(51) International Patent Classification 6:
C07D 471/04, 221/04, A61K 31/435

(11) International Publication Number: WO 99/47521
(43) International Publication Date: 23 September 1999 (23.09.99)

(21) International Application Number: PCT/IB99/00494
(22) International Filing Date: 17 March 1999 (17.03.99)
(30) Priority Data: 09/042,990 17 March 1998 (17.03.98) US


(54) Title: HYPNOTIC β-CARBOLINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR USE AS MEDICINAL PRODUCTS


Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(57) Abstract

The present invention concerns derivatives of general formula I (I' and I''), in which X represents a divalent radical of formula (a) or (b). R1, R2, R3, and R4 represent, independently of each other, a hydrogen atom, a hydroxy radical, a lower alkyl, lower alkoxy, aryloxy, halo or nitro radical or an unsaturated aliphatic chain, lower alky carbonyl, lower alky carbonyloxy, carboxyl, these groups being optionally substituted. R5 represents a hydrogen atom, a lower alkyl, cycloalkyl, aryl, lower alkanol, lower alkoxy, a lower alky carbonyl, halo(lower)alky carbonyl, lower alky carbonyloxy, amino, these groups being optionally substituted. R6, R7, R8, R9, R10, R12, R13, R14 and R15 represent, independently of each other, a hydrogen atom, a lower alkyl, a lower cycloalkyl, halo(lower)alky carbonyl, perhalo(lower)alkyl, aryl, alkanol, lower alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, alkenyloxy, hydroxyalkyl, alkoxyalkyl, lower alkoxythio, lower cycloalkylthio, these groups being optionally substituted. R9 represents a lower alkyl, a lower cycloalkyl, hydroxyalkyl, alkoxyalkyl, halo(lower)alkyl, perhalo(lower)alkyl, aryl, these groups being optionally substituted. R11 represents an oxygen atom or a sulfur atom optionally substituted.
FOR THE PURPOSES OF INFORMATION ONLY

Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

<table>
<thead>
<tr>
<th>Code</th>
<th>Country</th>
<th>Code</th>
<th>Country</th>
</tr>
</thead>
<tbody>
<tr>
<td>AL</td>
<td>Albania</td>
<td>LS</td>
<td>Lesotho</td>
</tr>
<tr>
<td>AM</td>
<td>Armenia</td>
<td>LT</td>
<td>Lithuania</td>
</tr>
<tr>
<td>AT</td>
<td>Austria</td>
<td>LU</td>
<td>Luxembourg</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>LV</td>
<td>Latvia</td>
</tr>
<tr>
<td>AZ</td>
<td>Azerbaijan</td>
<td>MC</td>
<td>Monaco</td>
</tr>
<tr>
<td>BA</td>
<td>Bosnia and Herzegovina</td>
<td>MD</td>
<td>Republic of Moldova</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>MG</td>
<td>Madagascar</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>MK</td>
<td>The former Yugoslav Republic of Macedonia</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>ML</td>
<td>Mali</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>MN</td>
<td>Mongolia</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>BY</td>
<td>Belarus</td>
<td>MX</td>
<td>Mexico</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>NE</td>
<td>Niger</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d'Ivoire</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>PT</td>
<td>Portugal</td>
</tr>
<tr>
<td>CN</td>
<td>China</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>CU</td>
<td>Cuba</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>CZ</td>
<td>Czech Republic</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>SG</td>
<td>Singapore</td>
</tr>
<tr>
<td>EE</td>
<td>Estonia</td>
<td>SI</td>
<td>Slovenia</td>
</tr>
<tr>
<td>SK</td>
<td>Slovakia</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>SZ</td>
<td>Swaziland</td>
<td>SZ</td>
<td>Singapore</td>
</tr>
<tr>
<td>TD</td>
<td>Chad</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>TJ</td>
<td>Tajikistan</td>
<td>TR</td>
<td>Turkey</td>
</tr>
<tr>
<td>TM</td>
<td>Turkmenistan</td>
<td>TT</td>
<td>Trinidad and Tobago</td>
</tr>
<tr>
<td>UA</td>
<td>Ukraine</td>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>UG</td>
<td>Uganda</td>
<td>UZ</td>
<td>Uzbekistan</td>
</tr>
<tr>
<td>VN</td>
<td>Viet Nam</td>
<td>YU</td>
<td>Yugoslavia</td>
</tr>
<tr>
<td>ZW</td>
<td>Zimbabwe</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
HYPNOTIC β-CARBOLINE DERIVATIVES,
PROCESS FOR THEIR PREPARATION
AND THEIR USE AS MEDICINAL PRODUCTS

The present invention relates to novel β-carboline derivatives, to a process for their preparation and to their use as medicinal products.

Melatonin, N-acetyl-5-methoxytryptamine, is a hormone from the pineal gland, isolated by Lerner & al. (J. Am. chem. Soc., 80, 1958, 2587), which has formed the subject of numerous studies for its circadian activity, in the rhythm of sleep, for its effects on the production of testosterone, for its activity on the hypothalamus and in psychiatric disorders.

It has thus been envisaged to employ melatonin and analogues thereof especially for the treatment of depression and psychiatric disorders, in particular stress, anxiety, depression, insomnia, schizophrenia, psychoses and epilepsy, and also for the treatment of sleeping disorders associated with travelling ("jet lag"), neurodegenerative diseases of the central nervous system such as Parkinson's disease or Alzheimer's disease, for the treatment of cancers or, alternatively, as a contraceptive or as an analgesic.

However, the direct use of melatonin in vivo has not proved to be very satisfactory, on account of the facts that the first passage through the liver extracts more than 90 % of the active principle and that hypnotic activity of melatonin has not been clearly demonstrated.

We have demonstrated that melatonin does not exhibit any hypnotic activity; but is the bioprecursor of acetylated metabolites which induce sleep.

The present patent application proposes a novel route for the development of novel carboline derivatives which are analogues of endogenous acetylated metabolites of melatonin.

The present invention relates to novel carboline derivatives of general formula I (I' and I'') :

![Chemical structures](image)

In which X represents a divalent radical of formula

\[ N-R_5 \quad \text{or} \quad R_6-CR_7 \]

R_1, R_2, R_3, and R_4 represent, independently of each other, a hydrogen atom, a hydroxy radical, a lower alkyl, lower cycloalkyl, lower alkoxy, aryloxy, lower aralkyloxy, halo or nitro radical or an unsaturated aliphatic chain, formyl, lower alkylcarbonyl, lower alkylcarbonyloxy, halo(lower)alkylcarbonyl, halo(lower)alkylcarbonyloxy, halo-(lower)alkyl, halo(lower)alkyloxy, lower alkoxy carbonyl, carboxyl, optionally substituted carboxamide, two adjacent
radicals R₁, R₂, R₃ or R₄ being able to form together a 2,3-
dihydropyran-1-yl group which is possibly bearing an oxo group,
R₁, R₂, R₃, and R₄ also represent, independently of each
other, a perhalo(lower)alkyl, aryl, aralkyl, lower
cycloalkoxy, polyhaloalkoxy, a thiol radical, lower
alkylthio, lower cycloalkylthio, mono or polyhaloalkylthio,
arylthio, aralkylthio, formate, a lower cycloalkyl-
carbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, lower
dialkylaminoalkyl, aminoalkyl, lower alkylaminoalkyl,
arylaminoalkyl, diarylaminoalkyl, arylalkylaminoalkyl,
amino, alkylamino, dialkylamino, arylamino, diarylamino,
aralkylamino, diaralkylamino, formamide, a lower alkyl-
carbonylamino, a lower cycloalkylcarbonylamino, halo(lower)-
alkylcarbonylamino, polyhalo(lower)alkylcarbonylamino, aryl-
carbonylamino, lower aralkylcarbonylamino, a lower cyclo-
alkylcarbonyl, polyhalo(lower)alkylcarbonyl, arylcarbonyl,
aralkylcarbonyl, lower cycloalkoxycarbonyl, haloalkoxy-
carbonyl, aryloxy carbonyl, aralkyloxy carbonyl, a lower
alkylsulfonyl, a lower cycloalkylsulfonyl, halo(lower)alkyl-
sulfonyl, perhalo(lower) alkylsulfonyl, arylsulfonyl,
aralkylsulfonyl, cyano radical.

R₅ represents a hydrogen atom, a lower alkyl,
cycloalkyl, aryl, lower aralkyl, lower alkoxy, a lower
alkylcarbonyl, halo(lower)alkylcarbonyl, lower alkyl oxy-
carbonyl, amino, alkylamino, dialkylamino, alkylarylamino,
diaryl amino, halo(lower)alkylsulfonyl, alkylsulfonyl or
aryl sulfonyl radical.

R₅ also represents a halo(lower)alkyl, perhalo
(lower)alkyl, a hydroxy radical, lower cycloalkoxy, aryloxy,
aralkyloxy, a thiol radical, lower alkylthio, lower
cycloalkylthio, arylthio, aralkylthio, dialkylaminoalkyl,
arlamino, aralkylamino, diaralkylamino, optionally
substituted carboxamide, formamide, formyl, a lower cycloalkylcarbonyl, perhalo(lower)alkylcarbonyl, aryl-carbonyl, aralkylcarbonyl, lower cycloalkoxycarbonyl, haloalkoxycarbonyl, aryloxy-carbonyl, aralkyloxy carbonyl, a lower cycloalkylsulfonyl, perhalo(lower)alkylsulfonyl, aralkylsulfonyl, cyano radical.

R₆, R₇, R₉, R₁₀, R₁₂, R₁₃, R₁₄ and R₁₅ represent, independently of each other, a hydrogen atom, a lower alkyl, a lower cycloalkyl, halo(lower)alkyl, perhalo(lower)alkyl, aryl, aralkyl, lower alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, aralkyloxy, hydroxyalkyl, alkyloxy-alkyl, lower alklythio, lower cycloalkylthio, mono or polyhaloalkylthio, arythio, aralkylthio, formate, lower alkylcarbonyl-oxy, a lower cycloalkylcarbonyloxy, halo-(lower)alkycarboxyloxy, arylcarboxyloxy, aralkyl-carboxyloxy, dialkylaminoalkyl, dialkylamino, diarylamino, diaralkylamino, optionally substituted carboxamide, formamide, a lower alkylcarbonylamino, a lower cycloalkylcarbonylamino, halo(lower)alkylcarbonylamino, perhalo-(lower)alkylcarbonylamino, lower arylcarbonylamino, lower alkylcarbonylamino, formyl, a lower alkylcarbonyl, a lower cycloalkylcarbonyl, halo(lower)alkylcarbonyl, perhalo-(lower)alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, lower cycloalkoxycarbonyl, haloalkoxycarbonyl, aryloxy carbonyl, aralkyloxy carbonyl, a lower alkylsulfonyl, a lower cycloalkylsulfonyl, halo-(lower)alkylsulfonyl, perhalo(lower) alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, halo, cyano or nitro radical.

R₈ represents a lower alkyl, a lower cycloalkyl, hydroxyalkyl, alkyloxyalkyl, halo(lower)alkyl, perhalo-(lower)alkyl, aryl, lower-alkyl aryl, halo aryl, lower-alkoxy aryl, nitro aryl, amino aryl, di(lower)alkylamino
aryl, pyridyl, aralkyl, lower alkoxy, lower cycloalkoxy, mono or poly haloalkoxy, aryloxy, aralkyloxy, lower alkylthio, lower cycloalkylthio, mono or poly haloalkylthio, arythio, aralkylthio, lower alkylcarbonyloxy, a lower cyclo-alkylcarbonyloxy, halo(lower)alkylcarbonyloxy, aryl-carbonyloxy, aralkylcarbonyloxy, dialkylaminoalkyl, dialkylamino, diaryl amino, diaralkylamino, optionally substituted carboxamide, formamide, a lower alkylcarbonylamino, a lower cycloalkylcarbonylamino, halo(lower)-alkylcarbonylamino, poly halo(lower)alkylcarbonylamino, aryl-carbonylamino, lower aralkyl-carbonylamino, formyl, a lower alkylcarbonyl, a lower cyclo-alkylcarbonyl, halo(lower)-alkylcarbonyl, perhalo(lower)alkylcarbonyl, aryl-carbonyl, aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, lower cycloalkoxycarbonyl, haloalkoxycarbonyl, aryloxy-carbonyl, aralkyloxycarbonyl, a lower alkylsulfonyl, a lower cycloalkylsulfonyl, halo(lower) alkylsulfonyl, perhalo(lower)alkylsulfonyl, arylsulfonyl, aralkylsulfonyl, halo, cyano or nitro radical.

R₆, R₇, R₈, R₉, R₁₀, R₁₂, R₁₃ and R₁₅ can represent, but not simultaneously R₈ and R₁₅, R₉ and R₁₀, R₁₂ and R₁₃ a hydroxyl radical, a thiol radical, amino, alkylamino, arylamino, aralkylamino, alkoxy, lower cycloalkoxy, mono or poly haloalkoxy, aryloxy, aralkyloxy, lower alkylthio, lower cycloalkylthio, mono or polyhalogenoalkylthio, arylthio, aralkylthio, alkylamino, arylamino.
Furthermore

\[ C \quad C \quad C \]
\[ R_8 \quad R_{15} \quad R_9 \quad R_{10} \quad R_{12} \quad R_{13} \]

can also represent a carbonyl group C=O, a thiocarbonyl group C=S, a radical C=N-R_{16}, or a radical

\[ C = C \]
\[ R_{18} \quad R_{17} \]

R_{11} represents an oxygen atom, a sulfur,

R_{16} represents a hydrogen atom, a lower alkyl, a lower cycloalkyl, aryl, aralkyl, a hydroxy radical, lower alkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, amino, alkyl-amino, dialkylamino, arylamino, diarylamino, aralkylamino, alkylcarbonylamino, arylcarbonylamino.

R_{17} and R_{18} represent independently of each other a hydrogen atom, a lower alkyl, a lower cycloalkyl, aryl, aralkyl, lower alkoxy, lower cycloalkoxy, aryloxy, aralkyloxy, lower alkylthio, arylthio, aralkylthio, lower alkylcarbonyloxy, lower cycloalkylcarbonyloxy, aryl-carbonyloxy, aralkyl-carbonyloxy, dialkylamino, aryl-alkylamino, diarylamino, optionally substituted carboxamide, formamide, lower alkylcarbonylamino, lower cyclo-alkylcarbonylamino, aryl-carbonylamino, formyl, lower alkylcarbonyl, lower cycloalkylcarbonyl, arylcarbonyl,
aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, aryl oxycarbonyl, aralkyloxycarbonyl, lower alkyl sulfanyl, aryl sulfanyl.

