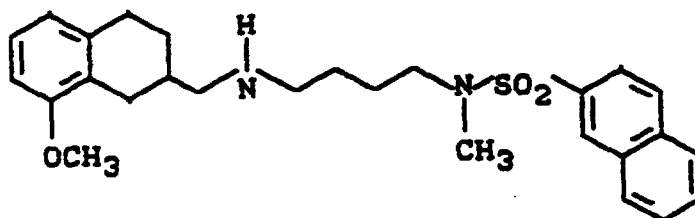
M.p.: 144°C

TLC: $R_f = 0.44$

Silica gel/toluene-methanol 70:30

Example 49

2-{N-[4-N-methyl-naphthalenyl-2-sulphonamido)butyl]-aminomethyl}-8-methoxy-tetralin



The compound is prepared from 1g of 2-aminomethyl-8-methoxytetralin (5.2 mmol), 1.9 g of N-methyl-N-(4-bromobutyl)-naphthalene-2-sulphonamide (5.2 mmol) and 0.73 ml

of triethylamine (5.2 mmol) in 20 ml of dimethylformamide analogously to the working directions of Example 47.

The final product is chromatographed on silica gel using toluene/methanol 85:15.

- 5 The final product is dissolved in dichloromethane and precipitated as the hydrochloride using ethereal hydrogen chloride solution.

Yield: 900 mg = 35% of theory

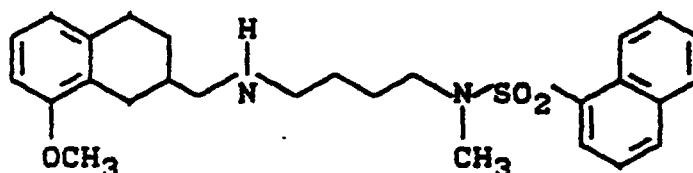
M.p.: 194-196°C

10 TLC: $R_f = 0.13$

Silica gel/toluene-methanol 85:15

Example 50

2-{N-[4-(N-Methyl-naphthalenyl-1-sulphonamido)butyl]-aminomethyl}-8-methoxy-tetralin



- 15 The compound is prepared from 2 g of 2-aminomethyl-8-methoxytetralin (10.5 mmol), 3.7 g of N-methyl-N-(4-bromobutyl)-naphthalene-2-sulphonamide (10.5 mmol) and 1.46 ml of triethylamine (10.5 mmol) in 40 ml of dimethyl-formamide analogously to the working direction
- 20 of Example 47.

The final product is chromatographed on silica gel using ethanol.

- 25 The final product is dissolved in ethanol and precipitated as the hydrochloride using ethereal hydrogen chloride solution.

Yield: 1.0 g = 19% of theory

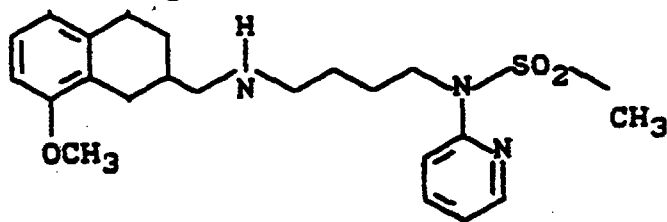
M.p.: 161-164°C

TLC: R_f = 0.45

Silica gel/toluene-methanol 70:30

5 Example 51

2-{N-[4-(N-Pyridinyl-2-methanesulphonamido)butyl]-amino-methyl}-8-methoxy-tetralin



1.60 g of 2-aminomethyl-8-methoxytetralin (8.4 mmol),
2.28 g of N-(4-bromobutyl)-pyridinyl-2-methanesulphon-
10 amide (7.4 mmol) and 0.85 g of triethylamine (8.4 mmol)
are stirred under argon at 40°C for 24 h in 32 ml of
dimethylformamide.

The reaction solution is then stirred into a mixture of
160 ml of 5 % strength sodium chloride solution, 80 ml of
15 toluene and 8.5 ml of 1 n sodium hydroxide solution. The
organic phase is washed once with 40 ml of water and
dried over sodium sulphate.

After the solvent has been distilled off in vacuo, the
crude product obtained is chromatographed on silica gel
20 60 (Merck) using methanol.

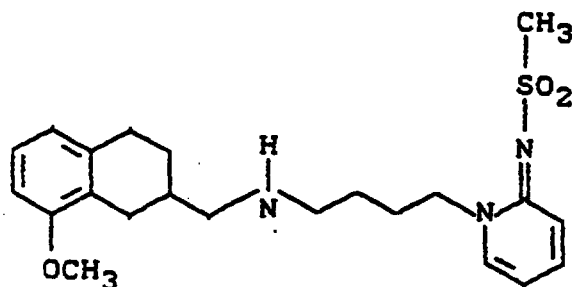
Yield: 1.9 g = 61% of theory

TLC: R_f = 0.25

Silica gel/methanol

Example 52

8'-Methoxy-2'-[4(2-methylsulphonylimino-1,2-dihydropyridin-1-yl)butyl]aminomethyl-1,2,3,4-tetrahydronaphthalene



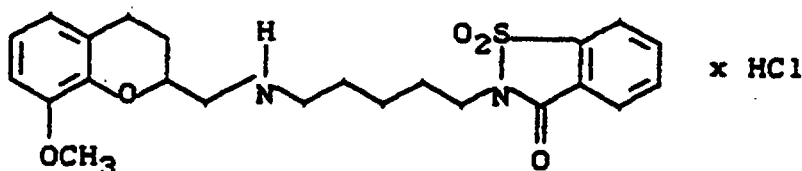
The compound is prepared from 1.60 g of 2-aminomethyl-8-methoxytetralin (8.4 mmol), 2.28 g of 1-(4-bromobutyl-2-methylsulphonylimino-1,2-dihydropyridine (7.4 mmol) and 0.85 ml of triethylamine (8.4 mmol) in 32 ml of dimethylformamide analogously to the working directions of Example 51.

10 Yield: 2.1 g = 68% of theory

TLC: R_f = 0.15
Silica gel/toluene-methanol 70:30
 R_f = 0.43
Silica gel/methanol-triethylamine 95:5

15 Example 53

2-{N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)pentyl] amino}-8-methoxy-chroman hydrochloride

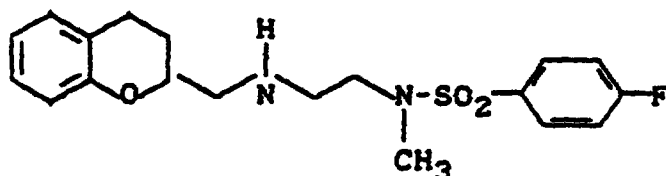


The title compound was prepared in analogy to the directions for Example 20.

20 M.p.: 110°C-118°C (after sintering)

Example 54

2-{N-[2-(N-Methyl-4-fluorophenylsulphonamido)ethyl]amino-
methyl}chroman hydrochloride

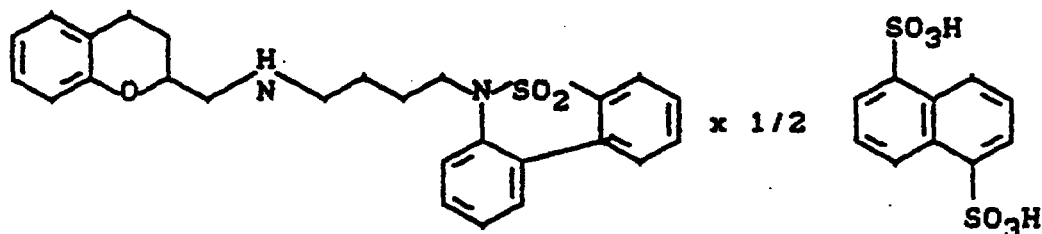


The title compound was prepared in analogy to the direc-
5 tions for Example 20.

