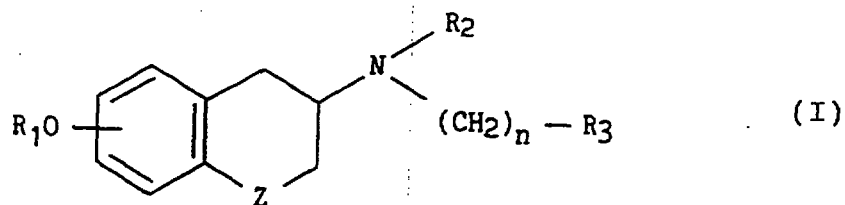


The present invention relates to new 3-aminochroman compounds, a process for the preparation thereof and pharmaceutical compositions containing them.

3-aminochromans and 3-aminothiochromans are known to be ligands of central nervous system receptors that can be used, in particular, as ligands of serotonin receptors, in the treatment of disorders of the central nervous system, depression and anxiety.

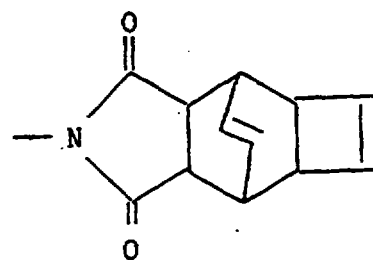
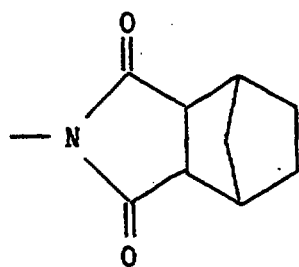
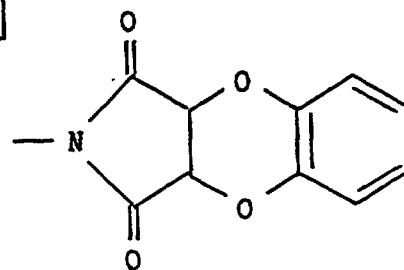
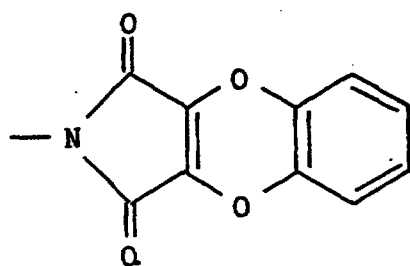
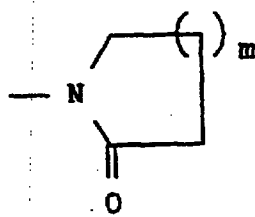
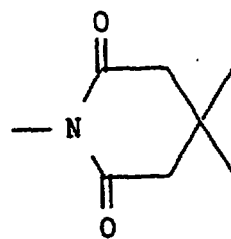
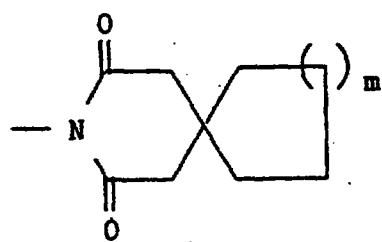
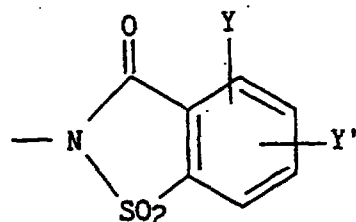
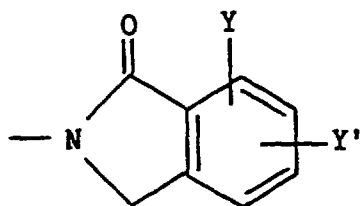
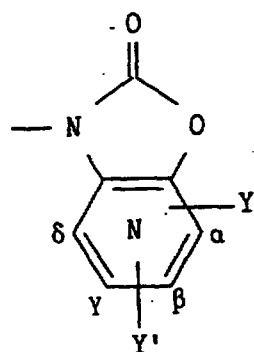
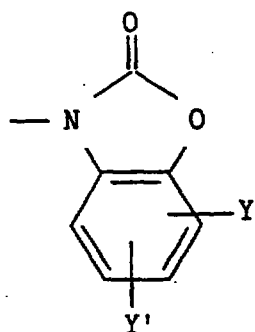
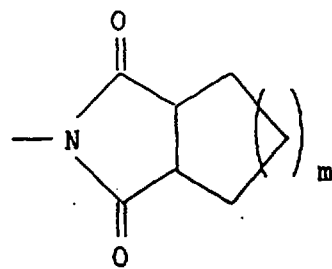
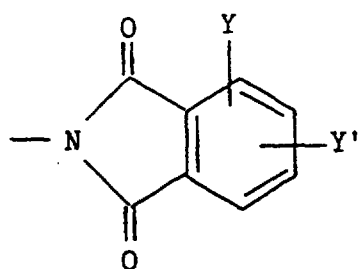
Aminochroman and aminothiochroman compounds have been described, for example, in European Patents EP 279150 and EP 222996. The compounds described in those patents have a certain affinity for 5-HT_{1A} receptors but also for D₂ receptors, which means that the degree of selectivity is very low. A factor of 10 separates the 5-HT_{1A} affinities from those for D₂. On the other hand, the compounds of the present invention, which are 3-aminochroman and 3-aminothiochroman compounds, apart from the fact that their structures are new, possess remarkable pharmacological properties. They are very powerful ligands of 5-HT_{1A} receptors. That very strong affinity is all the more valuable because it is accompanied by a very high degree of selectivity in respect of those receptors compared with D₂ and α_2 receptors. The affinity of the compounds of the invention in respect of 5-HT_{1A} receptors is, respectively, 10² times and 10⁴ times greater than that observed for D₂ and α_2 receptors. Those remarkable pharmacological properties mean that the compounds of the present invention can be used in the treatment of disorders of the central nervous system, especially of the serotonergic system, such as depression, anxiety, stress, schizophrenia, and pain and also in the treatment of hypertension, in the prevention of atheromas and as modifiers of eating and sexual behaviour.

More specifically, the present invention relates to compounds of the general formula (I):



wherein:

- Z represents an oxygen atom or a sulphur atom,
- R₁ represents a hydrogen atom, or a linear or branched (C₁-C₆)-alkyl grouping,
- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆)-alkyl grouping,
- n is an integer from 1 to 6, and
- R₃ represents a nitrile grouping, or an amino grouping optionally substituted by:
 - . a linear or branched acyl grouping containing from 2 to 7 carbon atoms,
 - . an alkylsulphonyl grouping,
 - . an arylsulphonyl grouping optionally substituted by an alkyl, alkoxy or hydroxy grouping or a halogen atom, or
 - . a linear or branched (C₁-C₆)-alkyl grouping,
- or R₃ represents any one of the following groupings:



wherein:

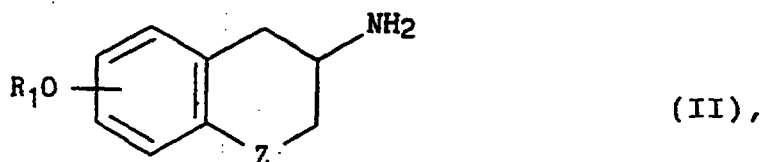
- . Y and Y', which may be identical or different, represent a hydrogen atom, a halogen atom, or an alkyl, alkoxy or hydroxy grouping,
- . m is an integer equal to 1 or 2,
- . and the nitrogen of the pyridine ring is in the α , β , γ or δ ring junction position,

their enantiomers, diastereoisomers and epimers and also their addition salts with a pharmaceutically acceptable acid.

Of the pharmaceutically acceptable acids, there may be mentioned by way of non-limiting examples hydrochloric acid, sulphuric acid, tartaric acid, maleic acid, fumaric acid, oxalic acid, methanesulphonic acid, camphoric acid, etc..

The invention extends also to a process for the preparation of the compounds of the general formula (I), characterised in that there is used as starting material:

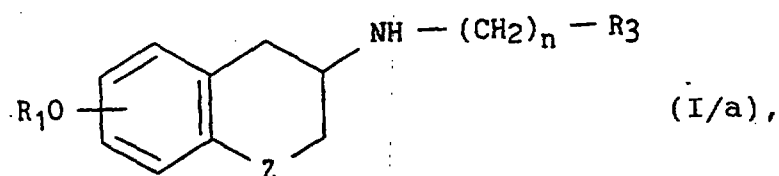
a a compound of formula (II):



wherein R_1 and Z are as defined in formula (I), which is reacted with a compound of formula (III):



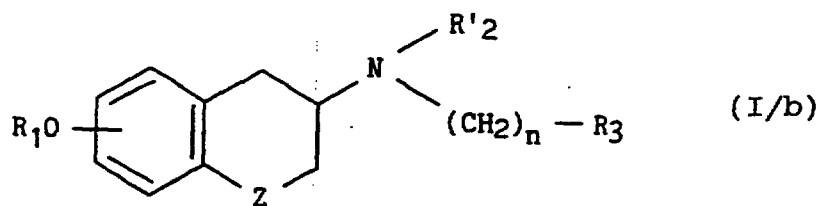
wherein R_3 and n are as defined in formula (I) and X is a halogen atom,
to yield a compound of formula (I/a), a particular case
of the compounds of formula (I):



wherein R_1 , R_3 , Z and n are as defined in formula (I),
which is optionally subjected to the action of a compound
of formula (IV):



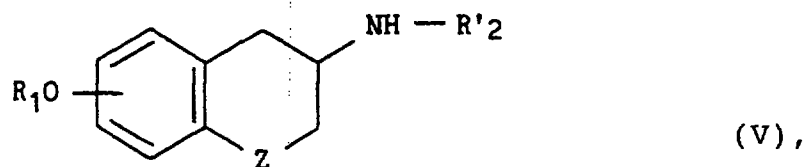
wherein R'_2 represents a linear or branched (C_1-C_6)-alkyl
grouping and X represents a halogen atom,
to yield a compound of formula (I/b), a particular case
of the compounds of formula (I):



wherein R , Z , R'_2 , R_3 and n are as defined above,

or

by a compound of formula (V):

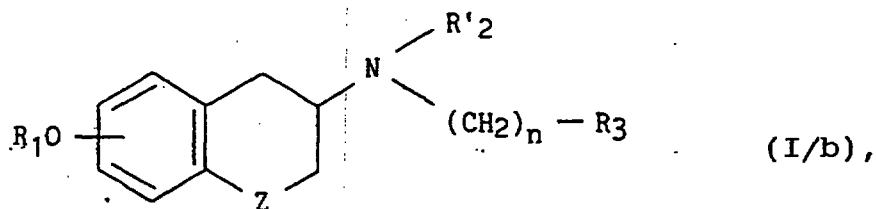


wherein R_1 , Z and R'_2 are as defined above, which is reacted:

- either with a compound of formula (III):



wherein R_3 , n and X are as defined above, to yield a compound of formula (I/b), a particular case of the compounds of formula (I):

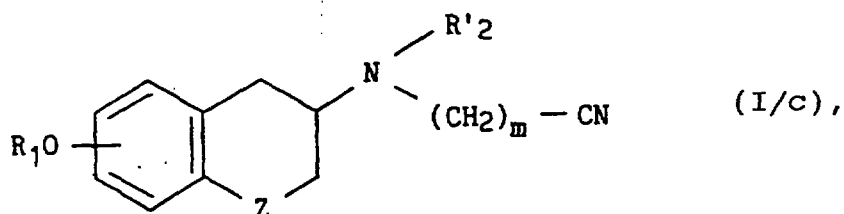


wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

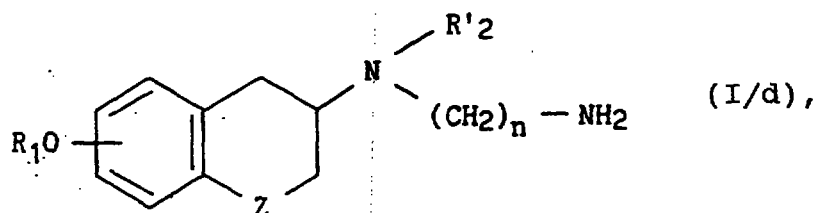
- or with a compound of formula (III/a):



wherein X is as defined above and m is an integer from 1 to 3, to yield a compound of formula (I/c), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 and m are as defined above,
 which is reduced catalytically in the presence of Raney
 nickel and ammonia, or chemically by lithium aluminium
 hydride or by sodium in alcohol,
 to yield the compound of formula (I/d), a particular case
 of the compounds of formula (I):

