

AUSTRALIA
Patents Act 1990

P/00/001 28/6/91
Section 29

647834

PATENT REQUEST: STANDARD PATENT/PATENT OF ADDITION

We, being the person(s) identified below as the Applicant, request the grant of a patent to the person identified below as the Nominated Person, for an invention described in the accompanying standard complete specification.

Full application details follow.

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[70] Nominated Person: ADIR ET COMPAGNIE
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[54] Invention Title: NEW PROCESS FOR THE SYNTHESIS OF ENANTIOMERS OF
3-AMINOCHROMAN COMPOUNDS

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BASIC CONVENTION APPLICATION(S) DETAILS

[31] Application Number	[33] Country	Country Code	[32] Date of Application
9108147	France	FR	1st July 1991

Drawing number recommended to accompany the abstract

By my/our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Louis C. Gebhardt

Registered Patent Attorney

.....29th June 1992.....
(Date)

AUSTRALIA

Patents Act 1990

NOTICE OF ENTITLEMENT

We, ADIR ET COMPAGNIE, of rue Carle Hebert, F-92415 Courbevoie Cedex, France,
being the applicant in respect of Application No. 18661/92 state the following:-

Part 1

The Person nominated for the grant of the patent has entitlement from the actual
inventors by assignment.

Part 3

The person nominated for the grant of the patent is the applicant of the basic
application listed on the patent request form.

The basic application listed on the request form is the first application made in a
Convention country in respect of the invention.

By our Patent Attorneys,
WATERMARK PATENT & TRADEMARK ATTORNEYS

Louis C. Gebhardt

Registered Patent Attorney

10 December 1993

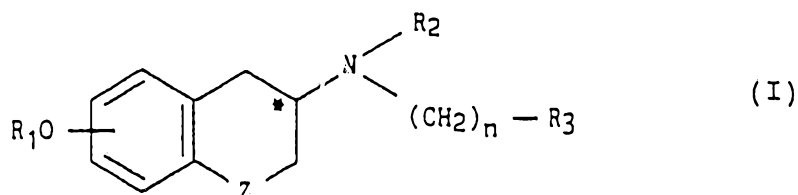


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(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 647634

- (54) Title
NEW PROCESS FOR THE SYNTHESIS OF ENANTIOMERS OF 3-AMINOCHROMAN COMPOUNDS
- International Patent Classification(s)
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- (71) Applicant(s)
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- (56) Prior Art Documents
AU 634368 74146/91 C07D 405/12 A61K 031/35
AU 45353/85 C07D 404/12
AU 38989/89 C07D 311/58
- (57) Claim

1. A process for the synthesis of enantiomers of compounds of general formula (I):



in which:

- Z represents an oxygen atom or a sulfur atom,
- R₁ represents a hydrogen atom, a linear or branched (C₁-C₆) alkyl group,
- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,
- n is an integer between 1 and 6,
- R₃ represents a nitrile group, an amino group which is optionally substituted by:
 - a linear or branched acyl group containing 2 to 7 carbon atoms,
 - an alkylsulfonyl group,
 - an arylsulfonyl group which is optionally

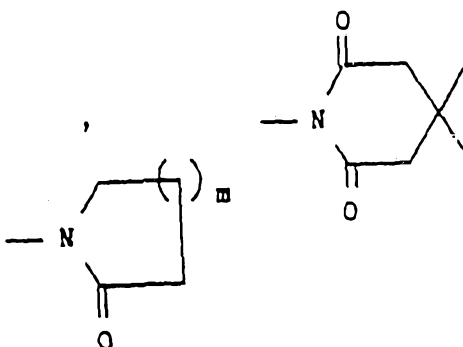
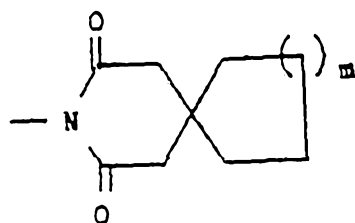
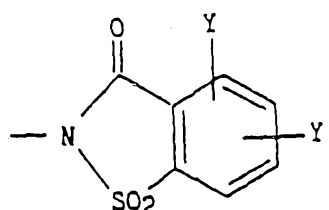
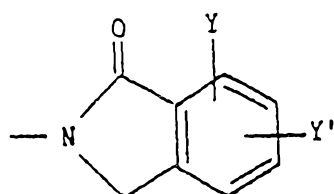
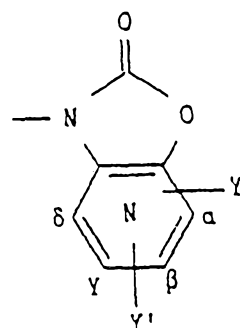
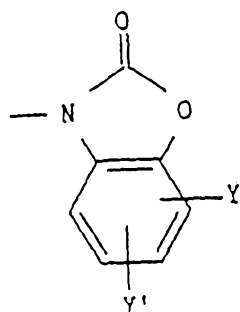
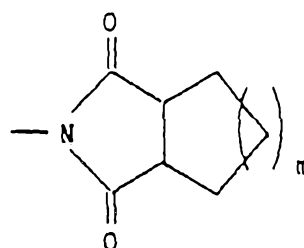
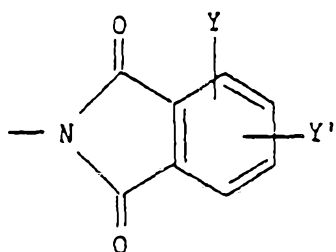
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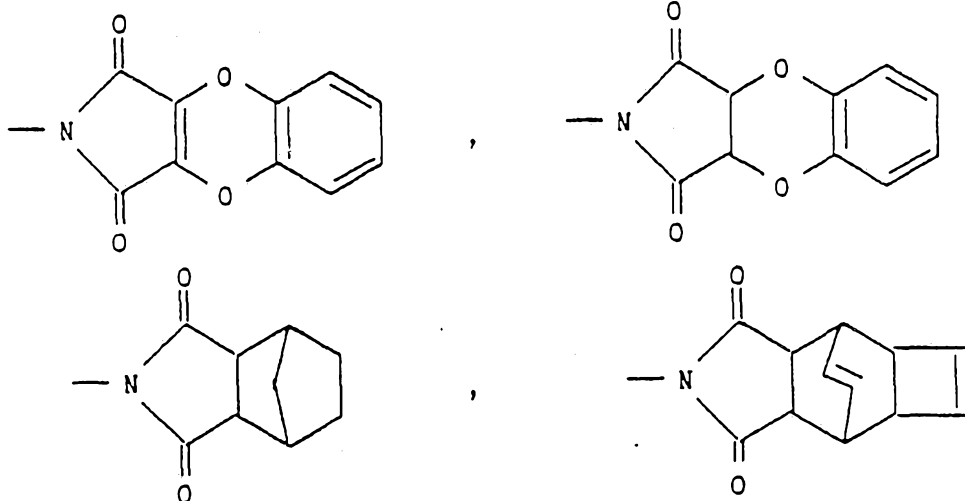
substituted by an alkyl, alkoxy or hydroxyl group or by a halogen atom,

