Our Ref: 443647

P/00/001
Section 29

AUSTRALIA

Patents Act 1990

650792

PATENT REQUEST : STANDARD PATENT

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

Full application details follow.

[71] [70] Applicant/s and Nominated Person/s:
Bayer Aktiengesellschaft, a company registered under the laws of the Federal Republic of Germany,
of D-5090 Leverkusen, Bayerwerk, GERMANY

[54] Invention Title:
Triazaspirodecanone-methylchromans

[72] Name/s of actual inventor/s: (optional)
Dr. Hans-Georg HEINE; Dr. Rudolf SCHOHE-LOOP; Dr. Thomas GLASER; Dr. Jean Marie VIKTOR DE VRY; Dr. Wolfgang DOMPERT; Dr. Henning SOMMERMEYER

[74] Address for service in Australia:
DAVIES COLLISON CAVE, Patent Attorneys
10 Barrack Street, SYDNEY NSW 2000 Attorney Code : CA

BASIC CONVENTION APPLICATION/S DETAILS:

[31] Appln No.:	[33] Country:	Code:	[32] Date:
P 41 35 473.7	GERMANY	DE	28 October 1991

DATED this SEVENTH day of OCTOBER 1992

Bayer Aktiengesellschaft
By Patent Attorneys
DAVIES COLLISON CAVE

Hector Cumming

HECTOR CUMMING, FIPAA

Fee: $ 365.00

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Our Ref: 443647/MKR/PAS

P/00/008 Section 29(1)
Regulation 3.1(2)

AUSTRALIA

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NOTICE OF ENTITLEMENT

We, BAYER AKTIENGESELLSCHAFT of D-51368 Leverkusen, Bayerwerk, Germany, the applicant in respect of Application No. 26265/92 state the following:

1. BAYER AKTIENGESELLSCHAFT is the Nominated Person in respect of the application.

2. The actual inventors of the invention, the subject of the application are, (1) Hans-Georg HEINE, (2) Rudolf SCHOHE-LOOP, (3) Thomas GLASER, (4) Jean Marie VIKTOR DE VRY (5) Wolfang DOMPERT, (6) Henning SOMMERMEYER.

3. The Nominated Person, BAYER AKTIENGESELLSCHAFT is entitled to the grant of a patent in respect of the application because (i) the said Nominated Person derives title to the invention from the inventors 1 & 2 by virtue of employment contract and (ii) the said Nominated Person derived title to the invention from Troponwerke GmbH & Co. by way of assignment and that Troponwerke GmbH & Co. had obtained entitlement to the invention from the inventors 3-6 by way of employment contract.

4. The Nominated Person is entitled to claim priority from the basic application listed on the patent request form because (i) the Nominated Person is the applicant in respect of the basic application and (ii) the basic application was the first application made in a Convention country in respect of the invention the subject of the application.

DATED this 15th day of April, 1994.

Peter Stearne

DR PETER A STEARNE

a member of the firm of DAVIES COLLISON CAVE
for and on behalf of the applicants

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(12) PATENT ABRIDGMENT (11) Document No. AU-B-26265/92
(19) AUSTRALIAN PATENT OFFICE (10) Acceptance No. 650792

(54) Title
TRIAZASPIRODECANONE-METHYLCHROMANS

International Patent Classification(s)
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(21) Application No. : 26265/92 (22) Application Date : 07.10.92

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(31) Number	(32) Date	(33) Country
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(43) Publication Date : 29.04.93

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(72) Inventor(s)
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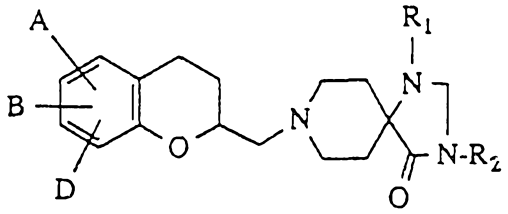
(57) Claim

1. Triazaspirodecanone-methylchromans of the general formula



(I)

in which

A, B and D are identical or different and represent hydrogen, halogen, cyano, azido, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, hydroxyl or carboxyl,

or

represent straight-chain or branched alkyl, alkenyl, acyl or alkoxycarbonyl each having up to 8 carbon atoms, or

represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen, straight-chain or branched alkyl having

.../2

up to 8 carbon atoms, phenyl or benzyl,

L denotes the -CO- or -SO_2- group,

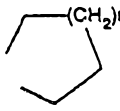
R^6 denotes straight-chain or branched alkyl having up to 8 carbon atoms or benzyl, or
denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

R^7 denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or phenyl

or

A has one of the abovementioned meanings

and

B and D together form a 5- to 7-membered saturated, partially unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 hetero-atoms from the series comprising S, N and O, where these rings can optionally have up to 2 carbonyl functions in the ring and are optionally monosubstituted or disubstituted by identical or different substituents from the series comprising straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, hydroxyl, cycloalkyl having 3 to 6 carbon atoms, phenyl, halogen, cyano, nitro or in spiro fashion by a radical of the formula 

,

in which

m denotes a number 1 or 2,

and

R^1 and R^2 are identical or different and represent hydrogen or straight-chain or branched alkyl, or

represent phenyl or benzyl, each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, hydroxyl, cyano, difluoromethyl, difluoromethoxy, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 8 carbon atoms,

if appropriate in an isomeric form, and their salts.