It is possible for R₁-R₂, R₂-R₃, and R₃-R₄, to form part of another aromatic or non-aromatic ring with or without a hetero atom and optionally bearing a carbonyl or thiocarbonyl group.

Compounds, according to the present invention, may contain one to three asymmetric centers, such compounds will exist as optical isomers (enantiomers).

The present invention concerns the racemic mixtures thereof, the pure enantiomers thereof or the mixtures thereof in all proportions, and the therapeutically acceptable salts thereof.

More particularly, the carbon atom bearing the R₈ group may be an asymmetric center, the present invention includes all such enantiomers and mixtures.

The expressions lower alkyl, lower alkoxy or perhalo (lower) alkyl are generally understood to refer to radicals whose alkyl residue comprises between 1 and 6 carbon atoms.

These are preferably linear or branched C₁-C₄ alkyl residues chosen more particularly from methyl, ethyl, n-propyl, i-propyl, n-butyl, i-butyl and t-butyl groups. The expression unsaturated aliphatic chain is preferably understood to refer to an unsaturated C₂-C₆ hydrocarbon chain.

The term aryl generally denotes aromatic and heteroaromatic groups, in particular aryls chosen from phenyl, thienyl, furanyl, pyridyl and naphthyl groups. The aryl radicals may also be substituted with one or more groups chosen in particular from a hydrogen atom, a lower alkyl, a lower cycloalkyl, halo(lower)alkyl, perhalo-
(lower)alkyl, aryl, aralkyl, a hydroxy radical, lower alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, aralkyloxy, a thiol radical, lower alkylthio, lower cycloalkylthio, mono or polyhaloalkylthio, arylthio, aralkylthio, formate, lower alkylcarbonyloxy, a lower cycloalkylcarbonyloxy, halo(lower)alkylcarbonyloxy, aryl-carbonyloxy, aralkylcarbonyloxy, dialkylaminoalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, diaralkylamino, optionally substituted carboxamide, formamide, a lower alkylcarbonylamino, a lower cycloalkylcarbonylamino, halo(lower)alkylcarbonylamino, perhalo-(lower)alkylcarbonylamino, lower arylcarbonylamino, lower aralkylcarbonylamino, formyl, a lower alkylcarbonyl, a lower cycloalkylcarbonyl, halo(lower)alkylcarbonyl, perhalo-(lower)alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, lower cycloalkoxycarbonyl, haloalkoxycarbonyl, aryloxycarbonyl, aralkyloxycarbonyl, a lower alkylsulfonfyl, a lower cycloalkylsulfonfyl, halo-(lower)alkylsulfonfyl, perhalo(lower) alkylsulfonfyl, aryl-sulfonfyl, aralkylsulfonfyl, halo, cyano or nitro radicals.

The expression lower aralkyl will be understood to refer to the combination of a lower alkyl and an aryl as defined above. This will preferably be the benzyl radical, which is optionally substituted.

The halo radicals are preferably chosen from fluorine, chlorine, bromine and iodine atoms.

The perhalo radicals are preferably perfluoro radicals.

When $R_1-R_2$, $R_2-R_3$ and $R_3-R_4$ form part of another aromatic ring, with or without a hetero atom, this is preferably another benzene ring, which is optionally substituted, or a pyridyl ring, which is optionally substituted.
When R₁-R₂, R₂-R₃ and R₃-R₄ form part of another non-aromatic ring, they preferably form together a divalent radical of formula \(-O-(CH₂)ₘ-\), \(m\) being equal to 2 or 3, which is optionally substituted, or a divalent radical of formula \(-O-(CH₂)ₚ-O-\), \(p\) being equal to 1 or 2, which is optionally substituted. When the derivatives comprise at least one asymmetric carbon, the present invention relates to the corresponding racemic mixtures, as well as to the pure enantiomers thereof or the mixtures thereof in all proportions.

The therapeutically acceptable salts of the derivatives according to the invention are the usual organic or inorganic salts of the art, in particular the hydrochlorides, the tosylates, the mesylates and the citrates, as well as solvates such as the hydrates or hemihydrates of the compounds of general formula I.

By comparison with the derivatives described in WO 96/08490, the derivatives according to the invention are characterised in that they contain a R₈ group which is different from an hydrogen atom, which increases dramatically the stability of such compounds in gastric acidic medium and allows oral administration to be used.

Without being bind to any theory, it has now been found that the group responsible of the hypnotic activity of the compounds according to the present invention is the ene-amide or dihydroene-amide group. This ene-amide or dihydroene-amide group is the group constituted by the Cₐ-N-Cₖ in formula I.

Derivatives according to the present invention and being of particular interest are these wherein:

R₁₁ represents preferably an oxygen atom or sulfur atom.
R₂ represents a hydroxy or lower alkoxy radical, preferably R₂ represents a methoxy radical.

R₁⁴ represents a hydrogen atom or a lower alkyloxy-carbonyl group.

The present invention relates more particularly to the derivatives of general formula Ia (Ia' and Ia'') :

When Ia represents Ia',

R₈ represents an alkyl radical, optionally substituted by alkyl, halide, amino, alkoxy groups, alkyloxy carbonyl, an aryl radical optionally substituted by alkyl, halide, nitro, dialkylamino, alkoxy group, alkyloxy carbonyl, alkylamino, this aryl radical being e.g. a phenyl group, a pyridyl group.

When Ia represents Ia'’,

If R₁⁵ is an hydrogen atom, R₈ represents preferably an ethyl, hexyl, isopropyl radical, a phenyl, fluorophenyl, methoxyphenyl, aminophenyl, dimethylaminophenyl, nitrophenyl, tolyl radical, an ethoxycarbonyl radical, a pyridyl radical.

If R₁⁵ is different of an hydrogen atom, R₈ and R₁⁵, identical, represent lower alkyl radicals or aryl radicals.
optionally substituted by alkyl, halide, amino, alkylxoy group.

X represents preferably a divalent radical of formula

\[ \text{NH} \quad \text{or} \quad \text{HC-CH} \]

\((R_5 = R_6 = R_7 = H)\)

\(R_{11}\) represents preferably an oxygen atom or sulfur atom.

\(R_2\) represents a hydroxyl or lower alkoxy radical and preferably a methoxy radical.

\(R_3\) represents an hydrogen atom or an alkyl radical and preferably a methyl radical.

The present invention also relates to the process for the preparation of the derivatives of general formula I as defined above.

In the particular of derivatives of general formula Ib.

For which \(R_2, R_3, R_6, R_{14}\) and \(X\) are defined above.

The derivative of formula Ib may be obtained directly by reacting the compound of general formula IIa.
For which R2, R3, R8, R14 and X are defined above, with a carboxylic acid (such as acrylic acid) in the presence or not of diphenylphosphorylazide or with acrylonitrile.

In order to obtain the derivatives of general formula IIa, a Bischler-Napieralski reaction is carried out by reacting the compounds of general formula IIIa.

In which R2, R3, R8, R14 and X are defined above, with phosphorus pentoxide (P2O5) or with phosphorus oxychloride (POCl3) in a suitable solvent, for example toluene, xylene, dichloromethane.

These derivatives IIa may also be prepared by permanganic oxidation of the derivatives of general formula IIb.

Wherein R2, R3, R8 and R14 are defined above.
In order to obtain the derivatives of general formula IIb, a Pictet-Spengler reaction is carried out by reacting the derivatives of general formula IIIb.

For which $R_2, R_3, R_{14}$ and $X$ are defined above, with compounds of formula $R_8-\text{CH}_2-\text{CHO}$ or chemical equivalents thereof such as a ketal, an enol ether, an enol ester or a nitrile of formula $R_8-\text{CH}_2-\text{CN}$ under reducing conditions, $R_8$ being defined above.

The derivatives of formula IIIa may be obtained by carrying out an acylation by an acylating agent (acid chloride, acid anhydride, ester) on the derivatives of formula IIIb for which $R_2, R_3, R_{14}$ and $X$ are defined above.

Also, when $X=NR_5$ the derivatives of formula IIIa may be obtained by Fischer reaction with the appropriate substituted phenylhydrazine of general formula IV and the suitable aldehyde or masked aldehyde such ketal of general formula V.
For which \( R_2, R_3, R_8, R_{14} \) are defined above

\( R_5 \) represents an hydrogen radical or a lower alkyl

In the particular case of derivatives of general formula IC

For which \( R_2, R_3, R_8, R_{14} \) and \( X \) are defined above, the derivative of formula IC may be obtained directly by catalytic reduction by hydrogen with Palladium on Carbon of compound of general formula IB.

In the particular case of derivatives of general formula ID
For which \( R_2, R_3, R_8, R_{14} \) and \( X \) are defined above, the derivatives of general formula \( \text{I}d \) may be obtained directly by reaction of the Lawesson's reagent or by \( P_2S_4 \) on the compounds of general formula \( \text{I}b \).

In the particular case of derivatives of general formula \( \text{I}e \)

\[
\begin{array}{c}
    \text{I}e \\
    \includegraphics[width=0.3\textwidth]{image}
\end{array}
\]

for which \( R_2, R_3, R_8, R_{14} \) and \( X \) are defined above, the derivative of formula \( \text{I}e \) may be obtained directly by reaction of the Lawesson's reagent or by \( P_2S_4 \) on the compound of general formula \( \text{I}c \).

In the particular case of derivatives of general formula \( \text{I}f \)

\[
\begin{array}{c}
    \text{I}f \\
    \includegraphics[width=0.3\textwidth]{image}
\end{array}
\]

for which \( R_2, R_3, R_8, R_{11}, R_{14} \) and \( X \) are defined above, the derivative of formula \( \text{I}f \) may be obtained directly with an oxidant (such \( O_2 \) in alkaline medium) on the compound of general formula \( \text{I}b \) or \( \text{I}d \).
The derivatives according to formula Ia wherein R₈ and R₁₅ are identical may be obtained by carrying out a reaction on the derivatives of general formula IIIb

\[
\begin{align*}
\text{IIIb} \\
\text{with compounds of formula EtO-CO-C(R₈)(R₁₅)-COH or chemical equivalents thereof under reducing conditions}
\end{align*}
\]

The derivatives according to the invention may be used as medical product for the treatment of diseases associated with disorders of melatonin activity. The derivatives according to the invention present myorelaxing properties and they also may be use for the treatment of depression and psychiatric disorders, in particular stress, anxiety, depression, insomnia, schizophrenia, psychoses and epilepsy, and also for the treatment of sleeping disorders associated with travelling ("jet lag"), neurodegenerative diseases of the central nervous system such as Parkinson's disease or Alzheimer's disease, for the treatment of cancers or, alternatively, as a contraceptive or as an analgesic. They present hypnotic and sedative effects.
STABILITY IN ACIDIC MEDIUM AND PHARMACOLOGICAL ACTIVITY

1. STABILITY IN ACIDIC MEDIUM AND ORAL BIOAVAILABILITY IN BEAGLE DOG

In order to study the influence of R₈ group on the stability of cycle A when comparing compounds EXAMPLE A and EXAMPLE B (R₈ = hydrogen atom) to compounds of Example 1, Example 4, Example 7, Example 8 and Example 11, 30 µM of each of these compounds were dissolved into 5 ml of pH=1 or pH=2 or pH=3 or pH=7 (reference) buffer. Solutions were stirred for 15 minutes at 37°C. Subsequent measurements of compounds amounts non hydrolyzed were measured using a high performance liquid chromatography method.

EXAMPLE A

EXAMPLE B
Table I:
Stability in acidic medium and oral bioavailability in beagle dogs

<table>
<thead>
<tr>
<th>Example n°</th>
<th>pH=1</th>
<th>pH=2</th>
<th>pH=3 (reference)</th>
<th>pH=7 (oral/IV in Beagle dogs)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>100</td>
<td>100</td>
<td>100</td>
<td>&lt;1%</td>
</tr>
<tr>
<td>1</td>
<td>79.5</td>
<td>14.5</td>
<td>8.7</td>
<td>&gt;35%</td>
</tr>
<tr>
<td>7</td>
<td>17.0</td>
<td>13.0</td>
<td>5.4</td>
<td>N.D.</td>
</tr>
<tr>
<td>4</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>&gt;20%</td>
</tr>
<tr>
<td>11</td>
<td>26.0</td>
<td>27.0</td>
<td>30.0</td>
<td>N.D.</td>
</tr>
<tr>
<td>B</td>
<td>95</td>
<td>95</td>
<td>90</td>
<td>&lt;5%</td>
</tr>
<tr>
<td>8</td>
<td>0</td>
<td>0</td>
<td>0</td>
<td>100%</td>
</tr>
</tbody>
</table>

N.D. : Not determined

Results are presented in Table I as percentage of compounds hydrolyzed, as shown in Table I, when compared to compounds EXAMPLE A and EXAMPLE B which are totally hydrolyzed between pH=1 and pH=3.
Compounds n°1, 4, 7, 8 and 11 are quite stable from pH=2, since less than 27 per cent of these compounds are hydrolysed at pH>2.

In conclusion, compounds wherein the Rₙ group (in general formula I) is different from a hydrogen atom do not undergo a total hydrolysis of cycle A. The stability in acidic gastric medium of compounds such as examples 1, 4, 8 allows their administration by oral route. Pharmacokinetic studies
of these compounds (Table I) have been carried out in beagle dogs; compounds 1, 4, 8 exhibit absolute bioavailability of oral route relative to intravenous route respectively higher than 35% (compound 1), 20% (compound 4) and equal to 100% (compound 8), since EXAMPLE A and EXAMPLE B absolute bioavailability are lower than 1% (EXAMPLE A) and 5% (EXAMPLE B).

Compounds n°1 (see Table II), as well as compounds n°4 and 7 (see Table III) exhibit significant hypnotic effect in Beagle dogs when given orally.