- a linear or branched (C_1-C_6) alkyl group,
- or R_3 represents any one of the following groups:



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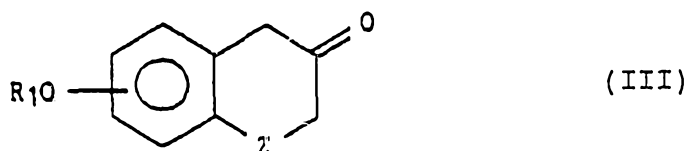


in which:

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

their enantiomers, diastereoisomers and epimers as well as their addition salts with a pharmaceutically acceptable acid,

wherein a compound of formula (III):



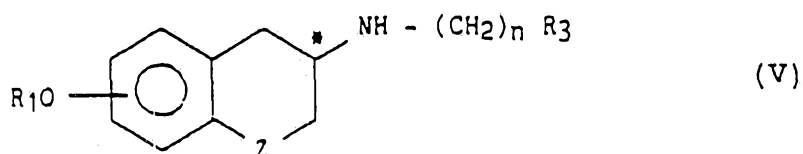
where R_1 and Z are defined as in formula (I), which is described in Patent Application EP-0,222,996, is used as raw material, and which compound is subjected to reductive amination preferably at ambient temperature and pressure in the presence of a catalyst, with a compound of general formula (IV):



where n and R_3 are defined as in formula (I), to give a compound of formula (V):

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where R_1 , R_3 , Z and n are defined as above,
which is a specific example of the compounds of formula
(I) for which R_2 represents a hydrogen atom,
the (+) and (-) isomers of which are separated by forming
an organic solution and by adding an optically active
acid thereto, and by subjecting to crystallization, one
of the two enantiomers crystallizing, the other remaining
in solution,

the chosen isomer is then treated, when, in the compound
of formula (I) which it is desired to obtain, R_2 repre-
sents a linear or branched C_1 - C_6 alkyl group,
with a compound of formula (VI):



in which X represents a halogen atom and R'_2 represents a
linear or branched C_1 - C_6 alkyl group,
specifically to give one enantiomer of the compound of
formula (I).

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Regulation 3.2(2)

Patents Act 1990

**ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT**

Application Number:

Lodged:

Invention Title:

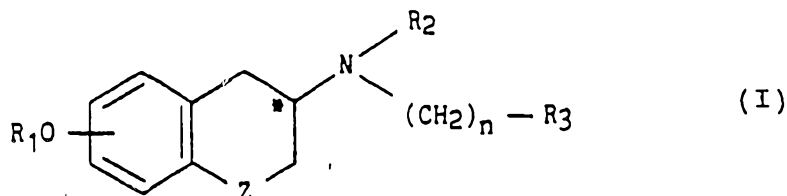
NEW PROCESS FOR THE SYNTHESIS OF ENANTIOMERS
OF 3-AMINOCHROMAN COMPOUNDS

The following statement is a full description of this invention, including the
best method of performing it known to :-

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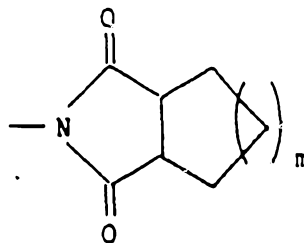
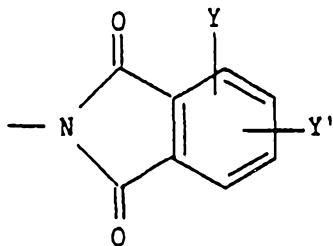
The present invention relates to a new process for the synthesis of enantiomers of 3-aminochroman compounds.