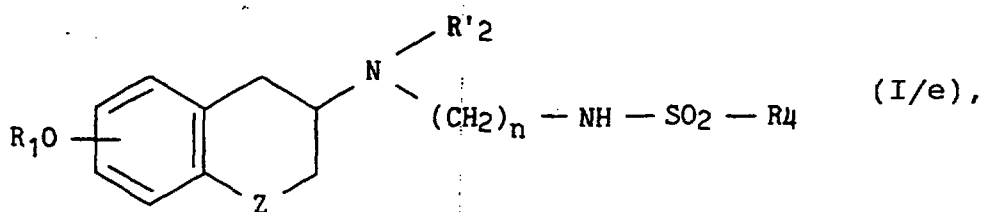


wherein R_1 , Z , R'_2 and n are as defined above,
 which is reacted:

either with a compound of formula (VI/A):



wherein R_{4A} is an alkyl grouping or an aryl grouping
 optionally substituted by an alkyl grouping and X is a
 halogen atom,
 to yield a compound of formula (I/e), a particular case
 of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_4 and n are as defined above,

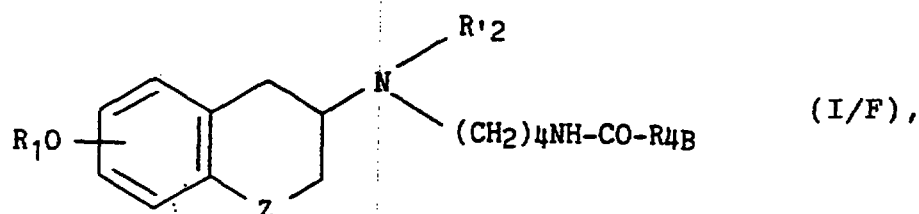
or with a compound of formula (VI/B):



wherein R_{4B} represents a linear or branched alkyl grouping having from 1 to 6 carbon atoms and T is a leaving group selected from halogen, and lower alkoxy or with a compound of formula (VI/C):



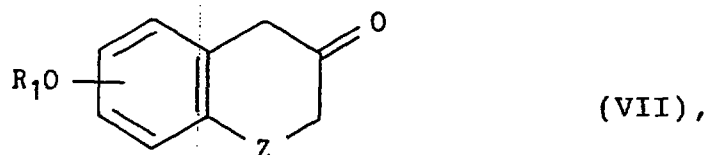
wherein R_{4B} is as defined above,
to yield a compound of formula (I/F):



wherein R_1 , Z , R'_2 , R_{4B} and n are as defined above, a particular case of the compounds of formula (I) in which R_3 represents an amino grouping substituted by a linear or branched acyl grouping having from 2 to 7 carbon atoms,

or

Ⓒ a compound of formula (VII):



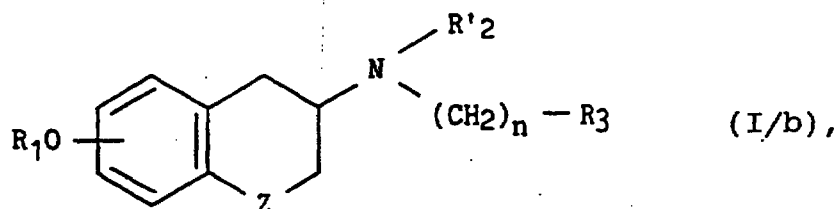
wherein R_1 and Z are as defined in formula (I), which is subjected to a reductive amination in the presence of a compound of formula (VIII):



wherein R_2 , R_3 and n are as defined in formula (I), to yield a compound of formula (I) which, when R_2 represents a hydrogen atom, may be subjected to the action of a compound of formula (IV):



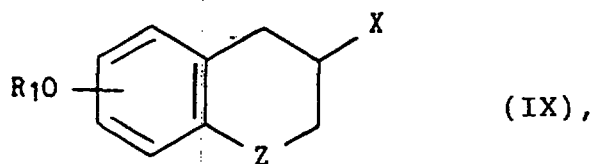
wherein R'_2 and X are as defined above, to yield a compound of formula (I/b), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

or

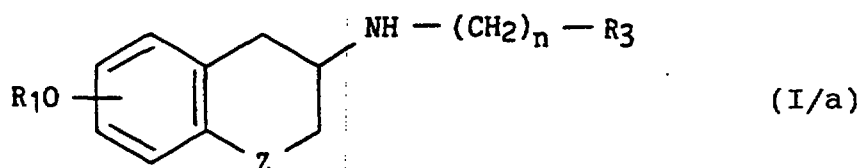
and a compound of formula (IX):



wherein R_1 and Z are as defined in formula (I) and X is a halogen atom, which is subjected to the action of a compound of formula (X):



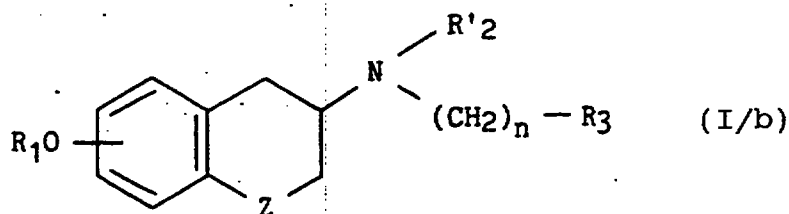
wherein n and R_3 are as defined above, to yield a compound of formula (I/a), a particular case of the compounds of formula (I):



wherein R_1 , Z, n and R_3 are as defined above, which is optionally subjected to the action of a compound of formula (IV)



wherein R'_2 and X are as defined above, to yield a compound of formula (I/b), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

the isomers of which compounds of formulae (I/a), (I/b), (I/c), (I/d) and (I/e) are optionally separated in accordance with a conventional separation technique, and which compounds are purified by a conventional purification technique and are converted, if desired, into their addition salts with a pharmaceutically acceptable acid.

The compounds of formula (I) possess very valuable pharmacological properties.

Binding assays have shown that the compounds of the invention behave as very powerful ligands of 5-HT_{1A} receptors, with an agonistic or antagonistic activity at the level of the central nervous system. That very great affinity is accompanied by a very high degree of selectivity in respect of those receptors compared with D₂ and α_2 receptors.

The compounds of the invention can therefore be used in the treatment of stress, anxiety, depression, schizophrenia and pain, cardiovascular disorders and hypertension. They can also modify eating and sexual behaviour.

The present invention relates also to pharmaceutical compositions containing as active ingredient at least one

compound of the general formula (I) or one of its addition salts with a pharmaceutically acceptable acid, alone or in combination with one or more inert, non-toxic excipients or carriers.

Of the pharmaceutical compositions according to the invention, there may be mentioned more especially those that are suitable for oral, parenteral and nasal administration, tablets and dragées, sublingual tablets, sachets, packets, gelatin capsules, glossettes, lozenges, suppositories, creams, ointments, dermal gels, etc....

The dosage varies in accordance with the age and weight of the patient, the nature and severity of the disorder and also the mode of administration, which may be oral, nasal, rectal or parenteral.

In general, the unit dose ranges from 0.1 to 100 mg for a treatment in 1 to 3 doses per 24 hours.

The following Examples illustrate the invention.

EXAMPLE 1:

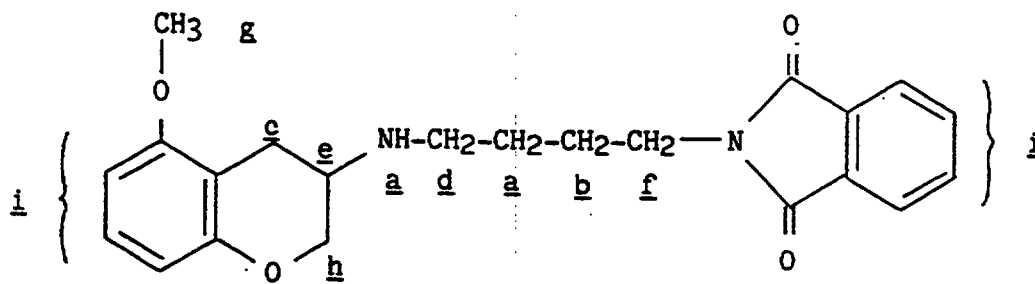
3-[N-(4-PHTHALIMIDOBUTYL)-AMINO]-5-METHOXYCHROMAN

In a round-bottomed flask, 2.2 mmol of 3-amino-5-methoxychroman (described in Patent EP 279150) are dissolved in 6 ml of dimethylformamide in the presence of 2.4 mmol of N-(4-bromobutyl)-phthalimide, 6.6 mmol of potassium carbonate and a catalytic amount of potassium iodide. The mixture is stirred at 60°C for 6 hours. After cooling, the solvent is evaporated and the crude reaction product is extracted with dichloromethane after aqueous hydrolysis. After washing, drying and evaporating the organic phase, the expected product is obtained after purifica-

tion by chromatography on a silica column (elution solvent: ether/petroleum ether: 5/95).

Yield: 67 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 1.56 ppm (3H,m)
- b δ = 1.75 ppm (2H,m)
- c δ between 2.47 and 2.92 ppm (2H,dd)
- d δ = 2.75 ppm (2H,t)
- e δ = 3.09 ppm (1H,m)
- f δ = 3.62 ppm (2H,t)
- g δ = 3.80 ppm (3H,s)
- h δ between 3.84 and 4.13 ppm (2H,m)
- i δ between 6.42 and 7.83 ppm (7H,m)

EXAMPLE 2:

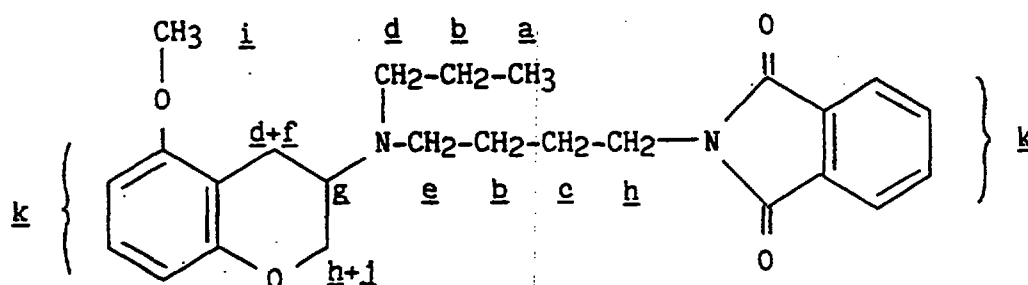
3-[N-PROPYL-N-(4-PHTHALIMIDOBUTYL)-AMINO]-5-METHOXY-
CHROMAN

1.5 mmol of the compound prepared in Example 1 are dissolved in 10 ml of dimethylformamide in the presence of 4.4 mmol of 1-iodopropane and 4.4 mmol of potassium carbonate. After stirring for 24 hours at 60°C, the solvent is evaporated and the crude reaction product is taken up in 10 ml of water and extracted with dichloromethane. The organic phase is dried and evaporated and

the expected product is obtained after purification by chromatography on a silica column (eluant solvent: ether/petroleum ether: 1/99).

Yield: 81 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.88 ppm (3H,t)
- b δ = 1.48 ppm (4H,m)
- c δ = 1.72 ppm (2H,m)
- d δ = 2.50 ppm (3H,m)
- e δ = 2.60 ppm (2H,m)
- f δ = 2.88 ppm (1H,dd)
- g δ = 3.12 ppm (1H,m)
- h δ = 3.70 ppm (3H,m)
- i δ = 3.80 ppm (3H,s)
- j δ = 4.24 ppm (1H,m)
- k δ between 6.42 and 7.84 ppm (7H,m)

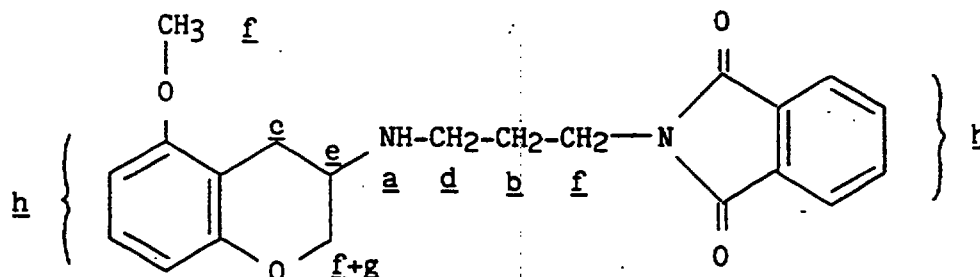
EXAMPLE 3:

3-[N-(3-PHTHALIMIDOPROPYL)-AMINO]-5-METHOXYCHROMAN

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(3-bromopropyl)-phthalimide, the expected product is obtained.