2. HYPNOTIC ACTIVITY IN BEAGLE DOGS: EFFECTS ON WAKEFULNESS / SLEEP STATES IN BEAGLE DOGS

Beagle dogs are kept in a metal cage, connected to 2 Schwartzter ED 24 Polygraph equipped with BRAINLAB* software, through a flexible cable. Test and control products are administered via the oral or intravenous routes by means of gastric tubes. Records are scored in 30 seconds epochs for active wake, drowsy, slow wave sleep (light sleep + deep sleep) and REM sleep. These criteria are according to SHELTON et al. (in SHELTON J., NISHINO S., VAUGHT J., DEMENT W.C. and MIGNOT E. Comparative effects of modafinil and amphetamine on daytime sleepiness and cataplexy of narcoleptic dogs. Sleep 19(1) ; 29-38, 1996.), based upon frequency and amplitude patterns of EEG cortical tracing (fronto-frontal), EMG (upper neck muscles) and EOG (bilateral). Behaviour is also continuously monitored for each observation period of 120 minutes. Prior acclimatisation of the dogs take 5 days; and, to mimic similar stress caused by gastric tubing, a mixture water/PEG (50/50 ; V/V) was administered orally together with intravenous boluses.
• **Wake** : includes all episodes with low voltage mixed frequency tracing in which the EMG is not inhibited. During wakefulness dogs stand, sit, or lay down, and eyes are open.

• **Sleepiness** : the drowsy state is scored when dogs lie quietly with eyes closed (50 p. cent or more per one epoch) and cortical EEG shows trains of relatively slow waves (4 - 7 Hz) without the development of sleep spindles. Synchronous waves at 4 - 7 Hz and 50 - 100 µV appear on a background of low voltage fast-wave activity. EMG is moderately decreased compared to wake stage.

• **Light deep sleep** = slow wave sleep (SWS) (light sleep + deep sleep) : canines are relaxed with prone posture. EEG patterns are of higher amplitude than in the previous stage and sleep spindles (10 - 14 Hz) and / or K complexes must be present in light sleep, as EOG show slow eye movements or no movement. Deep sleep is scored when slow delta waves (< 4 Hz) constitute 20 p. cent of an epoch or more during deep sleep.

• **REM** : rapid eye movement sleep is scored when dogs lay down, eyes closed with intermittent apparent fast muscle twitches. A low voltage mixed frequency EEG tracing is observed together with rapid eye movements and a drop in EMG activity.

Repartition and duration of wakefulness / sleep states in Beagle dogs have been measured after oral (and intravenous route for compound of EXAMPLE 1) administrations of Placebo (vehicle = 10 ml of mixture ethanol / PEG 400 / water ; 10 /
40 /50 ; V/V/V) compounds of Example 1, Example 4 and Example 7.

Results are presented in Tables II and III as Durations and Latencies of each stage.

Compounds of Example 1, Example 4 and Example 7 exhibit a potent hypnotic activity inducing a sleep characterized by a high proportion of slow wave sleep. Regarding duration and latencies of wake, drowsy and SWS stages, these 3 compounds induce a significant hypnotic effect.
TABLE II: Sleep stages and sleep latencies during a 120 minutes observation period, following Example 1 (test), and vehicle alone (Placebo: 10 ml of ethanol/PEG/water; 10/40/50; V/V/V) administrations via the oral and the intravenous routes.

<table>
<thead>
<tr>
<th>Dose (μmol/Kg)</th>
<th>Route</th>
<th>Wake</th>
<th>Drowsy</th>
<th>SWS</th>
<th>REM</th>
<th>Sleep</th>
<th>Drowsy</th>
<th>SWS</th>
<th>REM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>oral</td>
<td>110.1</td>
<td>4.4</td>
<td>5.2</td>
<td>0.3</td>
<td>9.9</td>
<td>86.2</td>
<td>94.6</td>
<td>116.2</td>
</tr>
<tr>
<td>Compound of Example 1</td>
<td>IV</td>
<td>77.4</td>
<td>14.9</td>
<td>23.9</td>
<td>3.8</td>
<td>42.6</td>
<td>33.0</td>
<td>49.4</td>
<td>79.9</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>81.1</td>
<td>12.2</td>
<td>23.6</td>
<td>3.3</td>
<td>39.1</td>
<td>49.1</td>
<td>56.3</td>
<td>82.9</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>79.7</td>
<td>14.3</td>
<td>23.0</td>
<td>3.1</td>
<td>40.4</td>
<td>41.0</td>
<td>51.3</td>
<td>79.3</td>
</tr>
<tr>
<td></td>
<td>oral</td>
<td>84.0</td>
<td>14.8</td>
<td>18.8</td>
<td>2.4</td>
<td>36.1</td>
<td>49.6</td>
<td>64.0</td>
<td>101.9</td>
</tr>
</tbody>
</table>

**Anova**

<table>
<thead>
<tr>
<th>Treatment Effect</th>
<th>p&lt;0.001</th>
<th>p&lt;0.01</th>
<th>not treated</th>
<th>p&lt;0.001</th>
<th>p&lt;0.001</th>
<th>not treated</th>
</tr>
</thead>
</table>

Student test - Newman - Keuls: means designed by the same letter (A, B or C) are not significantly different.
Table III: Sleep stages and sleep latencies during a 120 minutes observation period, following compound of example 4 (test), compound of example 7 (test) and vehicle alone (Placebo: 10 ml of ethanol/PEG/water; 10/40/50; V/V/V) administrations via the oral route

<table>
<thead>
<tr>
<th>Dose (μmol/Kg)</th>
<th>Route</th>
<th>Mean (± S.D.) duration of stages in 8 dogs (minutes)</th>
<th>Mean (± S.D.) latencies after administration (minutes)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Wake</td>
<td>Drowsy</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 oral</td>
<td>98.2 (13.9)</td>
<td>7.9 (4.3)</td>
</tr>
<tr>
<td>Compound of Example 4</td>
<td>10 oral</td>
<td>73.8 (21.3)</td>
<td>10.4 (3.9)</td>
</tr>
<tr>
<td>Anova</td>
<td></td>
<td>Treatment Effect</td>
<td>p&lt;0.01</td>
</tr>
<tr>
<td>Placebo</td>
<td>0 oral</td>
<td>98.2 (13.9)</td>
<td>7.9 (4.3)</td>
</tr>
<tr>
<td>Compound of Example 7</td>
<td>5.0 oral</td>
<td>83.7 (25.1)</td>
<td>13.0 (8.6)</td>
</tr>
<tr>
<td>Anova</td>
<td></td>
<td>Treatment Effect</td>
<td>p&lt;0.01</td>
</tr>
</tbody>
</table>
3. HYPNOTIC AND SEDATIVE EFFECTS IN CHICKS

The hypnotic and sedative effects of the derivatives, according to the invention, prepared above (the test results of which are given in Table IV below) were compared with those of 3 reference products, diazepam, pentobarbital sodium and melatonin, as well as with 2 psychostimulant compounds with hallucinogenic properties: 10-methoxyharmaline and harmaline, which are 3,4-dihydro-β-carbolines, in 10- to 14-day-old chicks of chair label JA657 strain. The animals are subjected to alternating programmes of lighting consisting of 12 h of darkness (20.00 h to 8.00 h) and 12 h of light (8.00 h to 20.00 h). The ambient temperature is 25°C during the first week of rearing of the chicks and 22°C from the second week onwards. During the day, the lighting is provided by a halogen lamp (300 W) placed 30 cm above the floor of the vivarium. During the tests, the live weights of the chicks ranged between 85 and 120 g. The tests are carried out between 14.00 and 15.00 h.

The chicks are allotted, in groups of 3, in identical 30 cm x 50 cm x 30 cm vivariums. The test products are administered intramuscularly (IM) into the pectoralis major muscle, as a solution in a 25/50/25 (V/V/V) ethanol / PEG 400 / water mixture, at the rate of 0.2 ml of solution per 100 g of live weight. The doses administered for the test products (novel compounds of the invention and reference substances) ranged from 0.25 µmol to 2 µmol per 100 g of live weight. The placebo corresponds to 0.2 ml of the 25/50/25 (V/V/V) ethanol / PEG 400 / water mixture.

The solutions of the test products in the 25/50/25 (V/V/V) ethanol / PEG 400 / water / mixture were prepared at the times of use by successive dilution of a stock solution, obtained from 2.5 to 20 µmol of accurately weighed product,
to which were successively added 0.5 ml of pure ethanol and then 1 ml of PEG 400, agitated by ultrasound and then made up to 2 ml with 0.5 ml of distilled water for an injectable preparation. Table IV gives the results obtained after IM administration of doses of between 0.25 and 2 µmol of test products dissolved in 0.2 ml of the ethanol / PEG 400 / distilled water mixture (25/50/25 ; V/V/V), per 100 g of live weight. For each chick, the volume injected is adjusted, as a function of the actual live weight, to 0.2 ml per 100 g of live weight.

The parameters observed are the locomotor activity and state of consciousness of the chicks for 2 h, i.e. the equivalent of 6 theoretical awake/asleep cycles for a chick of this age. They are recorded by video camera for 90 minutes, the first 30 minutes being the time for adaptation to the device.

The hypnotic and sedative effects of the test products on the diurnal activity of 10- to 14-day-old chicks subjected to a program of permanent lighting from birth for 48 h, and then to alternate lighting program of 12 h of daylight (8.00 h - 20.00 h) and 12 h of darkness (20.00 h - 8.00 h) up to the test date, are given in Table I below. The tests are carried out during the day between 14.00 h and 15.00 h.

For each test product, several series of measurements were taken on batches of 3 animals, each value indicated being the average in each batch of 3 chicks. When the number of batches is greater than or equal to 2, the figures indicated are the average limit values observed.
<table>
<thead>
<tr>
<th>Compound</th>
<th>Dose (μmol/100 g)</th>
<th>Dose (mg/kg)</th>
<th>FAT (min.)</th>
<th>ST (min.)</th>
<th>Sedation time (min.)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>(24 batches)</td>
<td>NA</td>
<td>0</td>
<td>10 - 35</td>
<td></td>
</tr>
<tr>
<td>Melatonin</td>
<td>0.5 (5 batches)</td>
<td>1.16</td>
<td>NA</td>
<td>0</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>1 (5 batches)</td>
<td>2.32</td>
<td>NA</td>
<td>0</td>
<td>16 - 36</td>
</tr>
<tr>
<td></td>
<td>2 (5 batches)</td>
<td>4.64</td>
<td>NA</td>
<td>0</td>
<td>47 - 105</td>
</tr>
<tr>
<td>Pentobarbital</td>
<td>0.5 (3 batches)</td>
<td>1.24</td>
<td>NA</td>
<td>0</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>2.48</td>
<td>13</td>
<td>36</td>
<td></td>
</tr>
<tr>
<td>Diazepam</td>
<td>0.5 (4 batches)</td>
<td>1.42</td>
<td>3 - 6</td>
<td>10 - 50</td>
<td>Not determined</td>
</tr>
<tr>
<td></td>
<td>1 (10 batches)</td>
<td>2.85</td>
<td>2 - 7</td>
<td>24 - 70</td>
<td>17 - 20</td>
</tr>
<tr>
<td></td>
<td>2 (3 batches)</td>
<td>3.69</td>
<td>2 - 5</td>
<td>81 - 100</td>
<td>14 - 15</td>
</tr>
<tr>
<td>10-methoxyharmaline</td>
<td>1.4</td>
<td>3</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Harmaline</td>
<td>1.4</td>
<td>3</td>
<td>NA</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Example 1</td>
<td>0.25</td>
<td>0.74</td>
<td>10</td>
<td>16</td>
<td>15</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>1.48</td>
<td>9</td>
<td>18</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>1 (8 batches)</td>
<td>2.96</td>
<td>6 - 14</td>
<td>28 - 101</td>
<td>5 - 20</td>
</tr>
<tr>
<td>Example 2</td>
<td>0.75</td>
<td>2.32</td>
<td>12</td>
<td>23</td>
<td>1</td>
</tr>
<tr>
<td>Example 4</td>
<td>0.25</td>
<td>0.86</td>
<td>10</td>
<td>9</td>
<td>17</td>
</tr>
<tr>
<td></td>
<td>0.50</td>
<td>1.72</td>
<td>12</td>
<td>11</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1 (4 batches)</td>
<td>3.44</td>
<td>13 - 15</td>
<td>13 - 27</td>
<td>22 - 32</td>
</tr>
<tr>
<td>Example 5</td>
<td>0.75</td>
<td>2.44</td>
<td>12</td>
<td>10</td>
<td>10</td>
</tr>
<tr>
<td>Example 6</td>
<td>1</td>
<td>3.24</td>
<td>8</td>
<td>102</td>
<td>5</td>
</tr>
<tr>
<td>Example 7</td>
<td>0.5</td>
<td>1.56</td>
<td>8</td>
<td>28</td>
<td>10</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>1.12</td>
<td>5</td>
<td>35</td>
<td>30</td>
</tr>
<tr>
<td>Example 8</td>
<td>2</td>
<td>5.97</td>
<td>15</td>
<td>15</td>
<td>37</td>
</tr>
<tr>
<td>Example 9</td>
<td>1</td>
<td>3.07</td>
<td>11</td>
<td>43</td>
<td>16</td>
</tr>
<tr>
<td>Example 11</td>
<td>0.5</td>
<td>1.80</td>
<td>9</td>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>3.60</td>
<td>8</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>Example 13</td>
<td>1</td>
<td>3.62</td>
<td>15</td>
<td>29</td>
<td>23</td>
</tr>
<tr>
<td>Example 14</td>
<td>1</td>
<td>3.74</td>
<td>10</td>
<td>15</td>
<td>29</td>
</tr>
<tr>
<td>Example 16</td>
<td>1</td>
<td>3.82</td>
<td>6.5</td>
<td>15</td>
<td>42</td>
</tr>
<tr>
<td>Example 17</td>
<td>1</td>
<td>3.89</td>
<td>11</td>
<td>7</td>
<td>38</td>
</tr>
<tr>
<td>Example 18</td>
<td>1</td>
<td>3.58</td>
<td>5</td>
<td>16</td>
<td>58</td>
</tr>
<tr>
<td>Example 19</td>
<td>1</td>
<td>3.46</td>
<td>2</td>
<td>35</td>
<td>33</td>
</tr>
</tbody>
</table>

**Key:**
- NA: not applicable, the animals remained conscious throughout the period of observation;
- FAT: falling-asleep time, equal to the time required to pass from the state of active consciousness to a non-conscious state;
- ST: sleep time, equal to the duration of the period of sleep from falling asleep to waking up;
- Sedation time: after waking up, period of inactivity corresponding to stage 2 defined above.
In the conditions under which the test is carried out (times of administration, in the phase during which the animals receive light, between 14.00 h and 15.00 h) melatonin has no hypnotic activity.