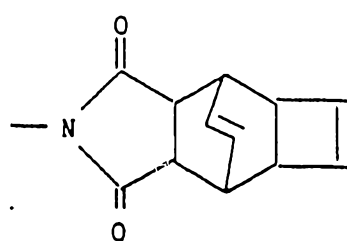
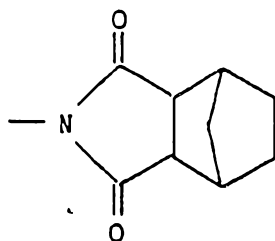
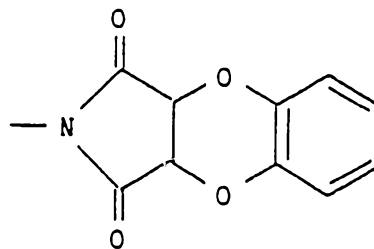
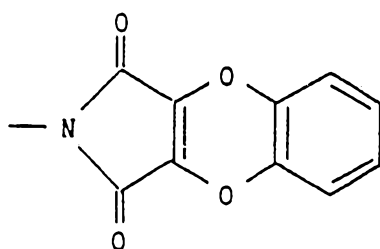
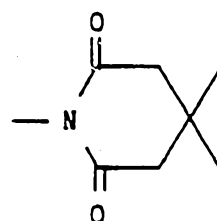
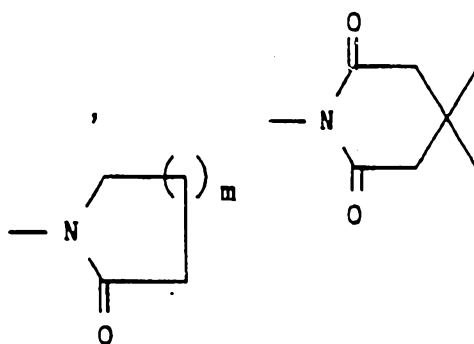
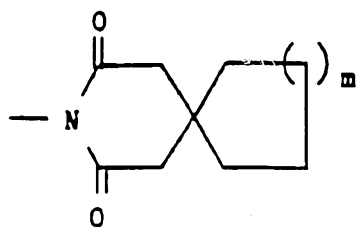
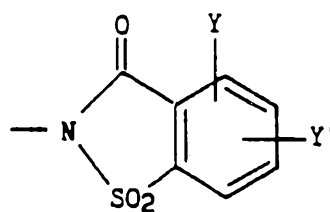
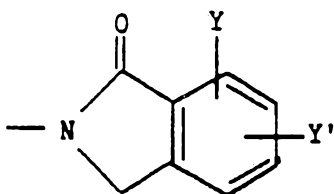
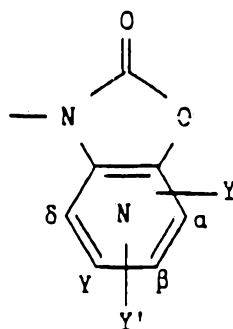
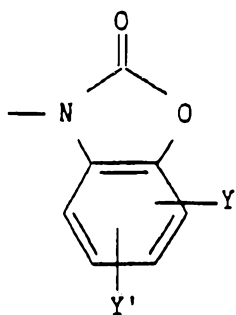
More specifically, the present invention relates to a new process for the synthesis of enantiomers of compounds of general formula (I):



in which:

- Z represents an oxygen atom or a sulfur atom,
- R_1 represents a hydrogen atom, a linear or branched (C_1-C_6) alkyl group,
- R_2 represents a hydrogen atom or a linear or branched (C_1-C_6) alkyl group,
- n is an integer between 1 and 6,
- R_3 represents a nitrile group, an amino group which is optionally substituted by:
 - a linear or branched acyl group containing 2 to 7 carbon atoms,
 - an alkylsulfonyl group,
 - an arylsulfonyl group which is optionally substituted by an alkyl, alkoxy or hydroxyl group or by a halogen atom,
 - a linear or branched (C_1-C_6) alkyl group,
- or R_3 represents any one of the following groups:





in which:

- Y and Y', which are identical or different, represent a hydrogen atom, a halogen atom, an alkyl, alkoxy or hydroxyl group,
- 5 • m is an integer equal to 1 or 2,
- and the nitrogen of the pyridine ring is situated in the α , β , γ or δ position of the ring junction,

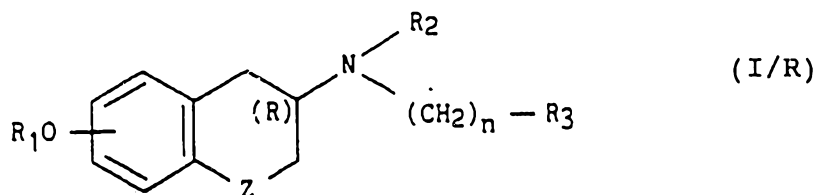
their enantiomers, diastereoisomers and epimers as well as their addition salts with a pharmaceutically acceptable acid.

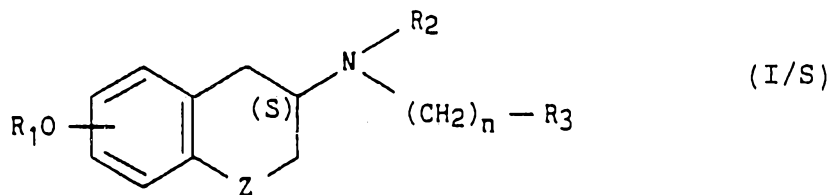
The compounds of formula (I) as well as their addition salts with a pharmaceutically acceptable acid have useful pharmacological properties.

15 Binding assays have shown that the compounds of formula (I) behave as very potent 5-HT_{1A} receptor ligands, with an agonist or antagonist activity at a level of the central nervous system. This very high affinity is accompanied by a very high selectivity towards these
20 receptors compared with the D₂ and α_2 receptors.

