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.

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[54] Invention Title:
New hetaryloxy-beta-carbolines, their production and use in pharmaceutical agents

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BASIC CONVENTION APPLICATION/S DETAILS:

<table>
<thead>
<tr>
<th>[31] Appln No.:</th>
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<th>Code:</th>
<th>[32] Date:</th>
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<td>P4118741.5</td>
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DATED this FIFTH day of JUNE 1992

Schering Aktiengesellschaft
By Patent Attorneys
DAVIES COLLISON CAVE

HECTOR CUMMING, FIPAA
Fee: $ 312.00

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NEW HETARYLOXY-BETA-CARBOLINES, THEIR PRODUCTION AND USE IN PHARMACEUTICAL AGENTS

The compounds of formula I as well as their acid addition salts can be used as pharmaceutical agents because of their affinity to benzodiazepine receptors and have a partial agonistic effect on the properties known by the benzodiazepines, which is characterized in that the compounds, for example, have an anticonvulsive and anxiolytic effect and are not atactic/muscle-relaxing.

Claim

1. Compounds of formula I

![Chemical Structure](image)

in which

$R^A$ means a triazine or benzocondensed hetaryl radical with 1-2 nitrogen atoms optionally substituted with halogen, $C_{1-6}$
-2-
alkyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkylthio, trifluoromethyl or SO\textsubscript{2}-R\textsuperscript{1} or a 5- or 6-membered hetaryl radical with 1-2 nitrogen atoms substituted with halogen, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkylthio, trifluoromethyl or SO\textsubscript{2}-R\textsuperscript{1}, and R\textsuperscript{1} is C\textsubscript{1-4} alkyl or phenyl optionally substituted 1-2 times with C\textsubscript{1-4} alkyl and RA can be substituted once to twice, and the substituent is not halogen, if RA means pyridine,

R\textsuperscript{4} means hydrogen, C\textsubscript{1-6} alkyl, C\textsubscript{1-6} alkoxy-C\textsubscript{1-2} alkyl- and
R\textsuperscript{3} means -CO\textsubscript{2}-C\textsubscript{1-6} alkyl, -CO-R\textsuperscript{2}, -CO\textsubscript{2}H,

and

R\textsuperscript{2} means C\textsubscript{1-4} alkyl, C\textsubscript{3-7} cycloalkyl, C\textsubscript{7-9} bicycloalkyl or a monocyclic or bicyclic C\textsubscript{6-12} aryl radical optionally substituted with C\textsubscript{1-4} alkyl, C\textsubscript{1-4} alkoxy or amino,

R\textsuperscript{a} and R\textsuperscript{b} are the same or different and respectively mean hydrogen, C\textsubscript{1-6} alkoxy, C\textsubscript{1-6} alkyl, -CH\textsubscript{2}-O-C\textsubscript{1-4} alkyl, phenyl or benzyl,

R\textsuperscript{c} and R\textsuperscript{d} respectively mean hydrogen or together--a bond and

R\textsuperscript{5} is hydrogen, C\textsubscript{1-4} alkyl or C\textsubscript{3-7} cycloalkyl,
as well as their isomers and acid addition salts.
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SYDNEY NSW 2000

Invention Title: New hetaryloxy-beta-carbolines, their production and use in pharmaceutical agents

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

The invention relates to new hetaryloxy-β-carboline derivatives, their production and use in pharmaceutical agents.

In EP-A-237 467 and EP-A-305 322, β-carbolines substituted with a hetaryloxy radical are described, which influence the central nervous system and are used as psychopharmaceutical agents. According to these patent applications, it was not to be expected that with the introduction of the hetaryl substituents according to the invention, a displacement of the active profile of the compounds takes place and that the compounds show an improved side effect profile because of the absent muscular relaxation.