By successively subjecting chicks to programmes of alternate and permanent lighting, we have demonstrated experimentally that melatonin has no direct hypnotic activity which is intrinsic to its structure. Its hypnotic activity depends on the activity of the enzyme N-acetyltransferase (NAT) in the pineal gland of the chick at the time of administration of the melatonin. The NAT enzyme is an acetylation enzyme. In the presence of the NAT enzyme in the pineal gland of the chick, the IM administration of melatonin induces a hypnotic effect of strong intensity (sleep time of between 250 and 300 minutes for a dose equal to 1 µmol of melatonin/100 g of live weight). Melatonin is thus the precursor of acetylated metabolites with direct hypnotic activity. Compounds of the invention are analogues of the hypnotic acetyl metabolites of melatonin.

In contrast with melatonin, all of the derivatives of the invention described above have direct hypnotic and sedative activities, which are independent of the time of administration, i.e. of the level of N-acetyltransferase enzyme in the CNS.

The results obtained show, for the derivatives according to the invention, a hypnotic effect which is higher than that of the reference products (pentobarbital, melatonin) and equivalent or even superior to that of diazepam. The derivatives according to the invention are thus particularly advantageous for the treatment of sleep disorders and diseases associated with disorders of melatonin activity.
EXAMPLES

Example 1: ETCARBO7

Formula: $C_{18}H_{20}N_2O_2$  \[ M = 296.36 \text{ g.mol}^{-1} \]

Structure:

\[ \text{9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one} \]

Preparation:

Paramethoxyphenylhydrazine sulphonate (5 g - 20.7 mmol) and N(4,4'-diethoxybutyl)butanamide (4.8 g – 20.7 mmol) are mixed in commercial THF (85 ml) in a 500 ml flask. The medium is then heated to the THF reflux and acetic acid (25\%) is added dropwise (35 ml). The limpid yellow mixture is stirred for 6 h at a temperature comprised between 80 and 85°C. After cooling, the reacting medium is transferred in a 2 litre Erlenmeyer flask and it is basified by addition of a sodium carbonate saturated solution (~100 ml) pH > 7. The organic phase is decanted, and the aqueous phase is twice extracted with ethyl acetate (2 x 100 ml). The organic phases are jointed and successively washed with a sodium carbonate saturated solution (70 ml) and with water (70 ml).

The obtained organic phase is dried over MgSO$_4$ and the solvent is evaporated under reduced pressure until crystals appear (~5 ml ethyl acetate). After dilution with diethyl ether (50 ml) this solution is left overnight in the refrigerator. The crystals are obtained by a filtration, washed with diethyl ether and dried under vacuum. N1-(2-(5-methoxy-1H-3-indolyl)ethyl)butanamide (3.3 g - R=61%) is then obtained.
A Bischler-Napieralski reaction on N1-(2-(5-methoxy-1H-3-indolyl)ethyl)butanamide leads to the 1-propyl-6-methoxy-3,4-dihydro-2-carboline.

Method 1:
Acrylic acid (0.71 ml, 1.1 eq.) is added to a solution of 1-propyl-6-methoxy-3,4-dihydro-2-carboline (2.34 g) in DMF (20 ml). Diphenylphosphoryl azide (2.1 ml, 1.06 eq.) dissolved in DMF (3 ml) is then added dropwise, followed by triethylamine (2.85 ml, 2.1 eq.). After recrystallization from ethyl acetate, 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one is recovered (1.6 g, 56%).

Method 2:
Acrylic acid (1 eq.) dissolved in xylene is added to a solution of 1-propyl-6-methoxy-3,4-dihydro-2-carboline in xylene. The reaction flask is equipped with a water separator and the medium is heated to reflux of the xylene for 24 h. The xylene is then distilled off under reduced pressure. The product is purified as above.

NMR: $^1$H (CDCl$_3$): 1.29 (t, 3H); 2.44 and 2.54 (2m, 6H); 2.86 (t, 2H); 3.86 (s, 3H); 4.08 (t, 2H); 6.07 (dd 2.4 and 8.7 Hz, 1H); 6.95 (d 2.4 Hz, 1H); 7.27 (d 8.7 Hz, 1H); 8.04 (broad s, 1H)

Mass spectrum:
m/z: 296(M+.), 281(100)

Exact mass: calculated 296.1524
found 296.1545

Melting point: 223°C
Example 2: HECARBO7

Formula: C_{22}H_{28}N_{2}O_{2} \quad M = 352.47 \text{ g mol}^{-1}

Structure:

9-methoxy-1-hexyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one

Preparation:

A Bischler-Napieralski reaction on N1-(2-(5-methoxy-1H-3-indolyl)ethyl)octanamide leads to the 1-heptyl-6-methoxy-3,4-dihydro-2-carboline.

Acrylic acid (1 eq.) dissolved in xylene is added to a solution of 1-heptyl-6-methoxy-3,4-dihydro-2-carboline in xylene. The reaction flask is equipped with a water separator and the medium is heated to reflux of the xylene for 48 h. The xylene is then distilled off under reduced pressure. The product is recrystallized from ethyl acetate.

NMR: \text{^1}H (CDCl_3): 0.92 (t, 3H); 1.42 (m, 8H); 2.40 (t, 2H); 2.50 (m, 4H); 2.56 (t, 2H); 3.86 (s, 3H); 4.08 (t, 2H); 6.87 (dd 2.4 and 8.7 Hz, H); 6.94 (d 2.4 Hz, 1H); 7.23 (d 8.7 Hz, 1H); 8.04 (broad s, 1H)

Mass spectrum:
m/z: 352(M^+) 281(100)

Melting point: 140°C
Example 3 : IPCARBO7 :

Formula : C_{19}H_{22}N_{2}O_{2} \quad M = 310.39 \text{ g.mol}^{-1}

Structure :

9-methoxy-1-isopropyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one

Preparation :

A Bischler-Napieralski reaction on N1-(2-(5-methoxy-1H-3-indolyl)ethyl)-3-methylbutanamide leads to the 1-isobutyl-6-methoxy-3,4-dihydro-2-carboline.

Acrylic acid (1 eq.) dissolved in xylene is added to a solution of 1-isobutyl-6-methoxy-3,4-dihydro-2-carboline in xylene. The reaction flask is equipped with a water separator and the medium is heated to reflux of the xylene for 48 h. The xylene is then distilled off under reduced pressure. The product is recrystallized from ethyl acetate.

NMR: \text{^1H (CDCl}_3\text{)}: 1.20 (d, 6H); 2.35 and 2.47 (2m, 4H); 2.87 (t, 2H); 3.38 (m, 1H); 3.86 (s, 3H); 4.06 (t, 2H); 6.87 (dd 2.4 and 9 Hz, 1H); 6.95 (d 2.4 Hz, 1H); 7.32 (d 9 Hz, 1H);

Mass spectrum :

m/z: 310(M\text{+}), 295(100)

Melting point: 251-252°C
Example 4: PHCARBO7

Formula: C_{22}H_{20}N_{2}O_{2} \quad M = 344.41 \text{ g mol}^{-1}

Structure:

\[ \text{H}_3\text{C}^\text{O} \]
\[ \text{N} \]
\[ \text{H} \]
\[ \text{O} \]

9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quolinizin-4-one

Preparation:

A Bischler-Napieralski reaction on N1-(2-(5-methoxy-1H-3-indolyl)ethyl)-2-phenylacetamide leads to the 1-benzyl-6-methoxy-3,4-dihydro-2-carboline.

Acrylic acid (0.75 ml, 1.1 eq.) is added to a solution of 1-benzyl-6-methoxy-3,4-dihydro-2-carboline (2.8 g) in DMF (20 ml). Diphenylphosphoryl azide (2.1 ml, 1.06 eq.) dissolved in DMF (3 ml) is then added dropwise, followed by triethylamine (2.85 ml, 2.1 eq.). After separation on silica gel (chloroform/methanol eluent), 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quolinizin-4-one is recovered (1.6 g, 56%).

NMR: \( ^1\text{H} \) (CDCl\textsubscript{3}): 2.71 (m, 4H); 2.91 (t, 2H); 3.83 (s, 3H); 4.20 (t, 2H); 6.76 (dd 2.4 and 8.7 Hz, 1H); 6.84 (d 8.7 Hz, 1H); 6.90 (d 2.4 Hz, 1H); 6.93 (broad s, 1H); 7.42 and 7.50 (m, 5H)

Mass spectrum:

m/z: 344 (M+) (100), 253

Melting point: 235°C
Example 5: CO2ETCARBO7

Formula: $\text{C}_{19}\text{H}_{20}\text{N}_{2}\text{O}_{4}$  \( M = 340.37 \text{ g.mol}^{-1} \)

Structure:

![Structure Diagram]

1-carbethoxy-9-methoxy-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one

Preparation:

A Bischler-Napieralski reaction on ethyl 3-((2-(5-methoxy-1H-3-indolyl)ethyl)amino)-3-oxopropanoate leads to the corresponding carboline.

Sodium hydroxide solution (1N, 3 ml) is added to a solution of the carboline obtained (800 mg) in benzene (10 ml), followed by tetrabutylammonium hydrogen sulphate (0.1 eq.). Acryloyl chloride (0.27 ml) is then added at 0°C and the mixture is allowed to return to room temperature overnight.

The product is separated on silica gel (chloroform/methanol) and 1-carbethoxy-9-methoxy-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one is thus obtained.

NMR: $^1\text{H} (\text{CDCl}_3): 1.42 \text{ (t, 3H)}; 2.60 \text{ (t, 2H)}; 2.85 \text{ (t, 2H)};
2.97 \text{ (t, 2H)}; 3.89 \text{ (s, 3H)}; 4.30 \text{ (t, 2H)}; 4.35 \text{ (q, 2H)}; 6.96 
\text{ (d 2.1 Hz, 1H)}; 7.01 \text{ (dd 2.1 and 7.5 Hz, 1H)}; 7.35 \text{ (d 7.5 Hz, 1H)};

Mass spectrum:

m/z: 340(M'), 294(100)

Melting point: 174-175°C
Example 6: 6ETETCARBO7

Formula: C_{20}H_{24}N_{2}O_{2} \quad M = 324.42 \text{ g.mol}^{-1}

Structure:

9-methoxy-1,10-diethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one

Preparation:

A Bischler-Napieralski reaction on N1-(2-(5-methoxy-6-ethyl-1H-3-indolyl)ethyl)butanamide leads to the 7-ethyl-1-propyl-6-methoxy-3,4-dihydro-2-carboline.

Acrylic acid (0.22 ml, 1.1 eq.) is added to a solution of 7-ethyl-1-propyl-6-methoxy-3,4-dihydro-2-carboline (764 mg) in DMF (20 ml), acrylic acid (0.22 ml, 1.1 eq.) is added. Diphenylphosphoryl azide (1.06 eq.) dissolved in DMF (3 ml) is then added dropwise, followed by triethylamine (2.1 eq.). After separation on silica gel (chloroform/methanol eluent) 9-methoxy-1,10-diethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one is recovered (28%).

NMR: \text{^{1}H (CDCl}_3\text{):} 1.26 (m, 6H); 2.41 and 2.58 (2m, 6H); 2.70 (q, 2H); 2.87 (t, 2H); 3.07 (s, 3H); 4.07 (t, 2H); 6.88 (1s, 1H); 7.19 (s, 1H); 8.33 (broad s, 1H).

Mass spectrum:

m/z: 324(M+), 309(100)

Melting point: 204°C
Example 7: ETCARBO7S

Formula: C_{18}H_{20}N_{2}O_{5}S \quad M = 312.42 \text{ g.mol}^{-1}

Structure:

9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine-4-thione

Preparation:
Lawesson's reagent (0.5 mmol) is added portionwise, at 110°C, to a solution of 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (300 mg, 1.01 mmol) in anhydrous toluene (15 ml). After refluxing for 30 min. and evaporation of the toluene, the product is chromatographed on silica gel (99/1 chloroform/methanol eluent) and 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine-4-thione is thus recovered (60% yield).

NMR: $^1H$ (CDCl$_3$): 1.32 (t, 3H); 2.32 (t, 2H); 2.65 (q, 2H); 2.98 (t, 2H); 3.08 (t, 2H); 3.89 (s, 3H); 4.80 (t, 2H); 6.91 (dd 2.4 and 8.7 Hz, 1H); 6.98 (d 2.4 Hz, 1H); 7.34 (d 8.7 Hz, 1H); 8.11 (broad s, 1H)

Mass spectrum:
m/z: 312 (M+) (100), 297

Melting point: 118°C
Example 8: ETDCARBO7

Formula: C_{18}H_{22}N_{2}O_{2} \quad M = 298.38 \text{ g mol}^{-1}

Structure:

\[
\begin{align*}
    &\text{H}_3\text{C}^\text{O} \quad \text{N} \quad \text{N} \\
    &\text{O} \quad \text{H}
\end{align*}
\]

9-methoxy-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (500 mg) and palladium-on-charcoal are successively added to a solution of 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (500 mg) in ethanol, and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 9-Methoxy-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (76%).

NMR: $^1H$ (CDCl$_3$): 0.79 (t, 3H); 1.13 (2m, 2H); 1.95 (m, 2H); 2.20 (m, 1H); 2.45 (m, 2H); 2.77 (m, 2H); 3.87 (s, 3H); 4.88 (s, 1H); 5.09 (m, 1H); 6.78 (dd 2.4 and 8.7 Hz, 1H); 6.92 (d 2.4 Hz, 1H); 7.25 (d 8.7 Hz, 1H); 8.77 (broad s, 1H)

Melting point: 207°C
Example 9: ETNAPH7

Formula: \( \text{C}_{20}\text{H}_{21}\text{NO}_2 \) \( \text{M} = 307.39 \text{ g.mol}^{-1} \)

Structure:

11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one

Preparation:

POCl\(_3\) (4.6 ml) is added to a refluxing solution of the \( N(2-(7\text{-methoxy-napht-1-yl}ethyl)\)butanamide (2.27 g, 11.1 mmol) in toluene (80 ml). After 3 h, the toluene is removed under reduced pressure. The residue is taken up in KOH solution (40%). The mixture is then extracted with EtOAc (x 3). After drying the organic phase over MgSO\(_4\), the solvent is removed. The crude reaction product is dissolved in DMF (5 ml) and acryl acid (0.94 ml, 1.2 eq.) is then added. Diphenylphosphoryl azide (2.7 ml, 1.1 eq.) dissolved in DMF (3 ml) is then added dropwise, followed by triethylamine (3.67 ml, 2.6 eq.). 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one (329 mg) is obtained by recrystallization from a 20/80 EtOAc/P.E. mixture.

