(51) International Patent Classification:  
C07D 401/12, 409/14, 401/14  
A61K 31/40

(11) International Publication Number:  WO 92/12977
(43) International Publication Date:  6 August 1992 (06.08.92)

(21) International Application Number:  PCT/US92/00162
(22) International Filing Date:  10 January 1992 (10.01.92)
(30) Priority data:  
647,398  
28 January 1991 (28.01.91)  
US

(71) Applicant: WARNER-LAMBERT COMPANY [US/US];  
2800 Plymouth Road, Ann Arbor, MI 48105 (US).

(72) Inventors: WISE, Lawrence, David; 1241 Barrister, Ann  
Arbor, MI 48105 (US). WUSTROW, David, Juergen;  
5101 John Holmes Road, Ann Arbor, MI 48103 (US).

(74) Agents: TINNEY, Francis, J.; Warner-lambert Company,  
2800 Plymouth Road, Ann Arbor, MI 48105 (US) et al.

(81) Designated States:  AT (European patent), BE (European  
patent), CA, CH (European patent), DE (European  
patent), DK (European patent), ES (European patent), FR  
(European patent), GB (European patent), GR (European  
patent), IT (European patent), JP, LU (European  
patent), MC (European patent), NL (European patent),  
SE (European patent).

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.

(54) Title:  SUBSTITUTED INDOLES AS CENTRAL NERVOUS SYSTEM AGENTS

(57) Abstract

Substituted indoles and derivatives of formula (I), wherein R is (a) or (b) wherein R⁴ is aryl or some 5- or 6- membered  
heterocycle, which are useful as central nervous system agents and are particularly useful as dopaminergic,  
antipsychotic, and antihypertensive agents as well as for treating hyperprolactinaemia-related conditions and central nervous  
system disorders.
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></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>AT</td>
<td>Austria</td>
<td>FI</td>
<td>Finland</td>
<td>MI</td>
<td>Mali</td>
</tr>
<tr>
<td>AU</td>
<td>Australia</td>
<td>FR</td>
<td>France</td>
<td>MN</td>
<td>Mongolia</td>
</tr>
<tr>
<td>BB</td>
<td>Barbados</td>
<td>GA</td>
<td>Gabon</td>
<td>MR</td>
<td>Mauritania</td>
</tr>
<tr>
<td>BE</td>
<td>Belgium</td>
<td>GB</td>
<td>United Kingdom</td>
<td>MW</td>
<td>Malawi</td>
</tr>
<tr>
<td>BF</td>
<td>Burkina Faso</td>
<td>GN</td>
<td>Guinea</td>
<td>NL</td>
<td>Netherlands</td>
</tr>
<tr>
<td>BG</td>
<td>Bulgaria</td>
<td>GR</td>
<td>Greece</td>
<td>NO</td>
<td>Norway</td>
</tr>
<tr>
<td>BJ</td>
<td>Benin</td>
<td>HU</td>
<td>Hungary</td>
<td>PL</td>
<td>Poland</td>
</tr>
<tr>
<td>BR</td>
<td>Brazil</td>
<td>IE</td>
<td>Ireland</td>
<td>RO</td>
<td>Romania</td>
</tr>
<tr>
<td>CA</td>
<td>Canada</td>
<td>IT</td>
<td>Italy</td>
<td>RU</td>
<td>Russian Federation</td>
</tr>
<tr>
<td>CF</td>
<td>Central African Republic</td>
<td>JP</td>
<td>Japan</td>
<td>SD</td>
<td>Sudan</td>
</tr>
<tr>
<td>CG</td>
<td>Congo</td>
<td>KP</td>
<td>Democratic People's Republic of Korea</td>
<td>SE</td>
<td>Sweden</td>
</tr>
<tr>
<td>CH</td>
<td>Switzerland</td>
<td>KR</td>
<td>Republic of Korea</td>
<td>SN</td>
<td>Senegal</td>
</tr>
<tr>
<td>CI</td>
<td>Côte d'Ivoire</td>
<td>LI</td>
<td>Liechtenstein</td>
<td>SU</td>
<td>Soviet Union</td>
</tr>
<tr>
<td>CM</td>
<td>Cameroon</td>
<td>LK</td>
<td>Sri Lanka</td>
<td>TD</td>
<td>Chad</td>
</tr>
<tr>
<td>CS</td>
<td>Czechoslovakia</td>
<td>LU</td>
<td>Luxembourg</td>
<td>TG</td>
<td>Togo</td>
</tr>
<tr>
<td>DE</td>
<td>Germany</td>
<td>MC</td>
<td>Monaco</td>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>DK</td>
<td>Denmark</td>
<td>MG</td>
<td>Madagascar</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ES</td>
<td>Spain</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
SUBSTITUTED INDOLES AS CENTRAL NERVOUS SYSTEM AGENTS

BACKGROUND OF THE INVENTION

The present invention relates to novel substituted indoles and derivatives thereof useful as pharmaceutical agents, to methods for their production, to pharmaceutical compositions which include these compounds and a pharmaceutically acceptable carrier, and to pharmaceutical methods of treatment. The novel compounds of the present invention are central nervous system agents. More particularly, the novel compounds of the present invention are dopaminergic agents.

European Published Patent Application EP 345808-A discloses compounds of Formula I

\[
\begin{align*}
A & \text{ or } C \quad R^6 \quad (R^6 = \text{H or Me); or } \\
R^1, R^2 &= \text{H or 1-4C alkyl; } \\
R^3, R^4, R^8, R^9 &= \text{H, lower alkyl, lower alkoxy, carbamide, halo, CF, or thio-lower alkyl; provided that } R^8 \text{ and } R^9 \text{ are not both H; } \\
A &= 5-7C \text{ cycloalkyl or cycloalkenyl, or } -(\text{CH}_2)_n-\text{CHR}^5-; \\
n &= 1, 2, \text{ or } 3; \\
R^5 &= R^1; \\
R^6, R^7 &= \text{H or Me; or}
\end{align*}
\]
R⁺⁺ + R⁻ = a methylene bridge; useful in the treatment of depression, anxiety disorders, panic disorders, obsessive-compulsive disorder, and feeding disorders.

The aforementioned reference does not teach nor suggest the combination of structural variations of the compounds of the present invention nor their use as dopaminergic agents described hereinafter.