Our Ref: 443647

650792

P/00/011
Regulation 3:2

AUSTRALIA

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ORIGINAL
COMPLETE SPECIFICATION
STANDARD PATENT

Applicant(s): Bayer Aktiengesellschaft
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GERMANY

Address for Service: DAVIES COLLISON CAVE
Patent & Trade Mark Attorneys
Level 10, 10 Barrack Street
SYDNEY NSW 2000

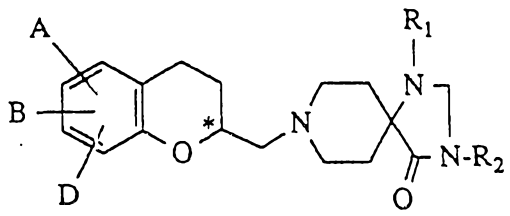
Invention Title: Triazaspirodecanone-methylchromans

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

The invention relates to new 1,3,8-triazaspiro[4.5]decan-4-one-2-methylchromans, to a process for their preparation and to their use in medicaments, in particular as agents for the control of diseases of the central nervous system.

DE 2,165,276 discloses 1,3,8-triazaspiro[4.5]decan-4-one-substituted 2-methyl-benzofurans. In addition US Patent 3,826,835 describes 8-benzofurylmethyl-1,3,8-triazaspiro-[4.5]decanes as neuroleptics.

The invention relates to 1,3,8-triazaspiro[4.5]decan-4-one-2-methylchromans of the general formula (I)



(I) (I)

in which

A, B and D are identical or different and

represent hydrogen, halogen, cyano, azido, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, hydroxyl or carboxyl,

or

represent straight-chain or branched alkyl, alkenyl,

acyl or alkoxycarbonyl each having up to 8 carbon atoms, or

represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, phenyl or benzyl,

L denotes the -CO- or $-SO_2-$ group,

R^6 denotes straight-chain or branched alkyl having up to 8 carbon atoms or benzyl, or

denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

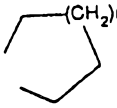
R^7 denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or phenyl

or

A has one of the abovementioned meanings

and

B and D together form a 5- to 7-membered saturated, partially unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 heteroatoms from the series comprising S, N and O, where these rings can optionally have up to 2 carbonyl functions in the ring and are optionally monosubstituted or disubstituted by identical or different substituents

from the series comprising straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, hydroxyl, cycloalkyl having 3 to 6 carbon atoms, phenyl, halogen, cyano, nitro or in spiro fashion by a radical of the formula  ,

in which

m denotes a number 1 or 2,

and

R^1 and R^2 are identical or different and

represent hydrogen or straight-chain or branched alkyl, or

represent phenyl or benzyl, each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, hydroxyl, cyano, difluoromethyl, difluoromethoxy, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 8 carbon atoms,

if appropriate in an isomeric form, and their salts.

In the context of the present invention, physiologically acceptable salts are preferred. Physiologically acceptable salts of the substituted 1,3,8-triazaspiro[4.5]-decan-4-one-2-methylchromans can be salts of the substances according to the invention with mineral acids, carboxylic acids or sulphonic acids. Particularly preferred salts are, for example, those with hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methanesulphonic acid, ethanesulphonic acid,

toluenesulphonic acid, benzenesulphonic acid, naphthalenedisulphonic acid, acetic acid, propionic acid, lactic acid, tartaric acid, citric acid, fumaric acid, maleic acid or benzoic acid.

Salts in the context of the present invention are additionally salts of the univalent metals, such as alkali metals, and the ammonium salts. Sodium salts, potassium salts and ammonium salts are preferred.

In the context of the present invention, the compounds according to the invention can exist in various stereoisomeric forms. The compounds according to the invention exist in stereoisomeric forms which behave either as image and mirror image (enantiomers), or which do not behave as image and mirror image (diastereomers). The invention relates both to the antipodes and to the racemic forms as well as the diastereomer mixtures. Like the diastereomers, the racemic forms can be separated into the stereoisomerically uniform constituents in a known manner [cf. E.L. Eliel, Stereochemistry of Carbon Compounds, McGraw Hill, 1962].

Preferred compounds of the general formula (I) are those in which

A, B and D are identical or different and

represent hydrogen, fluorine, chlorine, bromine, cyano, trifluoromethyl, difluoromethoxy, trifluoromethoxy or hydroxyl, or

represent straight-chain or branched alkyl, alkenyl,

acyl or alkoxycarbonyl each having up to 6 carbon atoms, or

represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

L denotes the -CO- or $-SO_2-$ group,

R^6 denotes straight-chain or branched alkyl having up to 6 carbon atoms or benzyl, or

denotes phenyl which is optionally substituted by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

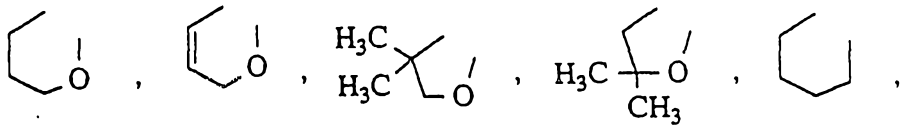
R^7 denotes straight-chain or branched alkyl or alkenyl having up to 6 carbon atoms, each of which is optionally substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl,

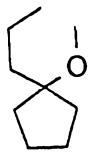
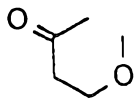
or

A has one of the abovementioned meanings

and

B and D together form a radical of the formula



 or 

R^1 and R^2 are identical or different and

represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or

represent phenyl or benzyl, each of which is optionally monosubstituted or disubstituted by identical or different substituents from the series comprising fluorine, chlorine, bromine, hydroxyl, cyano, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

if appropriate in an isomeric form, and their salts.

