PHARMACEUTICAL COMPOSITIONS CONTAINING MESEMBRINE AND RELATED COMPOUNDS

There is disclosed the use of mesembrine and related compounds (e.g., mesembranol, mesembranone) as serotonin-uptake inhibitors, pharmaceutical compositions comprising such compounds or dry material or an extract of plants from the Mesembryanthemaceae family (e.g., Sceletium (Aizoaceae) tortuosum) containing a standardised content of said compounds, for use in the treatment of depressive states, psychological or psychiatric disorders with an anxiety component, alcohol and drug dependence, bulimia nervosa and obsessive-compulsive disorders. Also disclosed are new derivatives of mesembrine.
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PHARMACEUTICAL COMPOSITIONS CONTAINING MESEMBRINE AND RELATED COMPOUNDS

BACKGROUND OF THE INVENTION

This invention relates to the use of mesembrine and related compounds as serotonin-uptake inhibitors, to pharmaceutical compositions comprising as an active ingredient dry material or an extract of a plant of the family Mesembryanthemaceae, standardised as to its active content, and to new compounds.

It is known that the naturally occurring alkaloid mesembrine is useful as a medicament having CNS-stimulating action (see JP71043539 to Tanabe Šeiyaku Company Limited).
It is also known that a plant and plant products known colloquially as "kougoed", "channa" or "kanna" in the Cape of South Africa, are used traditionally by some communities as inebriants, sedatives and to elevate mood. The plants called "kougoed", "channa" or "kanna" are all members of the family Mesembryanthemaceae, and contains varying amounts of (−)-mesembrine and related alkaloids.

An article entitled Psychoactive constituents of the genus Sceletium N.E.Br. and other Mesembryanthemaceae: a review, by Smith et al, in Journal of Ethnopharmacology, 50 (1996), Pages 119 to 130, reviews the historical data recorded over a 300 year period of the use of Sceletium plants in psychoactive preparations, describes techniques for the preparation and use of "kougoed" from plants of Sceletium and documents the subjective experiences of a number of contemporary users. The alkaloid distribution in Sceletium and other members of the family Mesembryanthemaceae are also considered. Chemical studies have indicated as many as nine alkaloids in Sceletium, which fall into three distinct structural categories.

SUMMARY OF THE INVENTION

According to a first aspect of the invention there is provided the use of a compound having the formula I

```
R1
\[\text{\textcircled{A}}\]
R2
Q1
R3
```

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wherein the ring A is selected from the group consisting of:

\[
\begin{align*}
\text{R}_1 &\text{ and } \text{R}_2 \text{ are independently selected from H, OH, OCH}_3 \text{ and O(CH}_2)_n\text{CH}_3; \\
\text{R}_3 &\text{ is selected from H, CH}_3 \text{ and (CH}_2)_n\text{CH}_3; \\
n &\text{ is an integer from 1 to 6;}
\end{align*}
\]

and Q₁ and Q₂ are independently selected from CH₂, C=O and CHO秌;
in the manufacture of a medicament for the treatment of diseases that respond to treatment with a serotonin-uptake inhibitor.

In their role as serotonin-uptake inhibitors, these compounds may be used in the treatment of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, i.e., single episode and recurrent depression with associated anxiety, in alcohol and drug dependence, in the treatment of bulimia nervosa, and in the treatment of obsessive-compulsive disorders.

According to a second aspect of the invention there is provided a pharmaceutical composition in unit dosage form comprising a serotonin-uptake inhibitor having the formula I as set out above, in a dose of from 20 micrograms to 2 milligrams inclusive, preferably in a dose of from 50 micrograms to 500 micrograms inclusive, more preferably in a dose of from 100 micrograms to 300 micrograms inclusive.

According to a third aspect of the invention there is provided a method of treating diseases that respond to treatment with a serotonin-uptake inhibitor comprising administering to a patient in need thereof an effective amount
of a compound having the formula I as set out above.

According to a fourth aspect of the invention there is provided a pharmaceutical composition comprising as an active ingredient plant material or an extract of a plant of the family Mesembryanthemaceae, containing in each unit dose an amount of from 20 micrograms to 2 milligrams inclusive, preferably from 50 micrograms to 500 micrograms inclusive, more preferably from 100 micrograms to 300 micrograms inclusive, of a compound selected from the group consisting of mesembrine, mesembranol and mesembranone, or a mixture of two or more thereof.