The compounds according to the invention have formula I

![Chemical Structure](image)

in which

RA means a triazine or benzocondensed hetaryl radical with 1-2 nitrogen atoms optionally substituted with halogen, C_1-6 alkyl, C_1-6 alkoxy, C_1-6 alkylthio, trifluoromethyl or SO_2-R^1 or represents a 5- or 6-membered hetaryl radical with 1-2 nitrogen atoms substituted with halogen, C_1-6 alkyl, C_1-6 alkoxy, C_1-6 alkylthio, trifluoromethyl or -SO_2-R^1, and R^1 is C_1-4 alkyl or phenyl optionally substituted 1-2 times with C_1-4 alkyl and RA
can be substituted once to twice, and the substituent is not halogen, if R\text{A} means pyridine,

\begin{align*}
R^4 & \text{ means hydrogen, } C_{1-6} \text{ alkyl, } C_{1-6} \text{ alkoxy-C}_{1-2} \text{ alkyl and } \\
R^3 & \text{ means } -\text{CO}_2- C_{1-6} \text{ alkyl, } -\text{CO-R}^2, -\text{CO}_2 \text{H,}
\end{align*}

\begin{align*}
\text{and } \\
R^2 & \text{ means } C_{1-4} \text{ alkyl, } C_{3-7} \text{ cycloalkyl, } C_{7-9} \text{ bicycloalkyl or a monocyclic or bicyclic } C_{6-12} \text{ aryl radical optionally substituted with } C_{1-4} \text{ alkyl, } C_{1-4} \text{ alkoxy or amino, } \\
R^a & \text{ and } R^b \text{ are the same or different and respectively mean hydrogen, } C_{1-6} \text{ alkoxy, } C_{1-6} \text{ alkyl, } -\text{CH}_2-\text{O-C}_{1-4} \text{ alkyl, phenyl or benzyl, } \\
R^c & \text{ and } R^d \text{ respectively mean hydrogen or together a bond and } \\
R^5 & \text{ is hydrogen, } C_{1-4} \text{ alkyl or } C_{3-7} \text{ cycloalkyl, as well as their isomers and acid addition salts.}
\end{align*}

Substituent R\text{A} can be in the A-ring in position 5-8, preferably in 5-, 6- or 7-position.

Alkyl contains respectively both straight-chain and branched-chain radicals, such as, for example, methyl, ethyl,
propyl, isopropyl, butyl, isobutyl, sec-butyl, tert-butyl,
pentyl, isopentyl and hexyl.

By halogen is respectively to be understood fluorine,
chlorine, bromine and iodine.

Cycloalkyl respectively stands for cyclopropyl, cyclobutyl,
cyclopentyl, cyclohexyl, cycloheptyl.

As a benzocondensed hetaryl radical with 1-2 nitrogen atoms,
for example, quinoline, isoquinoline, quinoxaline, benzimidazole
can be mentioned. Generally, these have two rings, each of which
can be a four-, five- or six-membered ring, there being generally
about 8-12 ring atoms in total.

If RA means a substituted nitrogen-containing hetaryl
radical, for example, pyridine, pyrimidine, pyrazine, pyridazine,
imidazole can be mentioned.

By a bicycloalkyl radical R² is to be understood
bicycloheptyl and bicyclooctyl. As monocyclic or bicyclic aryl
radical R², for example, phenyl, biphenyl, naphthyl and indenyl
can be mentioned.

The substituents of hetaryl radicals RA, phenyl radical R¹
and aryl radical R² can be once to twice in any position.

As preferred embodiments for RA, quinoline, isoquinoline and
quinazoline radicals optionally substituted with halogen, C₁₋₆
alkyl or C₁₋₆ alkoxy, triazine optionally substituted once to
twice with halogen, C₁₋₆ alkyl, C₁₋₆ alkoxy or C₁₋₆ alkylthio,
pyridine, pyrimidine, pyrazine and pyridazine radicals
substituted with C₁₋₆ alkyl, C₁₋₆ alkoxy, C₁₋₆ alkylthio,
trifluoromethyl or \( \text{SO}_2-R^1 \) and pyrimidine, pyridazine and pyrazine radicals substituted with halogen can be considered.

For \( R^3 \), \(-\text{CO}_2-C_{1-6} \) alkyl, \(-\text{CO}-R^2 \) with \( R^2 \) meaning a \( \text{C}_{3-7} \) cycloalkyl or an optionally substituted phenyl radical and the isoxazol-3-yl radical is to be considered as preferable.