Particularly preferred compounds of the general formula (I) are those

in which

A, B and D are identical or different and

represent hydrogen, fluorine, chlorine, bromine, cyano, trifluoromethyl, trifluoromethoxy or hydroxyl,

represent straight-chain or branched alkyl or alkenyl each having up to 4 carbon atoms,

represent a group of the formula $-NR^2R^3$ or $-OR^6$,

in which

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

hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

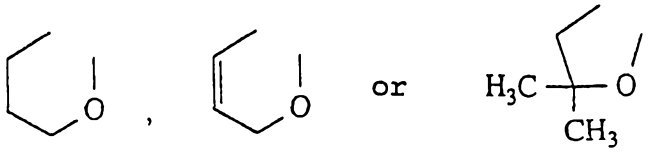
R^6 denotes straight-chain or branched alkyl or alkenyl having up to 4 carbon atoms, each of which is optionally substituted by cyclopropyl or phenyl,

or

A has one of the abovementioned meanings

and

B and D together denote a radical of the formula



R^1 and R^2 are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or represent phenyl or benzyl, each of which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl or trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

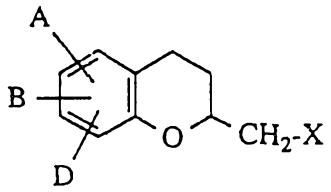
if appropriate in an isomeric form, and their salts.

Very particularly preferred compounds of the general formula (I) are those

in which

A, B and D represent hydrogen or methoxy, R^1 represents phenyl and R^2 represents hydrogen.

In addition, a process for the preparation of the compounds of the general formula (I) according to the invention has been found, characterised in that compounds of the general formula (II)



(II)

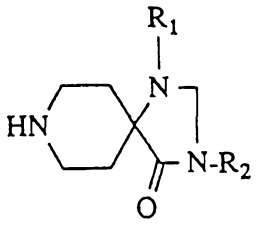
in which

A, B and D have the abovementioned meaning

and

X represents hydroxyl or a typical leaving group, such as tosyloxy, mesyloxy, chlorine or bromine,

are reacted in inert solvents, in the presence of a base and if appropriate of a catalyst, with compounds of the general formula (III)



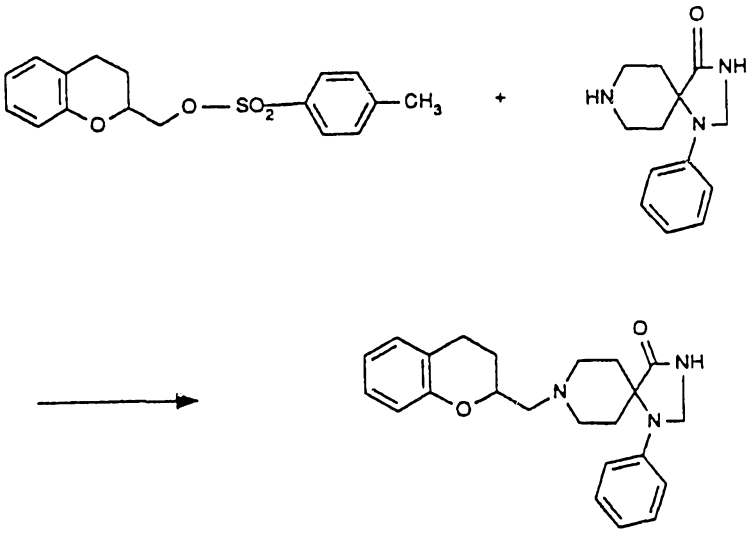
(III)

in which

R^1 and R^2 have the abovementioned meaning,

and if appropriate the substituents A, B and D are varied according to a customary method.

The process according to the invention can be illustrated by way of example by the following reaction scheme:



Suitable solvents are the customary solvents which do not change under the reaction conditions. These preferably include alcohols such as methanol, ethanol, propanol or isopropanol, or ethers such as diethyl ether, dioxane, tetrahydrofuran, glycol dimethyl ether or butyl methyl ether, or ketones such as acetone or butanone, or amides such as dimethylformamide or hexamethylphosphoric triamide, or dimethylsulphoxide, acetonitrile, ethyl acetate, or halogenohydrocarbons such as methylene chloride, chloroform or carbon tetrachloride, or pyridine, picoline or N-methylpiperidine. Mixtures of the solvents mentioned can also be used. Dimethylformamide is

preferred.