The plant of the family Mesembryanthemaceae is preferably a plant of the genus Sceletium, more preferably a plant of the species Sceletium tortuosum(L.) N.E. Br..

The pharmaceutical composition of the invention is also useful in the treatment of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, ie single episode and recurrent depression with associated anxiety, in alcohol and drug dependence, in the treatment of bulimia nervosa, and in the treatment of obsessive-compulsive disorders.

According to a fifth aspect of the invention there is provided a compound having the formula I
wherein the ring A is selected from the group consisting of:

R₁ and R₂ are independently selected from H, OH, OCH₃ and O(CH₂)ₙCH₃;
R₃ is selected from H, CH₃ and (CH₂)ₙCH₃;
n is an integer from 1 to 6;
and Q₁ and Q₂ are independently selected from CH₂, C=O and CHOH;

with the provisos that:

(1) when the ring A is

R₁ and R₂ are OCH₃, R₃ is CH₃, and Q₁ is CH₂, then Q₂ is not C=O or CHOH;

(2) when the ring A is

R₁ and R₂ are OCH₃ or R₁ is OH and R₂ is H, R₃ is CH₃, and Q₁ is CH₂, then Q₂ is not C=O; and

(3) when the ring A is
R₁ and R₂ are OCH₃, R₃ is CH₃, and Q₁ is C=O, then Q₂ is not C=O.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1 is a graph for a serotonin-uptake assay comparing (-)-mesembrine, identified by the code number 18532, as compared with the known serotonin-uptake inhibitor imipramine HCl;

Figure 2 is a graph for a serotonin-uptake assay of a whole plant extract of a plant from the family Mesembryanthaceae, identified by the code number 18639, as well as some comparisons with the known serotonin-uptake inhibitor imipramine HCl;

Figure 3 is a graph for a serotonin-uptake assay for mesembranol, identified by the code number 18623, as well as some comparisons with the known serotonin-uptake inhibitor imipramine HCl; and

Figure 4 is a graph for a serotonin-uptake assay for mesembranone, identified by the code number 18622, as well as some comparisons with the known serotonin-uptake inhibitor imipramine HCl.

DESCRIPTION OF EMBODIMENTS

The first aspect of the invention is the use of compounds of the formula I as serotonin-uptake inhibitors.

The compounds of the formula I may be utilised in either of their isomeric forms i.e as the (-)isomer or as the (+)isomer, or as the racemic mixture
of the two isomers. The preferred form is the (-)-isomer.

The compounds of the formula I may be divided into three sub groups:

![Chemical Structures]

I.1  I.2  I.3

In the compounds of the formula I, preferably R₁ and R₂ are both OCH₃, R₃ is CH₃, Q₁ is CH₂ and Q₂ is selected from C=O and CHOH.

The preferred compound of formula I.1, is that in which R₁ and R₂ are OCH₃, R₃ is CH₃, Q₁ is CH₂ and Q₂ is C=O.

This is the compound known as mesembrine.

The structure of mesembrine, also known as 3a-(3,4-dimethoxyphenyl)-octahydro-1-methyl-6H-indol-6-one, has been reported by Popelak et al., Naturwiss.47,156 (1960), and the configuration by P W Jeffs et al., J.Am.Chem.Soc.91,3831 (1969).

Mesembrine is preferably used as its (-)-isomer i.e (-)-mesembrine.

Another preferred compound of the formula I.1 is that in which R₁ and R₂
are \( \text{OCH}_3 \), \( R_3 \) is \( \text{CH}_3 \), \( Q_1 \) is \( \text{CH}_2 \) and \( Q_2 \) is \( \text{CHOH} \), i.e. the compound known as mesembranol.

Preferred compounds of the formula I.2 are those in which \( R_1 \) is selected from \( \text{OH} \) and \( \text{OCH}_3 \), \( R_2 \) is selected from \( \text{H} \) and \( \text{OCH}_3 \), \( R_3 \) is \( \text{CH}_3 \), \( Q_1 \) is \( \text{CH}_2 \) and \( Q_2 \) is \( \text{C}=\text{O} \).

A particularly preferred compound of the formula I.2 is that in which \( R_1 \) and \( R_2 \) are \( \text{OCH}_3 \), \( R_3 \) is \( \text{CH}_3 \), \( Q_1 \) is \( \text{CH}_2 \) and \( Q_2 \) is \( \text{C}=\text{O} \), i.e. the compound known as mesembranone.