The physiologically compatible acid addition salts are derived from the known inorganic and organic acids, such as, for example, hydrochloric acid, hydrobromic acid, sulfuric acid, phosphoric acid, formic acid, acetic acid, benzoic acid, maleic acid, fumaric acid, succinic acid, tartaric acid, citric acid, oxalic acid, glyoxylic acid as well as from alkanesulfonic acids, such as, for example, methanesulfonic acid, ethanesulfonic acid, benzenesulfonic acid, \( p \)-toluenesulfonic acid, i.a.

The compounds of formula I as well as their acid addition salts can be used as pharmaceutical agents because of their affinity to benzodiazepine receptors and have a partial agonistic effect on the properties known by the benzodiazepines, which is characterized in that the compounds, for example, have an anticonvulsive and anxiolytic effect and are not atactic/muscle-relaxing. To test the anxiolytic effect, the compounds are tested in the 4-plate test according to the method of Boissier et al., Eur. J. Pharmacol. 4, 145-150 (1968). In the table, the minimal effective dose (MED) is indicated, which increases the locomotor activity of the afflicted mice after i.p. treatment.
TABLE

<table>
<thead>
<tr>
<th>Compound</th>
<th>MED mg/kg i.p.</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>1.56</td>
</tr>
<tr>
<td>B</td>
<td>0.39</td>
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</table>

A = 6-(1-isoquinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester

B = 6-(2,6-dimethoxy-4-pyrimidyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester

Because of the good effectiveness in the PTZ convulsion test and in the 4-plate test, the compounds according to the invention are suitable especially for treatment of epilepsy and anxiety conditions.

To use the compounds according to the invention as pharmaceutical agents, the latter are brought into the form of a pharmaceutical preparation, which in addition to the active ingredient for enteral or parenteral administration contains suitable pharmaceutical, organic or inorganic inert vehicles, such as, for example, water, gelatin, gum arabic, lactose, starch, magnesium stearate, talc, vegetable oils, polyalkylene glycols, etc.

The pharmaceutical preparations can be present in solid form, for example, as tablets, coated tablets, suppositories, capsules or in liquid form, for example, as solutions, suspensions or emulsions. They further optionally contain auxiliary agents such as preservatives, stabilizers, wetting
agents or emulsifiers, salts to change the osmotic pressure or buffers.

For parenteral use, especially injection solutions or suspensions, especially aqueous solutions of the active compounds in polyhydroxyethoxylated castor oil, are suitable.

As vehicle systems, surface-active auxiliary agents such as salts of bile acids or animal or vegetable phospholipids but also their mixtures as well as liposomes or their components can also be used.

For oral use, tablets, coated tablets or capsules with talc and/or hydrocarbon vehicles or binding agents, such as, for example, lactose, corn or potato starch, are especially suitable. The use can also take place in liquid form, such as, for example, as juice, to which a sweetener optionally is added.

The compounds according to the invention are introduced in a dosage unit of 0.05 to 100 mg of active substance in a physiologically compatible vehicle.

The compounds according to the invention are generally used in a dose of 0.1 to 300 mg/day, preferably 0.1 to 30 mg/day, especially preferably 1-20 mg/day, for example as anxiolytic agents analogous to diazepam.

The production of the compounds according to the invention takes place according to methods known in the art. For example, compounds of formula I are attained in that
a) compounds of formula II

\[
\text{II,}
\]

in which \( R^4 \) and \( R^3 \) have the above-named meaning, with \( R^A Y \), in which \( R^A \) has the above-named meaning and \( Y \) is halogen or a reactive group, are etherified or

b) compounds of formula III

\[
\text{III,}
\]

in which \( R^4 \) has the above-named meaning, \( R^{A'} \) is hydrogen or \( R^A \) and \( Z \) is hydrogen, \( C_{1-4} \) alkoxy or a reactive acid derivative, are reacted with a lithium-organic compound, optionally after introducing a protecting group in 9-position to compounds of formula I with \( R^3 = -\text{CO-}R^2 \) or
c) compounds of formula IV

\[
\begin{align*}
&\text{IV,} \\
&\text{RA'} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA'} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA'} \quad \text{O} \\
\end{align*}
\]

in which RA' is hydrogen or RA and RA has the above-named meaning, are cyclized with a compound of formula V

\[
\begin{align*}
&\text{V,} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
\end{align*}
\]