NMR: \(^1\text{H} \) (CDCl\(_3\) : 1.17 (t, 3H); 2.38 (m, 4H); 2.58 (t, 2H); 3.16 (t, 2H); 3.82 (t, 2H); 3.95 (s, 3H); 7.17 (dd, 1H); 7.29 (d, 1H); 7.33 (d, 1H); 7.66 (d, 1H); 7.76 (d, 1H)

Melting point: 105-107°C
Example 10: PHNAPH7

Formula: $C_{24}H_{21}NO_2$  \[ M = 355.43 \text{ g.mol}^{-1} \]

Structure:

3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo[f]pyrido [2,1-a]isoquinolin-8-one

Preparation:

POCl$_3$ (1.4 ml) is added to a refluxing solution of the N(2-(7-methoxy-napht-1-yl)ethyl)phenylacetamide (600 mg) in toluene (100 ml). After 3 h, the toluene is removed under reduced pressure. The residue is taken up in KOH solution (40%). The mixture is then extracted with EtOAc ($\times$ 3). After drying the organic phase over MgSO$_4$, the solvent is removed. The crude reaction product is dissolved in DMF (4.5 ml) and acrylic acid (0.15 ml, 1.1 eq.) is then added. Diphenylphosphoryl azide (0.45 ml, 1.1 eq.) dissolved in DMF (1 ml) is then added dropwise, followed by triethylamine (0.55 ml, 2.1 eq.). The 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo[f]pyrido [2,1-a]isoquinolin-8-one is recovered (170 mg, yield = 25%).

NMR: $^1H$ (CDCl$_3$) : 2.70 (m, 4H); 3.32 (t, 2H); 3.88 (t, 2H); 3.94 (s, 3H); 6.74 to 7.60 (10H)

Melting point: 152-154°C
Example 11: PHCARBO7S

Formula: C_{22}H_{20}NO_{5} \quad M = 360.47 \text{ g.mol}^{-1}

Structure:

9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo [2,3-a] (beta)quinolizin 4-thione

Preparation:

Lawesson's reagent (180 mg, 0.47 mmol) is added portionwise, at 110°C, to a solution of 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (164 mg, 0.47 mmol) in anhydrous toluene (10 ml). After refluxing for 30 min. and evaporation of the toluene, the product is chromatographed on silica gel (chloroform eluent) and the 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine-4-thione is thus recovered (130 mg, 76% yield).

NMR: \text{^{1}H} (CDCl_{3}): 1.32 (t, 3H); 2.32 (t, 2H), 2.65 (q, 2H); 2.98 (t, 2H); 3.08 (t, 2H); 3.89 (s, 3H); 4.80 (t, 2H); 6.91 (dd 2.4 and 8.7 Hz, 1H); 6.98 (d 2.4 Hz, 1H); 7.34 (d 8.7 Hz, 1H); 8.11 (broad s, 1H)

Melting point: 180°C
Example 12: DEETCARBO7S

Formula: C_{18}H_{18}N_{2}S\quad M = 310.41 \text{g.mol}^{-1}

Structure:

9-methoxy-1-ethyl-2,3,4,12-tetrahydroindolo[2,3-a]quinolizin-4-thione

Preparation:

Potassium tert-butoxide (665 mg, 5.9 mmol) is added to a solution of 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizine-4-thione (500 mg, 1.6 mmol) in DMF (42 ml). After placing the reaction assembly under vacuum, the mixture is stirred under normal oxygen pressure overnight. Water (15 ml) and concentrated hydrochloric acid (3 ml) are then successively added. The solution is stored in a refrigerator for 4 hours. After filtration, 9-methoxy-1-ethyl-2,3,4,12-tetrahydroindolo [2,3-a] quinolizine-4-thione is obtained (150 mg, \% = 30%).

NMR: $^1$H (CDCl$_3$) : 1.38 (t, 3H), 2.93 (q, 2H), 3.06 (t, 2H), 3.90 (s, 3H), 5.06 (t, 2H), 7.03 (d+s, 2H), 7.19 (d, 1H), 7.38 (d, 1H), 7.62 (d, 1H), 8.43 (broad s, 1H)

Mass spectrum:

m/z: 310 (M+), 295, 155

Melting point: 212°C
Example 13: FPHCARBO7

Formula: \( \text{C}_{22}\text{H}_{19}\text{N}_{2}\text{O}_{2}\text{F} \)  \( M = 362.40 \text{g.mol}^{-1} \)

Structure:

![Chemical Structure Image]

9-methoxy-1-(p-fluorophenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one

Preparation:

A Bischler-Napieralski reaction, carried out on \( \text{N-}[2'-\text{(5-methoxy-1H-3-indolyl)}\text{ethyl}]\text{-2-(p-fluorophenyl)acetamide} \) (1.15 g, 3.5 mmol), results in the \( \text{1-(parafluorobenzyl)}\text{-6-methoxy-3,4-dihydro-2-carboline} \) (1.06 g), which is dissolved directly in anhydrous dimethylformamide (DMF) (10 ml). This mixture is cooled to 0°C and acrylic acid (0.24 ml, 3.5 mmol), diphenylphosphoryl azide ((PhO)\text{2}P(\text{O})\text{N}_3) (0.74 ml, 3.5 mmol) in solution in DMF (2 ml), dropwise, and triethylamine (1 ml, 7.8 mmol) are successively added. After separation on silica gel (chloroform), 9-methoxy-1-(p-fluorophenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one is recovered (750 mg, \( Y = 58\% \))

NMR: \( ^{1}\text{H (CDCl}_3 \): 2.71 (m, 4H), 2.89 (t, 2H), 3.82 (s, 3H), 4.19 (t, 2H), 6.77 (dd, 9 Hz and 3 Hz, 1H), 6.9-7.20 and 7.38 (3m, 7H)

Mass spectrum:

m/z: 362 (M+.), 319, 253

Melting point: 191°C
Example 14 : ANCARBO7

Formula : $C_{23}H_{22}N_2O_3$  \[ M = 374.43 g\cdot mol^{-1} \]

Structure :

9-methoxy-1-(p-methoxyphenyl)-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one

Preparation :

A Bischler-Napieralski reaction, carried out on N-(2′-(5-methoxy-1H-3-indolyl)ethyl)-2-(p-methoxyphenyl)acetamide (800 mg, 2.1 mmol), results in the 1-(paramethoxybenzyl)-6-methoxy-3,4-dihydro-2-carboline, which is dissolved directly in anhydrous dimethylformamide (DMF) (10 ml).

This mixture is cooled to 0°C and acrylic acid (0.15 ml, 2.2 mmol), diphenylphosphoryl azide ($\text{Ph}_2\text{P}(\text{O})\text{N}_3$) (0.45 ml, 2 mmol) in solution in DMF (2 ml), dropwise, and triethylamine (0.53 ml, 4 mmol) are successively added. After separation on silica gel (chloroform), 9-methoxy-1-(p-methoxyphenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one is recovered (213 mg, Y = 27%).

NMR: $^1H$ (CDCl$_3$) : 2.67 (m, 4H), 2.90 (t, 6 Hz, 2H), 3.83 (s, 3H), 3.91 (s, 3H), 4.20 (t, 6 Hz, 2H), 6.77, 6.88, 7.04 and 7.33 (m, 7H)

Mass spectrum:
m/z: 374 (M+ 100), 359, 253, 187

Melting point: 154-155°C
Example 15: DMAGARBO7

Formula: \( C_{24}H_{25}N_3O_2 \) \( \text{M} = 387.48 \text{ g mol}^{-1} \)

5 Structure:

\[
\begin{array}{c}
\text{H}_3^+ \\
\text{O} \\
\text{N} \\
\text{C} \\
\text{CH}_3
\end{array}
\]

9-méthoxy-1-(p-diméthylaminophényl)-2,3,4,6,7,12-hexahydrindolo[2,3-a]quinolizin-4-one

Préparation:

A Bischler-Napieralski reaction, carried out on N-[2-(5-méthoxy-1H-3-indolyl)ethyl]-2-(p-diméthylaminophenyl)-acetamide, results in the 1-(paradiméthylaminobenzyl)-6-méthoxy-3,4-dihydro-2-carboline, which is dissolved directly in anhydrous dimethylformamide (DMF).

This mixture is cooled to 0°C and acrylic acid, diphenylphosphoryl azide \((\text{PhO})_2\text{P(O)}\text{N}_3\) in solution in DMF, dropwise, and triéthylamine are successively added. After separation on silica gel (chloroform), 9-méthoxy-1-(p-diméthylaminophenyl)-2,3,4,6,7,12-hexahydrindolo[2,3-a]-quinolizin-4-one is recovered.

25 NMR: \( ^1\text{H} \) (CDCl\(_3\)): 2.69 (m, 4H), 2.89 (t, 2H), 3.04 (s, 6H), 3.82 (s, 3H), 4.20 (t, 2H), 6.80 (m, 3H), 6.89 (m, 2H), 7.25 (d, 2H), 7.29 (broad s, 1H)

Mass spectrum: m/z: 387 (M+.), 194, 142, 134 (100)
Example 16: PYRCARBO7

Formula: C_{21}H_{19}N_{3}O_{2}  \quad M = 345.40 \text{ g.mol}^{-1}

Structure:

\[
\begin{array}{c}
\text{9-methoxy-1- (pyrid-2'-yl)-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one}
\end{array}
\]

Preparation:

A Bischler-Napieralski reaction on the N1- (2- (5-methoxy-1H-3-indolyl)ethyl)-2- (pyrid-2'-yl)-acetamide (1.2g - 3.9 mmol) leads to 1- (2-pyridylmethyl)-6-methoxy-3,4-dihydro-2-carboline.

To a solution of 1- (2-pyridylmethyl)-6-methoxy-3,4-dihydro-2-carboline (760mg - 2.6 mmol) in the DMF (9ml), acrylic acid is added (0.18 ml). Diphenylphosphorylazide (0.55 ml) is then added drop in solution in the DMF (3 ml), then the trietyleamine (0.75 ml).

After separation on silica gel (Chloroform/methanol), 9-methoxyl-1- (pyrid-2'-yl)-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one (230mg-17.5%) is recovered.

NMR: 1H (CDCl3) : 2.73 (m, 2H); 2.85 (m, 2H); 2.94 (t, 2H); 3.18 (s, 3H), 4.24 (t, 2H); 6.85 (dd 2.4 et 9Hz, 1H); 6.93 (d 2.4Hz, 1H); 7.10 (d 9Hz, 1H); 7.30 (dd, 1H); 7.45 (d, 1H); 7.80 (dd, 1H); 8.75 (d, 1H)

Mass Spectrum:

m/z : 345(M^{+} , 100), 330, 316, 302

Melting point: > 260°C
Example 17: NPHCARBO7

Formula: $C_{23}H_{19}N_3O_4$  
\[ M = 389.41 \text{ g.mol}^{-1} \]

Structure:

9-methoxy-1-p-nitrophenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]
quinalizin-4-one

Preparation:

A Bischler-Napieralski reaction on the N1-(2-(5-methoxy-1H-
3-indolyl)ethyl)-2-p-nitrophenyl-acetamide (360mg - 1mmol)
leads to 1-(paranitrobenzyl)-6-methoxy-3,4-dihydro-2-carboline.

To a solution of 1-(paranitrobenzyl)-6-methoxy-3,4-dihydro-2-
carboline in the DMF (10ml), acrylic acid (0.07ml) is added.
Diphenylphosphorylazide (0.21 ml) is then added drip and
then triethylamine (0.26ml). After separation on silica gel
(eluent AcOEt/EP - 50/50), 9-methoxy-1-p-nitrophenyl-
2,3,4,6,7,12-hexahydroindolo[2,3-a]quinalizin-4-one (163mg-
41%) is recovered.

NMR: $^1H$ (CDCl3): 2.75 (m, 4H); 2.92 (t, 2H); 3.82 (s, 3H);
4.17 (t, 2H); 6.80 (dd 3 et 9 Hz, 1H); 6.90 (d 3 Hz, 1H);
6.92 (d 9Hz, 1H); 7.59 (d, 9Hz, 1H); 8.32 (, 9Hz, 1H).

Melting point: 138-140°C
Example 18: TOLCARBO7

Formula: C_{23}H_{22}N_{4}O_{2} \quad M = 358.43 \text{ g mol}^{-1}

Structure:

9-méthoxy-1-p-tolyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one

Preparation:

A Bischler-Napieralski reaction on the N1-(2-(5-méthoxy-1H-3-indolyl)ethyl)-2-p-tolyl-acetamide (2.12mg = 6.6mmol) leads to 1-(paramethylbenzyl)-6-méthoxy-3,4-dihydro-2-carboline.

To a solution of 1-(paramethylbenzyl)-6-méthoxy-3,4-dihydro-2-carboline in the DMF (15ml), acryllic acid (0.46ml) is added. Diphenylphosphorylazide (1.4 ml) is then added drip and then triethylamine (1.75ml). After separation on silica gel (eluent Chloroform/methanol), 9-méthoxy-1-p-tolyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one is recovered.

NMR: \text{\textsuperscript{1}H} (CDCl\textsubscript{3}): 2.46 (s, 3H); 2.73 (m, 4H); 2.88 (t, 2H); 3.82 (s, 3H); 4.20 (t, 2H); 6.75 (dd 2 et 9Hz, 1H); 6.84 (d 9Hz, 1H); 6.88 (d 2Hz, 1H); 7.03 (s large, 1H); 7.30 (m, 4H)

Melting point: 198°C
Example 19: PHDHCARBO7

Formula: $C_{22}H_{22}N_2O_2$  \[ M = 346.42 \text{g.mol}^{-1} \]

Structure:

9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (900 mg) and palladium on charcoal are successively added to a solution of 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (2.4 g) in mixture ethyl acetate - ethanol 1/1 (160 mL), and the mixture is stirred overnight under a hydrogen atmosphere.

After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (2.3 g, yield = 95%).