M.p.: 143°C-155°C

Example 55

2-{N-[4-(5,5-Dioxido-6H-dibenzo[c,1][1,2]thiazin-6-yl)-
butyl]aminomethylchroman-1,5-naphthalenedisulphonic acid
10 salt (stoichiometry 2:1)}



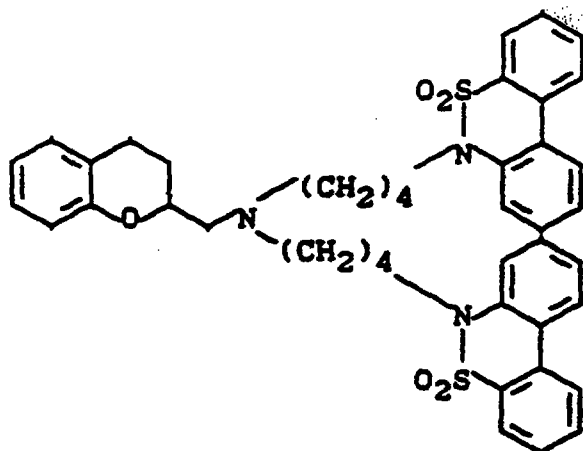
The free base [$R_f(\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH } 10:1) = 0.39$] was converted
into the 2:1 salt in acetone/ether by treating with 1,5-
naphthalenedisulphonic acid. Pale beige solid.

M.p.: > 240°C (decomposition)

15 The compound of Example 56 was additionally obtained in
the reaction.

Example 56

2-{N,N-bis(5,5-Dioxido-6H-dibenzo[c,e][1,2]-thiazin-6-
yl)butyl}aminomethylchroman-1,5-naphthalenedisulphonic
20 acid salt (2:1)

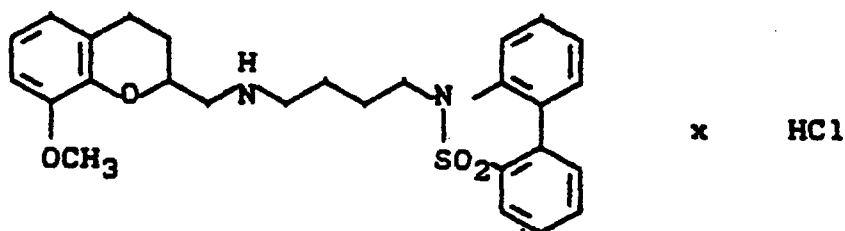


The free base was obtained as a non-polar component in addition to the compound of Example 55; $R_f(\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH } 10:1) = 0.91$.

The 2:1 salt with 1,5-naphthalenedisulphonic acid was obtained as in Example 55 (colourless solid). M.p.: from 170°C (decomposition).

Example 57

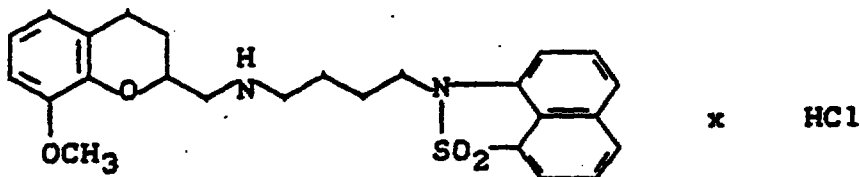
2-{N-[4-(5,5-Dioxido-6H-dibenzo[c,e][1,2]-thiazin-6-yl)-butyl]}aminomethyl-8-methoxy-chroman hydrochloride



10 The free base [$R_f(\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH } 10:1) = 0.25$] gave the hydrochloride as an amorphous, beige solid after treating with ethereal hydrogen chloride in methanol.

Example 58

15 2-{N-[4-(1,1-Dioxido-2H-naphth[1,8-cd]isothiazol-2-yl)-butyl]}aminomethyl-8-methoxy-chroman hydrochloride

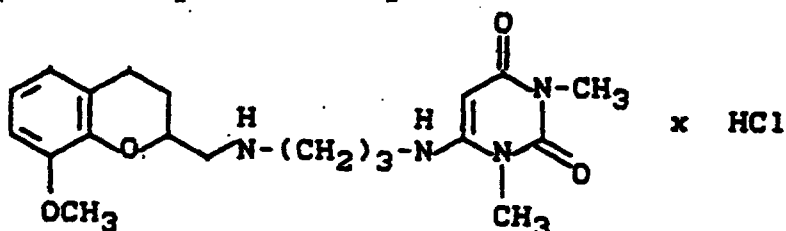


The free base [$R_f(\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH } 10:1) = 0.3$] gave the hydrochloride as slightly greenish crystals after treating with ethereal hydrogen chloride in ethyl acetate.

M.p. = 159°-162°C

5 Example 59

2-{N-[3-(1,3-Dimethyl-uracil-6-yl)amino]propyl}amino-methyl-8-methoxy-chorman hydrochloride

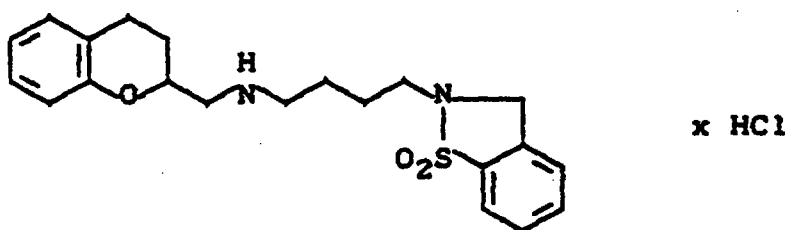


The title compound was prepared in analogy to the directions for Example 20.

- 10 The free base ($R_f(\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH } 10:1) = 0.19$], dissolved in methanol, was treated with ethereal hydrogen chloride. After addition of ether, the hydrochloride was obtained as a colourless solid. M.p.: from 195°C with decomposition (foaming).

15 Example 60

2-{N-[4-(2,3-Dihydro-1,1-dioxido-benzisothiazol-2-yl)-butyl]}amino-methyl-chroman hydrochloride



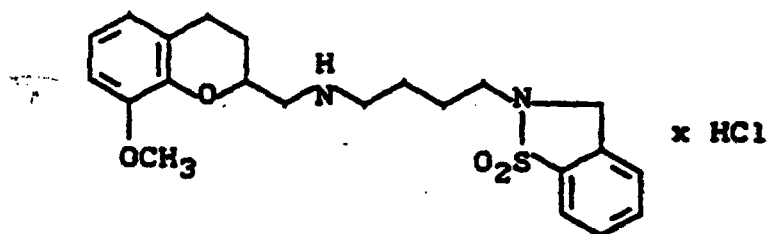
- 20 The title compound was prepared in analogy to the directions for Example 20.

The hydrochloride was recrystallized from isopropanol.

M.p.: 215-216°C

Example 61

2-{N-[4-(2,3-Dihydro-1,1-dioxido-benzisothiazol-2-yl)-
5 butyl]}amino-methyl-8-methoxy-chroman hydrochloride



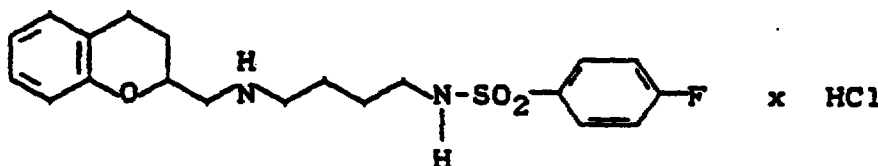
The title compound was prepared in analogy to the directions for Example 20.

The free base [R_f ($\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}$ 10:1) = 0.27] was dissolved
10 in methanol and treated with etherial hydrogen chloride,
and the hydrochloride precipitated after addition of
ether was recrystallized from ethyl acetate.

M.p. : 135°-138°C

Example 62

2-{N-[4-(4-Fluorophenylsulphonamido)butyl]}aminomethyl-
15 chroman hydrochloride



The title compound was prepared in analogy to the directions for Example 24.

M.p. 202-206°C

The compounds (63-70) shown in Table 1 were prepared
20 analogously to the following working procedure:

1.89 g of 8-methoxy-2-aminomethyl-1,3-dihydronaphthalene (10 mmol), x g of I (10 mmol) and 1.39 ml of triethylamine (10 mmol) are stirred under argon in 19 ml of dimethylformamide - for 24 h at 40°C.