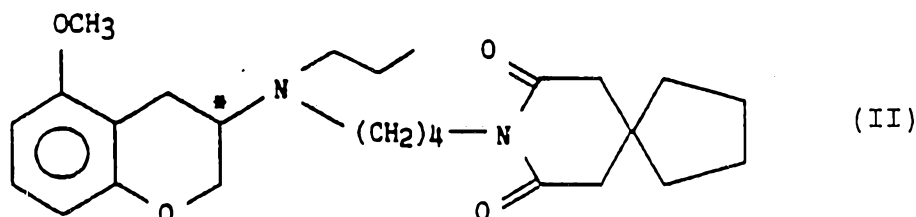
The compounds of formula (I) find their application in the treatment of stress, anxiety, depression, schizophrenia and pain, cardiovascular diseases and hypertension. They can also modify dietary and sexual
25 behavior.

The compounds of formula (I) possess an asymmetric carbon carrying the nitrogen-containing functional group and therefore exist in the form of two isomers which, according to the nomenclature introduced
30 by R.S. Cahn, Sir C. Ingold and V. Prelog, are termed (R) and (S).





The activities of the compounds of formula (I/R) and (I/S) are quite different. The configuration of the asymmetric carbon causes substantial modifications in the affinity and the selectivity of the relevant product towards the various categories of receptors and consequently, on its pharmacological activity and its side effects. For example, the compound of formula (II):



exists in the form of two enantiomers R and S whose specific rotation is evidently different. This specific rotation is noted (+) or (-) depending on whether the enantiomer deflects polarized light to the right or to the left.

If conventional binding techniques are used, the affinity of the (+) isomer of the compound of formula (II), expressed as $K_{0.5}$, is 2×10^{-10} for the 5HT_{1A} receptors and 2×10^{-8} for the D₂ receptors, which is equivalent to a selectivity of the order of 100.

In the case of the (-) isomer, the K_i is 2×10^{-9} for the 5HT_{1A} receptors and 10^{-8} for the D₂ receptors, which is equivalent to a selectivity of the order of 5.

Consequently, the affinity of the (+) isomer for the 5HT_{1A} receptors is about 10 times higher than that of the (-) isomer and the specificity is 20 times better.

It is therefore essential, in the case of these compounds, to be able to use a synthesis process which enables one of these two enantiomers to be selectively obtained.

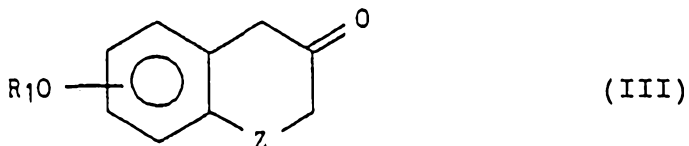
Processes for the synthesis of the racemates of the compounds of formula (I) have been described in Application FR 90,04481.

However, Application FR 90,04481 performs the separation of the isomers at the level of 3-amino-2-chroman which is the raw material, and continues the synthesis from the enantiomer chosen. Now, the separation is a complex stage which is costly in terms of product, and performing a synthesis from raw materials which need to be resolved beforehand is not industrially viable since it is very costly. There is loss of raw material and therefore financial loss at each stage of the synthesis, the yields never being totally quantitative.

The Applicant has now discovered the means for improving this synthesis by performing the separation of the enantiomers only at the stage corresponding to the products of formula (I), which is the final stage of the synthesis.

To this end, the Applicant uses a raw material with a chroman structure lacking an asymmetric carbon, such as a known chromanone or its sulfur-containing homolog, and which is of low cost price.

The process according to the invention is more specifically one in which a compound of general formula (III):

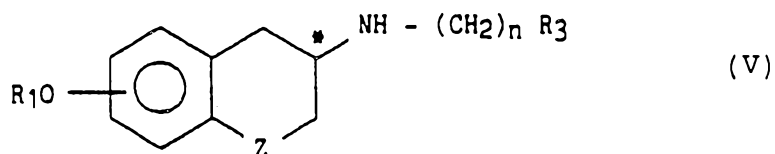


where R_1 and Z are as defined in formula (I), which is described in Patent Application EP-0,222,996, is used as raw material, and which compound is subjected to reductive amination preferably at ambient temperature and pressure in the presence of a catalyst, with a compound of general formula (IV):



where n and R_3 are defined as in formula (I),

to give a compound of formula (V):



where R_1 , R_3 , Z and n are defined as above,
 which is a specific example of the compounds of formula
 5 (I) for which R_2 represents a hydrogen atom,
 the (+) and (-) isomers of which are separated by forming
 an organic solution and by adding an optically active
 acid thereto, preferably chosen from citric, tartaric,
 diacyl tartaric, maleic, malic, tosyl glutamic,
 10 camphorsulfonic, camphoric, camphanic, mandelic or quinic
 acid, and then subjecting to crystallization and
 separation of the two enantiomers, one precipitating and
 the other remaining in suspension, thus permitting their
 separation,

15 the chosen isomer is treated, when, in the compound of
 formula (I) which it is desired to obtain, R_2 represents
 a linear or branched C_1 - C_6 alkyl group,
 with a compound of formula (VI):



20 in which X represents a halogen atom and R'_2 represents a
 linear or branched C_1 - C_6 alkyl group,
 specifically to give one enantiomer of the compound of
 formula (I).

A variant of the process according to the
 25 invention consists, when, in the compound of formula (I)
 which it is desired to obtain, R_2 represents a C_1 - C_6 alkyl
 group, in treating the compound of formula (V) as defined
 above with a compound of formula (VI) as defined above,
 to give a compound of formula (I) in the form of a
 30 racemate, the (+) and (-) isomers of which are separated
 in a manner similar to that described above in a general
 manner, to give the compounds of formula (V).