Yield: 70 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 1.56 ppm (1H,s)
- b δ = 1.87 ppm (2H,m)
- c δ between 2.44 and 2.90 ppm (2H,dd)
- d δ = 2.79 ppm (2H,m)
- e δ = 3.06 ppm (1H,m)
- f δ = 3.78 ppm (6H,m)
- g δ = 4.12 ppm (1H,m)
- h δ between 6.40 and 7.83 ppm (7H,m)

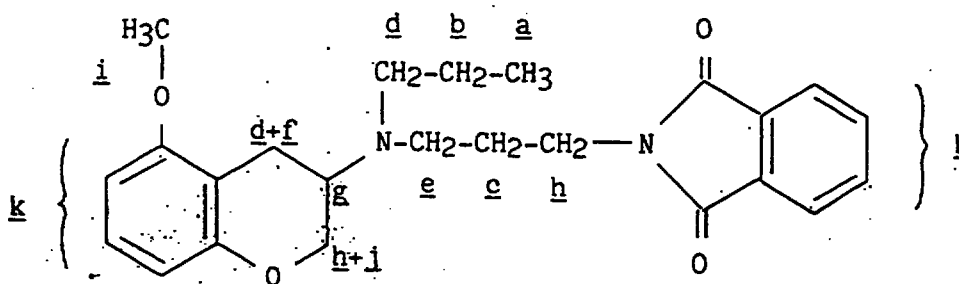
EXAMPLE 4:

3-[N-PROPYL-N-(3-PHTHALIMIDOPROPYL)-AMINO]-5-METHOXY-CHROMAN

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound of Example 3, the expected product is obtained.

Yield: 76 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.90 ppm (3H,t)
- b δ = 1.46 ppm (2H,m)
- c δ = 1.81 ppm (2H,m)
- d δ = 2.50 ppm (3H,m)
- e δ = 2.64 ppm (2H,m)
- f δ = 2.82 ppm (1H,dd)
- g δ = 3.10 ppm (1H,m)
- h δ = 3.72 ppm (3H,m)
- i δ = 3.79 ppm (3H,s)
- j δ = 4.23 ppm (1H,m)
- k δ between 6.40 and 7.83 ppm (7H,m)

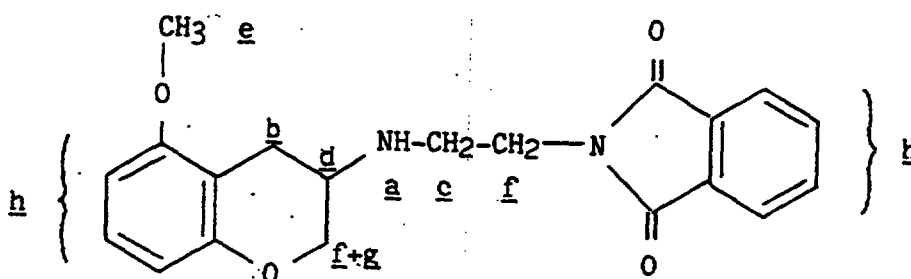
EXAMPLE 5:

3-[N-(2-PHTHALIMIDOETHYL)-AMINO]-5-METHOXYCHROMAN

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(2-bromoethyl)-phthalimide and stirring for 40 hours, the expected product is obtained.

Yield: 30 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 1.48 ppm (1H,s)
- b δ between 2.44 and 2.88 ppm (2H,m)
- c δ = 3.03 ppm (2H,m)
- d δ = 3.15 ppm (1H,m)

e δ = 3.78 ppm (3H,s)
f δ = 3.81 ppm (3H,m)
g δ = 4.1 ppm (1H,m)
h δ between 6.40 and 7.85 ppm (7H,m)

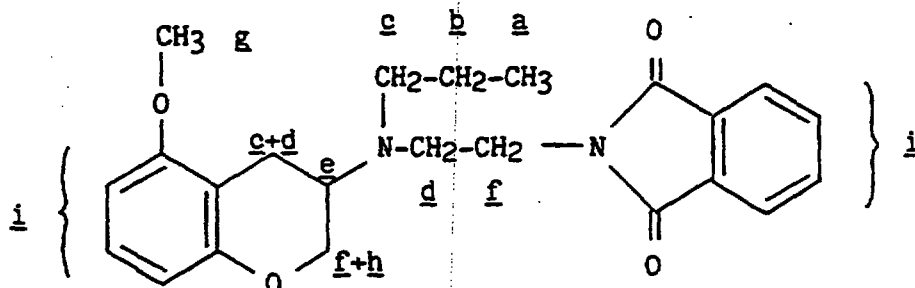
EXAMPLE 6:

3-[N-PROPYL-N-(2-PHTHALIMIDOETHYL)-AMINO]-5-METHOXY-
 CHROMAN

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound of Example 5, the expected product is obtained.

Yield: 70 %

Proton nuclear magnetic resonance: (CDCl₃):



a δ = 0.79 ppm (3H,t)
b δ = 1.40 ppm (2H,m)
c δ = 2.50 ppm (3H,m)
d δ = 2.84 ppm (3H,m)
e δ = 3.19 ppm (1H,m)
f δ = 3.71 ppm (3H,m)
g δ = 3.79 ppm (3H,s)
h δ = 4.15 ppm (1H,m)
i δ between 6.40 and 7.83 ppm (7H,m)

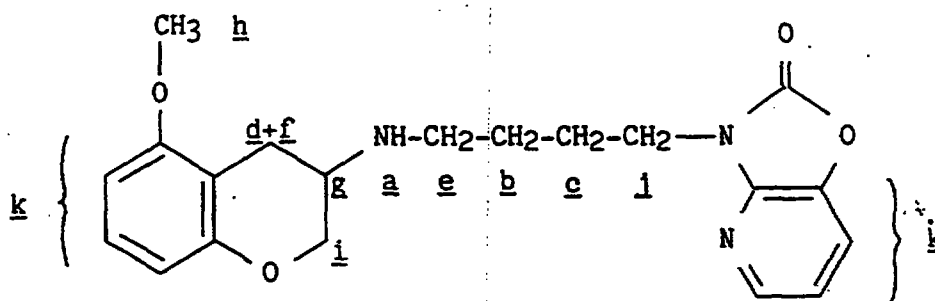
EXAMPLE 7:

3-[4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-2-OXO-2,3-DIHYDRO-OXAZOLO[4,5-b]PYRIDINE

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)phthalimide with N-(4-bromobutyl)-2-oxo-oxazolo[4,5-b]pyridine and stirring for 48 hours, the expected product is obtained.

Yield: 53 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 1.34 ppm (1H, s)
- b δ = 1.63 ppm (2H, m)
- c δ = 1.90 ppm (2H, m)
- d δ = 2.48 ppm (1H, dd)
- e δ = 2.78 ppm (2H, m)
- f δ = 2.92 ppm (1H, dd)
- g δ = 3.07 ppm (1H, m)
- h δ = 3.82 ppm (3H, s)
- i δ between 3.84 and 4.14 ppm (2H, m)
- j δ = 3.97 ppm (2H, m)
- k δ between 6.44 and 8.10 ppm (6H, m)

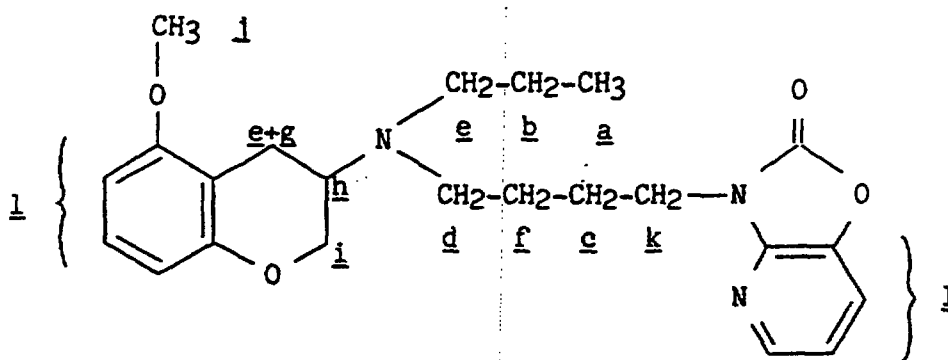
EXAMPLE 8:

3-[4-[N-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-2-
OXO-2,3-DIHYDRO-OXAZOLO[4,5-b]PYRIDINE

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound of Example 5, the expected product is obtained.

Yield: 65 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.84 ppm (3H,t)
- b δ = 1.40 ppm (2H,m)
- c δ = 1.50 ppm (2H,m)
- d δ = 1.85 ppm (2H,m)
- e δ = 2.49 ppm (3H,m)
- f δ = 2.62 ppm (2H,m)
- g δ = 2.83 ppm (1H,m)
- h δ = 3.08 ppm (1H,m)
- i δ = 3.66 ppm and 4.23 ppm (2H,m)
- j δ = 3.81 ppm (3H,s)
- k δ = 3.94 ppm (2H,t)
- l δ = between 6.48 and 8.10 ppm (6H,m)

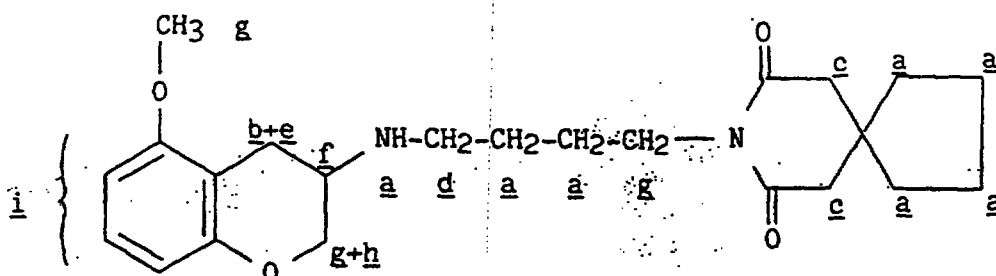
EXAMPLE 9:

3-[4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(4-bromobutyl)-2,4-dioxo-3-azaspiro[4.5]decane and stirring for 24 hours, the expected product is obtained.

Yield: 65 %

Proton nuclear magnetic resonance: (CDCl₃):



a δ between 1.45 and 1.85 ppm (13H,m)

b δ = 2.46 ppm (1H,dd)

c δ = 2.59 ppm (4H,s)

d δ = 2.74 ppm (2H,m)

e δ = 2.92 ppm (1H,dd)

f δ = 3.05 ppm (1H,m)

g δ = 3.80 ppm (6H,m)

h δ = 4.13 ppm (1H,m)

i δ between 6.41 and 7.04 ppm (3H,m)

EXAMPLE 10:

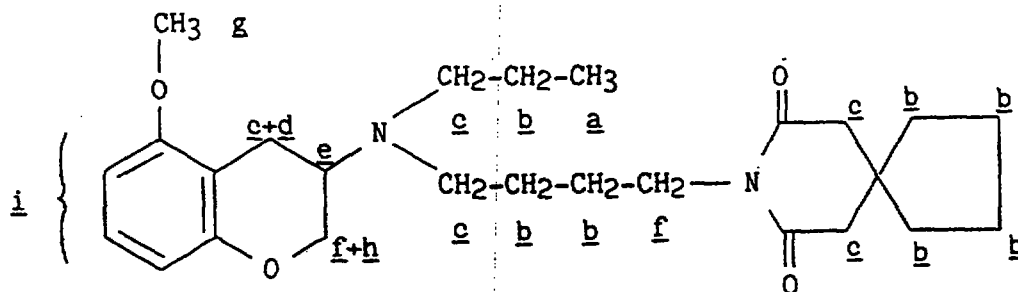
3-[4-[N-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

By proceeding as in Example 2, but replacing the compound

of Example 1 with the compound of Example 9, the expected product is obtained.