The preferred compounds of the formula I.3 are those in which \( R_1 \) and \( R_2 \) are \( \text{OCH}_3 \), \( R_3 \) is \( \text{CH}_3 \), and \( Q_1 \) and \( Q_2 \) are \( \text{C}=\text{O} \).

As stated above, it has been known that mesembrine is useful as a medicament having CNS stimulating action. However, it has now been discovered that the compounds of the invention have a totally different mode of action as serotonin-uptake inhibitors, and in specified doses act as antidepressants, minor tranquilizers and anxiolytics.

Thus, the compounds of the formula I are useful in the treatment of diseases selected from the group consisting of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, alcohol and drug dependence, bulimia nervosa, and obsessive-compulsive disorders.

The second aspect of the invention is a pharmaceutical composition in unit dosage form comprising a serotonin-uptake inhibitor having the formula I as set out above, in a unit dose of from 20 micrograms to 2 milligrams
inclusive, preferably from 50 micrograms to 500 micrograms inclusive, more preferably from 100 micrograms to 300 micrograms inclusive, preferably as a once-a-day administration.

The compounds of the formula I may be formulated in any suitable form for pharmaceutical administration, such as for example aqueous-ethanolic tinctures, tablets, capsules, nasal sprays and skin-patches. The formulations may be designed to be taken orally sublingually, intra-nasally and transdermally.

The third aspect of the invention is a method of treating diseases that respond to treatment with a serotonin-uptake inhibitor comprising administering to a patient in need thereof an effective amount of a compound having the formula I, in the doses described above.

The preferred compound for the pharmaceutical composition and for the method as described above is (−)-mesembrine, with mesembranol and mesembranone also being preferred.

The fourth aspect of the invention is a pharmaceutical composition comprising as an active ingredient plant material or an extract of a plant of the family Mesembryanthemaceae, more preferably a plant of the genus Sceletium, most preferably a plant of the species Sceletium tortuosum(L.) N.E. Br., containing in each unit dose an amount of 20 micrograms to 2 milligrams inclusive, preferably from 50 micrograms to 500 micrograms inclusive, more preferably from 100 micrograms to 300 micrograms inclusive, of a compound selected from the group consisting of mesembrine, mesembranol and mesembranone, or a mixture of two or more thereof.
In other words, this pharmaceutical composition, while derived from a
natural plant material, must contain a known and specified content of the
active component or components.

The pharmaceutical composition of the invention may comprise fresh or dry
portions of the plant, ground to a pulp or powder, or an aqueous or
alcoholic extract of the plant, all containing amounts of mesembrine,
mesembranol or mesembranone.

Again, the pharmaceutical composition may be formulated for example as
an aqueous-ethanolic tincture, tablet, capsule, nasal spray or skin-patch for
oral, sublingual, intra-nasal and transdermal application.

Methods for the extraction of (-)-mesembrine from a plant material
containing the product, and methods of analysis thereof are set out below.

1  EXTRATION METHODS
Dry material:
Material (or alcoholic extracts) are air-dried at maximum 40°C
before analysis. Yield figures for mesembrine are variable but
are typically between 15 and 35 mg per gram dry leaves (mean
value around 15 mg per gram dry weight). Finely ground
material (pestle and mortar) is mixed with 15 ml 0.05 M H₂SO₄
and left standing at room temperature for 20 minutes. After
filtration, the remaining solids are re-extracted with 5 ml 0,05
M H₂SO₄. The aqueous phases are combined, applied to glass
columns with a coarse grade celite (24 g), alkalinized with
ammonia (4 ml) and extracted (1X) with 100 ml CH₂Cl₂. The
CH₂Cl₂ extracts are dried with anhydrous Na₂SO₄ and the
solvent evaporated under reduced pressure to leave the alkaloid as a pale brown oil. The alkaloids can also be extracted with hot or cold water instead of H₂SO₄, or with methanol, ethanol, acetonitrile, chloroform or dichloromethane.

**Fresh material:**
The leaf sap of fresh leaves (or alcoholic extracts) can be studied directly, or the alkaloids may be directly extracted in hot or cold water, ethanol, ethanol/acetonitrile, chloroform or dichloromethane or any other suitable solvent. For HPLC or GC, the sample has to be filtered (e.g., 0.45 μm filter) in order to protect the columns from impurities. Yield figures for mesembrine are variable, but are typically between 0.8 and 6.5 mg per ml leaf sap (mean value around 3.3 mg per ml).