SUMMARY OF THE INVENTION

Accordingly, the present invention provides a compound of Formula I

\[ \text{I} \]

wherein R is

\[ \text{N} \]

or

\[ \text{N} \]

wherein R⁴ is aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy,
amino,
\[\text{-NH-C-R}^5, \text{wherein R}^5 \text{ is}\]
\begin{align*}
&\text{lower alkyl,} \\
&\text{halogen, or} \\
&\text{trifluoromethyl,}
\end{align*}
2-, 3-, or 4-pyridinyl, unsubstituted or substituted by
\begin{align*}
&\text{halogen,} \\
&\text{lower alkyl,} \\
&\text{hydroxy,} \\
&\text{lower acyloxy,} \\
&\text{lower alkoxy,}
\end{align*}
\begin{align*}
&\text{amino, or}
\end{align*}
\begin{align*}
\text{-NH-C-R}^5, \text{wherein R}^5 \text{ is as defined above,}
\end{align*}
2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by
\begin{align*}
&\text{halogen,} \\
&\text{lower alkyl,} \\
&\text{hydroxy,} \\
&\text{lower acyloxy,} \\
&\text{lower alkoxy,}
\end{align*}
\begin{align*}
&\text{amino, or}
\end{align*}
\begin{align*}
\text{-NH-C-R}^5, \text{wherein R}^5 \text{ is as defined above,}
\end{align*}
2-pyrazinyl, unsubstituted or substituted by
\begin{align*}
&\text{halogen,} \\
&\text{lower alkyl,} \\
&\text{hydroxy,} \\
&\text{lower acyloxy,} \\
&\text{lower alkoxy,}
\end{align*}
\begin{align*}
&\text{amino, or}
\end{align*}
\begin{align*}
\text{-NH-C-R}^5, \text{wherein R}^5 \text{ is as defined above,}
\end{align*}
2- or 3-furanyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{-NH-C-R}^5 \]
wherein \( R^5 \) is as defined above,

2-, or 3-thienyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{-NH-C-R}^5 \]
wherein \( R^5 \) is as defined above,

2-, 4-, or 5-imidazolyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{-NH-C-R}^5 \]
wherein \( R^5 \) is as defined above,

2-, 4-, or 5-thiazolyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy,
amino, or
\[ \text{-NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above, or} \]
2-, 3-, 4-, 5-, 6-, or 7-indolyl, unsubstituted or substituted by

- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,

lower alkoxy,
amino, or

\[ \text{-NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above;} \]

\( R^1 \text{ is hydrogen,} \)
\[ -\text{CN}, \text{ or} \]
\[ -\text{CO}_2\text{H}; \]

\( R^2 \text{ is hydrogen,} \)
- lower alkyl, or
cycloalkyl;

\( R^3 \text{ is hydrogen,} \)
- halogen,
- hydroxyl,
- lower alkoxy,
- lower alkyl,

\[ \text{-C-OR}^6, \text{ wherein } R^6 \text{ is hydrogen or lower alkyl,} \]

\[ \text{-NH-C-R}^7, \text{ wherein } R^7 \text{ is} \]
- hydrogen,
- lower alkyl,
cycloalkyl, or
aryl, unsubstituted or substituted by one to four substituents selected from
- lower alkyl,
- lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
aminoo,

$\text{O}$

$\text{-NH-C-R}^5$, wherein $R^5$ is as defined above,
halogen, or
trifluoromethyl,

$\text{O}$

$\text{-NH-S-R}^8$ wherein $R^8$ is

$\text{O}$

lower alkyl,
cycloalkyl or
aryl, unsubstituted or substituted by one to four substituents selected from
lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
aminoo,

$\text{O}$

$\text{-NH-C-R}^5$, wherein $R^5$ is as defined above,
halogen, or
trifluoromethyl, or

$\text{-NH}_2$;

$n$ is zero or an integer of 1, 2, or 3;

$\text{----}$ is a single or double bond; and corresponding geometric isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof.

As dopaminergic agents, the compounds of Formula I are useful as antipsychotic agents for treating psychoses such as schizophrenia. They are
also useful as antihypertensives and for the treatment of disorders which respond to dopaminergic activation. Thus, other embodiments of the present invention include the treatment, by a compound of Formula I, of hyperprolactinaemia-related conditions, such as galactorrhea, amenorrhea, menstrual disorders and sexual dysfunction, and several central nervous system disorders such as Parkinson’s disease, Huntington’s chorea, and depression.

A still further embodiment of the present invention is a pharmaceutical composition for administering an effective amount of a compound of Formula I in unit dosage form in the treatment methods mentioned above.

Finally, the present invention is directed to methods for production of a compound of Formula I.

DETAILED DESCRIPTION OF THE INVENTION

In the compounds of Formula I, the term "lower alkyl" means a straight or branched hydrocarbon radical having from one to six carbon atoms and includes, for example, methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, tert-butyl, n-pentyl, n-hexyl, and the like.

The term "aryl" means an aromatic radical which is a phenyl group or phenyl group substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy, 

\[
\text{amino, } -\text{NH-C-}R, \text{ wherein } R \text{ is lower alkyl, halogen, or trifluoromethyl.}
\]

"Lower alkoxy" and "thioalkoxy" are O-alkyl or S-alkyl of from one to six carbon atoms as defined above for "lower alkyl."
"Lower acyloxy" is \(-O-C\)-alkyl of from one to six carbon atoms as defined above for "lower alkyl". "Halogen" is fluorine, chlorine, bromine, or iodine.

"Alkali metal" is a metal in Group IIA of the periodic table and includes, for example, lithium, sodium, potassium, and the like.

"Alkaline-earth metal" is a metal in Group IIA of the periodic table and includes, for example, calcium, barium, strontium, magnesium, and the like.

"Noble metal" is platinum, palladium, rhodium, ruthenium, and the like.

The dotted line in a compound of Formula I means a single or double bond.

The compounds of Formula I are capable of further forming both pharmaceutically acceptable acid addition and/or base salts. All of these forms are within the scope of the present invention.

Pharmaceutically acceptable base addition salts of the compounds of Formula I include salts formed with metals or amines, such as alkali and alkaline earth metals or organic amines. Examples of metals used as cations are sodium, potassium, magnesium, calcium, and the like. Examples of suitable amines are \(N,N'\)-dibenzylethlenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, \(N\)-methylglucamine, and procaine (see, for example, Berge, S. M., et al., "Pharmaceutical Salts," *Journal of Pharmaceutical Science*, 66, pp. 1-19 (1977)).

The base addition salts of said acidic compounds are prepared by contacting the free acid form with a sufficient amount of the desired base to produce the salt in the conventional manner. The free acid form may be regenerated by contacting the salt form with an
acid and isolating the free acid in the conventional manner. The free acid forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free acid for purposes of the present invention.

Pharmaceutically acceptable acid addition salts of the compounds of Formula I include salts derived from nontoxic inorganic acids, such as hydrochloric, nitric, phosphoric, sulfuric, hydrobromic, hydriodic, phosphorous, and the like, as well as the salts derived from nontoxic organic acids, such as aliphatic mono- and dicarboxylic acids, phenyl-substituted alkanoic acids, hydroxy alkanoic acids, alkanedioic acids, aromatic acids, aliphatic and aromatic sulfonic acids, etc. Such salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, nitrate, phosphate, monohydrogen phosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, caprylate, isobutyrate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, mandelate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, phenylacetate, citrate, lactate, maleate, tartrate, methanesulfonate, and the like. Also contemplated are salts of amino acids such as arginate and the like and gluconate, galacturonate (see, for example, Berge, S. M., et al, "Pharmaceutical Salts," Journal of Pharmaceutical Science, Vol. 66, pages 1-19 (1977)).