Yield: 72 %

Proton nuclear magnetic resonance: (CDCl₃):



- a* δ = 0.87 ppm (3H,t)
- b* δ between 1.45 and 1.75 ppm (14H,m)
- c* δ = 2.52 ppm (9H,m)
- d* δ = 2.84 ppm (1H,m)
- e* δ = 3.11 ppm (1H,m)
- f* δ = 3.73 ppm (3H,m)
- g* δ = 3.81 ppm (3H,s)
- h* δ = 4.22 ppm (1H,m)
- i* δ between 6.39 and 7.02 ppm (3H,m)

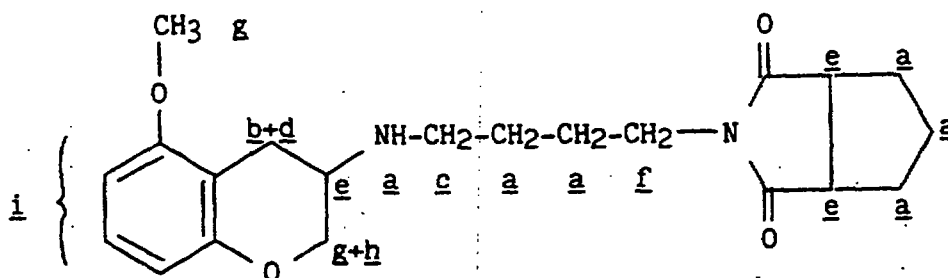
EXAMPLE 11:

3-[4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(4-bromobutyl)-2,4-dioxo-3-azabicyclo[3.3.0]octane and stirring for 24 hours, the expected product is obtained.

Yield: 66 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ between 1.18 and 2.19 ppm (11H,m)
- b δ = 2.54 ppm (1H,dd)
- c δ = 2.57 ppm (2H,m)
- d δ = 2.88 ppm (1H,m)
- e δ = 3.29 ppm (3H,m)
- f δ = 3.50 ppm (2H,t)
- g δ between 3.80 and 3.92 ppm (4H,m)
- h δ = 4.35 ppm (1H,m)
- i δ between 6.43 and 7.06 ppm (3H,m)

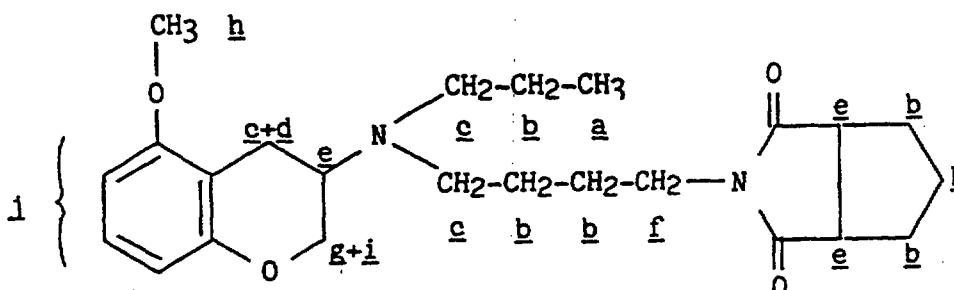
EXAMPLE 12:

3-[4-[N-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL]-
2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE

By proceeding as in Example 2, but replacing the compound of Example 2 with the compound of Example 11, the expected product is obtained.

Yield: 78 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.88 ppm (3H,m)
- b δ between 1.18 and 2.18 ppm (12H,m)
- c δ = 2.52 ppm (5H,m)
- d δ = 2.84 ppm (1H,dd)
- e δ = 3.12 ppm (3H,m)
- f δ = 3.48 ppm (2H,t)
- g δ = 3.74 ppm (1H,m)
- h δ = 3.82 ppm (3H,s)
- i δ = 4.21 ppm (1H,m)
- j δ between 6.41 and 7.06 ppm (3H,m)

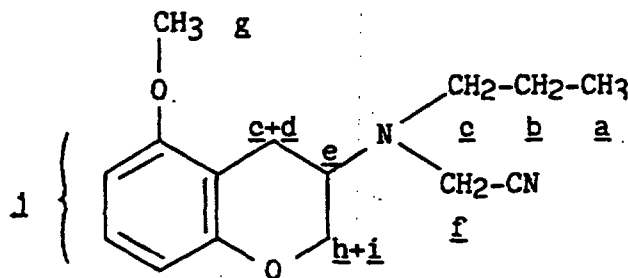
EXAMPLE 13:

5-METHOXY-3-[N-PROPYL-N-(CYANOMETHYL)-AMINO]-CHROMAN

In a round-bottomed flask, 6.8 mmol of 3-(N-propyl-amino)-5-methoxychroman (described in Patent EP 279150) are dissolved in 10 ml of dimethylformamide in the presence of 20 mmol of chloroacetonitrile, 20 mmol of potassium carbonate and a catalytic amount of potassium iodide. The mixture is stirred at 60°C for 24 hours. After cooling, the solvent is evaporated and the crude reaction product is extracted with dichloromethane after aqueous hydrolysis. After washing, drying and evaporating the organic phase, the expected product is obtained after purification by chromatography on a silica column (elution solvent: dichloromethane/methanol: 99/1).

Yield: 79 %

Proton nuclear magnetic resonance: (CDCl₃):



a δ = 0.92 ppm (3H,t)
b δ = 1.52 ppm (2H,m)
c δ = 2.68 ppm (3H,m)
d δ = 2.98 ppm (1H,dd)
e δ = 3.10 ppm (1H,m)
f δ = 3.70 ppm (2H,s)
g δ = 3.84 ppm (3H,s)
h δ = 3.91 ppm (1H,m)
i δ = 4.29 ppm (1H,m)
j δ between 6.45 and 7.08 ppm (3H,m)

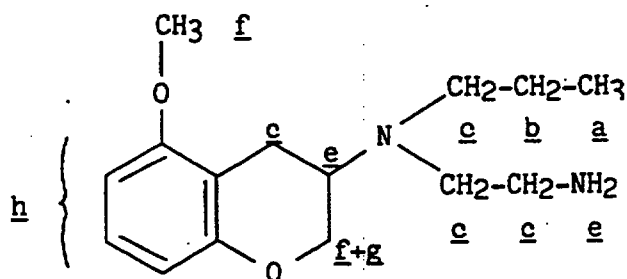
EXAMPLE 14:

5-METHOXY-3-[N-PROPYL-N-(2-AMINOETHYL)-AMINO]-CHROMAN

In a round-bottomed flask, 5.4 mmol of the compound prepared in Example 13 are dissolved in 30 ml of tetrahydrofuran. 11 mmol of LiAlH_4 are added slowly under an inert atmosphere. The reaction mixture is stirred for 30 minutes at ambient temperature. 15 ml of ice-water are then added to the mixture cooled in ice. The organic phase is then recovered, dried and evaporated and the expected product is obtained after purification by chromatography on a silica column (elution solvent: dichloromethane/methanol: 99/1).

Yield: 72 %

Proton nuclear magnetic resonance: (CDCl_3):



- a δ = 0.89 ppm (3H,t)
- b δ = 1.46 ppm (2H,m)
- c δ between 2.44 and 2.71 ppm (8H,m)
- d δ = 3.14 ppm (1H,m)
- e δ = 3.43 ppm (2H, unresolved peak)
- f δ = 3.80 ppm (4H,m)
- g δ = 4.25 ppm (1H,m)
- h δ between 6.40 and 7.04 ppm (3H,m)

EXAMPLE 15;

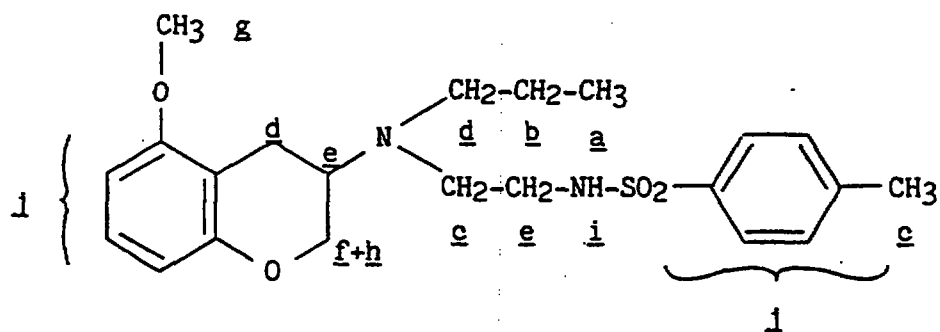
5-METHOXY-3-[N-PROPYL-N-[2-(4-TOLUENESULPHONYLAMINO)-ETHYL]-AMINO]-CHROMAN

4 mmol of the compound prepared in Example 14 are dissolved in 30 ml of dichloromethane cooled in ice.

11.4 mmol of triethylamine are added dropwise followed by 4 mmol of p-toluenesulphonyl chloride in solution in dichloromethane. The mixture is stirred for 30 minutes at ambient temperature. The solvent is then evaporated and the expected product is obtained after purification by chromatography on a silica column (elution solvent: dichloromethane).

Yield: 88 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.76 ppm (3H,t)
- b δ = 1.32 ppm (2H,m)
- c δ = 2.36 ppm (5H,m)
- d δ between 2.48 and 2.52 ppm (4H,m)
- e δ = 2.92 ppm (3H,m)
- f δ = 3.69 ppm (1H,m)
- g δ = 3.82 ppm (3H,s)
- h δ = 4.10 ppm (1H,m)
- i δ = 5.11 ppm (1H, unresolved peak)
- j δ between 6.43 and 7.73 ppm (7H,m)

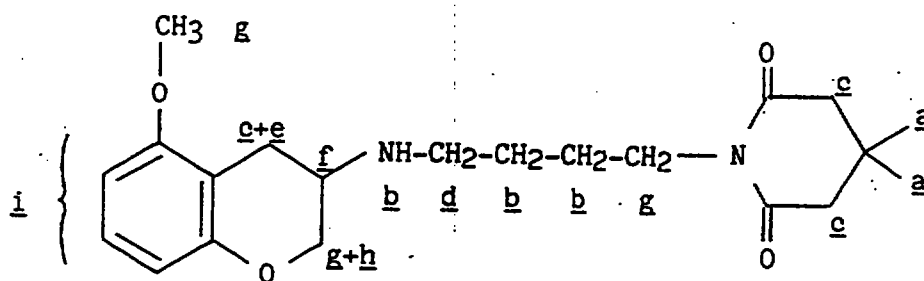
EXAMPLE 16:

5-METHOXY-3-[N-[4-(4,4-DIMETHYL-2,6-DIOXOPIPERIDIN-1-YL)-BUTYL]-AMINO]-CHROMAN

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(4-bromobutyl)-4,4-dimethyl-2,6-dioxopiperidine and stirring for 24 hours, the expected product is obtained.

Yield: 58 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 1.06 ppm (6H,s)
- b δ = 1.55 ppm (5H,m)
- c δ = 2.40 ppm (5H,m)
- d δ = 2.70 ppm (2H,m)

e δ = 2.90 ppm (1H,dd)
f δ = 3.09 ppm (1H,m)
g δ = 3.76 ppm (6H,m)
h δ = 4.17 ppm (1H,m)
i δ between 6.40 and 7.06 ppm (3H,m)

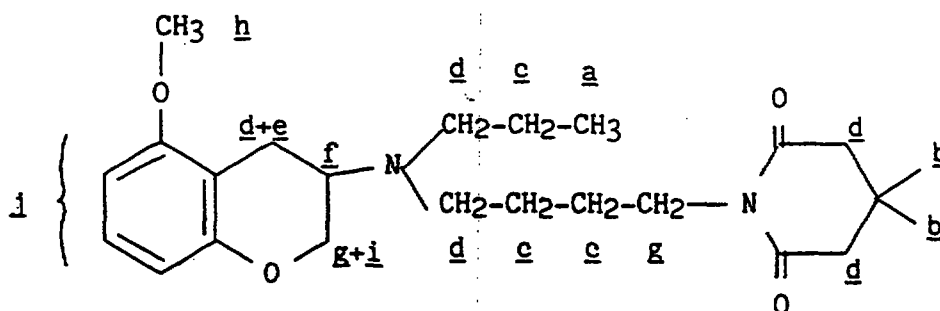
EXAMPLE 17:

5-METHOXY-3-[N-PROPYL-N-[4-(4,4-DIMETHYL-2,6-DIOXO-PIPERIDIN-1-YL)-BUTYL]-AMINO]-CHROMAN

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound of Example 16, the expected product is obtained.