NMR: $^1H$ (CDCl$_3$): 2.05 (m, 1H), 2.28 (m, 1H), 2.47 (m, 2H), 2.74 (m, 1H), 2.97 (m, 2H), 3.81 (m + s, 4H), 5.18 (m, 2H), 6.71 (dd, 2.4 Hz and 9 Hz, 1H), 6.89 (d, 2.4 Hz, 1H), 6.93 (d, 9Hz, 1H), 7.25 (m, 5H), 7.5 (broad s, 1H).

Mass spectrum:
m/z: 346 (M+.), 242, 200.

Melting point: 162°C
Example 20: FPHDHCARBO7

Formula: $C_{22}H_{21}N_2FO_2$ $M = 364.41$ g mol$^{-1}$

Structure:

9-methoxy-1-(parafluorophenyl)-1,2,3,4,6,7,12,12-bocatahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (50 mg) and palladium on charcoal are successively added to a solution of 9-methoxy-1-(parafluorophenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (64 mg) in ethyl acetate, and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 9-methoxy-1-(parafluorophenyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (21 mg, yield = 33%).

NMR: $^1H$ (CDCl$_3$): 2.05 (m, 1H), 2.40 (m, 3H), 2.74 (m, 1H), 2.90 (m, 2H), 3.80 (1s+1m, 4H), 5.19 (m, 2H), 6.71 (dd, 2.4 and 9 Hz, 1H), 6.92 (m, 3H), 6.97 (d, 8.7 Hz, 1H), 7.18 (m, 2H), 7.52 (broad s, 1H).

Mass spectrum:

m/z: 364 (M$^+$), 242, 200.

Melting point: 162-166$^\circ$C
Example 21: PHDHNAPH7

Formula: C_{24}H_{23}NO_{2} \quad M = 357.45 \text{g mol}^{-1}

Structure:

\[
\begin{array}{c}
\text{H}_{3}\text{C} \overset{O}{\text{N}} \\
\text{O} \\
\end{array}
\]

3-methoxy-11-phenyl-5,8,9,10,11,11a-hexahydro -6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one

Preparation:

Sodium bicarbonate (20 mg) and palladium-on charcoal are successively added to a solution of 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one (30 mg) in ethyl acetate (15 mL) and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 3-methoxy-11-phenyl-5,8,9,10,11,11a-hexahydro -6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one is thus recovered (25 mg, yield = 83%).

NMR: \[^1\text{H} (\text{CDCl}_3) : 2.14 \text{ (m, 1H)}, 2.48 \text{ to 3.16 (m, 5H)}, 3.13 \text{ (d, 15.6 Hz, 1H)}, 3.94 \text{ (m + s, 4H)}, 5.16 \text{ (ddd, 12.8 Hz, 5.1 Hz and 2.1 Hz, 1H)}, 5.28 \text{ (d, 4.4 Hz, 1H)}, 6.89 \text{ to 7.13 (m, 8H)}, 7.55 \text{ (d, 8.5Hz, 1H)}, 7.62 \text{ (d, 9.6Hz, 1H)}.}

Mass spectrum:

m/z : 357 (M\text{+}.), 329, 253, 211

Melting point: 175°C
Example 22: ETDHNAPH7

Formula: C_{20}H_{23}NO_{2} \quad M = 309.40 \text{g.mol}^{-1}

Structure:

![Chemical Structure]

11-ethyl-3-methoxy-5,8,9,10,11,11a-hexahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one

Preparation:

Sodium bicarbonate (30 mg) and palladium on charcoal are successively added to a solution of 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one (74 mg) in ethyl acetate (25 mL) and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 3-methoxy-11-ethyl-5,8,9,10,11,11a-hexahydro-6H-benzo[f]pyrido[2,1-a]isoquinolin-8-one is thus recovered (50 mg, yield = 67%).

NMR: \textsuperscript{1}H (CDCl\textsubscript{3}) : 0.73 (t, 6.8 Hz, 3H), 1.08 (m, 2H), 2.05 (m, 2H), 2.30 to 3.05 (m, 5H), 3.16 (d, 16.0 Hz, 1H), 3.96 (s, 3H), 5.02 (broad s, 1H), 5.17 (ddd, 12.4 Hz, 4.4 Hz and 16 Hz, 1H), 7.12 to 7.21 (m, 3H), 7.67 (d, 8.6 Hz, 1H), 7.73 (d, 8.6 Hz, 1H).

Mass spectrum:

m/z : 309 (M+.), 253, 225, 211.

Melting point: 206°C
Example 23: ANIDHCARBO7

Formula: \( \text{C}_{22}\text{H}_{23}\text{N}_{3}\text{O}_{2} \)

\[ M = 361.45 \text{g.mol}^{-1} \]

Structure:

![Chemical Structure Image]

9-methoxy-1-paraaminophenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (50 mg) and palladium on charcoal are successively added to a solution of 9-methoxy-1-paranitrophenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (91 mg) in ethyl acetate and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 9-methoxy-1-paraaminophenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (37 mg, yield 44%).

NMR: \( ^1\text{H} \) (CDCl\(_3\)) : 1.95 (m, 1H), 2.28 (m, 1H), 2.40 (m, 2H), 2.90 (m, 2H), 3.70 (m, 1H), 3.80 (m, 3H), 4.20 (broad s, 2H), 5.20 (m, 2H), 6.49 (d, 8.3 Hz, 1H), 6.65 (dd, 8.7 Hz, 2.4 Hz, 1H), 6.83 (d, 2.4 Hz, 1H), 6.90 (d, 8.4 Hz, 1H), 6.95 (d, 8.7 Hz, 1H).

Mass spectrum:

m/z : 361 (M+.), 242, 200, 181.

Melting point: 165-166°C
Example 24 : PHDHCARBO7S

Formula: C_{22}H_{22}N_{2}O_{5} \quad M = 362.48 \text{ g mol}^{-1}

Structure:

9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizin-4-thione

Preparation:

To 9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizin-4-one (520 mg) in anhydrous toluene (50mL) we added, at 110°C, Lawesson reactiv (640 mg), in small quantities. After refluxing for 30 min and evaporation of toluene, the product is isolated by column chromatography over SiO_{2} (Eluent chloroform/methanol, 99/1), we obtained the 9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizine-4-thione (160 mg, yield 30%).

NMR : \text{^1H (CDCl}_{3} \text{) : 1.95 (m, 1H), 2.20 (m, 1H), 2.72 (dd, 12 Hz, j = 2.8 Hz, 1H), 2.97 (m, 3H), 3.41 (m, 1H), 3.80 (m + s, 4H), 5.33 (d, j = 4 Hz, 1H), 5.93 (dd, 5.1 Hz and 1.3 Hz, 1H), 6.71 (dd, 8.7 Hz and 2.4 Hz, 1H), 6.83 (d, 2.4Hz, 1H), 6.94 (d, 8.7 Hz, 1H), 7.20 (m, 5H).}

Melting point: 242-244°C
Example 25 : ETNAPH7S

Formula: C_{20}H_{21}NOS \quad M = 323.45 \text{g.mol}^{-1}

Structure:

11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-thione

Preparation:

To 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-one (45 mg) in anhydrous toluene (10mL) we added, at 110°C, Lawesson reagent (70mmol), in small quantities. After refluxing for 30 min and evaporation of toluene the product is isolated by column chromatography over SiO₂ (Eluent dichloromethane), we obtained the 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-thione (32 mg, yield 70%).

NMR: \text{^1H (CDCl₃)} : 1.14 (t, 7.3 Hz, 3H), 2.35 (m, 4H), 3.13 (t, 7.7 Hz, 2H), 3.25 (t, 6 Hz, 2H), 3.99 (s, 3H), 4.27 (t, 6 Hz, 2H), 7.19 (dd, 8.5 and 2.4 Hz, 1H), 7.28 (m, 2H), 7.67 (d, 8.5 Hz, 1H), 7.76 (d, 8.9 Hz, 1H).

Melting point: 164-166°C
Example 26: PHNAPH7S

Formula: C_{24}H_{21}NOS  \quad M = 371.49 \text{ g/mol}^{-1}

Structure:

3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-thione

Preparation:

To 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-one (50 mg) in anhydrous toluene (10mL) we added, at 110°C, Lawesson reagent (66 mg), in small quantities. After refluxing for 30 min and evaporation of toluene the product is isolated by column chromatography over SiO_{2} (dichloromethane), we obtained the 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo [f] pyrido [2,1-a] isoquinolin-8-thione (37mg, yield 74%).

NMR: ^1H (CDCl_3): 2.71 (t, 7.8 Hz, 1H), 3.36 (m, 4H), 3.97 (s, 3H), 4.36 (t, 6.2 Hz, 1H), 6.68 (d, 8.5 Hz, 1H), 7.18 (m, 8H), 7.63 (d, 8.7 Hz, 1H).

Melting point: 136°C
Example 27: ETDHCARBO7S

Formula: \( C_{18}H_{22}N_{2}OS \) \( M = 314.44 \text{ g.mol}^{-1} \)

Structure:

1-ethyl -9-methoxy -1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-thione

Preparation:

To 1-ethyl -9-methoxy -1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizine-4-one (262 mg) in anhydrous toluene (20 mL) we added, at 110°C, Lawesson reactiv (208 mg) in small quantities. After refluxing for 30 min and evaporation of toluene, the product is isolated by column chromatography over SiO₂ (Eluent chloroform/methanol, 99/1) we obtained the 1-ethyl -9-methoxy -1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-thione (30 mg, yield 11.5%).

NMR: \(^1\text{H} (\text{CDCl}_3)\): 0.81 (t, 3H), 1.06 (m, 2H), 1.90 (m, 2H), 2.30 (m, 1H), 2.80 (m, 5H), 3.85 (s, 3H), 4.94 (s, 1H), 6.08 (m, 1H), 6.87 (dd, 2.4 and 8.7Hz, 1H), 6.96 (d, 2.4Hz, 1H), 7.26 (d, 8.7Hz, 1H), 7.82 (s large, 1H).

Melting point: 124°C
Example 28 : CO2ETDHCARBO7

Formula : C_{19}H_{22}N_{2}O_{4} \quad M = 342.39 \text{ g.mol}^{-1}

Structure :

1-carbethoxy-9-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation :

Sodium bicarbonate (10 mg) and palladium on charcoal are successively added to a solution of 1-carbethoxy-9-methoxy-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (50 mg) in ethyl acetate, and the mixture is stirred overnight under hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate. 1-carbethoxy-9-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (30 mg, yield = 60%).

NMR : ^1H (CDCl3) : 1.02 (t, 3H), 2.15 (m, 2H), 2.85 (m, 8H), 3.35 (m, 1H), 3.85 (s, 3H), 4.05 (t, 2H), 5.08 (m, 2H), 6.82 (dd, 8.7 and 2.4Hz, 1H), 6.92 (d, 2.4Hz, 1H), 7.21 (d, 8.7Hz, 1H), 8.24 (broad s, 1H).

Mass spectrum :

m/z : 342 (M+), 286, 269, 240, 199.

Melting point: 213°C
Example 29: TOLDHCARBO

Formula: C_{23}H_{24}N_{2}O_{2} \quad M = 360.46 \text{ g mol}^{-1}

Structure:

9-methoxy-1-paratolyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (50 mg) and palladium on charcoal are successively added to a solution of 9-methoxy-1-paratolyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (55 mg) in ethyl acetate and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate, 9-methoxy-1-paratolyl-1,2,3,4,6,7,12,12b-Octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (32 mg, yield 58%).

NMR: {^1}H (CDCl$_3$): 2.04 (m, 1H), 2.23 (m, 1H), 2.29 (s, 3H), 2.46 (m, 2H), 2.74 (m, 1H), 2.94 (m, 2H), 3.70 (m, 1H), 3.80 (s, 3H), 5.20 (m, 1H), 5.24 (d, 1H), 6.71 (dd, 2.4 Hz and 8.7 Hz, 1H), 6.87 (d, 2.4 Hz, 1H), 6.93 (d, 8.7 Hz, 1H), 7.08 (d, 8.0 Hz, 2H), 7.16 (d, 8.0 Hz, 2H), 7.2 (1H, NH).
Example 30: ANDHCARBO7

Formula: C_{23}H_{24}N_{2}O_{3} \quad M = 376.46 \text{g/mol}

Structure:

9-methoxy-1-paraanisyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one

Preparation:

Sodium bicarbonate (50 mg) and palladium on charcoal are successively added to a solution of 9-methoxy-1-paraanisyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one (43 mg) in ethyl acetate and the mixture is stirred overnight under a hydrogen atmosphere. After filtration and evaporation of the solvent, the crude product is recrystallized from ethyl acetate, 9-methoxy-1-paraanisyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizin-4-one is thus recovered (24 mg, yield 56%).

NMR: \text{^1H (CDCl}_3): 2.05 (m, 1H), 2.25 (m, 1H), 2.46 (m, 2H), 2.74 (d, 1H), 2.54 (m, 2H), 3.68 (m, 1H), 3.75 (s, 3H), 3.80 (s, 3H), 5.14 (m, 1H), 5.23 (d, 5.5Hz, 1H), 6.72 (dd, 2.4 and 8.7Hz, 1H), 6.82 (d, 8.7Hz, 2H), 6.87 (d, 2.4Hz, 1H), 6.96 (d, 8.7Hz, 1H), 7.17(d, 8.7Hz, 2H).

Melting point: 242°C
Example 31: DIETCARBO7

Formula: $C_{20}H_{26}N_2O_2$  
$M = 326.43 \text{g mol}^{-1}$

Structure:

1,1-diethyl -9-methoxy -1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-one

Preparation:

5-methoxytryptamine (494 mg - 2.59 mmol) and ethyl (-4-ethyl -4-formyl) caproate (522 mg - 2.61 mmol) are mixed in commercial toluene (27 mL) in a 50 mL flask.

The medium is then heated to the toluene reflux during 2 hours. After cooling, the toluene is evaporated under reduced pressure and acetic acid (1 mL) is added.

The medium is then heated to the acetic acid reflux during 2 hours. After cooling, water (25 mL) is added and a solid precipitates. This solid is diluted with ethyl acetate and washed with water. The resulting organic phase is dried over magnesium sulfate and the solvent is evaporated under reduced pressure.

After separation on silica gel (chloroform/methanol - 97.5/2.5 eluent), 1,1-diethyl -9-methoxy -1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-one is obtained (200 mg, yield 23%).