The optically active acid salts with the com-
 pounds of formula (I) are new and form part of the

invention as intermediates which are useful for its implementation.

The examples below illustrate the invention and do not imply any limitation thereto.

5 The preparation does not form part of the invention but is used for implementing the process according to the invention.

PREPARATION: 5-METHOXY-3,4-DIHYDRO-[2H]-1-BENZOPYRAN-3-ONE

10 0.4 ml of triethylamine is added to 0.5 g (2.4 mmol) of 3-carboxy-5-methoxy-2H-1-benzopyran, obtained as described in Application PCT 88/04654, in 5 ml of dichloromethane, followed dropwise by 0.65 g (2.4 mmol) of diphenylphosphoryl azide $[(C_6H_5O)_2P(O)N_3]$ in
15 solution in 2 ml of toluene. The solution is heated to 60°C in order to distil off the dichloromethane, and 5 ml of anhydrous toluene are added. The reaction mixture is then heated, with stirring at 80-85°C, for 1 h 30 min, and then 4 ml of a 6N solution of hydrochloric acid are
20 added. The mixture is refluxed again for 2 hours and then cooled to ambient temperature. The product is then extracted several times with dichloromethane and the extraction solvent is dried over $MgSO_4$ and then evaporated under reduced pressure.

25 Purification of the crude sample obtained, by chromatography on a silica column (eluent CH_2Cl_2), enables 0.246 g (57%) of the expected product to be obtained in the form of an oil which subsequently becomes crystalline at 4°C (m.p. = 53-54°C).

30 5-Methoxy-3,4-dihydro-2H-1-benzopyran-3-one may also be prepared as indicated in European Patent Application EP-0,222,996.

EXAMPLE 1: (+)-3-[4-[N-(5-METHOXYCHROMAN-3-YL)AMINO]-
BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE

STAGE A: 3-[4-[N-(5-METHOXYCHROMAN-3-YL)AMINO]BUTYL]-
2,4-DIOXO-3-AZASPIRO[4.5]DECANE (HYDRO-
CHLORIDE)

0.04 mole of 5-methoxychroman-3-one is dissolved
in 10 ml of ethanol. At the same time, 1 g of N-(4-amino-
butyl)-8-azaspiro[4.5]decane 7,9-dione hydrochloride is
dissolved in 10 ml of ethanol, and the solution of
chromanone obtained above is added to this solution.
0.16 g of sodium hydroxide in solution in 10 ml of
ethanol is then added thereto. The mixture is stirred for
one hour at ambient temperature, filtered and placed in
a hydrogenating apparatus. 0.5 g of palladized carbon is
added, the apparatus is purged with nitrogen and then
with hydrogen, and the mixture is hydrogenated at ambient
temperature and pressure. The mixture is filtered and the
filtrate is evaporated to dryness. The residue is taken
up in ethyl acetate and gaseous hydrochloric acid is
added thereto. The mixture is allowed to precipitate and
is drained.

Yield: 70%

STAGE B: (+)-3-[4-[N-(5-METHOXYCHROMAN-3-YL)AMINO]-
BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE (HYDRO-
CHLORIDE)

The product obtained in the preceding stage is
dissolved in 17 ml of ethanol and 0.03 mole of
L-(-)-malic acid dissolved in 12.5 ml of ethanol is
added. The mixture is stirred for 30 minutes. It is
allowed to stand at low temperature. The precipitate
formed is drained and dried.

Specific rotation $[\alpha]_D^{21}$ (1%, CHCl₃) : + 15.3°

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

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 moles of

potassium carbonate. After stirring for 24 hours at 60°C, the solvent is evaporated and the crude reaction mixture is taken up in 10 ml of water and extracted with dichloro-methane. The organic phase is dried and evaporated and the expected product is obtained after purification by chromatography on a silica column. It is salified with oxalic acid.

Yield: 83%

Specific rotation $[\alpha]_D^{21}$: +50°

10 **EXAMPLE 3:** (-)-3-[4-[N-(5-METHOXYCHROMAN-3-YL)AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE (HYDROCHLORIDE)

By carrying out the procedure as in Example 1, but replacing L-(-)-malic acid by D-(+)-malic acid, the title product is obtained.

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

By carrying out the procedure as in Example 2, but replacing the product obtained in Example 1 by the product obtained in Example 3, the title product is obtained. It is salified with oxalic acid.

Specific rotation α_D of the free amine $[\alpha]_D^{21}$: -50 (4% CHCl₃)

25 **EXAMPLE 5:** (+)-3-[4-[N-(5-METHOXYCHROMAN-3-YL)AMINO]-BUTYL]-2,4-DIOXO-3-AZASPIRO[4.5]DECANE (HYDROCHLORIDE)

2 g of the product obtained in Example 1, stage A, are dissolved in 3 cm³ of ethanol. A solution of 1.08 g of (-)-camphanic acid in 1.6 cm³ of ethanol is added to this solution. The mixture is stirred for 30 minutes. It is allowed to stand at low temperature. The precipitate formed is drained and dried.