The acid addition salts of said basic compounds are prepared by contacting the free base form with a sufficient amount of the desired acid to produce the salt in the conventional manner. The free base form may be regenerated by contacting the salt form with a
base and isolating the free base in the conventional manner. The free base forms differ from their respective salt forms somewhat in certain physical properties such as solubility in polar solvents, but otherwise the salts are equivalent to their respective free base for purposes of the present invention.

Certain of the compounds of the present invention can exist in unsolvated forms as well as solvated forms, including hydrated forms. In general, the solvated forms, including hydrated forms, are equivalent to unsolvated forms and are intended to be encompassed within the scope of the present invention.

Certain of the compounds of the present invention may exist as geometric isomers. Thus, the invention includes the geometric isomers such as cis or trans, E (entgegen) or Z (zusammen), isomers and mixtures thereof. The individual isomers may be prepared or isolated by methods known in the art.

A preferred compound of Formula I is one wherein

\[ R^4 \] is aryl, unsubstituted or substituted by one to four substituents selected from

- lower alkyl,
- lower alkoxy,
- lower thioalkoxy,
- hydroxy,
- lower acyloxy,
- amino,
- \[ \text{O} \]
- \[ \text{NH-C-R}^5 \], wherein \[ R^5 \] is

\[ \text{lower alkyl,} \]
\[ \text{halogen, or} \]
\[ \text{trifluoromethyl,} \]
\[ 2-, 3-, \text{or 4-pyridinyl,} \]
\[ 2-, 4-, \text{or 5-pyrimidinyl,} \]
\[ 2-, \text{or 3-furanyl,} \]
2-, or 3-thienyl,
2-, 4-, or 5-thiazolyl, or
2-, 3-, 4-, 5-, 6-, or 7-indolyl.
Another preferred embodiment is a compound of
5 Formula I wherein R^6 is
aryl,
2-, 3-, or 4-pyridinyl,
2-, 4-, or 5-pyrimidinyl,
2-, or 3-furanyl,
10 2-, or 3-thienyl,
2-, 4-, or 5-thiazolyl, or
2-, 3-, 4-, 5-, 6-, or 7-indolyl.
Particularly preferred compounds are:
Trans 3-[(4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 3-[(4-[2-[4-(2-pyridinyl)-1-piperazinyl]-ethyl]cyclohexyl]-1H-indole;
Trans 3-[(4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]-ethyl]cyclohexyl]-1H-indole, hydrochloride;
Cis 3-[(4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]-ethyl]cyclohexyl]-1H-indole, hydrochloride;
Trans 3-[(4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[(4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 3-[(4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[(4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 3-[(4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[(4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 5-methoxy-3-[(4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 5-methoxy-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Trans 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Trans 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole;
3-[4-[2-[4-[2-(Pyridinyl)-1-piperazinyl]]-ethyl]cyclohexen-1-y1]-1H-indole;
Trans 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]-ethyl]cyclohexyl]-1H-indol-5-ol;
Cis 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]-ethyl]cyclohexyl]-1H-indol-5-ol;
Trans 1-methyl-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole; and
Cis 1-methyl-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
or a pharmaceutically acceptable acid or base addition salt thereof.

The compounds of Formula I are valuable dopaminergic agents. The tests employed indicate that compounds of Formula I possess dopaminergic activity. Thus, the compounds of Formula I were tested for their ability to inhibit locomotor activity in mice according to the assay described by J. R. McLean, et al., Pharmacology, Biochemistry and Behavior, Volume 8, pages 97-99 (1978); and for their ability to inhibit [$^3$H]-spiroperidol binding in a receptor assay described by D. Grigoriadis and P. Seeman, Journal of Neurochemistry, Volume 44, pages 1925-1935 (1985). The above test methods are incorporated herein by reference. The data in the table show the
dopaminergic activity of representative compounds of Formula I.
<table>
<thead>
<tr>
<th>Example Number</th>
<th>Compound</th>
<th>Inhibition of Locomotor Activity in Mice (ED&lt;sub&gt;50&lt;/sub&gt;, mg/kg, IP)</th>
<th>Inhibition of [&lt;sup&gt;3&lt;/sup&gt;H]Spiroperidol Binding (IC&lt;sub&gt;50&lt;/sub&gt;, nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Trans 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole</td>
<td>1.4</td>
<td>69.8</td>
</tr>
<tr>
<td>5</td>
<td>Cis 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole</td>
<td>4.7</td>
<td>193</td>
</tr>
<tr>
<td>3</td>
<td>Trans 3-[4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole hydrochloride</td>
<td>3.3</td>
<td>224</td>
</tr>
<tr>
<td>4</td>
<td>Cis 3-[4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole, hydrochloride</td>
<td>8.6</td>
<td>349</td>
</tr>
<tr>
<td>5</td>
<td>Trans 3-[4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole</td>
<td>9.00</td>
<td>12.1</td>
</tr>
<tr>
<td>6</td>
<td>Cis 3-[4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole</td>
<td>16.6</td>
<td>39.3</td>
</tr>
<tr>
<td>10</td>
<td>Trans 3-[4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole</td>
<td>11.7</td>
<td>878</td>
</tr>
<tr>
<td>16</td>
<td>3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexen-1-yl]-1H-indole</td>
<td>6.25</td>
<td>270</td>
</tr>
</tbody>
</table>
SCHEME I

-15-
SCHEME II
SCHEME IV
SCHEME V

5

10

15

20

25

30

35
A compound of Formula Ia

wherein $R$ is

$$\text{N-N-R}^4 \quad \text{or} \quad \text{N-R}^4$$

wherein $R^4$ is aryl, unsubstituted or substituted by one to four substituents selected from

- lower alkyl,
- lower alkoxy,
- lower thioalkoxy,
- hydroxy,
- lower acyloxy,
- amino,
- $\text{NH-C-R}^5$, wherein $R^5$ is
  - lower alkyl,
  - halogen, or
  - trifluoromethyl,
- 2-, 3-, or 4-pyridinyl, unsubstituted or substituted by
  - halogen,
  - lower alkyl,
  - hydroxy,
  - lower acyloxy,
lower alkoxy, amino, or
\[ \text{O} \]
\(-\text{NH-C-R}^5\), wherein \(R^5\) is as defined above,