Suitable bases are the customary inorganic or organic bases. These preferably include alkali metal hydroxides such as, for example, sodium hydroxide or potassium hydroxide, or alkali metal carbonates such as sodium carbonate or potassium carbonate, or alkali metal alkoxides such as, for example, sodium methoxide or potassium methoxide, or sodium ethoxide or potassium ethoxide, or organic amines such as triethylamine, picoline or N-methylpiperidine, or amides such as sodium amide or lithium diisopropylamide, or organometallic compounds such as butyllithium or phenyllithium. Sodium carbonate and potassium carbonate and triethylamine are preferred.

The base is employed in an amount from 0.6 mol to 5 mol, preferably from 0.7 mol to 2 mol relative to 1 mol of the compound of the general formula (II).

The reaction is in general carried out in a temperature range from 0°C to 150°C, preferably from +20°C to +110°C.

The reaction can be carried out at normal, elevated or reduced pressure (for example 0.5 to 5 bar). In general, it is carried out at normal pressure.

Suitable catalysts are in general alkali metal halides such as, for example, sodium iodide or potassium iodide. Sodium iodide is preferred.

The catalyst is in general employed in an amount from 0.05 - 1.0 mol, preferably from 0.1 to 0.5 mol, relative to 1 mol of the compounds of the general formula (II).

The compounds of the general formula (II) are known or can be prepared by a customary method [cf. US 4,957,928; Farmaco, Ed. Sci. 42 (11), 805-13; Eur. J. Med. Chem. 22 (6), 539 - 44; EP 252,005; EP 199,400; Eur. J. Med. Chem.-Chim. Ther. 20(2), 117-20; Nouv. J. Chim. 6(3), 149-154].

The compounds of the general formula (III) are also known [cf. US 3,826,835]; [CAS, 1021-25-6].

The compounds according to the invention can be used as active substances in medicaments. The substances according to the invention have a particularly high affinity for cerebral 5-hydroxy-tryptamine receptors of the 5-HT_1 type. They also have high affinity for dopamine receptors of the D_2 type.

The substances according to the invention surprisingly exhibit an advantageous action on the central nervous system and can be used for the therapeutic treatment of humans and animals.

The compounds described in the present invention thus represent active substances for the control of diseases which are characterised by disorders of the serotoninergic and dopaminergic system, in particular with the

involvement of receptors which have high affinity for 5-hydroxytryptamine (5-HT_1 type) and/or for dopamine (D_2 type). They are therefore suitable for the treatment of disorders of the central nervous system such as anxiety, tension and depression states, central nervous system-related sexual dysfunctions and sleep disorders, and for controlling morbid disorders of the intake of food, stimulants and tobacco and addictive drugs. They are additionally suitable for the elimination of cognitive deficits, for the improvement of learning and memory power and for the treatment of Alzheimer's disease. They are also suitable for the control of psychoses (for example schizophrenia, mania). Compared to known neuroleptics, they have a lower side effect potential.

In addition, these active substances are also suitable for the modulation of the cardiovascular system. They also intervene in the regulation of the cerebral circulation and thus represent effective agents for the control of migraine.

They are also suitable for the prophylaxis and control of the sequelae of occurrences of cerebral infarct (apoplexia cerebri) such as stroke and cerebral ischaemia. In addition the compounds according to the invention can be used for the treatment of acute cranio-cerebral trauma and also for the control of pain states.

Affinity for the 5-HT_1 receptor

In Table 1, the high affinity of the compounds according

to the invention for 5-hydroxytryptamine receptors of the subtype 1 is represented by way of example. The values given are data which have been determined from receptor binding studies using calf hippocampus membrane preparations. The radioactively labelled ligand used for this was ^{3}H-serotonin.

Table [A]

Compound of example	K_i(nmol/l)
1	2
2	1.5
4	1

Affinity for the 5-HT_{1A} receptor

[W.U. Dompert et al., Naunyn-Schmiedeberg's Arch. Pharmacol. (1985), 328, 467-470].

In this test, the binding of ^{3}H-ipsapirone to 5-HT_{1A} receptors in calf hippocampus membranes is measured. It was found that the compounds according to the invention compete with the radioligand for binding and inhibit this.

Table [B]

Compound of example	K_i(nmol/l)
5	1
6	1

Dopamine D_2 receptor test

This test is carried out according to the following

reference: Imafuku J. (1987), Brain Research 402; 331-338.

In this test, the binding of the selective D_2-receptor antagonist ^{3}H-sulpiride on membranes from the striatum of the rat is measured. Compounds which bind to dopamine D_2-receptors inhibit the binding of ^{3}H-sulpiride in a concentration-dependent manner. IC_{50} values are determined from the displacement curves and the inhibition constants K_i are calculated from these.

Table [C]

Compound of example	K_i(nmol/l)
1	0.2
2	0.3
3	0.6

The present invention also includes pharmaceutical preparations which, in addition to inert, non-toxic, pharmaceutically suitable auxiliaries and excipients, contain one or more compounds of the general formula (I), or which consist of one or more active substances of the formula (I), and processes for the production of these preparations.

The active substances of the formula (I) should be present in these preparations in a concentration from 0.1 to 99.5% by weight, preferably from 0.5 to 95% by weight of the total mixture.