By carrying out the procedure as in the preceding examples without salifying either with hydrochloric acid or with oxalic acid, and by using the appropriate compound of formula NH₂-(CH₂)_n-R₃, the following are similarly obtained:

(+)-5-METHOXY-3-[4-[N-n-PROPYL-N-2-(4-TOLUENESULFONYL-AMINO)ETHYL]AMINO]CHROMAN

Specific rotation $[\alpha]_D^{21}$ (4%, CHCl₃) : +44°

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

and the diastereoisomers of the following compounds:

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

Specific rotation of the (+) diastereoisomer, $[\alpha]_D^{21}$ (4%, CHCl₃) : +52°

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

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

Specific rotation of the (+) diastereoisomer, $[\alpha]_D^{21}$ (4%, CHCl₃) : +57°

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

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

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

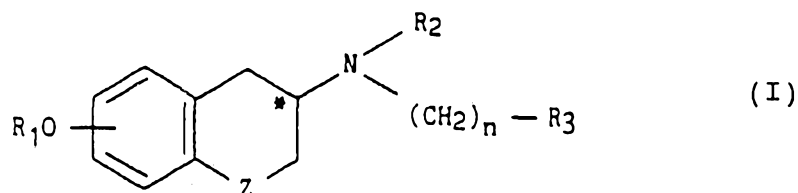
- 5-METHOXY-3-[N-n-PROPYL-N-[4-(4-TOLUENESULFONYL-AMINO)BUTYL]AMINO]-3,4-DIHYDRO-[2H]-BENZOTHIOPYRAN

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

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

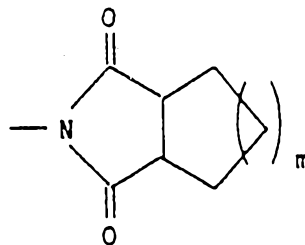
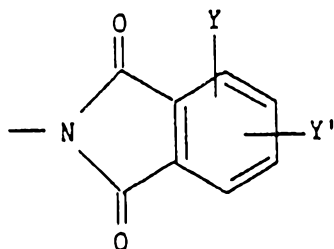
CLAIMS

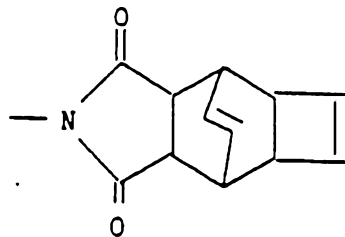
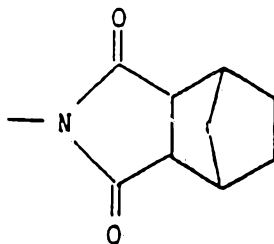
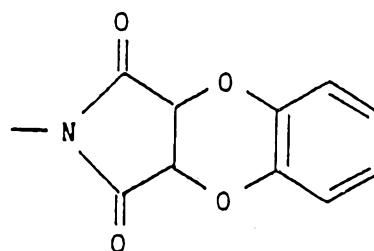
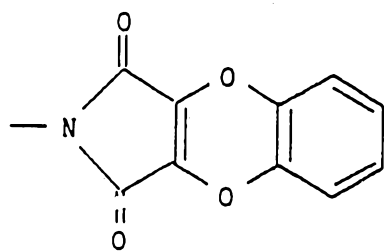
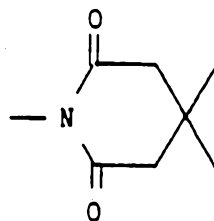
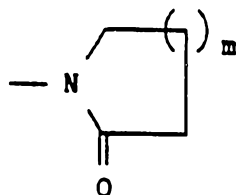
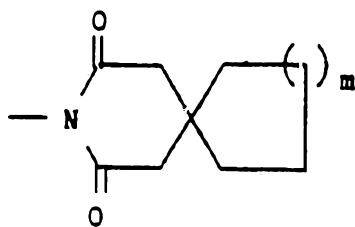
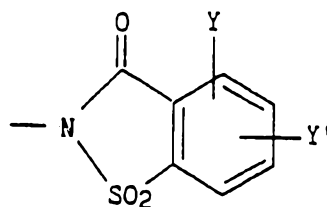
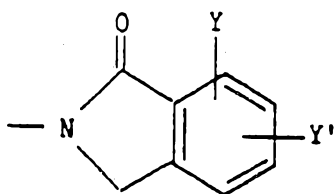
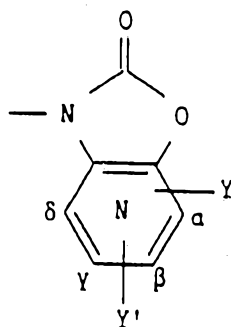
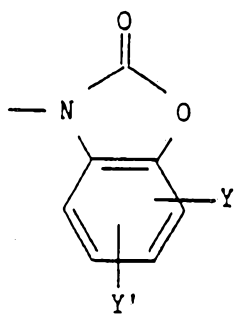
1. A process for the synthesis of enantiomers of compounds of general formula (I):



5 in which:

- Z represents an oxygen atom or a sulfur atom,
- R₁ represents a hydrogen atom, a linear or branched (C₁-C₆) alkyl group,
- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,
- n is an integer between 1 and 6,
- R₃ represents a nitrile group, an amino group which is optionally substituted by:
 - a linear or branched acyl group containing 2 to 7 carbon atoms,
 - an alkylsulfonyl group,
 - an arylsulfonyl group which is optionally substituted by an alkyl, alkoxy or hydroxyl group or by a halogen atom,
 - a linear or branched (C₁-C₆) alkyl group,
- or R₃ represents any one of the following groups:





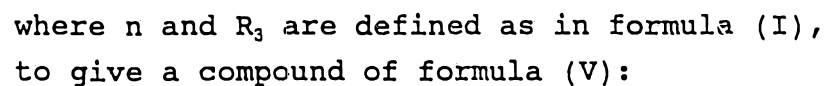
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- 10

wherein a compound of formula (III):



20



where R_1 , R_3 , Z and n are defined as above, which is a specific example of the compounds of formula (I) for which R_2 represents a hydrogen atom, the (+) and (-) isomers of which are separated by forming an organic solution and by adding an optically active acid thereto, and by subjecting to crystallization, one of the two enantiomers crystallizing, the other remaining

in solution,

the chosen isomer is then treated, when, in the compound of formula (I) which it is desired to obtain, R_2 represents a linear or branched C_1-C_6 alkyl group,

5 with a compound of formula (VI):



in which X represents a halogen atom and R'_2 represents a linear or branched C_1-C_6 alkyl group,

specifically to give one enantiomer of the compound of
10 formula (I).