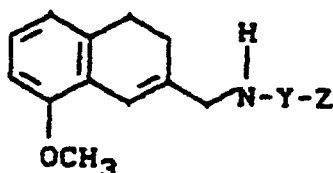
- 5 The reaction solution is then slowly poured into a stirred mixture of 90 ml of 5% strength sodium chloride solution, 10 ml of 1 N sodium hydroxide solution and 50 ml of toluene. Stirring of the mixture is continued for a further 10 min and the organic phase is then
- 10 separated off. The aqueous phase is extracted once more with 25 ml of toluene. The combined organic phases are washed twice with 25 ml of water and dried over sodium sulphate, and the solvent is distilled off at 40°C in vacuo.
- 15 The crude product obtained is purified by column chromatography on silica gel using ethanol (Example 63-67) or ethyl acetate (Example 68-70) as the eluent.

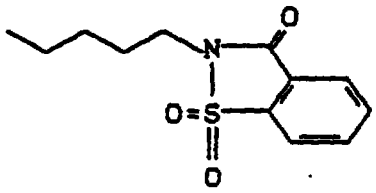
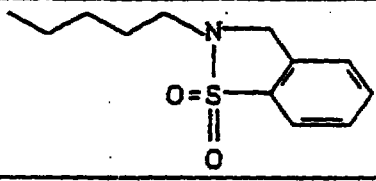
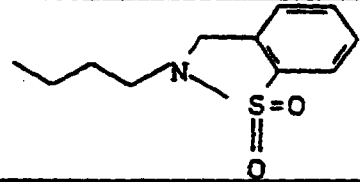
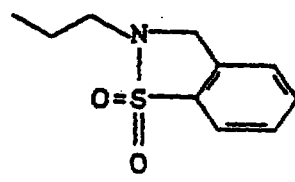
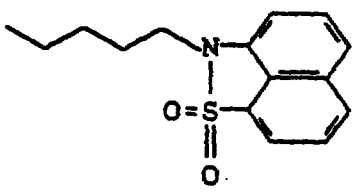
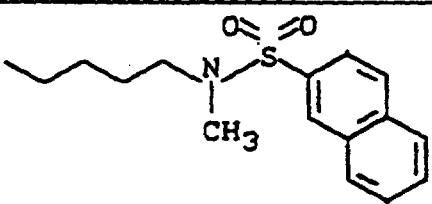
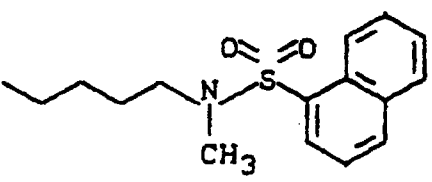
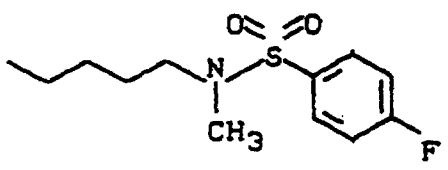
The acidic base is dissolved in ether/ethanol 90:10 (Example 63-67) or ether (Example 68-70) and precipitated

20 as the hydrochloride using ethereal hydrogen chloride solution.

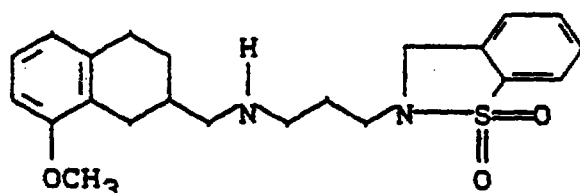
The yields are between 30 to 40% of theory.

Table 1



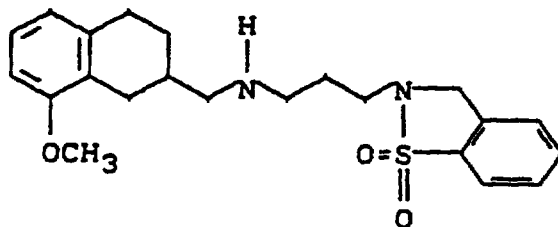
Ex. No.	Y-Z	RF on silica gel using toluene/methanol 70:30	M.p. °C
63		0.48	180°C
64		0.38	150-152°C
5 65		0.40	196-198°C
66		0.58	183-185°C
67		0.48	-
68		0.48	-
69		0.48	129-133°C
10 70		0.43	125°C

8-Methoxy-2-aminomethyl-N[3-benzisothiazole-1,1-dioxid-2-yl)propyl]-1,2,3,4-tetrahydronaphthalene



- ### Example 72

- 15 8-Methoxy-2-aminomethyl-N[2-(benzothiazole-1,1-dioxid-
2-yl)ethyl]-1,2,3,4-tetrahydronaphthalene



- R_f = 0.483 (hydrochloride), on silica gel using
toluene/methanol (70:30)
M.p.: 236-238°C (hydrochloride)
20 Yield: 38% of theory.

The compounds shown in Table 2 were prepared in analogy to the procedure of Example 20:

Table 2

Table 2

Ex. No.:	Y-Z	TLC RF or MS	M.p. °C	Salt
5				
73			195-197	x HCL
74		0.50 CH ₂ Cl ₂ /CH ₃ OH (10:1)		
10				
75				
76				
77				
15				
78		MS: (free base) 382, 219 (100%) 84		
79		MS: (free base) 430, 267 (100%) 105, 86, 84		amorphous
80				
20				
81		0.16 CHCl ₂ / C ₃ H ₈ OH (20:1)	158-159	Oxalate

The compounds shown in Tables 3, 4 and 5 were prepared in analogy to the procedure of Example 20:

Table 3

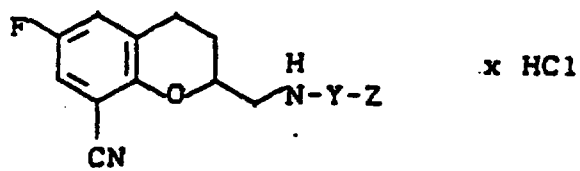
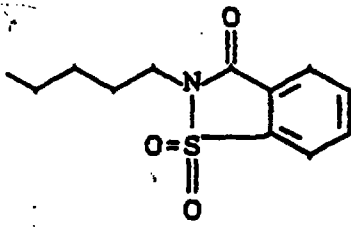
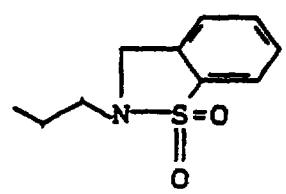
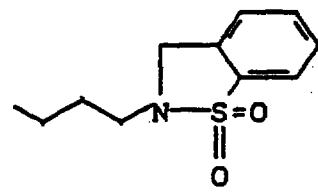
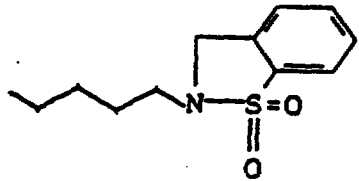
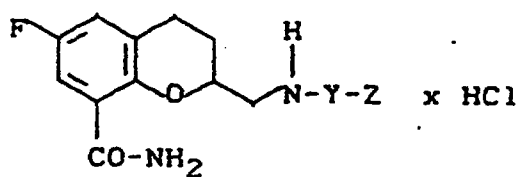
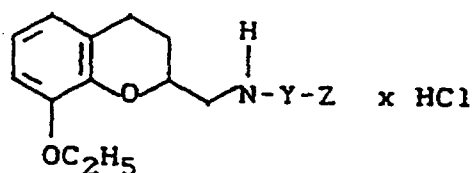
Ex. Y - Z No.		TLC/R _f on silica gel toluene/methanol (70:30)* or ethanol **		M.p. °C
5				
82		0.25**		109-111° C
83		0.49*		199-201° C
84				
85		0.38*		216-218° C