2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy,

lower acyloxy, lower alkoxy, amino, or

\[ \text{O} \]
\(-\text{NH-C-R}^5\), wherein \(R^5\) is as defined above,

2-pyrazinyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy,

lower acyloxy,

lower alkoxy, amino, or

\[ \text{O} \]
\(-\text{NH-C-R}^5\), wherein \(R^5\) is as defined above,

2- or 3-furanyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy,

lower acyloxy, lower alkoxy,

amino, or

\[ \text{O} \]
\(-\text{NH-C-R}^5\), wherein \(R^5\) is as defined above,

2-, or 3-thienyl, unsubstituted or substituted by

halogen, lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-22-

\[ \text{O} \]
\[ \text{NH-C-R}^5 \], wherein \( R^5 \) is as defined above, 2-, 4-, or 5-imidazolyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-27-

\[ \text{O} \]
\[ \text{NH-C-R}^5 \], wherein \( R^5 \) is as defined above, 2-, 4-, or 5-thiazolyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-32-

\[ \text{O} \]
\[ \text{NH-C-R}^5 \], wherein \( R^5 \) is as defined above, or 2-, 3-, 4-, 5-, 6-, or 7-indolyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or
-NH-C-R^2, wherein R^2 is as defined above;
R^2 is hydrogen, -CN, or -CO_2H;
R^3 is hydrogen, halogen, hydroxyl, lower alkoxy,
lower alkyl,
\[ \text{C-OR}^6, \text{wherein } R^6 \text{ is hydrogen or lower alkyl,} \]
\[ \text{NH-C-R}^7, \text{wherein } R^7 \text{ is} \]
hydrogen, lower alkyl, cycloalkyl, or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxyl, lower acyloxy, amino,
\[ \text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above, halogen, or} \]
\[ \text{trifluoromethyl,} \]
\[ \text{NH-S-R}^8 \text{ wherein } R^8 \text{ is} \]
lower alkyl, cycloalkyl or
aryl, unsubstituted or substituted by one to four substituents selected from
  lower alkyl,
  lower alkoxy,
  lower thioalkoxy,
  hydroxy,
  lower acyloxy,
  amino,

\[
\text{O} \quad \text{II} \quad \text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined}
\]
  above,
  halogen, or
  trifluoromethyl, or

\[
\text{NH}_2;
\]

and corresponding geometric isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme I.

Thus, a compound of Formula VIII wherein \( R^1 \) and \( R^3 \) are as defined above is reacted with

1,4-cyclohexanедione monoethylene ketal in the presence of a base such as, for example, an alkali metal hydroxide, alkali metal alkoxide and the like such as, for example, potassium hydroxide, sodium methoxide and the like and a solvent such as, for example, a lower alkyl alcohol such as methanol and the like at about 25°C to about the reflux temperature of the solvent to afford a compound of Formula VII wherein \( R^1 \) and \( R^3 \) are as defined above. Preferably the reaction is carried out with potassium hydroxide in refluxing methanol.

A compound of Formula VII is treated with hydrogen in the presence of a catalyst such as a noble metal, for example, palladium on carbon and the like in a solvent such as, for example, tetrahydrofuran, methanol and the like and mixtures thereof at about
0°C to about 70°C to afford a compound of Formula VI wherein R₁ and R₃ are as defined above. Preferably the reaction is carried out with 5% palladium on carbon in a mixture of tetrahydrofuran and methanol at room temperature.

A compound of Formula VI is treated with an acid such as, for example, an aqueous solution of hydrochloric acid and the like in a solvent such as, for example, acetone and the like at about 0°C to about 50°C to afford a compound of Formula V wherein R₁ and R₃ are as defined above. Preferably the reaction is carried out with a 10% aqueous solution of hydrochloric acid in acetone at room temperature. A solution of a compound of Formula V in a solvent such as, for example, tetrahydrofuran and the like is added to a ylide formed from triethyl phosphonoacetate and sodium hydride in a solvent such as, for example, tetrahydrofuran and the like at about 0°C to about 50°C followed by treatment of the resulting intermediate with hydrogen in the presence of a catalyst such as a noble metal, for example, palladium on carbon and the like in a solvent such as, for example, ethanol and the like at about 0°C to about 50°C to afford a compound of Formula IV wherein R₁ and R₃ are as defined above as a mixture of cis and trans isomers. Preferably the reaction is carried out in tetrahydrofuran at room temperature followed by treatment with hydrogen in the presence of 5% palladium on carbon in ethanol at room temperature.

A compound of Formula IV is hydrolyzed in the presence of a base such as, for example, an alkali hydroxide such as, for example, sodium hydroxide and the like and a solvent such as, for example, ethanol at about 0°C to about the reflux temperature of the solvent to afford a compound of Formula III wherein R₁
and $R^2$ are as defined above as a mixture of cis and trans isomers. Preferably the mixture is carried out with a 10% aqueous solution of sodium hydroxide in ethanol at room temperature.

A compound of Formula III is treated with isobutyl chloroformate in the presence of a base such as, for example, triethylamine and a solvent such as, for example, dichloromethane at about $-10^\circ C$ to about $25^\circ C$ followed by reaction with a compound of Formula A

\[
\text{RH}
\]

\[
\text{A}
\]

wherein $R$ is as defined above to afford a compound of Formula II wherein $R$, $R^1$, and $R^3$ are as defined above as a mixture of cis and trans isomers which are separated into the individual cis and trans isomers by conventional methodology such as, for example, chromatography on silica gel. Preferably the reaction is carried out in the presence of triethylamine in dichloromethane at 0°C followed by separation of the cis and trans isomers using silica gel chromatography and elution with mixtures of methanol in chloroform.

A compound of either Formula II (trans) or Formula II (cis) is reacted with a hydride reagent such as, for example, lithium aluminum hydride and aluminum chloride and the like in the presence of a solvent such as, for example, tetrahydrofuran and the like at about 0°C to about 50°C to afford either a compound of Formula Ia (trans) or a compound of Formula Ia (cis) wherein $R$, $R^1$, and $R^3$ are as defined above. Preferably the reaction is carried out with lithium aluminum hydride and aluminum chloride in tetrahydrofuran at room temperature.
A compound of Formula Ib (trans) or Formula Ib (cis)

wherein R, R¹, R³, and n are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme II.

Thus, a compound of Formula VIII is reacted with methyl 4-oxocyclohexanecarboxylate using the methodology used to prepare a compound of Formula VII from a compound of Formula VIII to afford a compound of Formula X wherein R², R³, and n are as defined above.

A compound of Formula X is converted to a compound of Formula IX wherein R¹, R³, and n are as defined above as a mixture of cis and trans isomers using the methodology used to prepare a compound of Formula VI from a compound of Formula VII.

A compound of Formula IX as a mixture of cis and trans isomers is converted to a compound of Formula IIb wherein R, R¹, R³, and n are as defined above as a mixture of cis and trans isomers using the methodology used to prepare a compound of II from a compound of Formula III. The cis and trans isomers of a compound of Formula IIb are separated as previously described using silica gel chromatography.

A compound of Formula IIb (trans) or a compound of Formula IIb (cis) is converted to a compound of
Formula Ib (trans) or a compound of Formula Ib (cis) respectively wherein R, R¹, R³, and n are as defined above using the methodology used to prepare a compound of Formula Ia (trans) or a compound of Formula Ia (cis) from a compound of Formula II (trans) or a compound of Formula II (cis), respectively.