NMR: $^1H$ (CDCl$_3$): 0.73 (t, 7.5 Hz, 3H), 1.02 (q, 7.5 Hz, 1H), 1.18 (t, 7.5 Hz, 3H) 1.50 (q 7.5 Hz, 1H), 1.60 (m, 1H), 1.80 (m, 4H), 2.49 (m, 1H), 2.76 (m, 3H), 3.85 (s, 3H), 4.83 (s, 1H), 5.17 (m, 1H), 6.84 (dd, 2.3 and 8.7 Hz, 1H), 6.85 (d, 2.3 Hz, 1H), 7.24 (d, 8.7 Hz, 1H), 7.77 (s broad, 1H).

Melting point: 229°C
Example 32: ETCARBO7TL

Formula: \( \text{C}_{21}\text{H}_{24}\text{N}_{2}\text{O}_{4} \)  \( M = 368.43 \text{ g.mol}^{-1} \)

Structure:

\[(6S)-6\text{-carbethoxy-9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one} \]

Preparation:

A Bischler-Napieralski reaction on \( \text{N1-(butyryl)-5-methoxy-(L)-tryptophan-ethyl ester (2.1 g)} \) lead to the \( (3S)-1\text{-propyl-3-carbethoxy-6-methoxy-3,4-dihydro-2-carboline (1.5 g)} \). To a solution of \( (3S)-1\text{-propyl-3-carbethoxy-6-methoxy-3,4-dihydro-2-carboline (1.5 g)} \) in DMF (20 mL) was added dropwise successively acrylic acid (0.35 mL), diphenylphosphoryl azide (1 mL) and triethylamine (2 mL). After separation on silica gel (eluent - ethyl acetate/petroleum ether - 30/70), \( (6S)-6\text{-carbethoxy-9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one} \) is recovered (400 mg - 17%)

NMR: \(^1\text{H} \) (CDCl\(_3\)): 1.1(t, 3H), 1.25(t, 3H), 2.3(m, 1H), 2.62(m, 5H), 3.08(dd, 6 and 16 Hz, 1H), 3.53(d, 16Hz, 1H), 3.85(s, 3H), 4.03(m, 2H), 6.00(d, 6Hz, 1H), 6.85(dd, 2.3 and 8.7 Hz, 1H), 6.94(d, 2.3Hz, 1H), 7.24(d, 8.7Hz, 1H), 8.13 (s broad, 1 H)

Melting point: 192°C

CLAIMS
1. Derivatives of general formula I (I' and I''):

\[
\begin{align*}
\text{I'} & : \\
\text{I''} & :
\end{align*}
\]

in which X represents a divalent radical of formula

\[
\begin{align*}
\text{or} \\
\end{align*}
\]

R₁, R₂, R₃, and R₄ represent, independently of each other, a hydrogen atom, a hydroxy radical, a lower alkyl, lower cycloalkyl, lower alkoxy, aryloxy, lower aralkyloxy, halo or nitro radical or an unsaturated aliphatic chain, formyl, lower alkylcarbonyl, lower alkylcarbonyloxy, halo(alower)alkylcarbonyl, halo(lower)alkylcarbonyloxy, halo-(lower)alkyl, halo(lower)alkyloxy, lower alkoxy carbonyl, carboxyl, optionally substituted carboxamide, two adjacent radicals R₁, R₂, R₃ or R₄ being able to form together a 2,3-dihydropyranyl group which is possibly bearing an oxo group, R₁, R₂, R₃, and R₄ also represent, independently of each other, a perhalo(lower)alkyl, aryl, aralkyl, lower cycloalkoxy, polyhaloalkoxy, a thiol radical, lower alkylthio, lower cycloalkylthio, mono or polyhaloalkylthio, arylthio, aralkylthio, formate, a lower cycloalkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, lower dialkylaminoalkyl, aminoalkyl, lower alkylaminoalkyl,
arylamoalkyl, diarylaminoalkyl, arylalkylaminoalkyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, diaralkylamino, formamide, a lower alkylcarbonylamino, a lower cycloalkylcarbonylamino, halo(lower)-alkylcarbonylamino, polyhalo(lower)alkylcarbonylamino, arylcarbonylamino, lower aralkyl-carbonylamino, a lower cycloalkylcarbonyl, polyhalo (lower)alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, lower cycloalkoxy carbonyl, haloalkoxy-carbonyl, aryloxy carbonyl, aralkyl oxy carbonyl, a lower alkylsulfonyl, a lower cycloalkylsulfonyl, halo(lower)alkylsulfonyl, perhalo(lower) alkylsulfonyl, aryloxy carbonyl, aralkylsulfonyl, cyano radical.

$R_5$ represents a hydrogen atom, a lower alkyl, cycloalkyl, aryl, lower aralkyl, lower alkoxy, a lower alkylcarbonyl, halo(lower)alkylcarbonyl, lower alkylamino, alkylamino, dialkylamino, alkylarylamino, diarylamino, halo(lower)alkylsulfonyl, alkylsulfonyl or arylsulfonyl radical.

$R_5$ also represents a halo(lower)alkyl, perhalo(lower)alkyl, a hydroxy radical, lower cycloalkoxy, aryloxy, aralkyloxy, a thiol radical, lower alkylthio, lower cycloalkylthio, arythio, aralkylthio, dialkylaminoalkyl, arylamino, aralkylamino, diaralkylamino, optionally substituted carboxamide, formamide, formyl, a lower cycloalkylcarbonyl, aryloxycarbonyl, aralkylcarbonyl, lower cycloalkoxy carbonyl, haloalkoxy carbonyl, aryloxy-carbonyl, aralkyloxycarbonyl, a lower cycloalkylsulfonyl, perhalo(lower)alkylsulfonyl, aralkylsulfonyl, cyano radical.

$R_6$, $R_7$, $R_9$, $R_{10}$, $R_{12}$, $R_{13}$, $R_{14}$ and $R_{15}$ represent, independently of each other, a hydrogen atom, a lower alkyl, a lower cycloalkyl, halo(lower)alkyl, perhalo(lower)alkyl,
aryl, aralkyl, lower alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, aralkyloxy, hydroxyalkyl, alkylxy-alkyl, lower alkylthio, lower cycloalkylthio, mono or polyhaloalkylthio, arylthio, aralkylthio, formate, lower alkylcarbonyloxy, a lower cycloalkylcarbonyloxy, halo- (lower)alkylcarbonyloxy, arylcarbonyloxy, aralkyl- carbonyloxy, dialkylaminoalkyl, dialkylamino, diarylamino, diaralkylamino, optionally substituted carboxamide, formamide, a lower alkylcarbonylamino, a lower cyclo-alkylcarbonylamino, halo(lower)alkylcarbonylamino, perhalo- (lower)alkylcarbonylamino, lower arylcarbonylamino, lower aralkylcarbonylamino, formyl, a lower alkylcarbonyl, a lower cycloalkylcarbonyl, halo(lower)alkylcarbonyl, perhalo (lower)alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, lower cycloalkoxy carbonyl, haloalkoxy carbonyl, aryloxy carbonyl, aralkyloxy carbonyl, a lower alkylsulfonyl, a lower cycloalkylsulfonyl, halo- (lower)alkylsulfonyl, perhalo(lower) alkylsulfonyl, ary- sulfonyl, aralkylsulfonyl, halo, cyano or nitro radical.

$R_8$ represents a lower alkyl, a lower cycloalkyl, hydroxyalkyl, alkylxyalkyl, halo(lower)alkyl, perhalo- (lower)alkyl, aryl, lower-alkyl aryl, halo aryl, lower- alkoxy aryl, nitro aryl, amino aryl, di(lower)alkylamino aryl, pyridyl, aralkyl, lower alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, aralkyloxy, lower alkylthio, lower cycloalkylthio, mono or polyhaloalkylthio, arylthio, aralkylthio, lower alkylcarbonyloxy, a lower cycloalkylcarbonyloxy, halo(lower)alkylcarbonyloxy, aryl- carbonyloxy, aralkylcarbonyloxy, dialkylaminoalkyl, dialkylamino, diarylamino, diaralkylamino, optionally substituted carboxamide, formamide, a lower alkylcarbonyl- amino, a lower cycloalkylcarbonylamino, halo(lower)- alkylcarbonylamino, polyhalo(lower)alkylcarbonylamino, aryl-
carbonylamino, lower aralkylcarbonylamino, formyl, a lower alkylcarbonyl, a lower cycloalkylcarbonyl, halo(lower)-alkylcarbonyl, perhalo(lower)alkylcarbonyl, arylicarbonyl, aralkylcarbonyl, carboxyl, lower alkoxy-carbonyl, lower cycloalkoxy carbonyl, haloalkoxy carbonyl, aryloxy carbonyl, aralkloxy carbonyl, a lower alkylsulfonfyl, a lower cycloalkylsulfonfyl, halo(lower) alkylsulfonfyl, perhalo-(lower)alkylsulfonfyl, arylsulfonfyl, aralkylsulfonfyl, halo, cyano or nitro radical.

R₆, R₇, R₈, R₉, R₁₀, R₁₂, R₁₃ and R₁₅ can represent, but not simultaneously R₈ and R₁₅, R₉ and R₁₀, R₁₂ and R₁₃ a hydroxyl radical, a thiol radical, amino, alkylamino, aminolino, aralkylamino, alkoxy, lower cycloalkoxy, mono or polyhaloalkoxy, aryloxy, aralkloxy, lower alkylthio, lower cycloalkylthio, mono or polyhalogenoalkylthio, arylthio, aralkylthio, alkylamino, arylamino.

Furthermore

\[ \text{C} \quad \text{C} \quad \text{C} \]
\[ R₈ \quad R₁₅ \quad R₉ \quad R₁₀ \quad R₁₂ \quad R₁₃ \]

can also represent a carbonyl group C=O, a thiocarbonyl group C=S, a radical C=N-R₁₆, or a radical

\[ \text{C} \quad \text{C} \]
\[ R₁₈ \quad R₁₇ \]
\( R_{11} \) represents an oxygen atom, a sulfur,
\( R_{16} \) represents a hydrogen atom, a lower alkyl, a lower cycloalkyl, aryl, aralkyl, a hydroxy radical, lower alkoxy, alkylcarbonyl, arylcarbonyl, aralkylcarbonyl, amino, alkylamino, dialkylamino, arylamino, diarylamino, aralkylamino, alkylcarbonylamino, arylcarbonylamino.

\( R_{17} \) and \( R_{18} \) represent independently of each other a hydrogen atom, a lower alkyl, a lower cycloalkyl, aryl, aralkyl, lower alkoxy, lower cycloalkoxy, aryloxy, aralkyloxy, lower alkylthio, arylthio, aralkylthio, lower alkylcarbonyloxy, lower cycloalkylcarbonyloxy, arylcarbonyloxy, aralkylcarbonyloxy, dialkylamino, arylalkylamino, diarylamino, optionally substituted carboxamide, formamide, lower alkylcarbonylamino, lower cycloalkylcarbonylamino, arylcarbonylamino, formyl, lower alkylcarbonyl, lower cycloalkylcarbonyl, arylcarbonyl, aralkylcarbonyl, carboxyl, lower alkoxy carbonyl, aryloxycarbonyl, aralkyloxycarbonyl, lower alkyloxysulfonyl, arylsulfonyle.

2. Derivatives according to claim 1 of general formula Ia (Ia' and Ia''): 

\[
\begin{align*}
Ia' & \\
Ia'' &
\end{align*}
\]
R₈ being an alkyl radical, optionally substituted by alkyl, halide, amino, alkoxy groups, alkyl oxycarbonyl, an aryl radical optionally substituted by alkyl, halide, nitro, dialkylamino, alkoxy group, alkyl oxycarbonyl, alkylamino, this aryl radical being e.g. a phenyl group, a pyridyl group

X represents preferably a divalent radical of formula

\[ \begin{align*} &N-H \quad \text{or} \quad =HC=CH- \\
& (R₅ = R₆ = R₇ = H) \\
\end{align*} \]

R₁₁ represents preferably an oxygen atom or sulfur atom.

R₂ represents a hydroxyl or lower alkoxy radical and preferably a methoxy radical.

R₃ represents an hydrogen atom or an alkyl radical and preferably a methyl radical.

3. Derivatives according to claim 2 wherein R₈ is an ethyl, hexyl, isopropyl radical, a phenyl, fluorophenyl, methoxyphenyl, aminophenyl, dimethylaminophenyl, nitrophenyl, p.methylphenyl radical, an ethoxycarbonyl radical, a pyridine radical.

4. Derivatives according to claim 1 of general formula Ia (Ia' and Ia''):
R_{15} is an hydrogen atom and R_{8} represents preferably an ethyl, hexyl, isopropyl radical, a phenyl, fluorophenyl, methoxyphenyl, aminophenyl, dimethylaminophenyl, nitrophenyl, tolyl radical, an ethoxycarbonyl radical, a pyridyl radical.

Or R_{8} and R_{15}, identical, represent lower alkyl radicals or aryl radicals optionally substitued by alkyl, halide, amino, alkylxy group.

X represents preferably a divalent radical of formula

\[
\begin{align*}
\text{or} & \\
\text{or} &
\end{align*}
\]

\[
\begin{align*}
(R_5 = R_6 = R_7 = H)
\end{align*}
\]

R_{11} represents preferably an oxygen atom or sulfur atom.

R_{2} represents a hydroxyl or lower alkoxy radical and preferably a methoxy radical.

R_{3} represents an hydrogen atom or an alkyl radical and preferably a methyl radical.