2. A process for preparing enantiomers of compounds of formula (I) as claimed in claim 1, for which R_2 does not represent a hydrogen atom, wherein a compound of formula (V), as claimed in claim 1, is reacted with a
15 compound of formula (VI), as claimed in claim 1, to give the racemate of a compound of formula (I), as claimed in claim 1, the enantiomers of which are separated by forming an organic solution by adding an optically active acid thereto, and by subjecting to crystallization, one
20 of the two enantiomers crystallizing, the other remaining in solution.

3. The process for preparing enantiomers of compounds of formula (I) as claimed in claim 1 or 2, wherein the acid used for the separation of the enantiomers is
25 chosen from (+) or (-) citric, tartaric, diacetyl tartaric, maleic, malic, tosyl glutamic, camphorsulfonic, camphoric, camphanic, mandelic and quinic acid, depending on the desired enantiomer of the product.

4. The process for preparing enantiomers of compounds of formula (I) as claimed in claim 1 or 2, wherein the acid used for separating the isomers is (+)-or (-)-malic acid, depending on the desired enantiomer.

5. The process for preparing enantiomers of compounds of formula (I) as claimed in claim 1 or 2,
35 wherein the acid used for separating the isomers is (+)-or (-)-camphanic acid, depending on the desired enantiomer.

6. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (+)-3-[4-[N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azaspiro[4.5]decane and its addition salts with a pharmaceutically acceptable acid.

7. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (-)-3-[4-[N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azaspiro[4.5]decane and its addition salts with a pharmaceutically acceptable acid.

8. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (+)-3-[4-[N-n-propyl-N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azaspiro[4.5]decane and its addition salts with a pharmaceutically acceptable acid.

9. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (-)-3-[4-[N-n-propyl-N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azaspiro[4.5]decane and its addition salts with a pharmaceutically acceptable acid.

10. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (+)-5-methoxy-3-[N-n-propyl-N-[4-(4-toluenesulfonylamino)butyl]amino]chroman and its addition salts with a pharmaceutically acceptable acid.

11. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (-)-5-methoxy-3-[N-n-propyl-N-[4-(4-toluenesulfonylamino)butyl]amino]chroman and its addition salts with a pharmaceutically acceptable acid.

12. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (+)-5-methoxy-3-[N-n-propyl-N-[2-(4-toluenesulfonylamino)ethyl]amino]chroman and its addition salts with a pharmaceutically acceptable acid.

13. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (-)-5-methoxy-3-[N-n-propyl-N-[2-(4-toluenesulfonylamino)ethyl]amino]-

chroman and its addition salts with a pharmaceutically acceptable acid.

14. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (+)-3-[4-[N-n-propyl-N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane and its salts with a pharmaceutically acceptable acid.

15. The process for preparing, as claimed in claim 1 or 2, the compound of formula (I) which is (-)-3-[4-[N-n-propyl-N-(5-methoxychroman-3-yl)amino]butyl]-2,4-dioxo-3-azabicyclo[3.3.0]octane and its addition salts with a pharmaceutically acceptable acid.

16. An addition salt of the compounds of formula (I) and its enantiomers as claimed in claim 1, with optically active acids, that is to say possessing one or more asymmetric carbon atoms in their structure.

17. An addition salt of the compound of formula (I) and its enantiomers as claimed in claim 1, with (+) or (-) citric, tartaric, diacyl tartaric, maleic, malic, tosyl glutamic, camphorsulfonic, camphoric, camphanic, mandelic and quinic acids.

18. An addition salt of the compounds of formula (I) and its enantiomers as claimed in claim 1, with (+)- or (-)-malic acid.

19. An addition salt of the compounds of formula (I) and its enantiomers as claimed in claim 1, with (+)- or (-)-camphanic acid.

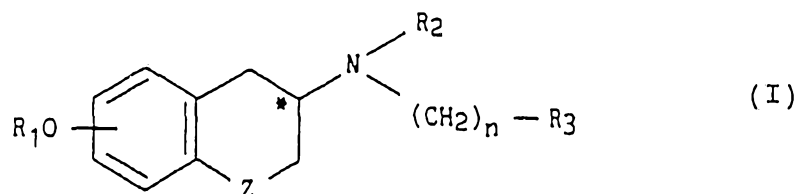
DATED this 29th day of June 1992.

ADIR ET COMPAGNIE

WATERMARK PATENT & TRADEMARK ATTORNEYS
"THE ATRIUM"
290 BURWOOD ROAD
HAWTHORN. VIC. 3122.