In addition to the active substances of the formula (I), the pharmaceutical preparations can also contain other pharmaceutical active substances.

The abovementioned pharmaceutical preparations can be prepared in a customary manner by known methods, for example using the auxiliary(ies) or excipient(s).

In general, it has proved advantageous to administer the active substance(s) of the formula (I) in total amounts from about 0.01 to about 100 mg/kg, preferably in total amounts of about 0.1 mg/kg to 5 mg/kg of bodyweight every 24 hours, if appropriate in the form of several individual doses, to achieve the desired result.

However, it may be advantageous to depart from the amounts mentioned, in particular depending on the nature and the bodyweight of the subject treated, on individual behaviour towards the medicament, the nature and severity of the disease, the type of preparation and administration, and the time or interval at which administration takes place.

The R_f values shown in each case were determined - if not stated otherwise - by thin layer chromatography on silica gel (aluminium foil, silica gel 60 F 254, E. Merck). The visualisation of the substance spots was carried out by examining under UV light and/or by spraying with 1% strength potassium permanganate solution.

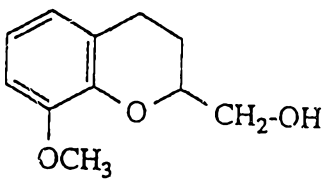
Flash chromatography was carried out on silica gel 60, 0.040 - 0.064 mm, E. Merck (see Still et al., J. Org. Chem. 43, 2923, 1978; for simpler separation problems see Aldrichimica Acta 18, 25, 1985). Elution with solvent gradient means: beginning with the pure, non-polar solvent mixture component the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

In the case of all products, the solvent was distilled off at the end at about 0.1 mm Hg. Salts were kept at this pressure overnight over potassium hydroxide and/or phosphorus pentoxide.

Starting Compounds

Example I

2-Hydroxymethyl-8-methoxy-chroman



59.0 g (0.25 mol) of ethyl 8-methoxy-chroman-2-carboxylate are added dropwise in 525 mol of anhydrous tetrahydrofuran in the course of 1 h with stirring at 20°C to the suspension from 9.5 g (0.25 mol) of lithium aluminium hydride in 525 ml of anhydrous diethyl ether. The mixture is stirred overnight and then treated drop-

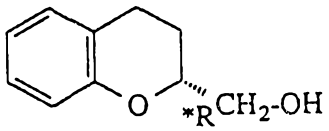
wise successively with cooling with 9.5 ml of water, 9.5 ml of 15% strength sodium hydroxide solution and 28.4 ml of water. The organic phase is decanted and evaporated. The residue is recrystallised twice from dichloromethane/petroleum ether.

Yield: 38.0 g (87%)

M.p.: 57-58°C

Example II

(2R)-2-Hydroxymethyl-chroman

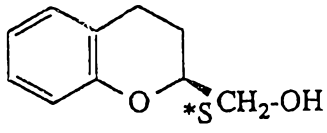


164 ml of a 1 M borane solution in tetrahydrofuran are added dropwise at an internal temperature of 0°C to the solution from 22.1 g (0.124 mol) of (2R)-chroman-2-carboxylic acid (ee = 98.3%) in 210 ml of anhydrous tetrahydrofuran under argon in the course of 30 minutes. The cooling is removed and the batch is subsequently stirred for 4 h. The internal temperature rises during the course of this to 34°C. 46 ml of a 1/1 mixture of tetrahydrofuran and water are then added dropwise with ice-cooling. After addition of 40.7 g of anhydrous potassium carbonate and vigorous stirring, the tetrahydrofuran solution is decanted and concentrated in a water jet vacuum. Short path distillation yields 18.8 g of colourless 2R-hydroxymethylchroman of b.p. 77-78°C/0.15 mbar.

ee > 99%.

Example III

(2S)-2-Hydroxymethyl-chroman



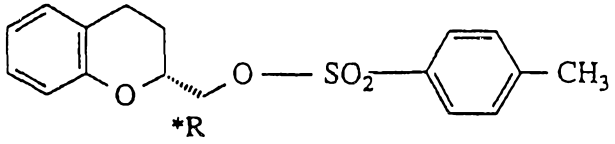
The title compound is prepared from (2S)-chroman-2-carboxylic acid in analogy to the procedure of Example II.

ee > 99%

B.p.: 79-81°C/0.15 mbar

Example IV

(2R)-2-Tosyloxymethyl-chroman

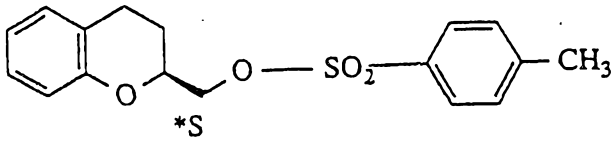


15.63 g of 4-toluenesulphonyl chloride are added in portions with stirring and ice-cooling to 12.8 g (0.78 mol) of (2R)-2-hydroxymethylchroman (Example II) in 50 ml of anhydrous pyridine. After allowing to stand overnight, the mixture is introduced into ice-water and extracted with diethyl ether. The ether phase is washed twice with 5% strength ice-cold hydrochloric acid and then with saturated sodium chloride solution, dried over anhydrous sodium sulphate and evaporated in a water jet vacuum. 22.4 g of homogeneous 4-toluenesulphonate of

2R-2-hydroxymethylchroman are obtained.
R_f = 0.6 (toluene/ethyl acetate 3:1) oil, $[\alpha]_D$ = 51.1° (c = 1, $CHCl_3$) M.p.°C = 61.5-64.5 (from dichloromethane/ petroleum ether).