in which RA, RB, RC, and RD have the above-named meaning, to compounds of formula I with RA meaning

\[
\begin{align*}
&\text{I,} \\
&\text{N} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
\end{align*}
\]

or

d) compounds of formula VI

\[
\begin{align*}
&\text{VI,} \\
&\text{RA'} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA'} \quad \text{O} \\
&\text{RA} \quad \text{C} = \text{C} \\
&\text{RA} \quad \text{O} \\
&\text{RA'} \quad \text{O} \\
\end{align*}
\]
in which R\(^{A'}\) is hydrogen or R\(^{A}\) and R\(^{4}\), R\(^{a}\), R\(^{c}\) and R\(^{d}\) have the above-named meaning, are cyclized with a nitrile oxide of formula VII

\[ R^{b}\text{C}N^{+}\text{O}^{-} \quad \text{VII}, \]

in which R\(^{b}\) has the above-named meaning, to compounds of formula I with R\(^{3}\) meaning

![Diagram of compound VII](image)

or

e) compounds of formula VIII

![Diagram of compound VIII](image)

in which R\(^{A'}\) is hydrogen or R\(^{A}\) and R\(^{4}\) has the above-named meaning, are cyclized with a compound of formula (R\(^{5}\text{CO})_{2}\text{O} with R\(^{5}\) in the above-named meaning to compounds with R\(^{3}\) meaning

![Diagram of compound VIII](image)

or
f) compounds of formula IX

\[
R^{A'} \rightarrow O \rightarrow R^{6} \quad \text{IX,}
\]

in which \(R^{A'}\) is hydrogen or \(R^{A}\), \(R^{4}\) has the above-named meaning and \(R^{6}\) means OH or a reactive acid derivative, are reacted with a compound of formula

\[
\begin{array}{c}
\text{NH} \\
\text{R}^{5} \\
\text{N-OH}
\end{array}
\]

to compounds with \(R^{3}\) meaning

\[
\begin{array}{c}
\text{N} \\
\text{R}^{5} \\
\text{O} \\
\text{N}
\end{array}
\]

and then optionally protecting groups are cleaved off or interesterified or the ester group is hydrolyzed or acid addition salts are formed or isomers are separated.

The introduction of substituent \(R^{A}\) according to process variant a) takes place according to the usual methods of etherification, which are described, for example, in EP-A-237467.

Reactive compound \(R^{A}-Y\), in which \(Y\) means, for example, halogen, tosylate, mesylate or triflate, is reacted in the
presence of a base such as alkaline-earth or alkali-alcoholate or -hydroxide, alkali or alkaline-earth carbonate in polar solvents, such as dimethylsulfoxide, dimethylformamide, acetonitrile or alcohols at room temperature or increased temperature, optionally in the presence of phase transfer catalysts.

The introduction of substituent R³ meaning -CO-R² according to process variant b) takes place according to the methods described in WO 91/09858. For example, a β-carboline-3-carboxylic acid-alkyl ester derivative or its reactive acid derivative, such as carboxylic acid imidazolide, is reacted with a lithium-organic compound R²Li in aprotic polar solvents, such as cyclic or acyclic ethers or hydrocarbons at temperatures of -70°C up to room temperature. Suitably, a protecting group can be present in 9-position of the β-carboline such as tosyl, mesyl or a trialkylsilyl group, which is cleaved off in the working up of the reaction mixture or thereafter in the usual way depending on the type of protecting group.

The cycloaddition of compounds of formulas IV and VI according to processes c) and d) takes place according to the methods described in EP-A-305 322. The addition is performed at temperatures of 0°C-40°C in an aprotic solvent, such as aliphatic or cyclic ethers, halogenated hydrocarbons, dimethylformamide, i.e. β-Carboline derivatives protected in 9-position optionally can be used in the reaction. The protecting group is cleaved off in the usual way with the working up of the reaction mixture or thereafter by treatment with bases or acids depending on the type of protecting group.
The production of the nitrile oxides takes place, for example, by reaction of β-carboline-3-carbaldehydes to the corresponding oximes, which can be converted, for example, with N-halogen-succinimide, tert-butoxychlorite or Na-hypochlorite in the above-mentioned aprotic solvents to hydroxamic acid halides. With bases such as Na- or K-alcoholates, trialkylamines, Hünig base, DBU or diazabicyclooctane, hydrogen halide is cleaved off from the hydroxamic acid halides and nitrile oxides are obtained, which are subjected to the cycloaddition without isolation (R. Annunziata et al., J. Chem. Soc. 1987, 529).