A compound of Formula Ic

wherein R, R¹, R³, and n are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme III.

Thus, a compound of Formula VIII is reacted with a compound of Formula XI wherein R and n are as defined above using the methodology used to prepare a compound of Formula VII from a compound of Formula VIII to afford a compound of Formula Ic.

A compound of Formula Id (trans) or Formula Id (cis)

Id (trans)            Id (cis)
wherein R¹, R², R³, and n are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme III.

Thus, a compound of Formula Ic-1

\[
\begin{array}{c}
\text{(CH}_2\text{)}_n\text{CH}_2\text{N} \quad \text{N-R}\frac{1}{4} \\
\text{R}^3 \quad \text{R}^1 \\
\text{N} \quad \text{R}^2 \\
\end{array}
\]

Ic-1

wherein R¹, R², R³, and n are as defined above is converted to a compound of Formula Id as a mixture of cis and trans isomers using the methodology used to prepare a compound of Formula VI from a compound of Formula VII. The cis and trans isomers of a compound of Formula Id are separated as previously described using silica gel chromatography.

A compound of Formula Ie (trans) or Formula Ie (cis)

\[
\begin{array}{c}
\text{(CH}_2\text{)}_n\text{CH}_2\text{R} \\
\text{R}^3 \quad \text{R}^1 \\
\text{R}^{2a} \\
\text{N} \quad \text{R}^2 \\
\end{array}
\]

\[
\begin{array}{c}
\text{(CH}_2\text{)}_n\text{CH}_2\text{R} \\
\text{R}^3 \quad \text{R}^1 \\
\text{R}^{2a} \\
\text{N} \quad \text{R}^2 \\
\end{array}
\]

Ie (trans) \hspace{1cm} Ie (cis)

wherein R²a is lower alkyl or cycloalkyl and R, R¹, R³, and n are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme III.
Thus, a compound of Formula I (trans) or Formula I (cis) is reacted with a compound of Formula B

\[ R^{2a}X \]

wherein \( X \) is a halogen or a leaving group such as, for example, arylsulfonyloxy, alkylsulfonyloxy, trihaloalkylsulfonyloxy and the like, for example, methanesulfonyloxy, trifluoromethanesulfonyloxy and the like and \( R^{2a} \) is as defined above in the presence of a base such as, for example, potassium hydride and the like and a solvent such as, for example, tetrahydrofuran and the like at about 0°C to about 50°C to afford a compound of Formula Ie (trans) or a compound of Formula Ie (cis), respectively. Preferably the reaction is carried out in tetrahydrofuran in the presence of potassium hydride.

A compound of Formula If

\[
\begin{align*}
\text{If} & \\
R^1 & \\
R^2a & \\
R^3 & \\
(CH_2)_n-CH_2-R &
\end{align*}
\]

wherein \( R, R^1, R^{2a}, R^3, \) and \( n \) are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme III.

Thus, a compound of Formula Ic is converted to a compound of Formula If using the methodology used to
-31-

prepare a compound of Formula Ie \(\text{trans}\) or Formula Ie \(\text{cis}\) from a compound of Formula Id \(\text{trans}\) or Formula Id \(\text{cis}\).

A compound of Formula Ih \(\text{trans}\) or Formula Ih \(\text{cis}\)

\[
\begin{align*}
\text{Ih (trans)} & \quad \text{Ih (cis)} \\
\end{align*}
\]

wherein \(R^2\) is hydrogen, lower alkyl, or cycloalkyl and \(R, R^1,\) and \(n\) are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme IV.

Thus, a compound of Formula Ig \(\text{trans}\) or Formula Ig \(\text{cis}\) wherein \(R^3\) is lower alkyl and \(R, R^1, R^2,\) and \(n\) are as defined above is reacted with pyridine hydrochloride and heated in a sealed tube to about 130°C for about 3 days to afford a compound of Formula Ih \(\text{trans}\) or a compound of Formula Ih \(\text{cis}\), respectively. Preferably the reaction is carried out at 130°C for 3 days.

A compound of Formula Ii \(\text{trans}\) or Formula Ii \(\text{cis}\)

\[
\begin{align*}
\text{Ii (trans)} & \quad \text{Ii (cis)} \\
\end{align*}
\]
wherein R, R', R'', and n are as defined above or a pharmaceutically acceptable acid or base addition salt thereof is prepared as outlined in Scheme V.

Thus, a compound of Formula V is reacted with the compound of Formula

\[
\text{\begin{array}{c}
\text{CH}_2 \text{OCH}_3 \\
\end{array}}
\]

in the presence of a base such as, for example, n-butyl lithium and the like and a solvent such as, for example, tetrahydrofuran and the like to afford a compound of Formula XII wherein R' and R'' are as defined above.

A compound of Formula XII is treated with an aqueous acid such as, for example, 10% aqueous hydrochloric acid and the like in the presence of a solvent such as, for example, tetrahydrofuran and the like to afford a compound of Formula XIVa wherein n is zero and R' and R'' are as defined above.

Additionally, a compound of Formula V is reacted with a compound of Formula

\[
\text{\begin{array}{c}
\text{CH}_2 \text{CH}_2 \text{OCH}_3 \\
\end{array}}
\]

wherein n is 2 or 3 using the methodology used to prepare a compound of Formula XII from a compound of Formula V to afford a compound of Formula XIII wherein n is 2 or 3 and R' and R'' are as defined above.

A compound of Formula XIII is treated with hydrogen in the presence of a catalyst such as, for example, palladium on carbon and the like in a solvent such as, for example, methanol followed by subsequent treatment with an acid using the methodology used to convert a compound of Formula XII to a compound of Formula XIVa to afford a compound of Formula XIVb.
wherein \( n \) is 2 or 3 and \( R^1 \) and \( R^3 \) are as defined above.

A compound of Formula XIVa or Formula XIVb is treated with a compound of Formula A in the presence of a reducing agent such as, for example, sodium cyanoborohydride (NaCNBH\(_3\)) and the like in a solvent such as, for example, acetonitrile and the like and a catalytic amount of acetic acid to afford a mixture of cis and trans isomers which are separated into the individual cis and trans isomers by conventional methodology as described above.

Compounds of Formula Ia (trans), Formula Ia (cis), Formula Ib (trans), Formula Ib (cis), Formula Ii (trans), and Formula Ii (cis) may be alkylated at the indole nitrogen with a compound of Formula B to afford N-alkylated derivatives using the methodology used to prepare a compound of Formula Ie (trans) or Formula Ie (cis) from a compound of Formula Id (trans) or Formula Id (cis).

Compounds of Formulas A, B, and XI are either known or capable of being prepared by methods known in the art.

The compounds of the present invention can be prepared and administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise as the active component, either a compound of Formula I or a corresponding pharmaceutically acceptable salt of a compound of Formula I.