Example V

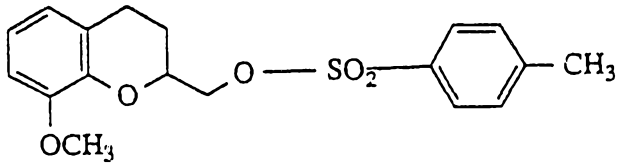
(2S)-2-Tosyloxymethyl-chroman



The title compound is prepared from Example III in analogy to the procedure of Example IV.
R_f = 0.6 (toluene/ethyl acetate 3:1) oil

Example VI

8-Methoxy-2-tosyloxymethyl-chroman

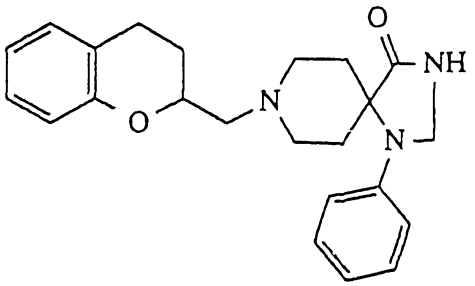


M.p.: 115-117°C (from dichloromethane)

Preparation Examples

Example 1

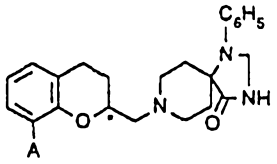
8-(Chroman-2-yl-methyl)-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one



The mixture from 31.8 g (0.1 mol) of 2-tosyloxymethyl-chroman, 7.1 g (0.07 mol) of anhydrous sodium carbonate and 23.1 g (0.1 mol) of 1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one in 240 mol of anhydrous dimethylformamide (DMF) is stirred at 110°C for 6 h and then poured onto ice (500 g). After extracting with ethyl acetate (5 x 100 ml), washing the organic extracts with water, drying over anhydrous sodium sulphate and evaporating the organic phase in a water jet vacuum, 65.7 g of solvent-containing crystalline crude product are obtained which, recrystallised twice from ethyl acetate, yields 20.6 g of the title compound of m.p. 192-193.5°C.
Yield: 55% of theory

The Examples shown in Table 1 are prepared in analogy to the procedure of Example I:

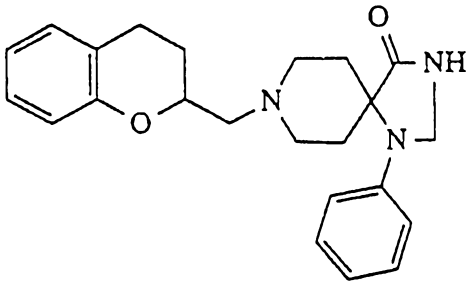
Table 1:



Ex.No.	A	*	M.p.°C	ee(%)	α(D)°
2	$-OCH_3$	R,S	169-172	-	-
3	H	S	170.5-172	>98	+56.0 (c=1,THF)
4	H	R	171-173	>98	-52.5 (c=1,THF)

Example 5

8-(Chroman-2-yl-methyl)-1-phenyl-1,3,8-triazaspiro[4.5]-decan-4-one HCl salt

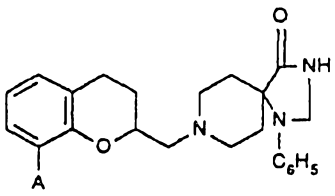


x HCl

3.34 g (0.01 mol) of 8-(chroman-2-yl-methyl)-1-phenyl-1,3,8-triazaspiro[4.5]decan-4-one are dissolved in 100 ml of diethyl ether with the addition of 20 ml of dichloromethane and treated with stirring with 6.9 ml of 1.45 N etherial hydrochloric acid with ice-cooling. After 2 h, the precipitate is filtered off with suction, washed with diethyl ether and dried in an oil pump vacuum at 60°C. 3.4 g of the title compound of m.p. 238-240°C (capillary) are obtained.

The compounds shown in Table 2 are prepared in analogy to the procedure of Example 5:

Table 2:

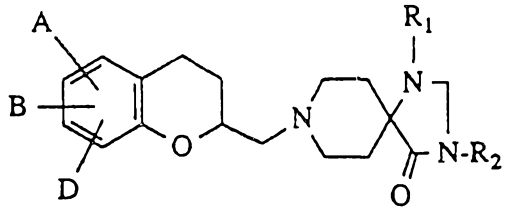


x HCl

Ex.No.	A	M.p. °C	
6	$-OCH_3$	250-252	
7	H	250-254	Configuration at C-2: R

The Claims defining the invention are as follows:

1. Triazaspirodecanone-methylchromans of the general formula



(I)

in which

A, B and D are identical or different and represent hydrogen, halogen, cyano, azido, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, hydroxyl or carboxyl,

or

represent straight-chain or branched alkyl, alkenyl, acyl or alkoxycarbonyl each having up to 8 carbon atoms, or

represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, phenyl or benzyl,

L denotes the -CO- or $-SO_2-$ group,

R^6 denotes straight-chain or branched alkyl having up to 8 carbon atoms or benzyl, or

denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl,

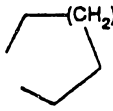
nitro, cyano, trifluoromethyl, trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

R^7 denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or phenyl

or

A has one of the abovementioned meanings

and

B and D together form a 5- to 7-membered saturated, partially unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 hetero-atoms from the series comprising S, N and O, where these rings can optionally have up to 2 carbonyl functions in the ring and are optionally monosubstituted or disubstituted by identical or different substituents from the series comprising straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, hydroxyl, cycloalkyl having 3 to 6 carbon atoms, phenyl, halogen, cyano, nitro or in spiro fashion by a radical of the formula 

,

in which

m denotes a number 1 or 2,

and

R^1 and R^2 are identical or different and represent hydrogen or straight-chain or branched alkyl, or

represent phenyl or benzyl, each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, hydroxyl, cyano, difluoromethyl, difluoromethoxy, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 8 carbon atoms,

if appropriate in an isomeric form, and their salts.

2. Triazaspirodecanone-methylchromans according to Claim 1

where

A, B and D are identical or different and represent hydrogen, fluorine, chlorine, bromine, cyano, trifluoromethyl, difluoromethoxy, trifluoromethoxy or hydroxyl, or represent straight-chain or branched alkyl, alkenyl, acyl or alkoxycarbonyl each having up to 6 carbon atoms, or represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms,

L denotes the -CO- or $-SO_2-$ group,

R^6 denotes straight-chain or branched alkyl having up to 6 carbon atoms or benzyl, or denotes phenyl which is optionally substituted

by fluorine, chlorine, bromine, trifluoromethyl, trifluoromethoxy, hydroxyl or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

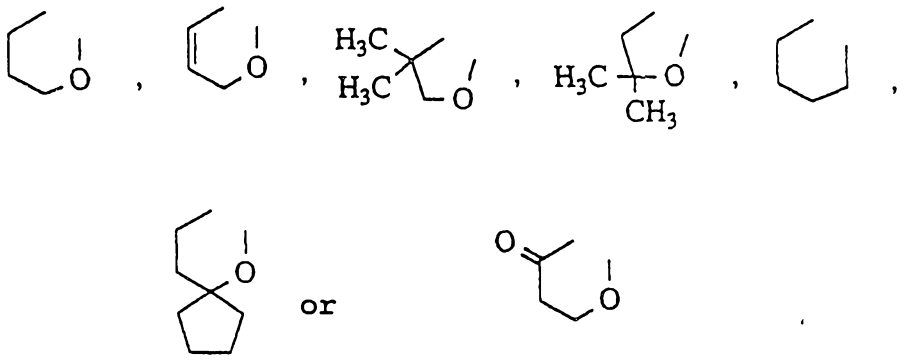
R^7 denotes straight-chain or branched alkyl or alkenyl having up to 6 carbon atoms, each of which is optionally substituted by cyclopropyl, cyclopentyl, cyclohexyl or phenyl,

or

A has one of the abovementioned meanings

and

B and D together form a radical of the formula



R^1 and R^2 are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 6 carbon atoms, or represent phenyl or benzyl, each of which is optionally monosubstituted or disubstituted by identical or different substituents from the

series comprising fluorine, chlorine, bromine, hydroxyl, cyano, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

if appropriate in an isomeric form, and their salts.

3. Triazaspirodecanone-methylchromans according to Claim 1

in which

A, B and D are identical or different and

represent hydrogen, fluorine, chlorine, bromine, cyano, trifluoromethyl, trifluoromethoxy or hydroxyl,

represent straight-chain or branched alkyl or alkenyl each having up to 4 carbon atoms,

represent a group of the formula $-NR^2R^3$ or $-OR^6$, in which

R^2 and R^3 are identical or different and denote hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms,

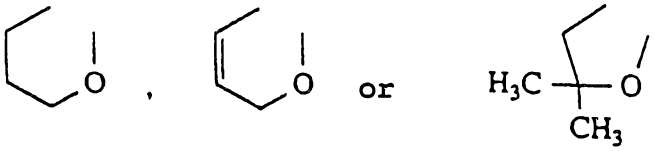
R^6 denotes straight-chain or branched alkyl or alkenyl having up to 4 carbon atoms, each of which is optionally substituted by cyclopropyl or phenyl,

or

A has one of the abovementioned meanings

and

B and D together denote a radical of the formu..

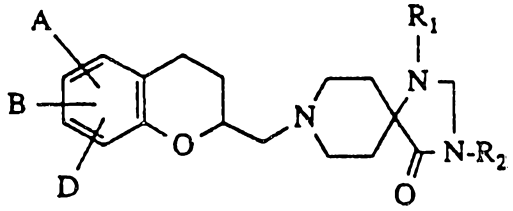


R^1 and R^2 are identical or different and represent hydrogen or straight-chain or branched alkyl having up to 4 carbon atoms, or represent phenyl or benzyl, each of which is optionally substituted by fluorine, chlorine, bromine, hydroxyl, trifluoromethyl or trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 4 carbon atoms,

if appropriate in an isomeric form, and their salts.