**METHODS OF ANALYSIS**

2.1 **Thin-layer Chromatography**

This method can be used only for rough screening purposes, as there is a poor separation between mesembrine alkaloids with a 4,5 double bond (such as mesembrenone) and those without (such as mesembrine). For routine screening, the following system is suitable (Rf of mesembrine = 0.6): Merck 60 F254 silica gel plates (0.25 mm layer thickness) developed in CHCl₃:cyclohexane:Et₂NH (4:5:1). The plates are dried at 100°C for 3 minutes, studied under UV254 and UV365 and then sprayed with iodoplatinate or dragendorff spray reagents.

2.2 **Gas Chromatography (GC)**
Extracts are dissolved in minimum MeOH and studied by comparative GC and GC-MS. Authentic mesembrine should be used as external standard to quantify the alkaloid content.

A Routine analyses for large numbers of samples (fast system): DB-1 fused silica capillary column (30 m x 0.25 mm internal diameter; He as carrier gas at 4 ml min\(^{-1}\); column temperature 200°C to 300°C at 100 min\(^{-1}\), 15 minute isotherm; injector 230°C; FID (Flame Ionization Detector) detection 300°C; split ratio 30:1; injection volume 1 μl).

B High resolution analyses (selected samples, slow): DB-1 fused silica capillary column (30 m x 0.25 mm internal diameter; He as carrier gas at 4 ml min\(^{-1}\); column temperature 150° to 320°C at 60 min\(^{-1}\) 15 minute isotherm; injector 230°C; PND (Phosphorus-Nitrogen Detector) detection 300°C; split ratio 30:1; injection volume 1μl).

C For GC-MS: Typical system such as DB-1 fused silica capillary column (30 m x 0.32 mm internal diameter; He as carrier gas; column temperature 150° to 300°C at 60 min\(^{-1}\), split ratio 20:1; injection volume 1 μl).

2.3 **High Performance Liquid Chromatography (HPLC)**

A phenomenex IB-Sil column is used (C18 reverse phase, 5 μm particle size, 250 mm x 4.6 mm internal diameter, flow rate 1 ml per minute, 20 μl sample
loop). An isocratic solvent system comprising 30% A in B (A = 1% triethylamine in water; B = 60% acetonitrile). Total run time is 10 minutes. Detection by diode array detector, using two channels (A set at 280 ± 30 nm, B set at 292 ± 10 nm). Results expressed in mg mesembrine per ml leaf sap (calculated from detector response, mean value of channels A and B). For concentrations below 0.05 mg per ml, channel A is more accurate (lower detection limit of ca. 0.01 mg per ml leaf sap). The method depends on a calibration curve which was calculated using five different concentration levels of pure mesembrine, using the System Gold (Beckman) software package. For yield figures see 'fresh material extraction'.

IDENTIFICATION OF MESEMBRINE BY MASS SPECTROMETRY AND 1H NMR SPECTROSCOPY

In the two populations of Sceletium tortuosum studied, mesembrine occurs in leaves as virtually the only compound (small but negligible amounts of mesembrenone and mesembrenol may sometimes be present). The alkaloid was isolated from the leaves using the methods described above and fully identified by mass spectrometry (relative structure) and 1H NMR spectroscopy (absolute configuration). The optical rotation was measured, which confirmed that the natural product is the (−)-form.

Mesembranol and mesembranone may be extracted from suitable plant material, analysed and identified as set out above for mesembrine.
Derivatives of mesembrine, mesembranol and mesembranone, within the group of compounds of formula I, may be prepared from these starting compounds by methods known in the art.

Higher order alkyl ethers of mesembrine, mesembranone or mesembranol may be prepared by acidolytic cleavage of the methoxy methyl groups (for example using anhydrous hydrogen fluoride) which gives the corresponding hydroxyl compound ($R_{1,2} = \text{OH}$) followed by alkylation using the appropriate alkyl halide (for example $\text{CH}_3(\text{CH}_2)_n\text{Br}$).

The hydroxyl compounds above may be reduced to the corresponding benzyl compound ($R_{1,2} = \text{H}$) by catalytic hydrogenation (for example over palladium).

Mesembranol may be prepared from mesembrine by catalytic hydrogenation (for example over palladium).

Compounds of formula I.3 may be prepared from the appropriate mesembrine derivatives described above by dehydrogenation with mercuric acetate.

Compounds of formulas I.2 and I.3 may be prepared from mesembrine by oxidation using selenium dioxide ($\text{SeO}_2$) in tertiary butanol with subsequent purification of the desired positional isomer.