For preparing pharmaceutical compositions from the compounds of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets,
suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavoring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding properties in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as a carrier providing a capsule in which the active component, with or without other carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid dosage forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glycerides or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogeneous mixture is then poured into
convenient sized molds, allowed to cool, and thereby to solidify.

Liquid form preparations include solutions, suspensions, and emulsions, for example, water or water propylene glycol solutions. For parenteral injection liquid preparations can be formulated in solution in aqueous polyethylene glycol solution.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavors, stabilizing and thickening agents as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, and other well-known suspending agents.

Also included are solid form preparations which are intended to be converted, shortly before use, to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. These preparations may contain, in addition to the active component, colorants, flavors, stabilizers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

The pharmaceutical preparation is preferable in unit dosage form. In such form the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packeted tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can
be the appropriate number of any of these in packaged form.

The quantity of active component in a unit dose preparation may be varied or adjusted from 1 mg to 1000 mg, preferably 10 mg to 100 mg, according to the particular application and the potency of the active component. The composition can, if desired, also contain other compatible therapeutic agents.

In therapeutic use as antipsychotic agents, the compounds utilized in the pharmaceutical method of this invention are administered at the initial dosage of about 1 mg to about 50 mg per kilogram daily. A daily dose range of about 5 mg to about 25 mg per kilogram is preferred. The dosages, however, may be varied depending upon the requirements of the patient, the severity of the condition being treated, and the compound being employed. Determination of the proper dosage for a particular situation is within the skill of the art. Generally, treatment is initiated with smaller dosages which are less than the optimum dose of the compound. Thereafter, the dosage is increased by small increments until the optimum effect under the circumstances is reached. For convenience, the total daily dosage may be divided and administered in portions during the day, if desired.

The following nonlimiting examples illustrate the inventors' preferred compounds of the invention and methods for their preparation.
EXAMPLE 1

Trans 3-[4-[2-[(2-pyridinyl)-1-piperazinyl]ethyl]-
cyclohexyl]-1H-indole

Step (a): Preparation of 4-(1H-3-indolyl)-3-
cyclohexenone ethylene ketal

Indole (45.3 g, 0.38 mol), 1,4-cyclohexanedione
monoethylene ketal (45.5 g, 0.29 mol) and potassium
hydroxide (9.12 g, 0.16 mol) are heated to reflux in
100 mL of methanol for 18 hours. The reaction is
cooled and the product is isolated by filtration and
washed with water to give a white solid (69.0 g).

Step (b): Preparation of 4-(1H-3-indolyl)cyclo-
hexanone ethylene ketal

4-(1H-3-indolyl)-3-cyclohexenone ethylene ketal

(66.6 g, 0.26 mmol) is dissolved in 500 mL of
tetrahydrofuran and 100 mL of methanol, 1.0 g 5%
palladium on carbon is added and the mixture is placed
under 60 pounds per square inch (psi) of hydrogen.
After 2 hours the reaction is filtered and
concentrated to give the product as a tan solid
(67.0 g). An analytical sample is recrystallized from
methanol; mp 163-5°C.

Step (c): Preparation of 4-(1H-3-indolyl)cyclo-
hexanone

4-(1H-3-indolyl)cyclohexanone ethylene ketal
(66.4 g, 0.258 mol) is dissolved in 350 mL of acetone
and 350 mL of 10% hydrochloric acid solution and
allowed to stir at room temperature for 6 hours. The
acetone is removed under reduced pressure and the
mixture is made basic with concentrated ammonium
hydroxide. The mixture is extracted with chloroform.
The organic fraction is dried with sodium sulfate and
volatiles are removed under reduced pressure. The
resulting solid is taken up in hot ethyl acetate and
upon cooling and filtration a crystalline solid is obtained (36.89 g).

Step (d): Preparation of Cis and Trans 2-(4-[(1H-3-indolyl)cyclohexyl]cyclohexyl]acetic acid

To a slurry of sodium hydride (8.60 g, 0.36 mol) in 230 mL of tetrahydrofuran at 0°C is added triethyl phosphonoacetate (73.53 g, 0.328 mol) in 100 mL tetrahydrofuran. The reaction is allowed to come to room temperature and a solution of 4-(1H-3-indolyl)-cyclohexanone (35.0 g, 0.164 mol) in 230 mL tetrahydrofuran is added. After 2 hours the reaction is quenched with 200 mL of saturated potassium dihydrogen phosphate (KH₂PO₄), the tetrahydrofuran is removed under reduced pressure and the resulting mixture is suspended in 200 mL saturated potassium dihydrogen phosphate (KH₂PO₄) and extracted with three 400 mL portions of ethyl acetate. The combined organic extracts are washed with brine, dried over sodium sulfate, and the solvents removed under reduced pressure. The resulting residue is dissolved in 600 mL of ethanol, treated with 5% palladium on carbon (5 g) and placed under 50 psi of hydrogen gas. After the appropriate amount of hydrogen has been taken up the mixture is filtered, and the solvents removed under reduced pressure. The residue is redissolved in 250 mL of ethanol, and 100 mL of 10% sodium hydroxide solution is added. After 18 hours the ethanol is removed under reduced pressure. The aqueous mixture is extracted with ethyl acetate, the aqueous layer is then made acidic and extracted with three 300 mL portions of methylene chloride. The methylene chloride extracts are combined, dried with sodium sulfate, and evaporated to give the product (35.1 g). The product is isolated as a mixture of diastereomers (trans to cis 1.4:1).
Step (e): Preparation of Cis and Trans 1-(2-{4-[(1H-3-indolyl)cyclohexyl]acetyl}-4-(2-pyridinyl)piperazine

The mixture of cis and trans 2-(4-[(1H-3-indolyl)-cyclohexyl]acetic acids (5.0 g, 19.43 mmol) are suspended in 90 mL of methylene chloride (90 mL). Triethylamine is added (4.5 mL) and the resulting solution is cooled to 0°C. Isobutyl chloroformate (2.77 mL, 21.37 mmol) is added and the reaction is stirred for 10 minutes. A solution of 1-(2-pyridinyl)piperazine (3.49 g, 21.37 mmol) in methylene chloride is added and the reaction is allowed to stir at 0°C for 3 hours and the reaction is then stirred at ambient temperature for 18 hours. A saturated solution of sodium bicarbonate (40 mL) is added and the organic phase is separated. The aqueous phase is extracted with two 90 mL portions of methylene chloride and the combined organic extracts are dried with sodium sulfate and evaporated. The residue is chromatographed on silica gel (2% methanol in chloroform) and 2 main fractions are isolated. The first fraction consists of trans 1-(2-{4-[(1H-3-indolyl)cyclohexyl]acetyl}-4-(2-pyridinyl)piperazine and the second fraction consists of the corresponding cis isomer.