4. A method of treatment and/or prophylaxis of disorders of the central nervous system or cardiovascular system in humans or animals, which comprises treating a human or animal suffering from, or prone to suffer from, said disorder with an effective amount of a compound according to claim 1, optionally in association with other pharmaceutically active compounds, pharmaceutically acceptable auxiliaries or excipients.

5. Process for the preparation of triazaspirodecanone-methylchromans of the general formula



(I)

in which

A, B and D are identical or different and represent hydrogen, halogen, cyano, azido, nitro, difluoromethyl, trifluoromethyl, difluoromethoxy, trifluoromethoxy, hydroxyl or carboxyl,

or

represent straight-chain or branched alkyl, alkenyl, acyl or alkoxycarbonyl each having up to 8 carbon atoms, or

represent a group of the formula $-NR^3R^4$, $-NR^5-L-R^6$ or $-OR^7$,

in which

R^3, R^4 and R^5 are identical or different and denote hydrogen, straight-chain or branched alkyl having up to 8 carbon atoms, phenyl or benzyl,

L denotes the -CO- or $-SO_2-$ group,

R^6 denotes straight-chain or branched alkyl having up to 8 carbon atoms or benzyl, or

denotes aryl having 6 to 10 carbon atoms, which is optionally substituted by halogen, hydroxyl, nitro, cyano, trifluoromethyl, trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms,

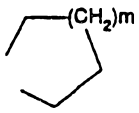
R^7 denotes straight-chain or branched alkyl or alkenyl each having up to 8 carbon atoms, each of which is optionally substituted by cycloalkyl having 3 to 6 carbon atoms or phenyl

or

A has one of the abovementioned meanings

and

B and D together form a 5- to 7-membered saturated,

partially unsaturated or aromatic carbocyclic ring or heterocyclic ring having up to 2 heteroatoms from the series comprising S, N and O, where these rings can optionally have up to 2 carbonyl functions in the ring and are optionally monosubstituted or disubstituted by identical or different substituents from the series comprising straight-chain or branched alkyl or alkoxy each having up to 6 carbon atoms, hydroxyl, cycloalkyl having 3 to 6 carbon atoms, phenyl, halogen, cyano, nitro or in spiro fashion by a radical of the formula 

,

in which

m denotes a number 1 or 2,

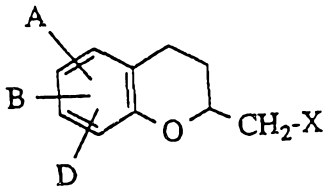
and

R^1 and R^2 are identical or different and

represent hydrogen or straight-chain or branched alkyl, or

represent phenyl or benzyl, each of which is optionally monosubstituted to trisubstituted by identical or different substituents from the series comprising halogen, hydroxyl, cyano, difluoromethyl, difluoromethoxy, trifluoromethyl and trifluoromethoxy or by straight-chain or branched alkyl or alkoxy each having up to 8 carbon atoms,

if appropriate in an isomeric form, and their salts, characterised in that compounds of the general formula (II)



(II)

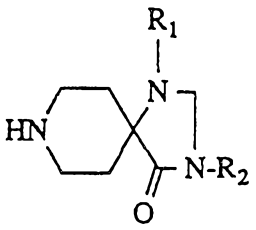
in which

A, B and D have the abovementioned meaning

and

X represents hydroxyl or a typical leaving group, such as tosyloxy, mesyloxy, chlorine or bromine,

are reacted in inert solvents, in the presence of a base and if appropriate of a catalyst, with compounds of the general formula (III)



(III)

in which

R^1 and R^2 have the abovementioned meaning,

and if appropriate the substituents A, B and D are varied according to a customary method.

6. Process according to Claim 5, characterised in that it is carried out at a temperature of 0°C to +150°C.

7. Medicament containing at least one triazaspirodecan-one-methyl chroman according to Claim 1 in association with one or more pharmaceutically acceptable auxiliaries or excipients.

8. Medicament according to Claim 7 for the treatment of diseases which are characterised by disorders of the serotoninergic and dopaminergic system.

9. Use of triazaspirodecanone-methylchromans according to Claim 1 for the production of medicaments.

10. Process for the production of medicaments according to Claim 7, characterised in that the triazaspirodecanone-methylchromans are converted into a suitable administration form, if appropriate with the aid of customary auxiliaries and excipients.

11. Triazaspirodecanone-methylchromans methods for their manufacture or pharmaceutical compositions or methods of treatment involving/containing them, substantially as hereinbefore described with reference to the Examples.

DATED this 15th day of April 1994.

BAYER AKTIENGESELLSCHAFT

By its Patent Attorneys

DAVIES COLLISON CAVE

Triazaspirodecanone-methylchromans

A b s t r a c t

Triazaspirodecanone-methylchromans are prepared by reacting methylchromans, which are substituted on the methyl group by appropriate leaving groups, with triazaspirodecanones. The substances can be employed for the production of medicaments, in particular for medicaments for the control of disorders of the central nervous system.