Yield: 77 %

Proton nuclear magnetic resonance: (CDCl₃):



a δ = 0.88 ppm (3H,t)
b δ = 1.06 ppm (6H,s)
c δ = 1.48 ppm (6H,m)
d δ = 2.52 ppm (9H,m)
e δ = 2.84 ppm (1H,m)
f δ = 3.10 ppm (1H,m)
g δ = 3.75 ppm (3H,s)
h δ = 3.83 ppm (3H,s)
i δ = 4.26 ppm (1H,m)
j δ between 6.42 and 7.05 ppm (3H,m)

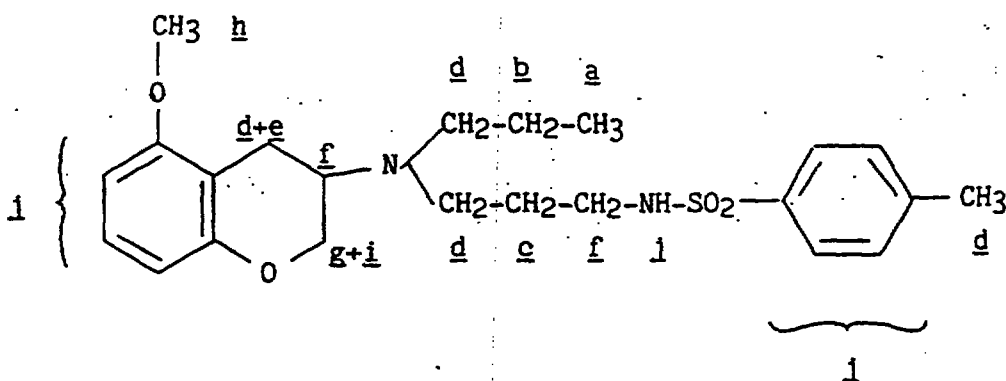
EXAMPLE 18:

5-METHOXY-3-[N-PROPYL-N-[3-(4-TOLUENESULPHONYLAMINO)-
PROPYL]-AMINO]-CHROMAN

By proceeding as in Example 1, but replacing the 3-amino-5-methoxychroman with 3-(N-propylamino)-5-methoxychroman and the N-(4-bromobutyl)-phthalimide with 1-bromo-3-(4-toluenesulphonyl)-aminopropane and stirring for 72 hours, the expected product is obtained.

Yield: 65 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.88 ppm (3H,t)
- b δ = 1.45 ppm (2H,m)
- c δ = 1.63 ppm (2H,m)
- d δ between 2.40 and 2.70 ppm (8H,m)
- e δ = 2.83 ppm (1H,dd)
- f δ = 3.08 ppm (3H,m)
- g δ = 3.75 ppm (1H,m)
- h δ = 3.83 ppm (3H,s)
- i δ = 4.17 ppm (1H,m)
- j δ between 6.25 and 7.75 ppm (8H,m)

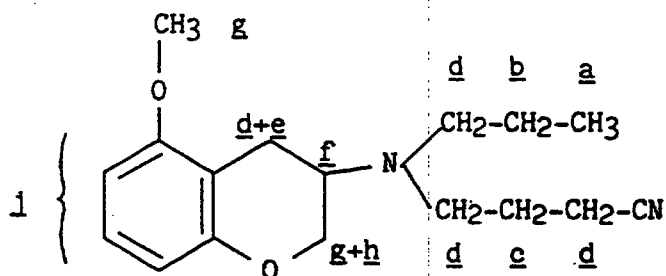
EXAMPLE 19:

5-METHOXY-3-[N-PROPYL-N-(3-CYANOPROPYL)-AMINO]-CHROMAN

By proceeding as in Example 13, but replacing the chloroacetonitrile with 4-bromobutyronitrile, the expected product is obtained.

Yield: 73 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.91 ppm (3H,t)
- b δ = 1.48 ppm (2H,m)
- c δ = 1.80 ppm (2H,m)
- d δ between 2.42 and 2.78 ppm (7H,m)
- e δ = 2.89 ppm (1H,dd)
- f δ = 3.16 ppm (1H,m)
- g δ = 3.82 ppm (4H,m)
- h δ = 4.24 ppm (1H,m)
- i δ between 6.44 and 7.07 ppm (3H,m)

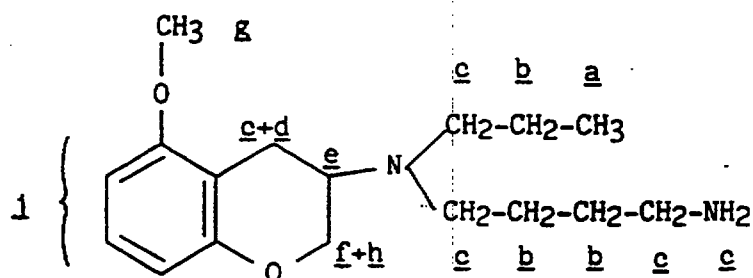
EXAMPLE 20:

5-METHOXY-3-[N-PROPYL-N-(4-AMINOBTYL)-AMINO]-CHROMAN

By proceeding as in Example 14, but replacing the compound of Example 13 with the compound of Example 19, the expected product is obtained.

Yield: 69 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.81 ppm (3H,t)
- b δ = 1.41 ppm (6H,m)
- c δ between 2.34 and 2.68 ppm (9H,m)
- d δ = 2.80 ppm (1H,dd)
- e δ = 3.07 ppm (1H,m)
- f δ = 3.68 ppm (1H,m)
- g δ = 3.76 ppm (3H,s)
- h δ = 4.18 ppm (1H,m)
- i δ between 6.33 and 6.98 ppm (3H,m)

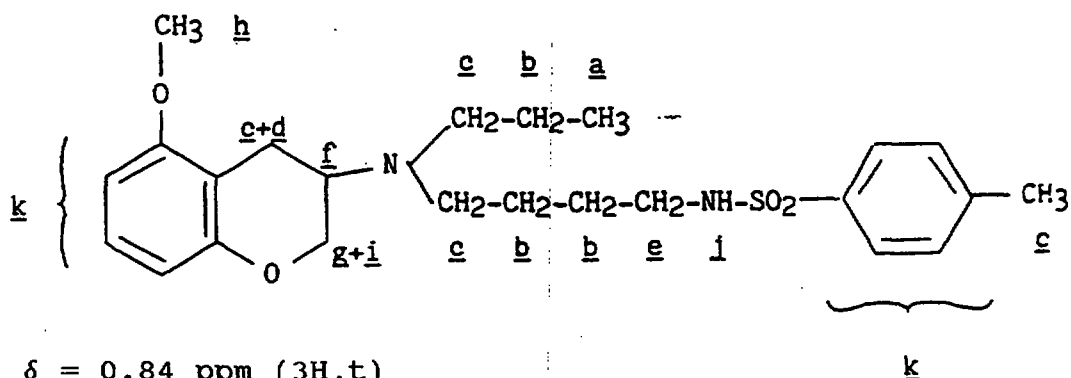
EXAMPLE 21:

5-METHOXY-3-[N-PROPYL-N-[4-(4-TOLUENESULPHONYLAMINO)-BUTYL]-AMINO]-CHROMAN

By proceeding as in Example 15, but replacing the compound of Example 14 with the compound of Example 20, the expected product is obtained.

Yield: 89 %

Proton nuclear magnetic resonance: (CDCl₃):



- a δ = 0.84 ppm (3H,t)
b δ between 1.35 and 1.57 ppm (6H,m)
c δ between 2.39 and 2.56 ppm (8H,m)
d δ = 2.83 ppm (1H,dd)
e δ = 2.94 ppm (2H,q)
f δ = 3.06 ppm (1H,m)
g δ = 3.73 ppm (1H,m)
h δ = 3.82 ppm (3H,s)
i δ = 4.21 ppm (1H,m)
j δ = 5.51 ppm (1H, unresolved peak)
k δ between 6.41 and 7.75 ppm (7H,m)

EXAMPLE 22:

3-[4-[N-PROPYL-N-(5-METHOXYTHIOCHROMAN-3-YL)-AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

By proceeding as in Example 10, but replacing the 3-amino-5-methoxychroman with 3-amino-5-methoxythiochroman, the expected product is obtained.

EXAMPLE 23:

5-METHOXY-3-{N-[4-(1,1-DIOXIDO-3-OXO-2,3-DIHYDRO-BENZISOTHIAZOL-2-YL)-BUTYL]-AMINO}-CHROMAN

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with 1,1-dioxido-3-oxo-2,3-dihydro-2-(4-bromobutyl)-benzisothiazole and stirring for 24 hours, the title product is obtained.

EXAMPLE 24:

5-METHOXY-3-{N-n-PROPYL-N-[4-(1,1-DIOXIDO-3-OXO-2,3-DIHYDROBENZISOTHIAZOL-2-YL)-BUTYL]-AMINO}-CHROMAN
(OXALATE)

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound obtained in Example 23, the expected product is obtained and is converted into a salt using oxalic acid.

Melting point: 85°C

Percentage composition:

calculated:	C 57.17	H 5.71	N 4.98	S 5.93
found:	C 56.92	H 5.88	N 5.11	S 5.84

EXAMPLE 25:

3-{2-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-ETHYL}-3-AZASPIRO-
[4.5]DECANE-2,4-DIONE

By proceeding as in Example 1, but replacing the N-(4-bromobutyl)-phthalimide with N-(2-bromobutyl)-2,4-dioxo-3-azaspiro[4.5]decane and stirring for 24 hours, the title product is obtained.

EXAMPLE 26:

3-{2-[N-n-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-ETHYL}-
3-AZASPIRO[4.5]DECANE-2,4-DIONE (OXALATE)

By proceeding as in Example 2, but replacing the compound of Example 1 with the compound obtained in Example 24, the expected product is obtained and is converted into a salt using oxalic acid.

Melting point: 56°C

EXAMPLE 27:

3-[4-[N-n-PROPYL-N-(5-HYDROXYCHROMAN-3-YL)-AMINO]-BUTYL]-3-AZASPIRO[4.5]DECANE-2,4-DIONE (OXALATE)

The product obtained in Example 10 is treated with the basic tribromide in methylene chloride at a temperature of -10°C. The title product is obtained and is converted into a salt.

Yield: 60 %

Melting point: 61°C

Percentage composition:

calculated: C 62.53 H 7.39 N 5.40

found: C 62.27 H 7.64 N 5.51

EXAMPLE 28:

⊕-3-{4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL}-2,4-DIOXO-3-AZASPIRO[4.5]DECANE OXALATE

By proceeding as in Example 9, but replacing the 3-amino-5-methoxychroman with ⊕-3-amino-5-methoxychroman (obtained by treating 3-amino-5-methoxychroman with ⊕-S-acetylvaline in a methanolic medium, filtering the solution obtained and carrying out successive crystallisations) the title product is obtained.

EXAMPLE 29:

⊕-3-{4-[N-n-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL}-2,4-DIOXO-3-AZASPIRO[4.5]DECANE OXALATE

By proceeding as in Example 10, but replacing the compound of Example 9 with the compound of Example 28, the title product is obtained and is converted into a salt using oxalic acid.

Melting point: 68°C

Rotatory power D: +50°

EXAMPLE 30:

⊖-3-(4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL)-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

By proceeding as in Example 28, but replacing the ⊕-3-amino-5-methoxychroman with ⊖-3-amino-5-methoxychroman (obtained by treating the 3-amino-5-methoxychroman with ⊖-S-acetylvaline in a methanolic medium, filtering the solution obtained and carrying out successive crystallisations) the title product is obtained.

EXAMPLE 31:

⊖-3-(4-[N-n-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL)-2,4-DIOXO-3-AZASPIRO[4.5]DECANE OXALATE

By proceeding as in Example 29, but replacing the compound of Example 28 with the compound of Example 30, the title product is obtained.