Step (f): Preparation of Trans 3-[4-{2-[4-(2-pyridinyl)-1-piperazinyl]ethyl}-cyclohexyl]-1H-indole

A slurry of lithium aluminum hydride (0.472 g, 12.4 mmol) in 20 mL of tetrahydrofuran at 0°C is treated with aluminum chloride (0.553 g, 4.15 mmol) and the mixture is stirred for 20 minutes. A slurry of trans 1-{2-{4-[(1H-3-indolyl)-cyclohexyl]acetyl}-4-(2-pyridinyl)piperazine (1.67 g, 4.15 mmol) in 20 mL of tetrahydrofuran is added and the reaction is stirred at ambient temperature for 18 hours. Water (1 mL) and 10% sodium hydroxide solution (2 mL) is
added the mixture is stirred for 2 hours, then filtered through celite and the volatiles are removed under reduced pressure. The resulting oil is triturated with diethyl ether to give the product as a white solid (1.57 g); mp 147-148°C.

Following the procedure of Example 1, the following compounds are prepared:

EXAMPLE 2

Cis 3-[4-[[2-[4-(2-pyridinyl)]-1-piperazinyl]ethyl]-cyclohexyl]-1H-indole; mp 99-101°C.

EXAMPLE 3

Trans 3-[4-[[2-[4-(2-pyrimidinyl)]-1-piperazinyl]ethyl]-cyclohexyl]-1H-indole, hydrochloride; mp 262°C (dec).

EXAMPLE 4

Cis 3-[4-[[2-[4-(2-pyrimidinyl)]-1-piperazinyl]ethyl]-cyclohexyl]-1H-indole, hydrochloride; mp 145°C (dec).

EXAMPLE 5

Trans 3-[4-[[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole; mp 209-210°C.

EXAMPLE 6

Cis 3-[4-[[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole; mp 123-124°C.

EXAMPLE 7

Trans 3-[4-[[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole; mp 192-194°C.
EXAMPLE 8
Cis 3-[4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)pyridinyl)ethyl]cyclohexyl]-1H-indole; m/e 383.

EXAMPLE 9
Trans 3-[4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole; m/e 383.

EXAMPLE 10
Cis 3-[4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole; m/e 383.

EXAMPLE 11
Trans 5-methoxy-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole; m/e 418.

EXAMPLE 12
Cis 5-methoxy-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole; m/e 418.

EXAMPLE 13
Trans 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole.

EXAMPLE 14
Cis 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole.
EXAMPLE 15

Trans 3-[4-{4-(2-pyridinyl)-1-piperazinylmethyl}-cyclohexyl]-1H-indole and

EXAMPLE 15a

Cis 3-[4-{4-(2-pyridinyl)-1-piperazinylmethyl}-cyclohexyl]-1H-indole

Method \

Step (a): Preparation of 4-(1H-3-indolyl)-cyclohexane carboxylic acid

To 50 mL of methanol is added sodium (3.32 g, 144.3 mmol). After the metal has dissolved indole (2.89 g, 24.6 mmol) and methyl 4-oxocyclohexane-carboxylate (5.0 g, 32.0 mmol) are added. The mixture is heated to reflux for 3 hours. The methanol is removed under reduced pressure and the residue partitioned between water and methylene chloride. The organic layer is discarded. The aqueous layer is acidified to pH 5 and extracted with three portions of methylene chloride. The combined organics are dried over sodium sulfate and evaporated to give 4-indolyl-3-cyclohexanecarboxylic acid (1.71 g). The material is hydrogenated in methanol (75 mL) under 50 psi of hydrogen in the presence of 5% palladium on carbon (0.5 g). After filtration and removal of solvent, the product is obtained as a mixture of diastereomers.

Step (b): Preparation of Trans 3-[4-{4-(2-pyridinyl)-1-piperazinylmethyl}cyclohexyl]-1H-indole and Cis 3-[4-{4-(2-pyridinyl)-1-piperazinylmethyl}cyclohexyl]-1H-indole

A mixture of 4-(1H-3-indolyl)-cyclohexane-carboxylic acid (1.60 g, 6.57 mmol) and methylene chloride (30 mL) is treated with triethylamine (1.53 mL, 10.97 mmol) and the resulting solution is cooled to 0°C. Isobutyl chloroformate (0.93 mL,
7.15 mmol) is added and the reaction is stirred at 0°C for 10 minutes. A solution of 1-(2-pyridinyl)piperazine (1.18 g, 7.23 mmol) in methylene chloride is added and the reaction is allowed to stir at 0°C for 3 hours and the reaction is then stirred at ambient temperature for 18 hours. A saturated solution of sodium bicarbonate (20 mL) is added and the organic phase is separated. The aqueous phase is extracted with two 40 mL portions of methylene chloride and the combined organic extracts are dried with sodium sulfate, and evaporated. The residue is chromatographed on silica gel (2% methanol in chloroform) and 2 main fractions are isolated. The first fraction consisted of trans 1-((4-[1H-3-indolyl]cyclohexyl)carboxyl)-4-(2-pyridinyl)piperazine and the second fraction consisted of the corresponding cis isomer. The resulting trans amide is reduced by the method described in Example 1 to give trans 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole (Example 15); m/e 374.

Following the procedure of Example 15, cis 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole (Example 15a) is obtained; m/e 374.

Method B
Step (a): Preparation of Mixture of Cis and Trans 2-(4-[1H-3-indolyl]cyclohexyl)carboxaldehyde

A mixture of (methoxymethyl)triphenylphosphonium chloride (10 g, 21.17 mmol) in 25 mL of tetrahydrofuran is cooled to -78°C and treated with a 1.6 M solution of butyllithium in hexanes (13.2 mL, 21.2 mmol). After 20 minutes a solution of 4-(1H-3-indolyl)cyclohexanone (2.25 g, 10.6 mmol) in 25 mL of tetrahydrofuran is added. The reaction is warmed to 10°C over 2 hours and then quenched with
saturated ammonium chloride. The tetrahydrofuran is removed under reduced pressure and the resulting mixture is extracted with chloroform and dried over sodium sulfate. The solvents are removed under reduced pressure and the resulting residue is chromatographed on silica gel (1% methanol, 80% hexanes, 19% chloroform) to yield the corresponding methyl enol ether. The enol ether is hydrolyzed by heating in a solution of tetrahydrofuran and 10% hydrochloric acid for 2 hours. The tetrahydrofuran is removed under reduced pressure and the reaction mixture is partitioned between methylene chloride and water. The organic layer is dried and solvents are evaporated under reduced pressure to obtain the desired aldehyde as a 1:5 mixture of cis and trans isomers (1.37 g). The compound was characterized by proton NMR.

Step (b): Preparation of Trans 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole and Cis 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole

A mixture of cis and trans 2-[4-[1H-3-indolyl]cyclohexyl]carboxaldehyde (0.75 g, 3.3 mmol) and 2-pyridinyl piperazine (0.54 g, 3.3 mmol) are dissolved in 20 mL of acetonitrile, cooled to 0°C and treated with 0.3 mL of acetic acid. The reaction is stirred for 15 minutes and is then treated with sodium cyanoborohydride (0.22 g, 3.5 mmol). The reaction is stirred for 3 hours, is diluted with water, the mixture is adjusted to pH 10 and extracted with chloroform. The chloroform extracts are dried with sodium sulfate and the solvents are evaporated under reduced pressure. The residue is chromatographed on silica gel (1% methanol, 99% chloroform) to give trans 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-
1H-indole (Example 15) (0.55 g) and cis 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole (Example 15a) (0.12 g).