The introduction of the oxadiazole radicals according to process variants e) and f) can take place according to the methods described in EP-161 574. The production of 1,2,4-oxadiazol-3-yl-carbolines takes place, for example, by reaction of β-carboline-3-carboxamide oximes with acid anhydrides \((R^5CO)_2O\) at room temperature up to boiling temperature of the mixture.

To introduce the 1,2,4-oxadiazol-5-yl radical, the β-carboline-3-carboxylic acid or its reactive acid derivative, such as halide, imidazolide or mixed anhydride or carboxylic acid alkyl ester is reacted in the presence of alcoholate with an amide oxime

\[
\text{R}^2\text{NOH}_2
\]

in aprotic solvents such as hydrocarbons, such as toluene, ethers or dimethylformamide at room temperature or increased temperature.
If an interesterification is desired, the methods described in EP-A-237 467 can be used by being interesterified with alkali alcoholates or the corresponding alcohol, optionally by adding titanium-tetra-isopropylate as catalyst at increased temperature. The introduction of the tert-butyl ester group takes place, e.g., by reaction of carboxylic acid with tert-butoxy-bis-dimethylaminomethane. The hydrolysis of the ester group can take place as acid or alkaline in the usual way, for example, with Na- or K-hydroxide in protic solvents or according to the processes described in EP-A-161 574.

The mixtures of isomers can be separated according to the usual methods such as, for example, crystallization, chromatography or salt formation in the diastereomers or enantiomers.

For the formation of physiologically compatible acid addition salts, a compound of formula I is dissolved, for example, in a little alcohol and mixed with a concentrated solution of the desired acid.

In so far as the production of the initial compounds is not described, the latter are known or can be produced analogously to known compounds or processes described here.

For example, the production of 3-carboxylic acid esters of formula II is described in EP-A-130 140.

The following examples are to explain the process according to the invention.
Example 1

6-(1-Isoquinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

1.3 g of potassium hydroxide powder is added to 25 ml of dimethyl sulfoxide at room temperature. Then, 3.14 g of 6-hydroxy-β-carboline-3-carboxylic acid isopropyl ester is added in portions to the batch and then a solution of 2 g of 1-chloroisoquinoline in 2 ml of dimethyl sulfoxide is instilled. After 3 hours of heating to a bath temperature of 90-95°C, 375 mg of 1-chloroisoquinoline is added once more and heated for 2 hours to 100°C. It is poured on ice, adjusted to pH 5 with glacial acetic acid, the precipitate is suctioned off and rewashed with ethyl acetate. This residue is chromatographed on silica gel with methylene chloride:ethanol = 13:1 as eluant. After concentration by evaporation of the correspondingly combined fractions and recrystallization, 2.5 g (55% of theory) of 6-(1-isooquinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester of melting point 10°C is obtained.

In an analogous way, there are produced:

6-(4-Quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 165-167°C

6-(4-methyl-2-quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 174-176°C

6-(2-quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 108°C

6-(3-chloro-2-quinoxalyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 223-228°C
5-(1-isoquinolylOXY)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 235-237°C
6-(5-tosyl-2-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 206-207°C
6-(2-tosyl-5-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 206-207°C
6-(5-bromo-2-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester, melting point 180-181°C
6-(5-bromo-2-pyrazinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid tert-butyl ester, melting point 195-196°C
6-(2-methylmercapto-4-pyrimidinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 209-210°C
6-(2-methylsulfonyl-4-pyrimidinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 178-179°C
6-(5-trifluoromethyl-2-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 215-216°C
6-(4,6-dimethoxy-2-pyrimidinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 130-132°C
6-(5-bromo-2-pyrimidinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 211-212°C
6-(4,6-dimethyl-2-pyrimidinyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 84-85°C
6-[(4,6-bis(methylthio)-1,3,5-triazin-2-yloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 167-170°C
6-(2,6-dimethoxy-4-pyrimidinyl)oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 159-161°C
6-(4,6-dimethoxy-1,3,5-triazin-2-yloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 159-162°C
6-(1,3,5-triazin-2-yloxy-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 168-170°C
6-(5-methyl-2-pyrazinyl)oxy-4-ethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 180°C
6-(5-methyl-2-pyrazinyl)oxy-4-ethyl-β-carboline-3-carboxylic acid-tert-butyl ester, melting point 196°C
6-(5-methyl-2-pyrazinyl)oxy-3-(5-methoxymethyl-3-isoxazolyl)-4-methoxymethyl-β-carboline, melting point 194-196°C
6-(5-methylpyrazine-2-yl)oxy-4-ethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 175-177°C
6-(5-bromopyrazine-2-yl)oxy-4-ethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 227-228°C
6-(5-bromopyrazine-2-yl)oxy-4-methyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 245-246°C
6-(6-methoxypyridine-2-yl)oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 92-99°C
6-(5-chloropyridazine-2-yl)oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 223°C
6-(5-chloropyridazine-2-yl)-oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-tert-butyl ester, melting point 197°C

6-(6-methoxypyridine-2-yl)-oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-tert-butyl ester, melting point 166°C.

5-(5-trifluoromethylpyridine-2-yl)-oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester, melting point 206°C

5-(5-trifluoromethylpyridine-2-yl)-oxy-4-methoxymethyl-β-carboline-3-carboxylic acid-tert-butyl ester, melting point 178-180°C.

Example 2

6-(1-Isocinolinoxy-4-methoxymethyl-3-(5-methoxymethylisoaxol-3-yl)-β-carboline

330 mg of 6-(1-isocinolinoxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester is mixed in 10 ml of toluene with 0.62 ml of triethylamine and 0.2 chlorotrimethylsilane and heated for 45 minutes to a bath temperature of 50-60°C. After concentration by evaporation to about 6 ml, it is cooled to -78°C under argon and 1.25 ml of a 1.2 molar diisobutyl aluminum
hydride is instilled in hexane. After 30 minutes at -78°C, it is mixed with 3 ml of ethanol and 0.75 ml of 1N NaOH. It is mixed with ethyl acetate and very little water. The organic phase is separated and concentrated by evaporation without drying. The residue is mixed with hexane and yields 440 mg of 6-(1-isoquinolyloxy)-4-methoxymethyl-β-carboline-3-carbaldehyde. 254 mg of it is mixed in 2.5 ml of dimethylfuran with 67.5 mg of hydroxylamine hydrochloride and 69 mg of potassium hydroxide powder and allowed to stand for 16 hours at room temperature. The batch is poured on ice and the precipitate is suctioned off and rewashed with water. 133 mg of 6-(1-isoquinolyloxy-4-methoxymethyl-β-carboline-3-carbaldehyde oxime of melting point 215-218°C is obtained.

450 mg of this oxime is dissolved in 7 ml of dimethylformamide and stirred with 218 mg of N-bromosuccinimide for 30 minutes at room temperature. After adding 0.8 ml of triethylamine and 0.16 ml of methyl propargyl ether, it is stirred for 3 hours at room temperature. After concentration by evaporation, it is dispersed in ethyl acetate/water and the organic phase is dried, filtered and concentrated by evaporation. The residue is chromatographed twice on silica gel first with methylene chloride:ethanol = 10:1 and then with methylene chloride:ethanol = 12:1. After recrystallization of the corresponding fractions that are combined and concentrated by evaporation, 200 mg of 6-(1-isoquinolyloxy)-4-methoxymethyl-3-(5-methoxymethylisoxazol-3-yl)-β-carboline of melting point 107-112°C (ethyl acetate/hexane) is obtained.
Example 3