Melting point: 68°C

Rotatory power D: -50°

EXAMPLE 32:

⊕-3-(4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL)-2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE

By proceeding as in Example 11, but replacing the 3-amino-5-methoxychroman with ⊕-3-amino-5-methoxychroman, the title product is obtained.

EXAMPLE 33:

⊕ -3-{4-[N-n-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-
BUTYL}-2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE (OXALATE)

The procedure is as in Example 12, except that the compound of Example 11 is replaced with the compound of Example 32. The product is converted into a salt using oxalic acid.

Rotatory power α_D of the free amine: +57° (20 mg in 3 ml of CHCl_3)

EXAMPLE 34:

⊖ -3-{4-[N-(5-METHOXYCHROMAN-3-YL)-AMINO]-BUTYL}-2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE

By proceeding as in Example 11, but replacing the 3-amino-5-methoxychroman with ⊖-3-amino-5-methoxychroman, the title product is obtained.

EXAMPLE 35:

⊖ -3-{4-[N-n-PROPYL-N-(5-METHOXYCHROMAN-3-YL)-AMINO]-
BUTYL}-2,4-DIOXO-3-AZABICYCLO[3.3.0]OCTANE OXALATE

By proceeding as in Example 12, but replacing the compound of Example 11 with the compound obtained in Example 34, the title product is obtained and is converted into a salt using oxalic acid.

Rotatory power α_D of the free amine (20 mg, 3 ml CHCl_3):
-57°

EXAMPLE 36:

⊕-5-METHOXY-3-[N-n-PROPYL-N-(CYANOMETHYL)-AMINO]-CHROMAN

By proceeding as in Example 13, but replacing the 3-amino-5-methoxychroman with ⊕-3-amino-5-methoxychroman, the title product is obtained.

EXAMPLE 37:

⊕-5-METHOXY-3-[N-n-PROPYL-N-(2-AMINOETHYL)-AMINO]-CHROMAN

By proceeding as in Example 14, but replacing the product of Example 13 with the product obtained in Example 36, the title product is obtained.

EXAMPLE 38:

⊕-5-METHOXY-3-[N-n-PROPYL-N-[2-(4-TOLUENESULPHONYLAMINO)-ETHYL]-AMINO]-CHROMAN (OXALATE)

By proceeding as in Example 15, but replacing the product prepared in Example 14 with the product obtained in Example 37, the title product is obtained and is converted into a salt using oxalic acid.

Melting point: 132°C

Rotatory power α_D of the free amine: +44° (20 mg in 3 ml of CHCl₃)

EXAMPLE 39:

⊖-5-METHOXY-3-[N-n-PROPYL-N-(CYANOMETHYL)-AMINO]-CHROMAN

By proceeding as in Example 13, but replacing the 3-amino-5-methoxychroman with ⊖-3-amino-5-methoxychroman (obtained in Example 30), the title product is obtained.

EXAMPLE 40:

⊖ -5-METHOXY-3-[N-n-PROPYL-N-(2-AMINOETHYL)-AMINO]-CHROMAN

By proceeding as in Example 14, but replacing the product of Example 13 with the product obtained in Example 39, the title product is obtained.

EXAMPLE 41:

⊖ -5-METHOXY-3-[N-n-PROPYL-N-[2-(4-TOLUENESULPHONYLAMINO)-ETHYL]-AMINO]-CHROMAN (OXALATE)

By proceeding as in Example 15, but replacing the product prepared in Example 14 with the product obtained in Example 40, the title product is obtained and is converted into a salt using oxalic acid.

Melting point: 132°C

Rotatory power α_D of the free amine: -44° (20 mg in 3 ml of CHCl_3)

EXAMPLE 42:

⊕ -5-METHOXY-3-[N-n-PROPYL-N-(3-CYANOPROPYL)-AMINO]-CHROMAN

By proceeding as in Example 19, but replacing the 3-amino-5-methoxychroman with ⊕-3-amino-5-methoxychroman, the title product is obtained.

EXAMPLE 43:

⊕ -5-METHOXY-3-[N-n-PROPYL-N-(4-AMINO BUTYL)-AMINO]-CHROMAN

By proceeding as in Example 20, but replacing the product of Example 19 with the product obtained in Example 42, the title product is obtained.

EXAMPLE 44:

⊕ -5-METHOXY-3-[N-n-PROPYL-N-[4-(4-TOLUENESULPHONYL-AMINO)BUTYL]-AMINO]-CHROMAN (OXALATE)

By proceeding as in Example 21, but replacing the product of Example 20 with the product of Example 43, the title product is obtained and is converted into a salt using oxalic acid.

Melting point: 95°C

Rotatory power α_D of the free amine: +52° (20 mg in 3 ml of CHCl_3)

EXAMPLE 45:

⊖ -5-METHOXY-3-[N-n-PROPYL-N-(3-CYANOPROPYL)-AMINO]-CHROMAN

By proceeding as in Example 19, but replacing the 3-amino-5-methoxychroman with ⊖ -3-amino-5-methoxychroman, the title product is obtained.

EXAMPLE 46:

⊖ -5-METHOXY-3-[N-n-PROPYL-N-(4-AMINO BUTYL)-AMINO]-CHROMAN

By proceeding as in Example 20, but replacing the product of Example 19 with the product of Example 45, the title product is obtained.

EXAMPLE 47:

⊖ -5-METHOXY-3-[N-n-PROPYL-N-[4-(4-TOLUENESULPHONYL-AMINO)BUTYL]-AMINO]-CHROMAN (OXALATE)

By proceeding as in Example 21, but replacing the product of Example 20 with the product of Example 46, the title

product is obtained and is converted into a salt using oxalic acid.

Melting point: 95°C

Rotatory power of the free amine: -52° (20 mg in 3 ml of CHCl₃)

EXAMPLE 48:

N-{2-[N'-n-PROPYL-N'-(5-METHOXYCHROMANYL)-AMINO]-ETHYL}-
ACETAMIDE OXALATE

In a round-bottomed flask, 17 mmol of the compound prepared in Example 13 are dissolved in 95 ml of tetrahydrofuran. 34 mmol of LiAlH₄ are added slowly under an inert atmosphere. The reaction mixture is stirred for 30 minutes at ambient temperature. 20 ml of ethyl acetate are then added to the mixture cooled in ice. Stirring is continued for approximately 10 minutes and then 20 ml of water are added dropwise. The organic phase is separated and dried over magnesium sulphate. The solvent is evaporated under reduced pressure and the sample is purified by column chromatography using a mixture of methylene chloride and methanol. The product is converted into a salt using oxalic acid.

Yield: 75 %

Melting point: 54°C

Spectral characteristics (free base):

Infrared: 3280 cm⁻¹ (νNH)

Nuclear magnetic resonance:

δ = 1.96 ppm, singlet, 3H, CO-CH₃

EXAMPLE 49:

3-[4-[N-(5-METHOXYBENZOTHIOPYRAN-3-YL)-AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

By proceeding as in Example 9, but replacing the 3-amino-5-methoxychroman with the 3-amino-3,4-dihydro-5-methoxy-[2H]-1-benzothiopyran described in Patent Application EP 0 222 996, the title product is obtained.

Spectral characteristics:

N(CO-CH₂)₂: d: 2.59 ppm singlet

EXAMPLE 50:

5-METHOXY-3-[N-n-PROPYL-N-(CYANOMETHYL)-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 13, but replacing the 3-(N-n-propylamino)-5-methoxychroman with 3-(N-n-propylamino)-5-methoxy-1-benzothiopyran, the title product is obtained.

EXAMPLE 51:

5-METHOXY-3-[N-n-PROPYL-N-(2-AMINOETHYL)-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 14, but replacing the product of Example 13 with the product obtained in Example 50, the title product is obtained.

EXAMPLE 52:

5-METHOXY-3-[N-n-PROPYL-N-[2-(4-TOLUENESULPHONYLAMINO)-ETHYL]-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

The procedure is the same as in Example 15, except that the product of Example 14 is replaced with the compound obtained in Example 51.

Spectral characteristics:

Nuclear magnetic resonance ^1H (CDCl_3)

$\delta = 3.82$ ppm, singlet, 3H, $\text{C}_6\text{H}_4\text{-CH}_3$

EXAMPLE 53:

5-METHOXY-3-[N-n-PROPYL-N-(3-CYANOPROPYL)-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 50, but replacing the chloroacetonitrile with 4-bromobutyronitrile, the expected product is obtained.

EXAMPLE 54:

5-METHOXY-3-[N-n-PROPYL-N-(4-AMINOBTYL)-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 51, but replacing the compound of Example 50 with the compound of Example 53, the title product is obtained.

EXAMPLE 55:

5-METHOXY-3-[N-n-PROPYL-N-[4-(4-TOLUENESULPHONYLAMINO)-BTYL]-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 52, but replacing the compound of Example 51 with the compound of Example 54, the title product is obtained.

Spectral characteristics:

Nuclear magnetic resonance ^1H (CDCl_3)

$\delta = 3.82$ ppm, singlet, 3H, $\text{C}_6\text{H}_4\text{-CH}_3$

EXAMPLE 56:

5-METHOXY-3-[N-n-PROPYL-N-[3-(4-TOLUENESULPHONYLAMINO)-PROPYL]-AMINO]-3,4-DIHYDRO[2H]-1-BENZOTHIOPYRAN

By proceeding as in Example 18, but replacing the 3-(N-propylamino)-5-methoxychroman with 3-(N-propylamino)-5-methoxy-3,4-dihydro[2H]-1-benzothiopyran, the title product is obtained.

EXAMPLE 57:

N-{2-[N-n-PROPYL-N-(5-METHOXYCHROMANYL)-AMINO]-ETHYL}-ISOBUTYRAMIDE

The procedure is as in Example 48 except that the ethyl acetate is replaced with ethyl isobutyrate.

By replacing the 3-amino-5-methoxychroman in the preceding Examples with 3-amino-6-methoxychroman, 3-amino-7-methoxychroman and 3-amino-8-methoxychroman, respectively, or by replacing the 3-amino-5-methoxy-3,4-dihydro[2H]-1-benzothiopyran with 3-amino-6-methoxy-3,4-dihydro[2H]-1-benzothiopyran, with 3-amino-7-methoxychroman and with 3-amino-8-methoxychroman, the isomers of Examples 1 to 56 methoxylated in positions 6, 7 and 8, respectively, are obtained.

PHARMACOLOGICAL STUDY OF THE COMPOUNDS OF THE INVENTION

EXAMPLE 58:

IN VITRO AFFINITY TESTS FOR 5-HT_{1A}, D₂ AND α_2 RECEPTORS

The in vitro affinity tests for 5-HT_{1A}, D₂ and α_2 receptors were carried out in accordance with customary binding techniques.

The results of the studies show that the compounds of the

invention possess $K_{0.5}$ of the order of 10^{-10} M in respect of 5-HT_{1A} receptors. That very great affinity is complemented by a very high degree of selectivity. The ratio of the 5-HT_{1A}/D₂ affinities is 10^2 ; that of the 5-HT_{1A}/ α_2 affinities is 10^4 .

EXAMPLE 59:

ACUTE TOXICITY STUDY

Acute toxicity was brought about after the oral administration to groups of five mice (20 $\pm$ 2 grams) of increasing doses (0.1 - 0.25 - 0.50 - 0.75 - 1 g.kg⁻¹) of the products of the invention.

The animals were observed at regular intervals in the course of the first day and daily for the two weeks following the treatment. It seems that the compounds of the invention are completely non-toxic. No deaths were observed after the administration of a dose of 1 g.kg⁻¹. No disorders were observed after the administration of that dose.

EXAMPLE 60:

5HT_{1A}-AGONISTIC ACTIVITY

LOWER LIP RETRACTION TEST IN RATS

The protocol used is that described by Berendsen et al. (Berendsen H.H.G., Jenck F; Broekkamp C.L.E. Pharmacology Biochemistry and Behavior 1989, 33, 821-827).

The compounds of the invention are administered to rats which are immediately placed in individual transparent plastics cages (20 x 10 x 10 cm).

The retraction of the lower lip is noted every 15 minutes for the three hours following injection in the following

manner:

- 0 = lower incisors not visible
- 1 = lower incisors partially visible
- 2 = lower incisors completely visible

The scores are added up for each rat and the effect obtained is expressed as a percentage of the possible maximum in three hours.