Table 4



5	Ex. Y - Z No.	TLC/R _f on silica gel/ ethanol	M.p. °C
86		0.28	140-142°C
87			
88			
89			

Table 5



Ex. No.	Y - Z	TLC/R _F	M.p. °C
5	90	<chem>CCCCN1C(=O)c2ccccc2S1(=O)=O</chem> 0.38 ClCH₂CH₂Cl/1PrOH 10:1	185°C
10	91	<chem>CCCCN1Cc2ccccc2S1(=O)=O</chem> 0.22 ClCH₂CH₂Cl/1PrOH 10:1	153°C

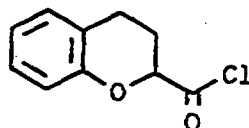
Example 92

(-)-{2-[N-(4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl)aminomethyl]chroman} and

15 (+)-{2-[N-(4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl)aminomethyl]chroman}

Example 92 A

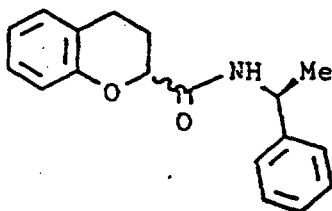
Chroman-2-carbonyl chloride



20 89.0 g (0.5 mol) of chroman-2-carboxylic acid and 71.4 g (0.6 mol) of thionyl chloride are heated at 80°C until evolution of gas is complete (4-5 hours). Distillation yields 96.0 g (98%) of chroman-2-carbonyl chloride of melting point of 77-80°C/13.3 Pa (0.1 torr).

Example 92 B

N-[1-(S)-Phenyl-ethyl]chroman-2-carboxamide
(diastereomers)



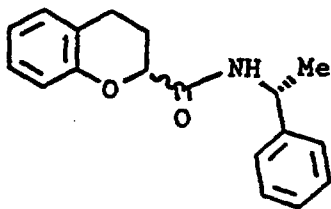
39.9 g (0.33 mol) of (S)-(-)-1-phenylethylamine and
5 30.9 g (0.3 mol) of triethylamine are added dropwise at
10°C with stirring to the solution of 59.0 g (0.3 mol) of
chroman-2-carbonyl chloride in 200 ml of dichloromethane.
After stirring overnight, the batch is poured onto ice.
Separation of the phases, washing of the organic phase
10 with saturated sodium chloride solution and drying over
anhydrous sodium sulphate yield 87.8 g of crude N-[1-(S)-
phenylethyl]chroman-2-carboxamide as a 1:1 mixture of the
diastereomers. After crystallization (4 x) from ethanol,
15.8 g of a homogeneous diastereomer (de $\geq$ 99.5) of
15 melting point 127-128°C are obtained; $\alpha_D^{25} = +17.5$ (c=1,
tetrahydrofuran).

$C_{18}H_{19}NO_2$	calc. C 76.84	H 6.81	N 4.98
281.4)	found 76.9	7.18	4.97

Evaporation of the mother liquors yielded 61.2 g of a
20 mixture of the diastereomers.

Example 92 C

N-[1-(R)-Phenylethyl]chroman-2-carboxamide (diastereomers)

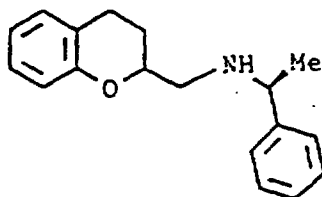


Corresponding to Example 92 B, when using (R)-(+)-1-phenylethylamine 15.0 g of a homogeneous diastereomer (de = 100%) of melting point 127-128°C are obtained after crystallization (4 x) from ethanol; $\alpha_D = -17.2$ (C = 1, tetrahydrofuran).

$C_{18}H_{19}NO_2$	calc. C 76.84	H 6.81	N 4.98
(281.4)	found 76.8	7.22	5.17

Example 92 D

N-[1-(S)-Phenylethyl]-2-aminomethyl-chroman (diastereomer A)



16.2 g (0.058 mol) of the homogeneous diastereomer (N-[(-S)-phenylethyl] chroman-2-carboxamide; $\alpha_D = +17.5^\circ$) in 300 ml of dry tetrahydrofuran are added dropwise with stirring to the solution, cooled to 0°C, of 0.2 mol of diborane in 400 ml of dry tetrahydrofuran. After stirring overnight at 20°C, the mixture is heated to reflux for 1 hour, cooled and cautiously decomposed using 10% strength aqueous hydrochloric acid.

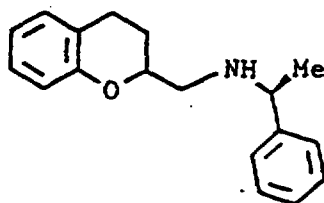
After stripping off the solvent in vacuo, the residue is rendered alkaline (pH ~ 8.5) using dilute sodium

hydroxide solution and extracted with ether. Washing of the combined organic extracts with saturated sodium chloride solution, drying over anhydrous sodium sulphate and evaporation yield 17.4 g of crude N-[1-(S)-phenethyl]-2-aminomethylchroman; de >99.5. For analysis, 0.5 g is distilled in a bulb tube at 190°C/2.66 Pa (0.2 torr).

$C_{18}H_{21}NO$	calc. C 80.86	H 7.92	N 5.24
(267.4)	found 80.7	8.01	5.41

10 Example 92 E

(+)-N-[1-(S)-Phenylethyl]-2-aminomethyl-chroman (diastereomer B)



According to Example 92 D, 42.2 g (0.15 mol) of the mixture of the diastereomers obtained in the separation of the homogeneous diastereomer as in Example 92 B are reacted with 0.3 mol of diborane in tetrahydrofuran. Working up yields 42.8 g of crude N-[1-(S)-phenylethyl]-2-aminomethylchroman as a mixture of the diastereomers, which is chromatographed on 600 g of silica gel using toluene/ethyl acetate. 9.0 g of a homogeneous N-[1-(S)-phenylethyl]-2-aminomethylchroman, which is identical to a preparation (diastereomer A) obtained as in Example 92 D, and 25.4 g of a homogeneous, less polar N-[1-(S)-phenylethyl]-2-aminomethylchroman; de >99.5 (diastereomer B) are obtained. For analysis, 0.5 g is distilled in a bulb tube at 195°C/6.65 Pa (0.05 torr) $\alpha_D = +42.3^\circ$ (c = 1, tetrahydrofuran)

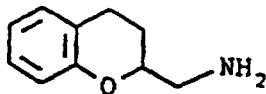
calc. C 80.7	H 8.08	N 5.38 found
$C_{18}H_{21}NO$		

30

(163.2)

Example 92 F

(-)-2-Aminomethylchroman

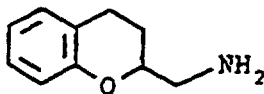


27.5 g (0.1 mol) of homogeneous N-[1-(S)-phenylethyl]-2-aminomethylchroman (prepared according to Example 92 D) are hydrogenated (Pd/C 5%) at 50°C and 10 bar for 24 hours in 400 ml of ethanol. After evaporation, 15.6 g of colourless oil are obtained. Filtration through silica gel using toluene/ethyl acetate and afterwards using methanol yield 12.5 g of 2-aminomethylchroman of melting point 100 - 110°C/5.32 Pa (0.04 torr) (bulb tube); ee ≥ 97.5% $\alpha_D = -122.8^\circ$ (C = 1, trichloromethane).

$C_{10}H_{13}NO$	calc. C 73.59	H 8.03	N 8.58
(163.2)	found 73.7	8.39	8.85

Example 92 G

15 (+)-2-Aminomethylchroman

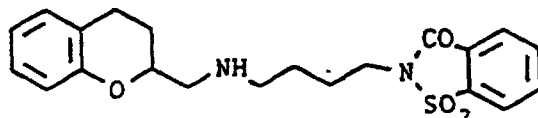


Analogously to Example 92 F, 21.5 g (0.08 mol) of homogeneous N-[1-(S)-phenylethyl]-2-aminomethylchroman (prepared according to Example 92 E, $\alpha_D = +42.3$) are hydrogenated (Pd/C 5%) in 400 ml of ethanol. 10.2 g of homogeneous (+)-2-aminomethylchroman of melting point 100 b 110°C/3.99 Pa (0.03 torr) (bulb tube) are obtained; ee ≥ 97.0%, $\alpha_D = +128.8^\circ$ (c = 1, trichloromethane).