6-(1-Isoquinolylloxy)-4-methoxymethyl-3-benzoyl-β-carboline

476 mg of 6-(1-isooquinolylloxy)-4-methoxymethyl-9-tosyl-β-carboline-3-carboxylic acid isopropyl ester is mixed in 10 ml of tetrahydrofuran under argon at -60°C with 0.79 ml of a 0.9 m solution of phenyllithium in benzene. After 1 hour at -60°C, it is stirred for 16 hours at room temperature. The batch is acidified with glacial acetic acid and concentrated by evaporation. The residue is dispersed in ethyl acetate/water and the organic phase is washed, dried, filtered and concentrated by evaporation in succession with respectively saturated sodium bicarbonate and common salt solution. The residue is chromatographed on silica gel with methylene chloride:ethanol = 10:1. The corresponding fractions are combined, concentrated by evaporation and recrystallized. 30 mg of 6-(1-isooquinolylloxy)-4-methoxymethyl-3-benzoyl-β-carboline of melting point 159-160°C (ethyl acetate/hexane) is obtained.
The Claims defining the invention are as follows:

1. Compounds of formula I

\[ R^A \text{ means a triazine or benzocondensed hetaryl radical with 1-2 nitrogen atoms optionally substituted with halogen, } C_{1-6} \text{ alkyl, } C_{1-6} \text{ alkoxy, } C_{1-6} \text{ alkylthio, trifluoromethyl or } SO_2-R^1 \text{ or a 5- or 6-membered hetaryl radical with 1-2 nitrogen atoms substituted with halogen, } C_{1-6} \text{ alkyl, } C_{1-6} \text{ alkoxy, } C_{1-6} \text{ alkylthio, trifluoromethyl or } SO_2-R^1, \text{ and } R^1 \text{ is } C_{1-4} \text{ alkyl or phenyl optionally substituted 1-2 times with } C_{1-4} \text{ alkyl and } R^A \text{ can be substituted once to twice, and the substituent is not halogen, if } R^A \text{ means pyridine,} \]

\[ R^4 \text{ means hydrogen, } C_{1-6} \text{ alkyl, } C_{1-6} \text{ alkoxy-}C_{2} \text{alkyl} \text{ and } \]

\[ R^3 \text{ means } -CO_2-C_{1-6} \text{ alkyl, } -CO-R^2, -CO_2H, \]

\[ \text{or} \]

\[ \text{or} \]

\[ \text{or} \]
and

$R^2$ means $C_{1-4}$ alkyl, $C_{3-7}$ cycloalkyl, $C_{7-9}$ bicycloalkyl or a monocyclic or bicyclic $C_{6-12}$ aryl radical optionally substituted with $C_{1-4}$ alkyl, $C_{1-4}$ alkoxy or amino,

$Ra$ and $R^b$ are the same or different and respectively mean hydrogen, $C_{1-6}$ alkoxy, $C_{1-6}$ alkyl, $-\text{CH}_2-O-C_{1-4}$ alkyl, phenyl or benzyl,

$R^c$ and $R^d$ respectively mean hydrogen or together a bond and

$R^5$ is hydrogen, $C_{1-4}$ alkyl or $C_{3-7}$ cycloalkyl,

as well as their isomers and acid addition salts.

2. 6-(1-isoquinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

6-(4-methyl-2-quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

6-(2-quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

6-(3-chloro-2-quinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

5-(2-isoquinolyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

6-(1-isoquinolyloxy-4-ethoxynethyl-3-benzoyl-3-carboline

6-(5-tosyl-2-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester

6-(2-tosyl-5-pyridyloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester
6-(5-bromo-2-pyrazinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid isopropyl ester
6-(5-bromo-2-pyrazinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-tert-butyl ester
6-(2-methylmercapto-4-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(2-methylsulfonyl-4-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(5-trifluoromethyl-2-pyridinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(4,6-dimethoxy-2-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(5-bromo-2-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(4,6-dimethyl-2-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-[4,6-bis(methylthio)-1,3,5-triazin-2-yloxy]-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(2,6-dimethoxy-4-pyrimidinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(4,6-dimethoxy-1,3,5-triazin-2-yloxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(1,3,5-triazin-2-yloxy-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(5-methyl-2-pyrazinyl oxy)-4-methoxymethyl-β-carboline-3-carboxylic acid-isopropyl ester
6-(5-methyl-2-pyrazinyl)-4-methoxymethyl-3-carboline-3-carboxylic acid-tert-butyl ester
6-(5-methyl-2-pyrazinyl)-3-(5-methoxymethyl-3-isoxazolyl)-4-methoxymethyl-3-carboline
6-(5-methylpyrazine-2-yl)-oxy-4-ethyl-3-carboline-3-carboxylic acid-isopropyl ester
6-(5-bromopyrazine-2-yl)-oxy-4-ethyl-3-carboline-3-carboxylic acid-isopropyl ester
6-(5-bromopyrazine-2-yl)-oxy-4-methyl-3-carboline-3-carboxylic acid-isopropyl ester
6-(6-methoxypyridine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-isopropyl ester
6-(5-chloropyridazine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-isopropyl ester
6-(5-chloropyridazine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-tert-butyl ester
6-(6-methoxypyridine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-tert-butyl ester
5-(5-trifluoromethylpyridine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-isopropyl ester
5-(5-trifluoromethylpyridine-2-yl)-oxy-4-methoxymethyl-3-carboline-3-carboxylic acid-tert-butyl ester.
3. Use of compounds according to claims 1 and 2 for the production of pharmaceutical agents.