Six rats are used per group. The experiment is carried out simultaneously on a blind control. The products were administered subcutaneously at doses of 0.5, 2 and 8 mg.kg⁻¹.

That test shows that the compounds of the invention exhibit an intense 5HT_{1A}-agonistic activity.

EXAMPLE 61:

STUDY OF ANTIDEPRESSIVE ACTIVITY

EFFECT ON ESCAPE FAILURES

The products are studied using the learned helplessness model which consists in inducing in the animal, by a series of uncontrollable aversive events, a deficiency during later avoidance tasks. (Martin *et al.*, 1986, Pharmacol. Biochem. Behav., 24, 177-181).

We use male Wistar A.F. rats of uniform CERJ breed weighing from 180 to 200 grams. The animals are kept in the animal house for one week before the test, in plastics boxes in groups of 10, at an ambient temperature of 21°C ± 1°C, with free access to water and food.

The animals are isolated in small boxes and are subjected to 60 unavoidable electric shocks (0.8 mA every minute ± 15 seconds). A group of control rats are not

subjected to electric shocks. The capacity of the animals to learn avoidance (shuttle-box) is evaluated 48 hours later and for 3 consecutive days. In the learning sessions, the animals undergo 2 tests per minute for 15 minutes. The number of escape failures is noted for each rat. The animals are treated (i.p.; 0.5 ml/100 g) 6 hours after the unavoidable shocks and for 4 consecutive days, in the morning 30 minutes before the shuttle-box session and in the evening between 6 p.m. and 7 p.m. The products studied are dissolved in distilled water. The products studied are administered at doses of 0.25 mg/kg/day.

The test proves that the products of the invention significantly reduce the number of escape failures, which demonstrates an activity of the antidepressive type.

EXAMPLE 62:

ANTIHYPERTENSIVE ACTIVITY

The animals are acclimatised for a period of six days before the start of the study.

At the beginning of the experiment the rats are anaesthetised with 1000 mg.kg⁻¹ of urethane administered intraperitoneally. A catheter is introduced into the jugular vein.

A catheter connected to a precision recorder is placed in the carotid artery. An interval of 10 minutes is allowed to elapse in order to allow the blood pressure to stabilise before the first measurement is taken.

In a first period, the solvent is administered intravenously to all the animals, the blood pressure is recorded

for 30 minutes after administration and readings of the blood pressure are taken 10, 20 and 30 minutes after administration.

The compounds of the invention are administered in saline solution likewise intravenously. The blood pressure is recorded for 30 minutes and the pressure is measured 10, 20 and 30 minutes after administration. The products of the invention bring about a significant reduction in blood pressure.

EXAMPLE 63:

ANXIOLYTIC ACTIVITY STUDY - CONFLICT TEST IN PIGEONS

Six White Carneaux pigeons that have not previously been used in experiments are trained to peck a Plexiglas key which is transilluminated with red or white lights. The response key is mounted on the front wall of the experimental chamber. The pigeons are reduced to 85 % of their normal weight before the start of the experiment, which is conducted using the successive approximations method (Frester 1953). At the beginning, each pecking of the key (illuminated with a red or white light) that exceeds a force of 0.15N permits access to a mixture of cereals by means of an automatic dispenser arranged under the key. After several days, the cereals are not delivered until the key is pecked for the thirtieth time. When that response to the 30th peck is obtained and when it occurs in a regular manner, permitting the delivery of food, the colour of the key light alternates every three minutes (from white to red and vice versa). The measurement of the rate of response to the 30th peck remains in force for each light phase. During that phase and for the duration of the experiment, a daily session consists of 5 cycles of 3 minutes of each light sequence, those sequences being separated by a pause of 30 seconds during

which the light keys are extinguished and the responses have no result. Consequently, a sequence lasts approximately from 35 to 40 minutes. When the response rates are stable and identical for each colour for a period of 5 days (which requires from 3 to 4 weeks) each 30th response in one of the coloured phases simultaneously brings about a release of food and a brief (200 milliseconds) and moderate (1.3 mA) electric shock delivered by electrodes arranged at the level of the pubic bones. The response rate is reduced in a first period and then returns to the initial level.

The products of the invention are administered when the response rate has been stable for a period of 5 days.

The intramuscular administration of the products of the invention at a dose of 0.3 mg.kg^{-1} brings about a significant increase in responses whether followed or not followed by electric shocks, which proves the anxiolytic activity of those products.

EXAMPLE 64:

PHARMACEUTICAL COMPOSITION

Tablets each containing 10 mg of $\odot$ -3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azaspiro[4.5]decane.

Formula for 1000 tablets:

$\odot$ -3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azaspiro[4.5]decane	10 g
wheat starch	15 g
corn starch	15 g
lactose	65 g

magnesium stearate	2 g
silica	1 g
hydroxypropylcellulose	2 g

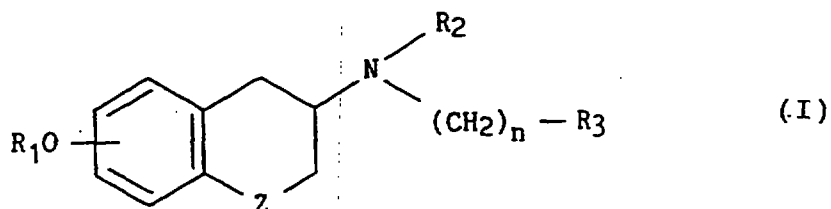


European Patent Application No. 91400942.8

CLAIMS for the Contracting States:

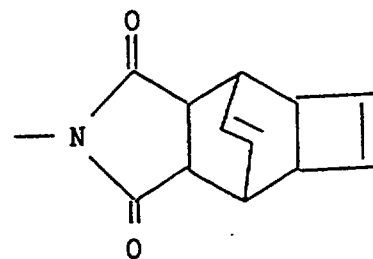
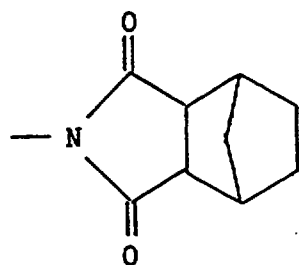
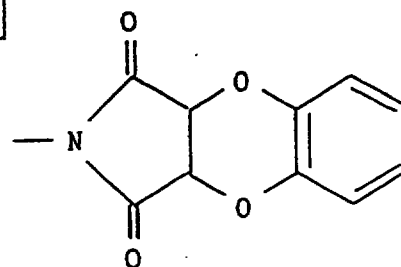
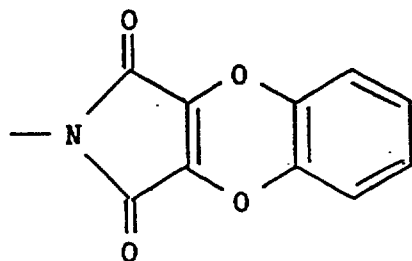
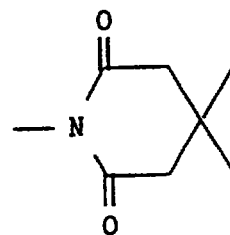
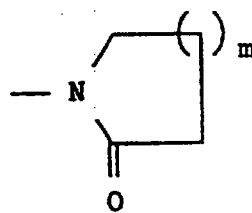
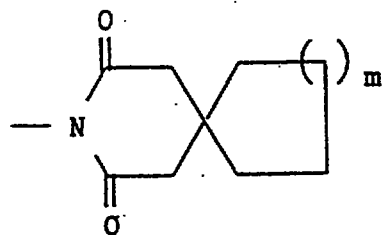
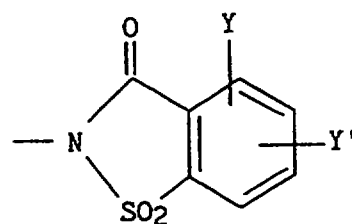
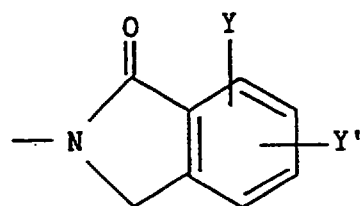
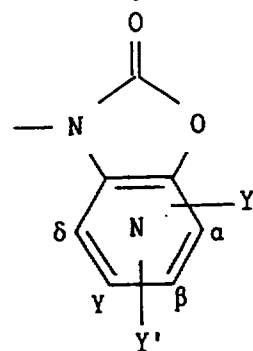
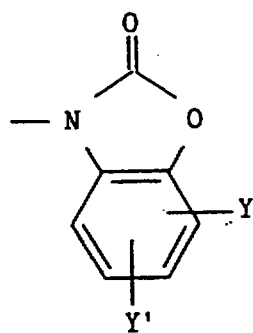
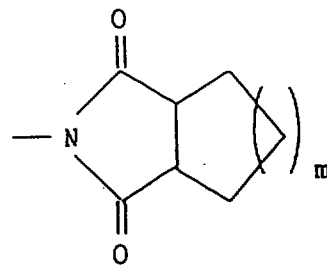
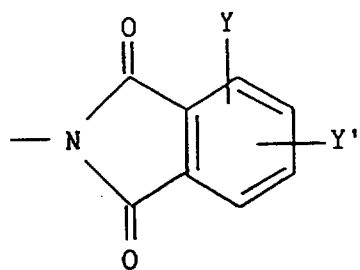
AT, LI, NL, BE, DE, FR,
IT, SE, CH, DK, GB, LU

1. Compounds of the general formula (I):



wherein:

- Z represents an oxygen atom or a sulphur atom,
- R₁ represents a hydrogen atom, or a linear or branched (C₁-C₆)-alkyl grouping,
- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆)-alkyl grouping,
- n is an integer from 1 to 6, and
- R₃ represents a nitrile grouping, or an amino grouping optionally substituted by:
 - . a linear or branched acyl grouping containing from 2 to 7 carbon atoms,
 - . an alkylsulphonyl grouping,
 - . an arylsulphonyl grouping optionally substituted by an alkyl, alkoxy or hydroxy grouping or a halogen atom, or
 - . a linear or branched (C₁-C₆)-alkyl grouping,
- or R₃ represents any one of the following groupings:





wherein:

- . Y and Y', which may be identical or different, represent a hydrogen atom, a halogen atom, or an alkyl, alkoxy or hydroxy grouping,
- . m is an integer equal to 1 or 2,
- . and the nitrogen of the pyridine ring is in the α , β , γ or δ ring junction position,

their enantiomers, diastereoisomers and epimers and also their addition salts with a pharmaceutically acceptable acid.

2. Compounds according to claim 1 such that R_1 is a methyl grouping.

3. Compounds according to claim 1 such that R_2 is an n-propyl grouping.

4. Compounds according to claim 1 such that OR_1 is in the 5-position.

5. Compounds according to claim 1 such that R_2 is a hydrogen atom.

6. Compound according to claim 1 which is 3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azaspiro[4.5]decane, its isomers and also its addition salts with a pharmaceutically acceptable acid.

7. Compound according to claim 1 which is $\ominus$ -3-[4-[N-n-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azaspiro[4.5]decane, and also its addition salts with a pharmaceutically acceptable acid.

8. Compound according to claim 1 which is $\oplus$ -3-[4-[N-n-



propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azaspiro[4.5]decane, and also its addition salts with a pharmaceutically acceptable acid.

9. Compound according to claim 1 which is 5-methoxy-3-[N-propyl-N-[2-(4-toluenesulphonylamino)-ethyl]-amino]-chroman, its isomers and also its addition salts with a pharmaceutically acceptable acid.

10. Compound according to claim 1 which is $\oplus$ -5-methoxy-3-[N-propyl-N-[2-(4-toluenesulphonylamino)-ethyl]-amino]-chroman, and also its addition salts with a pharmaceutically acceptable acid.

11. Compound according to claim 1 which is $\ominus$ -5-methoxy-3-[N-propyl-N-[2-(4-toluenesulphonylamino)-ethyl]-amino]-chroman, and also its addition salts with a pharmaceutically acceptable acid.

12. Compound according to claim 1 which is 5-methoxy-3-[N-n-propyl-N-[4-(4-toluenesulphonylamino)-butyl]-amino]-chroman, its isomers and also its addition salts with a pharmaceutically acceptable acid.