The isolated pure compound (-)-mesembrine was screened for biological activity by the National Institute of Mental Health in the United States of America, through a contract with Novascreen, a division of Oceanix Biosciences Corporation. As illustrated in Figure 1, in comparison to the
tricyclic anti-depressant imipramine HCl, (-)-mesembrine was found to be a highly potent serotonin-uptake inhibitor with an IC50 in nano-molar concentrations.

This testing of (-)-mesembrine also gave the following results set out in Table 1, and below.

### Table 1

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<th>Receptor</th>
<th>Percent Inhibition (Average: N=2) Concentration 5.0E1</th>
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<td>GABA B</td>
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<td>Serotonin-uptake</td>
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The inhibitory constant (Ki) of (-)-mesembrine, with reference to imipramine HCl was found to be Ki = 3.6E-8.

In addition, the whole plant extract of Sceletium N.E.Br., mesembranol and mesembranone were screened for biological activity by the National Institute of Mental Health in the United States of America through the contract with Novascreen. The results of these assays are illustrated in Figures 2 to 4. These assays show that the whole plant extract, as well as mesembranol and mesembranone are highly potent serotonin-uptake inhibitors.

Various in vitro studies of the effects of the compounds of the invention were carried out in adult volunteers as follows:
Study 1. N=3 Healthy adult volunteers, all health professionals
13 September 1996.

A single dose of standardised preparation of dried whole plant, standardised
to contain 400 micrograms of mesembrine was taken sublingually.

Rapid onset of action (10-15 minutes) noted by all.
Anxiolytic effect noted by all.
Sustained elevation of mood noted by all.
Duration of anxiolytic action ranged from five hours to eight hours.

Study 2. N=2 Healthy adult volunteers, all health professionals
21 September 1996.

A single 200 microgram dose of pure (-)-mesembrine dissolved in 1ml of
60% ethanol was taken sublingually.

Rapid onset of action (7 and 12 minutes, respectively) noted by both.
Anxiolytic effect noted by both.
Sustained elevation of mood noted by both (for approximately eight hours
and eleven hours respectively).
Duration of anxiolytic action ranged from five hours to eight hours.

Study 3. N=2 Adult volunteers, both self-confessed alcoholics and
polysubstance abusers
21 September 1996.

A single 5ml dose of a whole-plant aqueous-ethanolic extract containing 100
micrograms of mesembrine per ml of extract (60% ethanol) was
administered orally (total dose of mesembrine 500 micrograms).

Rapid onset of action (15-20 minutes) noted by both.
Anxiolytic effect noted by both.
Neither volunteer imbibed alcohol or used any illicit or other drug for a twenty-four hour period following the administration of the single dose.

Examples of pharmaceutical compositions of the invention will now be given.

Example 1
A liquid composition comprises a 60% ethanol/water solvent containing about 200 \( \mu \text{g/ml} \) of (-)-mesembrine.

A typical dose of the liquid composition is from 1 ml to 5 ml inclusive daily.

Example 2
A sublingual tablet contains a spray-dried 30% aqueous-ethanolic extract of Sceletium tortuosum, containing 200 micrograms of (-)-mesembrine, and conventional pharmaceutical excipients.

Example 3
An oral tablet contains 200 micrograms of pure (-)-mesembrine, and conventional pharmaceutical excipients.
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CLAIMS

1. The use of a compound having the formula I.

\[
\begin{array}{c}
\text{R}_1 \\
\text{Q}_1 \\
\text{R}_3 \\
\text{A} \\
\text{R}_2
\end{array}
\]

wherein the ring A is selected from the group consisting of:

\[
\begin{array}{c}
\text{Q}_2 \\
\text{Q}_2 \\
\text{Q}_2
\end{array}
\]

R₁ and R₂ are independently selected from H, OH, OCH₃ and O(CH₂)ₙCH₃;
R₃ is selected from H, CH₃ and (CH₂)ₙCH₃;
n is an integer from 1 to 6; and
Q₁ and Q₂ are independently selected from CH₂, C=O and CHOH;
in the manufacture of a medicament for the treatment of diseases that respond to treatment with a serotonin-uptake inhibitor.

2. The use according to claim 1 wherein R₁ and R₂ are OCH₃, R₃ is CH₃, Q₁ is CH₂ and Q₂ is selected from C=O and CHOH.
The use according to claim 1 wherein the ring A is

\[
\begin{center}
\includegraphics[width=0.2\textwidth]{structure1.png}
\end{center}
\]

\(R_1\) and \(R_2\) are \(OCH_3\), \(R_3\) is \(CH_3\), \(Q_1\) is \(CH_2\) and \(Q_2\) is \(C=O\).