4. Process for the production of compounds of formula I characterized in that
   a) compounds of formula II

\[
\begin{align*}
\text{HO} & \quad \text{II}, \\
\text{R}^6 & \quad \text{R}^3 \\
\text{N} & \quad \text{N}
\end{align*}
\]

in which \( R^4 \) and \( R^3 \) have the above-named meaning, with \( R^4 Y \), in which \( R^4 \) has the above-named meaning and \( Y \) is halogen or a reactive group, are etherified or
b) compounds of formula III

![Formula III]

in which \( R^4 \) has the above-named meaning, \( R^{A'} \) is hydrogen or \( R^A \) and \( Z \) is hydrogen, \( C_{1-4} \) alkoxy or a reactive acid derivative, are reacted with a lithium-organic compound optionally after introducing a protecting group in 9-position to compounds of formula I with \( R^3 = -CO-R^2 \) or

c) compounds of formula IV

![Formula IV]

in which \( R^{A'} \) is hydrogen or \( R^A \) and \( R^4 \) has the above-named meaning, are cyclized with a compound of formula V

![Formula V]

in which \( R^a, R^b, R^c, \) and \( R^d \) have the above-named meaning to compounds of formula I with \( R^3 \) meaning
d) compounds of formula VI

\[
\begin{align*}
\text{R}^a & \quad \text{R}^b \\
\text{R}^c & \quad \text{R}^d
\end{align*}
\]

in which \(\text{R}^a\)' is hydrogen or \(\text{R}^4\), \(\text{R}^a\), \(\text{R}^c\) and \(\text{R}^d\) have the above-named meaning, are cyclized with a nitrile oxide of formula VII

\[
\text{R}^b - \text{C}=\text{N}^+ - \text{O}^-
\]

in which \(\text{R}^b\) has the above-named meaning, to compounds of formula I with \(\text{R}^3\) meaning

\[
\begin{align*}
\text{R}^a & \quad \text{R}^b \\
\text{R}^c & \quad \text{R}^d
\end{align*}
\]
e) compounds of formula VIII

\[
\begin{align*}
\text{VIII,}
\end{align*}
\]

in which \( R^A' \) is hydrogen or \( R^A \) and \( R^4 \) has the above-named meaning, are cyclized with a compound of formula \((R^5\text{CO})_2\text{O}\) with \( R^5 \) in the above-named meaning to compounds with \( R^3 \) meaning.

or

f) compounds of formula IX

\[
\begin{align*}
\text{IX,}
\end{align*}
\]

in which \( R^A' \) is hydrogen or \( R^A \), \( R^4 \) has the above-named meaning and \( R^6 \) means \( \text{OH} \) or a reactive acid derivative, are reacted with a compound of formula

\[
\begin{align*}
\text{to compounds with } R^3 \text{ meaning}
\end{align*}
\]
and then optionally protecting groups are cleaved off or interesterified or the ester group is hydrolyzed or acid-addition salts are formed or isomers are separated.

5. Process for the production of pharmaceutical agents in that a compound of formula I produced according to claim 4 is mixed with a pharmaceutical vehicle.

6. Any novel, starting or intermediate compound or process for the manufacture of same as herein described.

DATED this 5th day of June 1992

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