$C_{10}H_{13}NO$	calc. C 73.3	H 8.11	N 8.82
(163.2)			

Example 92 H

2-[N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]chroman and hydrochloride[(-)-isomer]



- 5 5.4 g (0.033 mol) of 2-aminomethylchroman (Example 92 F, $\alpha_D = -122.8^\circ$), 6.1 g (0.06 mol) of triethylamine, 9.5 g (0.03 mol) of N-4-bromobutylsaccharin and 80 ml of dry dimethylformamide are heated at 60°C for 4 hours. After stripping off the solvent at 1.33 Pa (0.01 torr), the
- 10 residue (13.5 g) is taken up in toluene/ethyl acetate (5:1) and chromatographed on 300 g of silica gel. The product (5.8 g) eluted using toluene/ethyl acetate (1:1) is rechromatographed on 150 g of silica gel and affords
- 15 3.7 g of homogeneous 2-[N-[4-(1,1-dioxido-3-oxo-2,3-dihydrobenzisothiazol-2-yl)butyl]aminomethyl]chroman.

Hydrochloride:

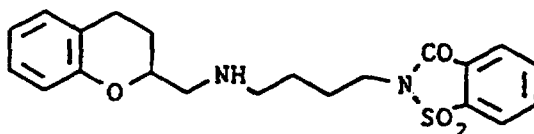
Melting point $192 - 194^\circ\text{C}$

(fused capillary) are obtained; ee $\geq 99\%$, $\alpha_D = -42.2$ (c = 1, trichloromethane).

20	$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{S} \times \text{CHl}$	calc. C 57.72	H 5.78	N 6.41
	(437)	found 57.5	5.81	6.40

Example 92 I

- 25 2-[N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]chroman and hydrochloride [(+)-isomer]



5.4 g (0.033 mol) of 2-aminomethylchroman from Example 92 G ($\alpha_D = +122.8^\circ$) are reacted with N-(4-bromobutyl)-saccharin analogously to Example 92 H; chromatography of the crude product (11.6 g) on silica gel using toluene/ethyl acetate (5:1 to 2:1) affords 5.4 g of crude product, which is rechromatographed on 175 g of silica gel. 4.2 g of homogeneous 2-[N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]chroman

Hydrochloride:

10 Melting point: $192 - 194^\circ\text{C}$ (fused capillary); ee $\geq 99\%$, $\alpha_D = +43.5^\circ$ (c = 1, trichloromethane).

$\text{C}_{21}\text{H}_{24}\text{N}_2\text{O}_4\text{S} \times \text{HCl}$ calc. C 57.4 H 5.72 N 6.33 (437)

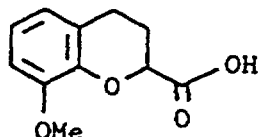
15 Example 93

(+)-{2-(N-[4-1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]-8-methoxy-chroman} and

(-)-{2-[N-[4-1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]-8-methoxy-chroman}

20 Example 93 A

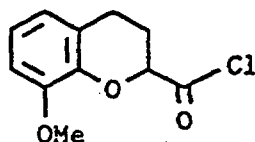
8-Methoxy-chroman-2-carboxylic acid



100.7 g (0.43 mol) of ethyl 8-methoxy-chroman-2-carboxy-
late and 20.1 g (0.50 mol) of sodium hydroxide are
stirred at 20°C for 24 hours in 800 ml of ethanol. After
concentration of the solution, the residue is treated
5 with water, the mixture is extracted with diethyl ether
and the aqueous phase is acidified. After customary
working up, extraction with diethyl ether yields 95.2
[lacuna] of crystalline 8-methoxy-chroman-2-carboxylic
acid.

10 Example 93 B

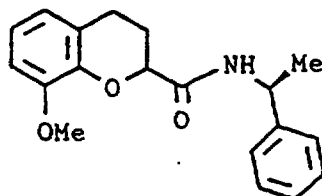
8-Methoxy-chroman-2-carbonyl chloride



Analogously to Example 92 A, 8-methoxy-chroman-2-carbonyl
chloride was obtained from Example 93 A and further
processed as the crude product.

15 Example 93 C

8-Methoxy-N-[1-(S)-phenylethyl]chroman-2-carboxamide
(diastereomers)



Analogously to Example 92 B, 88.7 g (0.39 mol) of crude
8-methoxy-chroman-2-carbonyl chloride (Example 93 B) in
20 600 ml of dichloromethane are reacted at 10°C with 64.9 g

(0.54 mol) of (S)-(-)-1-phenylethylamine and 54.1 g (0.54 mol) of triethylamine. Working up yields 135.2 g of crude 8-methoxy-N-[1-(S)-phenylethyl]chroman-2-carboxamide as a 1:1 mixture of the diastereomers.

- 5 Chromatography on 2000 g of silica gel using toluene/ethyl acetate affords 47.9 g of homogeneous diastereomer A and 33.9 g of homogeneous diastereomer B. 29.2 g of a mixture of the two diastereomers A and B are chromatographed again.

10 8-Methoxy-N-[1-(S)-phenylethyl]chroman-2-carboxamide

Diastereomer A

Melting point 123 - 124°C (dichloromethane/petroleum ether)

de > 99%, $\alpha_D = + 6.3^\circ$ (c=1, tetrahydrofuran)

15	$C_{19}H_{21}NO_3$	calc. C 73.29	H 6.80	N 4.50
	(311.4)	found 73.0	6.69	4.53

Diastereomer B

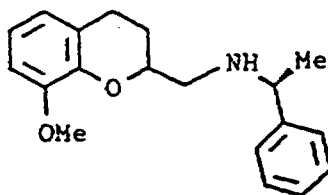
Melting point 108 - 109°C (dichloromethane/petroleum ether)

- 20 de 100%, $\alpha_D = + 40.2^\circ$ (C=1, tetrahydrofuran)

$C_{19}H_{21}NO_2$	found C 73.2	H 6.93	N 4.61
--------------------	--------------	--------	--------

Example 93 D

(+)-N-[1-(S)-Phenylethyl]-2-aminomethyl-8-methoxy-chroman



46.7 g (0.15 mol) of 8-methoxy-N-[1-(S)-phenylethyl]-chroman-2-carboxamide (diastereomer A from Example 93 C; melting point 123-124°C) are added dropwise analogously to Example 92 D in 500 ml of dry tetrahydrofuran to 0.35 mol of diborane in 650 ml of dry tetrahydrofuran at 10°C. Working up yields 50.8 g of crude N-[1-(S)-phenylethyl]-8-2-aminomethyl-8-methoxy-chroman.

Chromatography of the crude products obtained from two batches on silica gel (2000 g) using toluene/ethyl acetate (10:1 to 5:1) affords 69.2 g of homogeneous (+)-N-[1-(S)-phenylethyl]-2-aminomethyl-8-methoxy-chroman and 21.1 g of 8-methoxy-N-[1-(S)-phenylethyl]chroman-2-carboxamide.

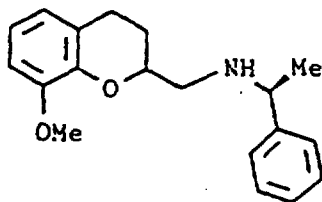
For analysis, 1 g is distilled in a bulb tube at 160-170°C/6.65 Pa (0.05 torr).

de = 100%, $\alpha_D = +30.3^\circ$ (c=1, tetrahydrofuran)

$C_{19}H_{23}NO_2$	calc. C 76.73	H 7.80	N 4.71
(297.4)	found 76.5	7.84	4.66

Example 93 E

N-[1-(S)-Phenylethyl]-2-aminomethyl-8-methoxy-chroman (other diastereomer)



Analogously to Example 93 D, the diastereomer to Example 93 D was obtained from diastereomer B of Example 93 C (melting point 108-109°C).

de = 100%.

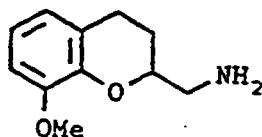
For analysis, [lacuna] is distilled in a bulb tube at

175°C/6.65 Pa (0.05 torr).