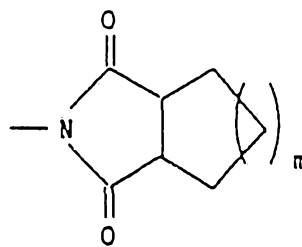
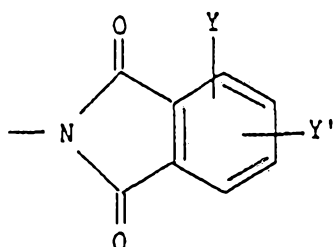
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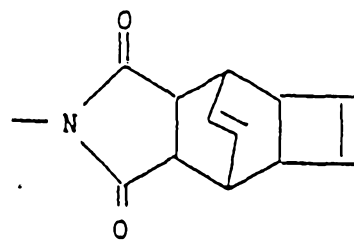
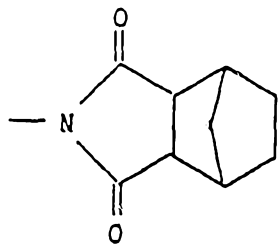
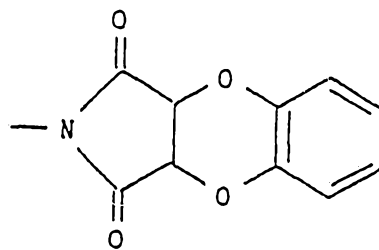
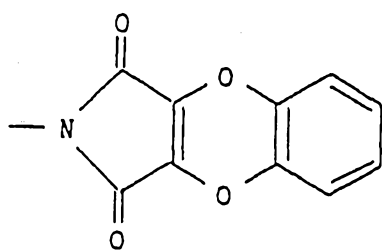
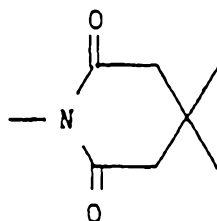
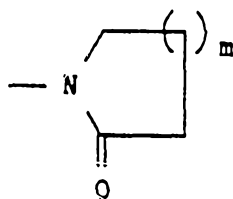
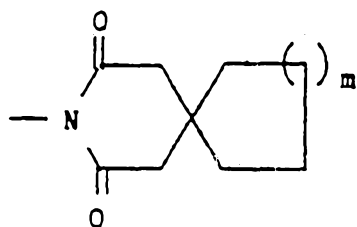
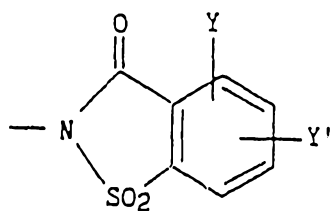
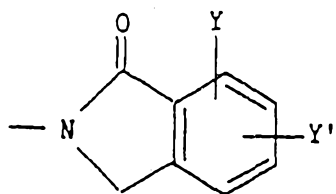
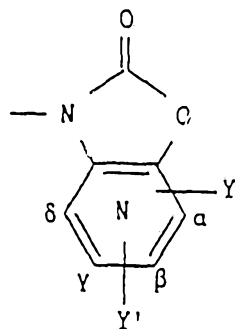
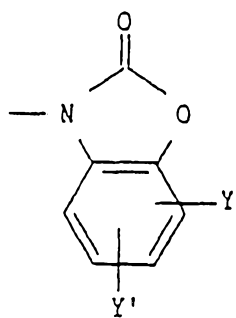
A process for the synthesis of enantiomers of compounds of general formula (I):



in which:

- Z represents an oxygen atom or a sulfur atom,
- R₁ represents a hydrogen atom, a linear or branched (C₁-C₆) alkyl group,
- R₂ represents a hydrogen atom or a linear or branched (C₁-C₆) alkyl group,
- n is an integer between 1 and 6,
- R₃ represents a nitrile group, an amino group which is optionally substituted by:
 - a linear or branched acyl group containing 2 to 7 carbon atoms,
 - an alkylsulfonyl group,
 - an arylsulfonyl group which is optionally substituted by an alkyl, alkoxy or hydroxyl group or by a halogen atom,
 - a linear or branched (C₁-C₆) alkyl group,
- or R₃ represents any one of the following groups:



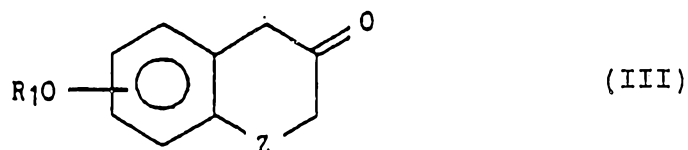


in which:

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

their enantiomers, diastereoisomers and epimers as well as their addition salts with a pharmaceutically acceptable acid,

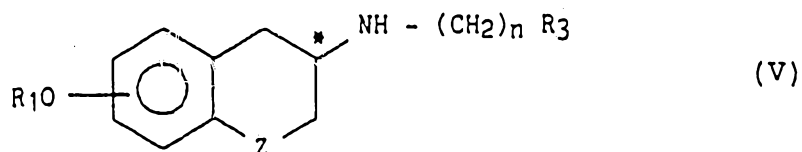
wherein a compound of formula (III):



where R_1 and Z are defined as in formula (I), which is described in Patent Application EP-0,222,996, is used as raw material, and which compound is subjected to reductive amination preferably at ambient temperature and pressure in the presence of a catalyst, with a compound of general formula (IV):



where n and R_3 are defined as in formula (I), to give a compound of formula (V):



where R_1 , R_3 , Z and n are defined as above, which is a specific example of the compounds of formula (I) for which R_2 represents a hydrogen atom, the (+) and (-) isomers of which are separated by forming an organic solution and by adding an optically active acid thereto, and by subjecting to crystallization, one of the two enantiomers crystallizing, the other remaining

in solution,

the chosen isomer is then treated, when, in the compound of formula (I) which it is desired to obtain, R_2 represents a linear or branched C_1-C_6 alkyl group, with a compound of formula (VI):



in which X represents a halogen atom and R'_2 represents a linear or branched C_1-C_6 alkyl group, specifically to give one enantiomer of the compound of formula (I).