The use according to claim 1 wherein the compound of formula I is \((-\)-mesembrine).

The use according to claim 1 wherein the ring A is

\[
\begin{center}
\includegraphics[width=0.2\textwidth]{structure2.png}
\end{center}
\]

\(R_1\) and \(R_2\) are \(OCH_3\), \(R_3\) is \(CH_3\), \(Q_1\) is \(CH_2\) and \(Q_2\) is \(CHOH\).

The use according to claim 1 wherein the ring A is

\[
\begin{center}
\includegraphics[width=0.2\textwidth]{structure3.png}
\end{center}
\]

\(R_1\) is selected from \(OH\) and \(OCH_3\), \(R_2\) is selected from \(H\) and \(OCH_3\), \(R_3\) is \(CH_3\), \(Q_1\) is \(CH_2\) and \(Q_2\) is \(C=O\).
The use according to claim 1 wherein the ring A is

\[
\text{R}_1 \text{ and } \text{R}_2 \text{ are } \text{OCH}_3, \text{ R}_3 \text{ is } \text{CH}_3, \text{ Q}_1 \text{ is } \text{CH}_2, \text{ and } \text{Q}_2 \text{ is } \text{C=O}. 
\]

The use according to claim 1 wherein the ring A is

\[
\text{R}_1 \text{ and } \text{R}_2 \text{ are } \text{OCH}_3, \text{ R}_3 \text{ is } \text{CH}_3, \text{ and } \text{Q}_1 \text{ and } \text{Q}_2 \text{ are } \text{C=O}. 
\]

The use according to any one of claims 1 to 8 wherein the disease is selected from the group consisting of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, alcohol and drug dependence, bulimia nervosa, and obsessive-compulsive disorders.

A pharmaceutical composition in unit dosage form comprising a serotonin-uptake inhibitor having the formula I

\[
\text{R}_1 \quad \text{R}_2 \\
\text{Q}_1 \quad \text{A} \\
\text{R}_3
\]

SUBSTITUTE SHEET (RULE 26)
wherein the ring A is selected from the group consisting of:

\[
\begin{align*}
\text{R}_1 \text{ and R}_3 \text{ are independently selected from H, OH, OCH}_3 \text{ and } \\
\text{O(C}_2\text{H}_5)_2\text{CH}_3;
\end{align*}
\]
\[
\begin{align*}
\text{R}_3 \text{ is selected from H, CH}_3 \text{ and } (\text{CH}_2)_n\text{CH}_3; \\
n \text{ is an integer from 1 to 6; and}
\end{align*}
\]
\[
\begin{align*}
\text{Q}_1 \text{ and Q}_2 \text{ are independently selected from CH}_2, \text{ C=O and } \\
\text{CHOH;}
\end{align*}
\]
in a dose of from 20 micrograms to 2 milligrams inclusive.

11 A pharmaceutical composition according to claim 10 comprising the serotonin-uptake inhibitor in a dose of from 50 mg to 500 mg inclusive.

12 A pharmaceutical composition according to claim 10 or 11 wherein the serotonin-uptake inhibitor is (-)-mesembrine.

13 A method of treating diseases that respond to treatment with a serotonin-uptake inhibitor comprising administering to a patient in need thereof an effective amount of a compound having the formula I

\[
\begin{align*}
\text{R}_1 \text{ R}_2 \\
\text{Q}_1 \text{ N} \\
\text{R}_3
\end{align*}
\]
wherein the ring A is selected from the group consisting of:

\[
\begin{align*}
R_1 & \text{ and } R_2 \text{ are independently selected from } H, \text{ OH, OCH}_3 \text{ and } O(CH_2)_nCH_3; \\
R_3 & \text{ is selected from } H, \text{ CH}_3 \text{ and } (CH_2)_nCH_3; \\
n & \text{ is an integer from 1 to 6; and} \\
Q_1 & \text{ and } Q_2 \text{ are independently selected from } CH_2, \text{ C}=O \text{ and } \text{CHOH.}
\end{align*}
\]

14 A method according to claim 13 wherein the serotonin-uptake inhibitor is administered in a unit dose of from 20 micrograms to 2 milligrams inclusive.

15 A method according to claim 14 wherein the serotonin-uptake inhibitor is administered in a unit dose of from 50 micrograms to 500 micrograms inclusive.