$C_{19}H_{23}NO_2$	calc. C 76.8	H 7.87	N 5.03
(297.4)			

Example 93 F

5 (+)-2-Aminomethyl-8-methoxy-chroman



49.2 g (0.16 mol) of 2-N-[1-(S)-phenylethyl]-aminomethyl-8-methoxy-chroman, obtained according to Example 93 D, are hydrogenated (Pd/C 5%) at 50°C and 10 bar for 24 hours in two batches in 400 ml of ethanol in each case.

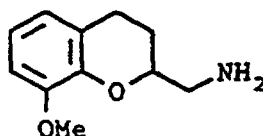
10 Filtration and evaporation yield 34.8 g of crude 2-aminomethyl-8-methoxy-chroman, which is chromatographed on 600 g of silica gel using toluene/ethyl acetate. The fraction obtained using toluene/ethyl acetate (1:2) is distilled in a bulb tube at 170-180°/2.66 Pa (0.02 torr)

15 and affords 20.1 g of homogeneous 2-aminomethyl-8-methoxy-chroman; ee = 96.7%, $\alpha_D = +111.5^\circ$ (c=1, tri-chloromethane)

$C_{11}H_{15}NO_2$	calc. C 68.37	H 7.82	N 7.25
(193.2)	found 68.3	8.02	7.34

20 Example 93 G

(-)-2-Aminomethyl-8-methoxy-chroman



Analogously to Example 93 F, the enantiomer to Example 93

F was obtained from Example 93 E.

Boiling point: 160-170°C/9.31 Pa (0.07 Torr) (bulb tube)

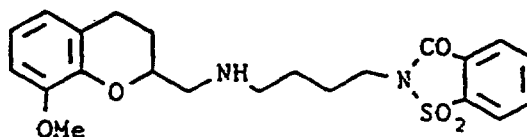
Melting range: 49-55°C

ee = 96.1%, $\alpha_D = -110.8^\circ$ (c=1, trichloromethane)

5 $C_{11}H_{15}NO_2$ calc. C 68.0 H 7.88 N7.23
 (193.2)

Example 93 H

10 2-[N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]-methoxy-chroman and hydrochloride
 [(+)-enantiomer]



15 The solution of 5.3 g (0.027 mol) of 2-aminomethyl-8-methoxy-chroman, 9.5 g (0.03 mol) of N-4-bromobutyl-saccharin, 3.03 g (0.03 mol) of triethylamine and 80 ml of dimethylformamide is stirred for 5 hours at 60°C.

20 Concentration of the solution in vacuo, taking up of the residue in dichloromethane, addition of dilute sodium hydroxide solution (0.1 n NaOH)) and water to pH 8 and separation of the phases yields, after washing the organic phase to pH 7 with saturated sodium chloride

25 solution and evaporation, 17.9 g of crude product, which is chromatographed on 250 g of silica gel using toluene/methanol (10:1).

 10.5 g of crude 2-[N-[4-(1,1-dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl]-methoxy-chroman are obtained, which is chromatographed on 300 g of silica gel. Using toluene/methanol (10:1), 6.6 g of homogeneous product are obtained.

Hydrochloride

Melting point: 205-208°C (fused capillary) after

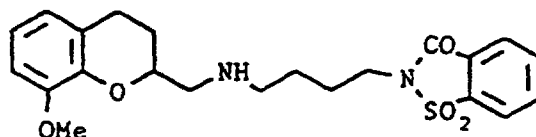
recrystallization from dichloromethane/petroleum ether.

ee $\geq$ 99%, $\alpha_D = + 53.1^\circ$, (c=1. trichloromethane).

$C_{22}H_{26}N_2O_5S \times HCl$	calc.	C 56.58	H 5.83	N 6.00
(467.0)	found	56.8	5.98	5.97

5 Example 93 I

2-[N-[4-(1,1-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl)butyl]aminomethyl-8-methoxy-chroman and hydrochloride [(-)-enantiomer]



5.3 g (0.027 mol) of 2-aminomethyl-8-methoxy-chroman, prepared according to Example 93 G, 9.5 g (0.03 mol) of N-4-bromobutylsaccharin, 3.05 g (0.03 mol) of triethylamine and 80 ml of dimethylformamide are heated at 50°C for 4 hours. Working up, as described in Example 93 H, yields 16.6 g of crude product, which is filtered through 175 g of silica gel using toluene/ethyl acetate. 3.4 g of dialkylation product and 7.1 g of monoalkylation product are obtained. Rechromatography of the monoalkylation product on 230 g of silica gel using toluene/methanol (10:1) yields 2.5 g of homogeneous 2-[N-[4-(1,1-dioxido-3-oxo-2,3-dihydrobenzisothiazol-2-yl)butyl]aminomethyl-8-methoxy-chroman.

Hydrochloride

Melting point: 208-210°C (fused capillary) after recrystallization from dichloromethane/petroleum ether:

25 ee $\geq$ 99%, $\alpha_D = -51.2^\circ$ (c=1, trichloromethane).

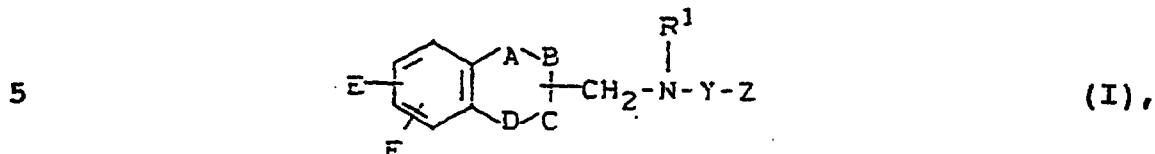
- 98 -

$C_{22}H_{26}N_2O_5S \times HCl$ calc. C 56.5 H 5.82 N 5.95
(467.0)



Patent Claims for the Contracting States AT, BE, CH, DE, FR, GB, GR, IT, LI, LU, NL, SE

1. Substituted aminomethyltetralins and their heterocyclic analogues of the general formula



in which

Y - denotes a straight-chain alkylene chain having 2-5 carbon atoms,

Z - denotes a group of the formula



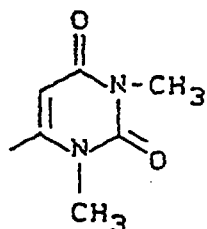
where

R² and R³ are identical or different and

- represent hydrogen, methyl, ethyl, propyl or

15 - represent phenyl, benzyl or pyridyl, which is optionally substituted by fluorine, chlorine, methyl or methoxy

- represent a group of the formula



20 - represent a group of the formula -COR⁹ or -SO₂R¹⁰,

in which



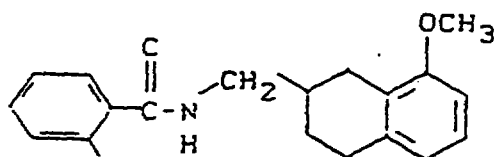
R^9 - represents methyl, ethyl or ethoxy or

- represents phenyl or benzyl, optionally substituted by methyl, methoxy, - fluorine or chlorine,

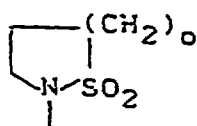
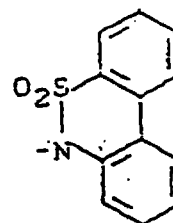
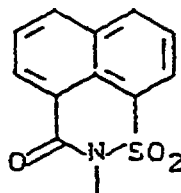
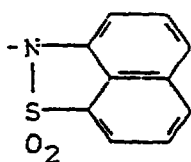
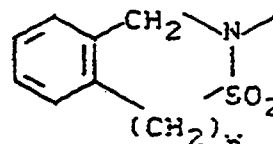
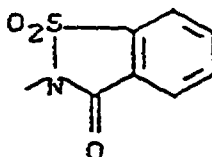
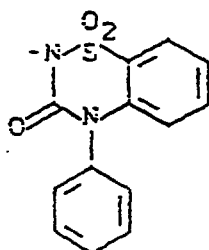
5 R^{10} - represents methyl, ethyl or propyl,