5. Derivatives according to one of the preceding claims, selected from the following derivatives:
1. 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one,
2. 9-methoxy-1-hexyl-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-4-one,
3. 9-methoxy-1-isopropyl-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one,
4. 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one,
5. 1-carbethoxy-9-methoxy-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one,
6. 9-methoxy-1,10-diethyl-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one,
7. 9-methoxy-1-ethyl-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizine-4-thione,
8. 9-methoxy-1-ethyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a] quinolizin-4-one,
9. 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-Benzo[f]pyrido[2,1-a] isoquinolin-8-one,
10. 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo[f]pyrido[2,1-a] isoquinolin-8-one,
11. 9-methoxy-1-phenyl-2,3,4,6,7,12-hexahydroindolo [2,3-a](beta)-quinolizine-4-thione,
12. 9-methoxy-1-ethyl-2,3,4,12-tetrahydroindolo [2,3-a] quinolizin-4-thione,
13. 9-methoxy-1- (p-fluorophenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one,
14. 9-methoxy-1-(p-methoxyphenyl)-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one,
15. 9-méthoxy-1-(p-diméthylaminophényle)-2,3,4,6,7,12-hexahydroindolo [2,3-a] quinolizin-4-one,
16. 9-methoxy-1-(pyrid-2'-yl)-2,3,4,6,7,12-hexahydroindolo [2,3-a]quinolizin-4-one,
17. 9-methoxy-1-p-nitrophenyl-2,3,4,6,7,12-hexahydroindolo[2,3-a] quinolizin-4-one
18. 9-methoxy-1-p-tolyl-2,3,4,6,7,12-hexahydroindolo [2,3-a] quinolizin-4-one,
19. 9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydro- indolo[2,3-a]quinolin-4-one,
20. 9-methoxy-1-(parafluorophenyl)-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolin-4-one
21. 3-methoxy-11-phenyl-5,8,9,10,11,11a-hexahydro-6H- benzo[f]pyrido[2,1-a]isoquinolin-8-one
22. 11-ethyl-3-methoxy-5,8,9,10,11,11a-hexahydro-6H- benzo[f]pyrido[2,1-a]isoquinolin-8-one
23. 9-methoxy-1-paraaminophenyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolin-4-one
24. 9-methoxy-1-phenyl-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizin-4-thione
25. 11-ethyl-3-methoxy-5,8,9,10-tetrahydro-6H-benzo[f] pyrido [2,1-a] isoquinolin-8-thione
26. 3-methoxy-11-phenyl-5,8,9,10-tetrahydro-6H-benzo [f]pyrido[2,1-a] isoquinolin-8-thione
27. 1-ethyl-9-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo [2,3-a]quinolizine-4-thione
28. 1-carbethoxy-9-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolin-4-one
29. 9-methoxy-1-para-tolyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolin-4-one
30. 9-methoxy-1-para-anisyl-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolin-4-one
31. 1,1-diethyl-9-methoxy-1,2,3,4,6,7,12,12b-octahydroindolo[2,3-a]quinolizine-4-one
32. (6S)-6-carbethoxy-9-methoxy-1-ethyl-2,3,4,6,7,12- hexahydroindolo[2,3-a]quinolizin-4-one

6. Derivatives according to one of the preceding claims, racemic mixtures thereof, pure enantiomers thereof, the
mixtures thereof in all proportions, and the therapeutically acceptable salts thereof.

7. Process for the preparation of derivatives according to one of the preceding claims.

8. Process according to claim 7 for the preparation of derivatives of general formula

\[ \text{II}_b \]

by directly reacting the compound of general formula

\[ \text{II}_a \]

with a carboxylic acid in the presence or not of diphenylphosphorylazide or with acrylonitrile.

9. Process for the preparation of derivatives of general formula \[ \text{II}_a \] as an intermediate, by carrying out a Bischler-Napieralski reaction on the compounds of general formula \[ \text{III}_a \].
with phosphorus pentoxide (P₂O₅) or with phosphorus oxychloride (POCl₃) in a suitable solvent.


with compounds of formula R₈-CH₂-CHO or chemical equivalents thereof under reducing conditions.
12. Process according to claim 7 for the preparation of derivatives of general formula Ic

![Chemical Structure Image]

by catalytic reduction by hydrogen with Palladium on Carbon of compound of general formula Ic

5

13. Process according to claim 7 for the preparation of derivatives of general Id

![Chemical Structure Image]

by reaction of the Lawesson's reagent or by P₂S₄ on the compounds of general formula Ic

10
14. Process according to claim 7 for the preparation of derivatives of general \textit{Ic}:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {R_2 \hspace{1cm} R_4 
R_3 \hspace{1cm} R_8 
\node at (-2,0) {X} \node at (0,0) {O} \node at (2,0) {N \hspace{1cm}} \node at (1,-1) {\text{Ic}}; 
\end{tikzpicture}
\end{center}

by reaction of the Lawesson's reagent or by \textit{P_2S_4} on the compound of general formula \textit{Ic}:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {R_2 \hspace{1cm} R_4 
R_3 \hspace{1cm} R_8 
\node at (-2,0) {X} \node at (0,0) {S} \node at (1,-1) {\text{Ic}}; 
\end{tikzpicture}
\end{center}

15. Process according to claim 7 for the preparation of derivatives of general \textit{If}:

\begin{center}
\begin{tikzpicture}
\node at (0,0) {R_2 \hspace{1cm} R_4 
R_3 \hspace{1cm} R_8 
\node at (-2,0) {X} \node at (0,0) {N} \node at (2,0) {R_{11}} \node at (1,-1) {\text{If}}; 
\end{tikzpicture}
\end{center}
By reaction with an oxidant (such O₂ in alkaline medium) on the compound of general formula Ib

![Chemical Structure Ib](image)

or Id

![Chemical Structure Id](image)

16. Process for the preparation of derivatives of general formula Ia, wherein R₈ and R₁₅ are identical by carrying out a reaction on the derivatives of general formula IIIb.

![Chemical Structure IIIb](image)

with compounds of formula EtO-CO-C(R₈) (R₁₅)-COH or chemical equivalents thereof under reducing conditions.

17. A medical product characterized in that it contains a derivative according to one of the claims 1 to 6 or obtained by a process according to one of the claims 7 to 16.
18. A medical product according to claim 17 having at least one activity selected in the myorelaxing (decontracting), hypnotic, sedative, contraceptive and analgesic activities, an activity for the treatment of diseases associated with disorders of melatonin activity, for the treatment of depression and psychiatric disorders, in particular stress, anxiety, depression, insomnia, schizophrenia, psychoses and epilepsy, for the treatment of sleeping disorders associated with travelling ("jet lag"), neurodegenerative diseases of the central nervous system, for the treatment of cancers.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

| IPC  | C07D471/04 | C07D221/04 | A61K31/435 |

According to International Patent Classification (IPC) or to both national classification and IPC.

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| IPC  | C07D |

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched.

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>H. HAMMER ET. AL.: &quot;Dreiringreaktionen in der Indolreihe&quot; CHEMISCHE BERICHTHE, vol. 112, 1979, pages 1889-1901, XP002108405 see page 1891, compound nos. 5 and 9</td>
<td>1, 6, 7</td>
</tr>
<tr>
<td>X</td>
<td>E. BÖSLING ET. AL.: &quot;Stereoselektive Totalsynthese von Eburamomin, eburnamin und Eburnamenin.&quot; CHEMISCHE BERICHTHE, vol. 112, 1979, pages 1902-12, XP002108406 see page 1906, compound nos. 20a and 20b</td>
<td>1, 6, 7</td>
</tr>
</tbody>
</table>

Further documents are listed in the continuation of box C.

**Date of the actual completion of the international search**

7 July 1999

**Date of mailing of the international search report**

21/07/1999

**Name and mailing address of the ISA**

European Patent Office, P.B. 5018 Patentlaan 2 NL - 2280 HV Rijswijk

Tel. (+31) 70 340-2040, Tx. 31 651 epo nl, Fax: (+31) 70 340-3016

Authorized officer

Helps, I

Form PCT/ISA/010 (second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>G. MASSIOT ET. AL.: &quot;Synthesis in the indole series. VIII. A novel approach to indoloquinolizidines through alkylation-cyclisation of an enamine derived from tryptamine.&quot; TETRAHEDRON LETTERS, vol. 23, no. 2, 1982, pages 177-180, XP002108407 see page 179, compound nos. 8a and 8b</td>
<td>1, 6, 7</td>
</tr>
<tr>
<td>X</td>
<td>H. TAKAYAMA ET. AL.: &quot;On the Indole Alkaloid, Nauclefidine; Structure Revision, Synthesis, and a Biomimetic Transformation from the Vincoside Lactam.&quot; TETRAHEDRON LETTERS, vol. 35, no. 47, 1994, pages 8813-6, XP002108408 see page 8815, compound no. 5</td>
<td>1, 6, 7</td>
</tr>
<tr>
<td>X</td>
<td>G. KALAUSS ET. AL.: &quot;Synthesis of Vinca Alkaloids and related compounds, XIII. Synthesis starting from 2-(Ethoxycarbonyl)tryptamine.&quot; CHEMISCHER BERICHT, vol. 114, 1981, pages 1476-83, XP002108409 see page 1477, compounds 5a and 6a and page 1478, compounds 11a and 12a</td>
<td>1, 6, 7</td>
</tr>
<tr>
<td>X</td>
<td>P. BENOVSKY ET. AL.: &quot;Aza-Annulation as a Versatile Approach to the Synthesis of Non-Benzodiazipine Compounds for the Treatment of Sleep Disorders.&quot; TETRAHEDRON LETTERS, vol. 38, no. 49, 1997, pages 8475-8, XP002108410 see page 8475, paragraph 1 and page 8477, compounds 25 and 27</td>
<td>1, 6, 7, 17, 18</td>
</tr>
<tr>
<td>X</td>
<td>J-Y LARONZE ET. AL.: &quot;Synthèses en série indolique V. Sur la réactivité de chloroindolénilines dérivés d'oxo-4 indolo'2,3a'quinolizidines.&quot; BULLETIN OF THE CHEMICAL SOCIETY OF FRANCE, vol. 1977, 1977, pages 1215-20, XP002108411 see page 1216, table II, compound F2 and page 1218, compounds 21 and 22</td>
<td>1, 6, 7</td>
</tr>
</tbody>
</table>

---

Form PCT/IB 99/00494 (continuation of second sheet) (July 1992)
<table>
<thead>
<tr>
<th>Category</th>
<th>Citation of document, with indication, where appropriate, of the relevant passages</th>
<th>Relevant to claim No.</th>
</tr>
</thead>
<tbody>
<tr>
<td>X</td>
<td>M. INCZE ET. AL.: &quot;Synthesis of Trifluoro-apovincamic Acid Ester&quot; ARCHIVE DER PHARMAZIE, vol. 323, 1990, pages 331-3, XP002108413 WEINHEIM; DE see page 331, compounds 6a and 6b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>M. IHARA ET. AL.: &quot;Novel synthesis of heterocyclic compounds having angular nitrogen atom by intramolecular Diels Alder reaction of 1-azadienes&quot; HETEROCYCLIC, vol. 23, no. 1, 1985, page 221 XP002108414 see page 221, compounds 4a and 4b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>M. NODE ET. AL.: &quot;Chiral Total Synthesis of Indole Alkaloids of the Aspidasperma and Hunteria Types.&quot; JOURNAL OF ORGANIC CHEMISTRY, vol. 55, 1990, pages 517-21, XP002108415 see page 518, scheme 1, compounds 5b and 6a</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>B. DANIELI ET. AL.: &quot;A One-Pot Synthesis of 2,6,7,12,Tetrahydroindolo'2,3a!quinolizin-4(3H)ones&quot; SYNTHESIS , no. 4, 1984, pages 353-6, XP002108417 see whole article</td>
<td>1,6-8</td>
</tr>
<tr>
<td>X</td>
<td>H. HAMMER ET. AL.: &quot;Aza- and oxo-eburnamone (Reactions with indole derivatives, Part XLVII).&quot; TETRAHEDRON, vol. 37, no. 21, 1981, pages 3609-13, XP002108418 see page 3611, compounds 15a and 15b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
</tr>
<tr>
<td>----------</td>
<td>--------------------------------------------------------------------------------</td>
<td>----------------------</td>
</tr>
<tr>
<td>X</td>
<td>A. R. STOIT ET. AL.: &quot;Models of Folate Cofactors. 20. An Approach to Deethylburnamamine&quot; TETRAHEDRON, vol. 45, no. 3, 1989, pages 849-54, XP002108419 see page 850, compounds 9,10a and 10b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>G. KALAUS ET. AL.: &quot;Synthesis of Vinca Alkaloids and Related Compounds. 8. Unusual Alkylation of an Enamine.&quot; JOURNAL OF ORGANIC CHEMISTRY, vol. 43, no. 26, 22 December 1978, pages 5017-8, XP002108420 see page 5017, compounds 1a and 1b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>S. B. MANDAL ET. AL.: &quot;Reduction of Lactams and Thiolactams by Sodium Borohydride: Application in the Synthesis of Some Alkaloids.&quot; JOURNAL OF ORGANIC CHEMISTRY, vol. 53, no. 18, 2 September 1988, pages 4236-41, XP002108421 see page 4236, compounds 4a-6b and page 4237, compound 15a, page 4239, column 2, paragraph 4</td>
<td>1,6,7,14</td>
</tr>
<tr>
<td>X</td>
<td>B. DANIELI ET. AL.: &quot;A new approach to Apovincamine.&quot; GAZZETTA CHIMICA ITALIANA, vol. 111, 1981, pages 257-66, XP002108422 see page 258, compounds 11 and 12</td>
<td>1,6,7,14</td>
</tr>
<tr>
<td>X</td>
<td>A. DANSCE ET. AL.: &quot;Synthesis of Vinca Alkaloids and Related Compounds. XXIX. stereochemistry of 1,1-disubstituted indolo'2,3a'quinolizidines.&quot; ACTA CHIMICA HUNGARICA, vol. 123, no. 3, 1986, pages 155-60, XP002108423 see page 156, compounds 1a and b</td>
<td>1,6,7</td>
</tr>
<tr>
<td>X</td>
<td>WO 96 08490 A (CEMAF ET LABORATOIRES BESINS ISCOVESCO) 21 March 1996 see claims; example 22</td>
<td>1-18</td>
</tr>
<tr>
<td>A</td>
<td>US 5 283 343 A (DUBOCOVICH ET. AL.) 1 February 1994 cited in the application see claims; examples</td>
<td>1-18</td>
</tr>
</tbody>
</table>
## INTERNATIONAL SEARCH REPORT

### Information on patent family members

<table>
<thead>
<tr>
<th>Patent document cited in search report</th>
<th>Publication date</th>
<th>Patent family member(s)</th>
<th>Publication date</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>AU 3475595 A</td>
<td>29-03-1996</td>
</tr>
<tr>
<td></td>
<td></td>
<td>EP 0781281 A</td>
<td>02-07-1997</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP 10505606 T</td>
<td>02-06-1998</td>
</tr>
<tr>
<td>US 5283343 A</td>
<td>01-02-1994</td>
<td>US 5093352 A</td>
<td>03-03-1992</td>
</tr>
</tbody>
</table>

---

Form PCT/ISA/910 (patent family annex) (July 1992)