16 A method according to any one of claims 13 to 15 wherein the serotonin-uptake inhibitor is \((-\text{-mesembrine).\)

17 A method according to any one of claims 13 to 16 wherein the disease is selected from the group consisting of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, alcohol and drug dependence, bulimia nervosa, and obsessive-compulsive disorders.
A pharmaceutical composition comprising as an active ingredient plant material or an extract of a plant of the family Mesembryanthemaceae containing in each unit dose an amount of from 20 micrograms to 2 milligrams inclusive of a compound selected from the group consisting of mesembrine, mesembranol and mesembranone, or a mixture of two or more thereof.

A pharmaceutical composition according to claim 18 for use in the treatment of a disease which is selected from the group consisting of mild to moderate depression, psychological and psychiatric disorders where anxiety is present, major depressive episodes, alcohol and drug dependence, bulimia nervosa, and obsessive-compulsive disorders.

A pharmaceutical composition according to claim 18 or claim 19 wherein each unit dose contains an amount of from 50 micrograms to 500 micrograms inclusive of the compound.

A pharmaceutical composition according to any one of claims 18 to 20 in the form of an aqueous-ethanolic tincture, a tablet, a capsule, a nasal spray or a skin patch.

A compound having the formula I

```
R₁  R₂

Q₁  A  N

R₃
```
wherein the ring A is selected from the group consisting of:

\[ \text{R}_1 \text{ and } \text{R}_2 \text{ are independently selected from } \text{H, OH, OCH}_3 \text{ and } \text{O(CH}_2\text{)}_n\text{CH}_3; \]
\[ \text{R}_3 \text{ is selected from } \text{H, CH}_3 \text{ and } (\text{CH}_2)_n\text{CH}_3; \]
\[ \text{n is an integer from 1 to 6; and} \]
\[ \text{Q}_1 \text{ and } \text{Q}_2 \text{ are independently selected from } \text{CH}_2, \text{C=O and CHO}_2; \]

with the provisos that:

(1) when the ring A is

\[ \text{R}_1 \text{ and } \text{R}_2 \text{ are } \text{OCH}_3, \text{R}_3 \text{ is } \text{CH}_3, \text{ and } \text{Q}_1 \text{ is } \text{CH}_2, \text{ then } \text{Q}_2 \text{ is not } \text{C=O or CHO}_2; \]

(2) when the ring A is

\[ \text{R}_1 \text{ and } \text{R}_2 \text{ are } \text{OCH}_3 \text{ or } \text{R}_1 \text{ is } \text{OH and } \text{R}_2 \text{ is } \text{H, R}_3 \text{ is } \text{CH}_3, \text{ and } \text{Q}_1 \text{ is } \text{CH}_2 \text{ then } \text{Q}_2 \text{ is not } \text{C=O}; \text{ and} \]
(3) when the ring A is

\[ \text{Diagram} \]

R₁ and R₂ are OCH₃, R₃ is CH₃, and Q₁ is C=O, then Q₂ is not C=O.
AMENDED CLAIMS
[received by the International Bureau on 11 November 1997 (11.11.97);
original claim 22 cancelled; remaining claims unchanged (1 page)]

18 A pharmaceutical composition comprising as an active ingredient
plant material or an extract of a plant of the family
Mesembryanthemaceae containing in each unit dose an amount
of from 20 micrograms to 2 milligrams inclusive of a compound
selected from the group consisting of mesembrine, mesembranol
and mesembranone, or a mixture of two or more thereof.

19 A pharmaceutical composition according to claim 18 for use in
the treatment of a disease which is selected from the group
consisting of mild to moderate depression, psychological and
psychiatric disorders where anxiety is present, major depressive
episodes, alcohol and drug dependence, bulimia nervosa, and
obsessive-compulsive disorders.

20 A pharmaceutical composition according to claim 18 or claim 19
wherein each unit dose contains an amount of from 50
micrograms to 500 micrograms inclusive of the compound.