- represents phenyl, naphthyl or benzyl, which is optionally substituted by fluorine or chlorine or

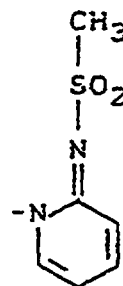
- represents a group of the formula



10 R^2 and R^3 together with the nitrogen atom form a heterocycle from the series comprising



or



where



w denotes a number 0, 1 or 2 and

o denotes a number 1 or 2

R¹ - denotes hydrogen, ethyl, methyl, propyl or benzyl or

5 - denotes the group -(Y¹-Z¹), where Y¹ and Z¹ may be identical or different to Y and Z and have the abovementioned meaning of Y and Z,

10 A and D represent a group of the formula -CH₂-, oxygen or the CH or N part of a C=C-C=N double bond, with the proviso that either only A or only D may represent oxygen,

B represents a group of the formula

$\diagup$ CH₂ or $\diagup$ CH or the CH part of a C=C or C=N double bond,

15 C - represents a group of the formula $\diagup$ CH or the C part of a C=C or C=N double bond,

20 E and F are identical or different and represent hydrogen, ethoxy, methoxy, fluorine, cyano or a group of the formula -CONR²R³ in which R² and R³ denote hydrogen,

[lacuna]

E and F together form a phenyl or cyclohexane ring, and their salts.

25 2. Substituted aminomethyltetralins and their heterocyclic analogues according to Claim 1

in which



Y - denotes a straight-chain alkylene chain having 2-5 carbon atoms,

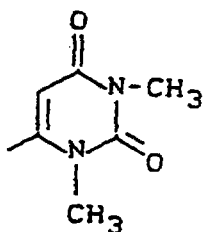
Z - denotes a group of the formula



in which

5 R^2 and R^3 are identical or different and

- represent hydrogen, methyl, benzyl or pyridyl
- represent a group of the formula



or

- represent a group of the formula $-\text{COR}^9$ or SO_2R^{10} ,

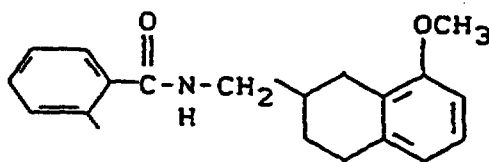
10 in which

R^9 - represents phenyl or ethoxy

R^{10} - represents phenyl or naphthyl which may be substituted by fluorine or

- represents methyl [lacuna]

15 - for a group of the formula

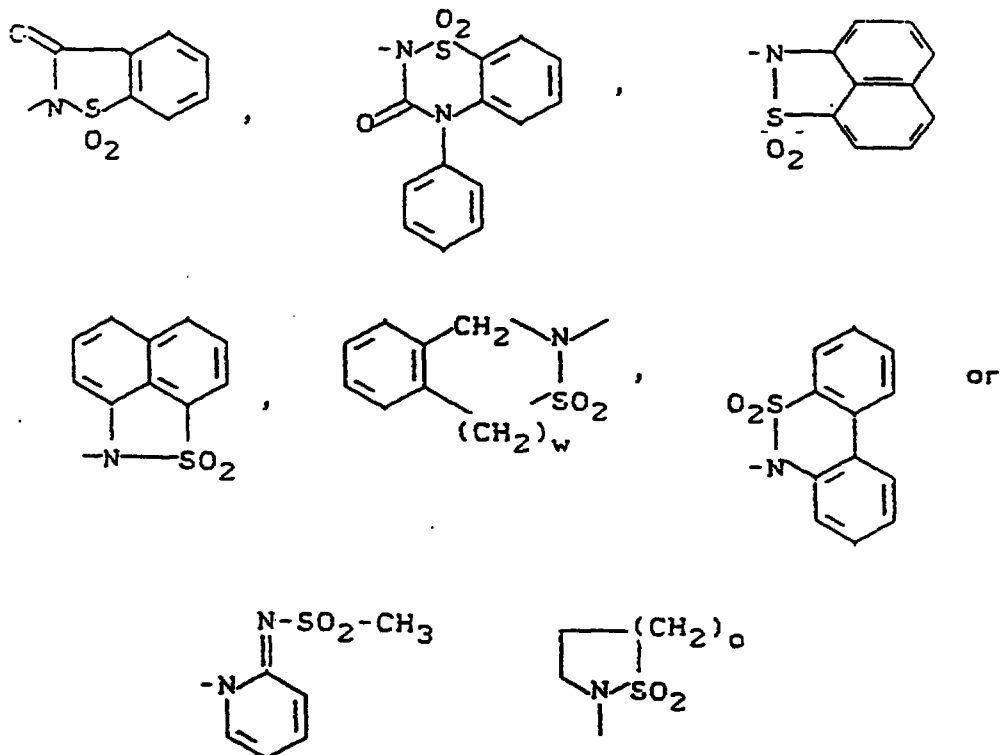


or

R^2 and R^3 together with the nitrogen atom form



a heterocycle of the formula



in which

w - denotes a number 0, 1 or 2 and

o - denotes a number 1 or 2,

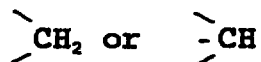
R¹ - denotes hydrogen, methyl, propyl or benzyl or

- denotes a group -(Y¹-Z¹),

where Y¹ and Z¹ may be identical or different to Y and Z and have the abovementioned meaning of Y and Z

A and D represent a group of the formula -CH₂-, oxygen or the CH or N part of a C=C [lacuna] C=N double bond, with the proviso that either only A or only D may represent oxygen,

B represents a group of the formula



or the CH part of a C=C or C=N double bond,



C - represents a group of the formula $\begin{array}{c} \diagup \\ \text{CH} \\ \diagdown \end{array}$ or the C part of a C=C or C=N double bond,

5 E and F are identical or different and represent hydrogen, ethoxy, methoxy, fluorine, cyano or a group of the formula $-\text{CONR}^2\text{R}^3$, in which R^2 and R^3 denote hydrogen

[lacuna]

E and F together form a cyclohexane or phenyl ring, and their salts.

10 3. $(-)-2-\{\text{N}-[4-(1,1\text{-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl})\text{butyl}]\text{aminomethyl}\}\text{chroman}$ and its salts according to Claim 1.

15 4. $(+)-2-\{\text{N}-[4-(1,1\text{-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl})\text{butyl}]\text{aminomethyl}\}\text{chroman}$ and its salts according to Claim 1.

5. $(+)-2-\{\text{N}-[4-(1,1\text{-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl})\text{butyl}]\text{aminomethyl}\}-8\text{-methoxy-chroman}$ and its salts according to Claim 1.

20 6. $(-)-2-\{\text{N}-[4-(1,1\text{-Dioxido-3-oxo-2,3-dihydro-benzisothiazol-2-yl})\text{-butyl}]\text{aminomethyl}\}-8\text{-methoxy-chroman}$ and its salts according to Claim 1.

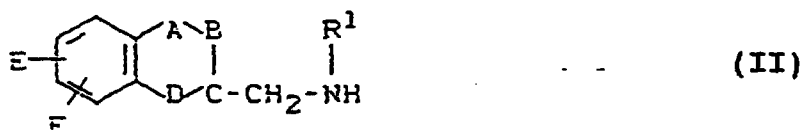
7. Substituted aminomethyltetralins and their heterocyclic analogues according to Claims 1 to 6 for therapeutic treatment.