13. Compound according to claim 1 which is $\oplus$ -5-methoxy-3-[N-n-propyl-N-[4-(4-toluenesulphonylamino)-butyl]-amino]-chroman, and also its addition salts with a pharmaceutically acceptable acid.

14. Compound according to claim 1 which is $\ominus$ -5-methoxy-3-[N-n-propyl-N-[4-(4-toluenesulphonylamino)-butyl]-amino]-chroman, and also its addition salts with a pharmaceutically acceptable acid.

15. Compound according to claim 1 which is 3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-



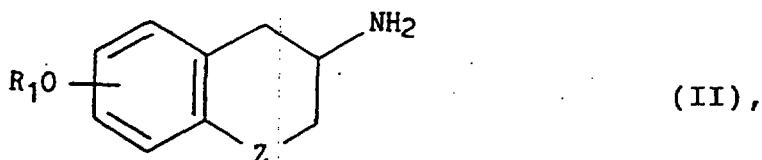
3-azabicyclo[3.3.0]octane, its isomers and also its addition salts with a pharmaceutically acceptable acid.

16. Compound according to claim 1 which is $\oplus$ -3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane, and also its addition salts with a pharmaceutically acceptable acid.

17. Compound according to claim 1 which is $\ominus$ -3-[4-[N-propyl-N-(5-methoxychroman-3-yl)-amino]-butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane, and also its addition salts with a pharmaceutically acceptable acid.

18. Process for the preparation of the compounds of formula (I), characterised in that there is used as starting material:

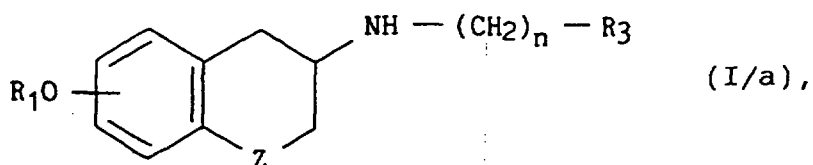
a a compound of formula (II):



wherein R_1 and Z are as defined in formula (I), which is reacted with a compound of formula (III):



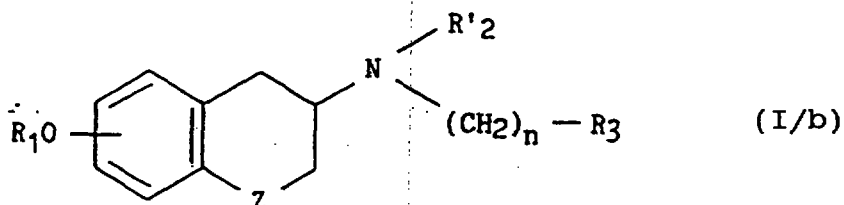
wherein R_3 and n are as defined in formula (I) and X is a halogen atom,
to yield a compound of formula (I/a), a particular case of the compounds of formula (I):



wherein R_1 , R_3 , Z and n are as defined in formula (I), which is optionally subjected to the action of a compound of formula (IV):



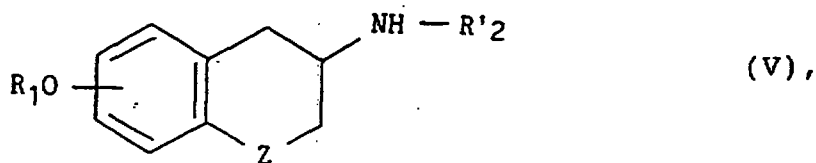
wherein R'₂ represents a linear or branched (C₁-C₆)-alkyl grouping and X represents a halogen atom, to yield a compound of formula (I/b), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

or

b a compound of formula (V):



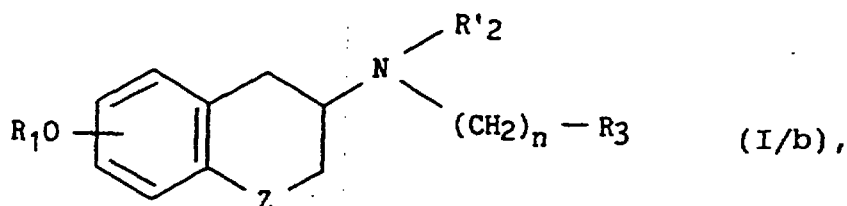
wherein R_1 , Z and R'_2 are as defined above, which is reacted:



- either with a compound of formula (III):



wherein R_3 , n and X are as defined above,
to yield a compound of formula (I/b), a particular case
of the compounds of formula (I):

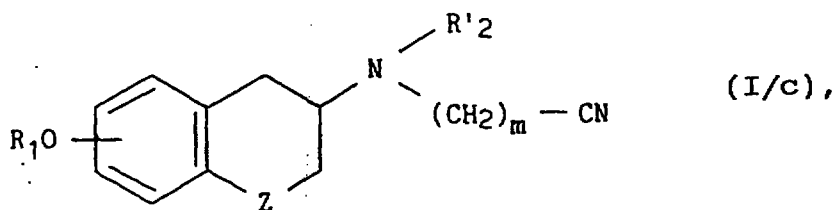


wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

- or with a compound of formula (III/a):



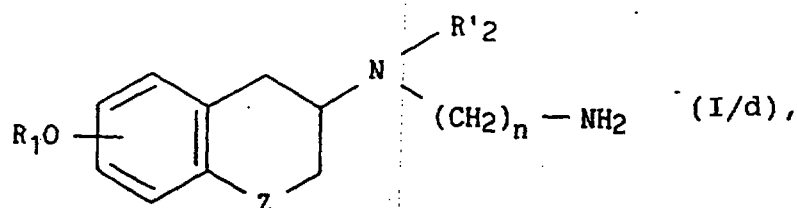
wherein X is as defined above and m is an integer from 1
to 3,
to yield a compound of formula (I/c), a particular case
of the compounds of formula (I):



wherein R_1 , Z , R'_2 and m are as defined above,
which is reduced catalytically in the presence of Raney



nickel and ammonia, or chemically by lithium aluminium hydride or by sodium in alcohol, to yield the compound of formula (I/d), a particular case of the compounds of formula (I):

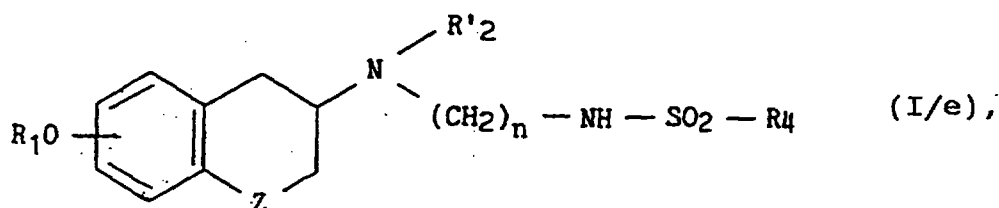


wherein R_1 , Z , R'_2 and n are as defined above, which is reacted:

either with a compound of formula (VI/A):



wherein R_{4A} is an alkyl grouping or an aryl grouping optionally substituted by an alkyl grouping and X is a halogen atom, to yield a compound of formula (I/e), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_4 and n are as defined above,

or with a compound of formula (VI/B):

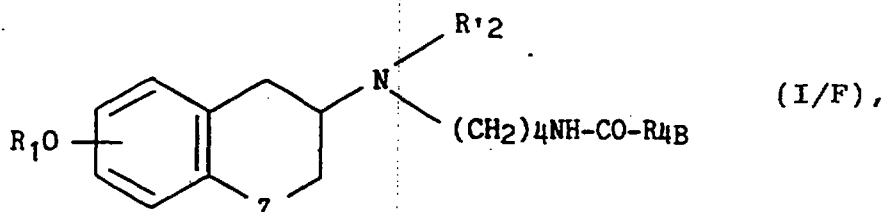




wherein R_{4B} represents a linear or branched alkyl grouping having from 1 to 6 carbon atoms and T is a leaving group selected from halogen, or lower alkoxy or with a compound of formula (VI/C):



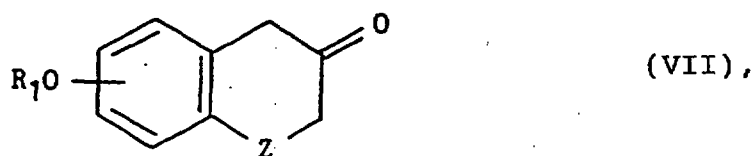
wherein R_{4B} is as defined above, to yield a compound of formula (I/F):



wherein R_1 , Z, R'_2 , R_{4B} and n are as defined above, a particular case of the compounds of formula (I) in which R_3 represents an amino grouping substituted by a linear or branched acyl grouping having from 2 to 7 carbon atoms,

or

or a compound of formula (VII):



wherein R_1 and Z are as defined in formula (I), which is



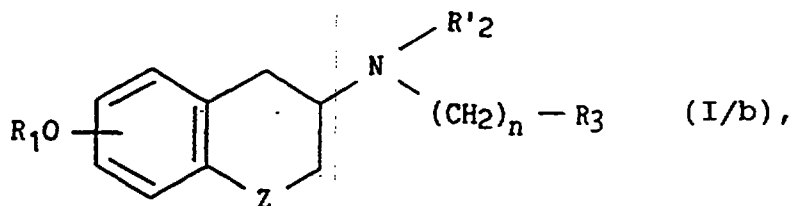
subjected to a reductive amination in the presence of a compound of formula (VIII):



wherein R_2 , R_3 and n are as defined in formula (I), to yield a compound of formula (I) which, when R_2 represents a hydrogen atom, may be subjected to the action of a compound of formula (IV):



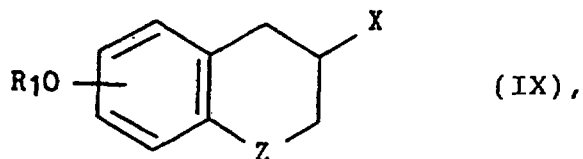
wherein R'_2 and X are as defined above, to yield a compound of formula (I/b), a particular case of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

or

d a compound of formula (IX):



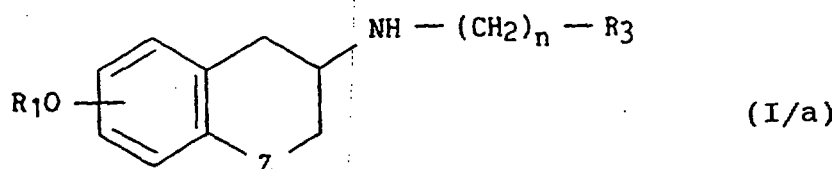
wherein R_1 and Z are as defined in formula (I) and X is a halogen atom, which is subjected to the action of a



compound of formula (X):



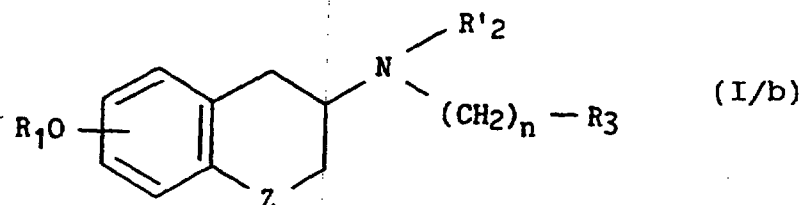
wherein n and R_3 are as defined above,
to yield a compound of formula (I/a), a particular case
of the compounds of formula (I):



wherein R_1 , Z , n and R_3 are as defined above, which is
optionally subjected to the action of a compound of
formula (IV)



wherein R'_2 and X are as defined above,
to yield a compound of formula (I/b), a particular case
of the compounds of formula (I):



wherein R_1 , Z , R'_2 , R_3 and n are as defined above,

the isomers of which compounds of formulae (I/a), (I/b),
(I/c), (I/d) and (I/e) are optionally separated in
accordance with a conventional separation technique, and



which compounds are purified by a conventional purification technique and are converted, if desired, into their addition salts with a pharmaceutically acceptable acid.

19. Pharmaceutical compositions containing as active ingredient at least one compound according to any one of claims 1 to 17, alone or in combination with one or more pharmaceutically acceptable inert, non-toxic excipients or carriers.

20. Pharmaceutical compositions according to claim 19 containing at least one active ingredient according to any one of claims 1 to 17, for use in the treatment of depression, stress, psychoses, anxiety, pain, schizophrenia, hypertension, prevention of atheromas and as modifiers of eating and sexual behaviour.