21 A pharmaceutical composition according to any one of claims 18
to 20 in the form of an aqueous-ethanolic tincture, a tablet, a
capsule, a nasal spray or a skin patch.
STATEMENT UNDER ARTICLE 19

The amendments involve a deletion of original claim 22.
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<th>Ki</th>
<th>Slope</th>
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SUBSTITUTE SHEET (RULE 26)
% Specific Binding

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### IC50 and K1 Table

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**Substitute Sheet (Rule 26)**
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<th>Slope</th>
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INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/40 C07D209/32 C07D209/08 //A61K35/78

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 6 A61K C07D

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

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

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>
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<td>X</td>
<td>TAGUCHI: &quot;Synthesis of octahydroindole derivatives&quot; CHEM. PHARM. BULL., vol. 18, no. 5, 1970, pages 1008-1014, XP002040519 see page 1008, compounds VII-IX (a) &amp; (b) see page 1010 compounds XIV, XVI, XVII, XIX.</td>
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<tr>
<td>X</td>
<td>JEFFS: &quot;Total synthesis of (+)-mesembrine, (+)-joubertinamine, and (+)-N-demethylmesembrenone&quot; J. ORG. CHEM., vol. 48, no. 21, 1983, pages 3861-3863, XP002040520 see page 3862 compounds 11, 13 see page 3863 compounds 2,15-17</td>
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</table>

X Further documents are listed in the continuation of box C. X Patent family members are listed in annex.

* Special categories of cited documents:
- "A" document defining the general state of the art which is not considered to be of particular relevance
- "D" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

Date of the actual completion of the international search 18 September 1997

Date of mailing of the international search report 26.09.97

Name and mailing address of the ISA
European Patent Office, P.B. 3818 Patentlaan 2 NL - 2280 HJ Rijswijk
Tel. (+31-70) 340-2048, Te. 31 651 e-po ni, Fax: (+31-70) 340-3016

Authorized officer
Gac, G
<table>
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<td>JEFFS: &quot;Sceletium alkaloids. VI. Minor alkaloids of S. namaquense and S. strictum&quot;</td>
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<td>J. ORG. CHEM., vol. 39, no. 18, 1974, pages 2703-2710, XP002040521 see page 2704</td>
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<td>LANGLOIS: &quot;Recherches dans la série des ary1-3-pyrrolidines-II. Synthèse de produits</td>
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<td>appentés à la mesembrine et à la crinine&quot; TETRAHEDRON, vol. 27, no. 22, 1971,</td>
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<td></td>
<td>pages 5641-5652, XP002040522 see page 5646 - page 5648</td>
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<td>1968, pages 5763-5766, XP002040523 see page 5763 compounds 1a and 1b</td>
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<td>KRUGER: &quot;Minor alkaloids from Sceletium strictum L. Bol. The structure of N-</td>
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<td>demethylmesembrenol and N-demethylmesembranol&quot; J. S. AFR. CHEM. INST., vol.</td>
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<td>24, no. 9, 1971, pages 235-237, XP002040524 see the whole document</td>
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<td>CAPPES: &quot;Sceletium alkaloids. Part 7. Structure and absolute stereochemistry of</td>
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<td>(-) mesembrane and 3'-methoxy-4'-O-methyljoubertamine, two minor bases from S.</td>
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<td>Nmamaquense L.Bolus: X-ray analysis of (-) mesembrane hydrochloride monohydrate&quot;</td>
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<td>J. CHEM. SOC., PERKINS TRANS. 2, vol. 8, 1977, pages 1098-1104, XP002040525</td>
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<td>see page 1098 compound 2</td>
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<td>1973, pages 347-355, XP002040526 see page 347 compounds 2-3</td>
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<td>A</td>
<td>SMITH : &quot;Psychoactive constituents of the genus Sceletium N.E.Br. and other Mesembryanthemaceae : a review&quot; J. ETHNOPHARMACOL., vol. 50, no. 3, March 1996, pages 119-130, XP002040528 cited in the application see page 124 - page 125 see page 127, right-hand column see page 128, left column first paragraph, and point 6: Conclusions</td>
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<td>DE 36 04 112 A (BESZEDES) 13 August 1987 see the whole document</td>
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<td>DATABASE CHEMABS CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US AN: 76:59442, XP002040529 see abstract &amp; JP 46 043 538 B (TANABE SEIYAKU CO LTD) 23 December 1971</td>
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<td>DATABASE WPI Week 7201 Derwent Publications Ltd., London, GB; AN 72-01352T XP002041042 cited in the application see abstract &amp; JP 46 043 539 B (TANABE SEIYAKU CO) 23 December 1971</td>
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INTERNATIONAL SEARCH REPORT

Box I  Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:  
   because they relate to subject matter not required to be searched by this Authority, namely:
   
   Remark: Although claim(s) 13-17
   is(are) directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:  
   because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:  
   because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II  Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

Form PCT/ISA/210 (continuation of first sheet (1)) (July 1992)
<table>
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<td>DE 3604112 A</td>
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