25 8. Process for the preparation of substituted aminomethyltetralins and their heterocyclic analogues according to Claim 1 to 6,

characterized in that



[A] compounds of the general formula (II)



in which

A, B, C, D, E, F and R¹ have the meaning indicated in Claim 1,

(A1) are reacted with alkylating agents of the formula (III)



in which

Y and Z have the meanings indicated in Claim 1, with the provisos that

Z does not represent amino and R² does not represent hydrogen if R³ represents alkyl or aryl, and

L denotes a leaving group for alkylating agents or

(A2) are reductively alkylated using aldehydes of the formula (IV)



in which

Z has the abovementioned meaning and Y² is an alkylene chain Y shortened by one methylene group,

or

(A3) are reacted with reactive acid derivatives of the general formula (V)





in which

Y^2 and Z have the meanings indicated under process variants [A1] and M denotes a leaving group for alkylating agents,

5 and the corresponding acid amides are reduced using hydrogen in the presence of a catalyst, using boranes or using complex metal hydrides,

or

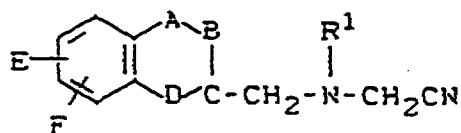
(A4) are alkylated using nitriles of the formula

10 $G - CN$

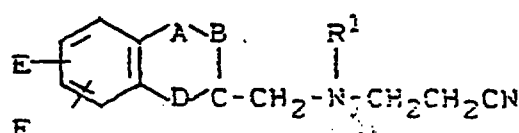
in which

G represents monochlorinated lower alkyl (C_1 to C_3), vinyl or lower alkyl (C_1 to C_3)-substituted vinyl,

15 to give compounds of the formula (VI) and (VII)



(VI)

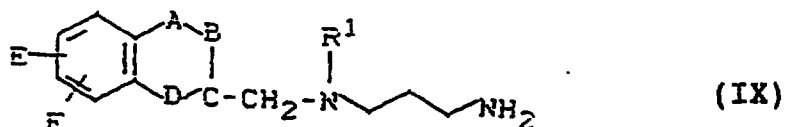
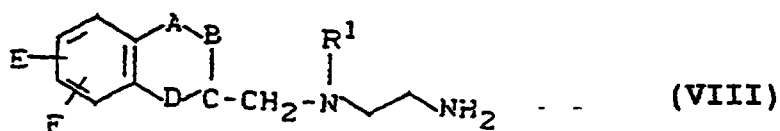


(VII)

in which

A , B , C , D , E , F and R^1 have the abovementioned meaning,

20 the nitriles obtained are hydrogenated to give the amines (VIII) and (IX)



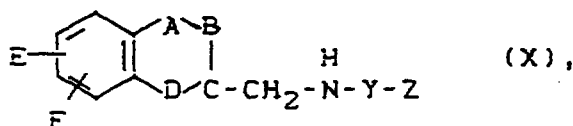
in which

A, B, C, D, E, F and R¹ have the abovementioned meaning,

and these are reacted in a manner known per se by alkylation, reductive alkylation, acylation, reaction with isocyanates or sulphonylations,

or in that

[B] compounds of the general formula (X)



in which

A, B, C, D, E, F, Y and Z have the abovementioned meanings,

with the provisos that

Z does not represent amino and
R² does not represent hydrogen if
R³ represents alkyl or aryl,

(B1) are alkylated using alkylating agents of the formula

(XI)



(XI)



in which

R^1 has the abovementioned meaning and

L denotes a leaving group for alkylating agents,

or

5 (B2) are reductively alkylated using aldehydes of the formula (XII)



in which R^{14} denotes a radical R^1 shortened by one methylene group,

10 or

(B3) are reacted with reactive acid derivatives of the general formula (XIII)



in which

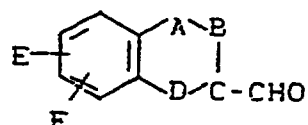
15 R^{14} has the abovementioned meaning and

M denotes a leaving group for acylating agents,

and the corresponding acid amides are reduced using hydrogen in the presence of a catalyst or using complex metal hydrides,

20 or in that

[C] aldehydes of the formula (XIV)

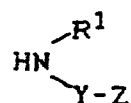


(XIV)

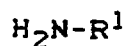
in which

A, B, C, D, E and F have the abovementioned meaning,

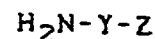
5 are reductively aminated using amines of the formula (XV), (XVI) or (XVII)



(XV)



(XVI)



(XVII)

in which

R¹, Y and Z have the abovementioned meaning

10 with the provisos that

Z does not represent amino and

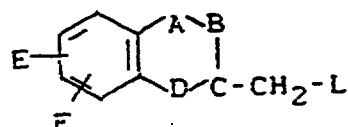
R² does not represent hydrogen if

R³ represents alkyl or aryl,

in a manner known per se,

15 or in that

[D] compounds of the general formula (XVIII)



(XVIII),

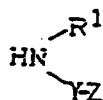
in which



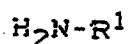
A, B, C, D, E and F and X have the abovementioned meaning and

L denotes a leaving group for -alkylating agents,

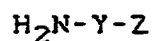
5 are reacted with amines of the formulae



(XV)



(XVI)



(XVII),

in which

R^1 , Y and Z have the abovementioned meaning,

with the provisos that

10 Z does not represent amino and

R^2 does not represent hydrogen if

R^3 represents alkyl or aryl,

or reacted with an alkali metal azide and the azido function is subsequently reduced to an amino function,

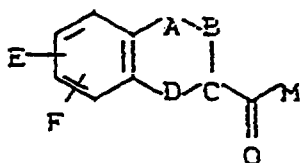
15

[lacuna] this is reacted in a manner known per se by alkylation, reductive alkylation, acylation, reaction with isocyanates or sulphonylations,

20

or in that

[E] reactive carboxylic acid derivatives of the formula (XIX)

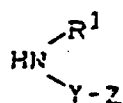


(XIX)

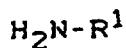
in which

A, B, C, D, E and F have the abovementioned meaning,
and

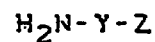
5 M denotes a leaving group for acylating agents,
are reacted with amines of the formulae



(XV)



(XVI)



(XVII)

in which

R¹, Y and Z have the abovementioned meaning,

10 with the provisos that

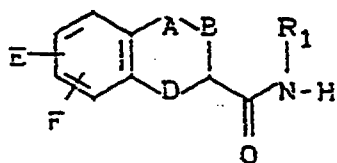
Z does not represent amino and

R² does not represent hydrogen if

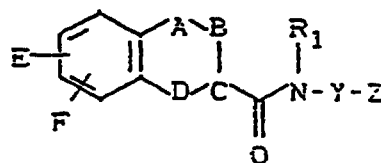
R³ represents alkyl or aryl,

and the amides thus obtained of the formulae (XX)
and (XXI)

15



(XX)



(XXI)



in which

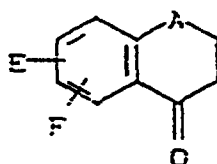
A, B, C, D, E, F, R¹, Y and Z have the abovementioned meaning,

5

are catalytically reduced using hydrogen, using complex metal hydrides or using boranes,

or in that

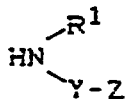
[F] compounds of the general formula (XXII)



(XXII)

10

in which A, E and F have the abovementioned meaning are reacted with formaldehyde and amines of the formula (XV)



(XV),

in which

R¹, Y and Z have the abovementioned meaning.

15

with the provisos that

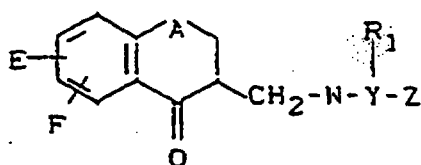
Z does not represent amino and

R² does not represent hydrogen if

R³ represents alkyl or aryl,

20

and the intermediates obtained of the general formula (XXIII)



(XXIII)

in which

A, E, F, R¹, Y and Z have the abovementioned meaning,

- 5 are reacted by reduction of the carbonyl function or by partial reduction of the carbonyl function to the alcohol function, subsequent elimination of water and, if desired, hydrogenation of the C=C double bond using hydrogen.
- 10 9. Medicaments, containing substituted aminomethyl-tetralins and/or their heterocyclic analogues according to Claims 1 to 6.
10. Medicaments according to Claim 9 for the treatment of disorders of the central nervous system.
- 15 11. Medicaments according to Claim 9 and 10 for the treatment of depression and cerebral infarct.
12. Use of substituted aminomethyltetralins and/or their heterocyclic analogues according to Claims 1 to 6 for the production of medicaments.
- 20 13. Use according to Claim 12 for the production of medicaments for the treatment of disorders of the central nervous system.