EXAMPLE 16

3-[4-[2-[4-(2-Pyridinyl)-1-piperazinyl]ethyl]cyclohexen-1-yl]-1H-indole

A mixture of 4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexanone (Example A) (4.0 g, 13.91 mmol), indole (1.63 g, 13.91 mmol) and potassium hydroxide (0.198 g, 3.48 mmol) are heated in 20 mL of methanol for 14 hours. The methanol is evaporated under reduced pressure and the residue is partitioned between water and methylene chloride. The organic layer is dried with sodium sulfate and the solvent evaporated. The residue is chromatographed (2% methanol in chloroform 0.1% ammonia) and the major fraction is recrystallized with ethyl acetate to give the product as a white solid (1.49 g); mp 258-260°C.

The cyclohexenyl compound may be hydrogenated in the presence of palladium on carbon to give a 1:1 mixture of diastereomers which are separated chromatographically to give both trans 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole (Example 1) and cis 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole (Example 2).

EXAMPLE 17

Trans 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole-5-ol

A mixture of trans 1-(2-[4-[1H-5-methoxy-3-indoly1]cyclohexyl]ethyl)-4-(2-pyridinyl)piperazine (Example 11) (2.0 g, 4.8 mmol) and pyridine hydrochloride (5.0 g, 43 mmol) is heated in a sealed tube to 130°C for 3 days. The reaction is partitioned between chloroform and concentrated ammonium
hydroxide. The organic layer is dried and solvents
evaporated. The residue is chromatographed (3% 
methanol in chloroform containing 0.1% ammonia) to
give the product as a white solid; m/e 404.

Following the procedure of Example 17, the
following compound is prepared:

EXAMPLE 18
Cis 3-[4-[(2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]-
cyclohexyl]-1H-indol-5-ol; m/e 404.

EXAMPLE 19
Trans 1-methyl-3-[4-[(2-[4-(2-pyridinyl)-1-pipera-
zinyl]ethyl]cyclohexyl]-1H-indole

A mixture of potassium hydride (0.24 g, 6 mmol)
in tetrahydrofuran is cooled to 0°C and a solution of 
trans 1-[(2-[4-1H-3-indolyl)cyclohexyl]ethyl]-4-(2-
pyridinyl)piperazine (Example 1) (2.0 g, 5.14 mmol) in 
20 mL of tetrahydrofuran is added. After 20 minutes 
3 mL of methyl iodide is added and the reaction is 
warmed to room temperature overnight. The reaction is 
quenched with ammonium chloride and the 
tetrahydrofuran is removed under reduced pressure.
The residue is partitioned between chloroform and 
ammonium chloride and the organics are dried with 
sodium sulfate and solvents are evaporated. The 
residue is chromatographed on silica gel (2% methanol 
in chloroform) to give the desired product.

Following the procedure of Example 19, the
following compound is prepared.

EXAMPLE 20
Cis 1-methyl-3-[4-[(2-[4-(2-pyridinyl)-1-piperazinyl]-
ethyl]cyclohexyl]-1H-indole.
PREPARATION OF STARTING MATERIALS

EXAMPLE A

4-[2-[4-(2-Pyridinyl)-1-piperazinyl]ethyl]cyclo-

decane-8-acetate

Step (a): Preparation of Ethyl 1,4-dioxaspiro[4,5]-
decane-8-acetate

A solution of triethyl phosphonoacetate
(158.7 mL) in 500 mL of tetrahydrofuran is added over
a period of 2 hours to an ice-cold suspension of 60%-
sodium hydride (38.5 g) in 500 mL of tetrahydrofuran
under nitrogen. The reaction mixture is stirred at
room temperature for 1 hour. A solution of
1,4-cyclohexanedione monoethylene ketal (100.0 g) in
500 mL of tetrahydrofuran is added dropwise and the
reaction mixture is stirred at room temperature for
10 hours. The reaction is concentrated in vacuo and
the residue taken up into ethyl acetate and washed
with brine. The organic extract is dried (magnesium
sulfate) and concentrated to leave 142.7 g of a light
yellow liquid consisting of a mixture of isomeric
unsaturated esters. A solution of these esters
(101.5 g) in 700 mL of ethanol containing 5 g of 5%
palladium on charcoal is hydrogenated at 50 pounds per
square inch (psi) (H₂) for 3 hours. The mixture is
filtered and evaporated in vacuo. The title compound
is obtained by distillation; bp₁ 110–115°C.

Step (b): Preparation of 1,4-Dioxaspiro[4,5]decane-8-

acetic acid

A solution of ethyl 1,4-dioxaspiro[4,5]decane-8-
acetate (50.0 g) in 50 mL of 4.8 N sodium hydroxide
solution and 400 mL of ethanol is refluxed under
nitrogen for 2 hours. The mixture is concentrated in
vacuo to remove the ethanol. The residue is acidified
with a saturated sodium bisphosphate solution and the
mixture is extracted with ethyl acetate (2 x 300 mL). The organic extract is dried over magnesium sulfate, and evaporated in vacuo to give an oily solid which is triturated with hexane and filtered to give 38.25 g of the title compound as a white solid; mp 110-113°C.

Step (c): Preparation of 1-(1,4-Dioxaspiro[4,5]dec-8-ylacetyl)-4-(2-pyridinyl)piperazine

An ice cold solution of 1,4-dioxaspiro[4,5]-decane-8-acetic acid (20.0 g) and triethylamine (20.9 mL) in 100 mL of dichloromethane is treated dropwise with a solution of isobutyl chloroformate (19.4 mL) in 100 mL of dichloromethane under nitrogen. The resulting solution is stirred at 0°C for 10 minutes and a solution of 1-(2-pyridyl)piperazine (32.59 g) in 100 mL of dichloromethane is added dropwise. The mixture is stirred at 0°C for 15 minutes and then at room temperature for 1 hour. After washing with 1 L of a saturated solution of sodium bicarbonate, the organic phase is dried over magnesium sulfate and concentrated in vacuo. The crude product is purified by MPLC (medium pressure liquid chromatography) (silica; ethyl acetate) to give 25.50 g of the title compound as a colorless solid; mp 113-116°C.

Step (d): Preparation of 4-[2-[4-(2-Pyridinyl)-1-piperazinyl]ethyl]cyclohexanone

A solution of 1-(1,4-dioxaspiro[4,5]dec-8-yl-acetyl)-4-(2-pyridinyl)piperazine (17.0 g) in 500 mL of dry tetrahydrofuran is treated with sodium borohydride (6.81 g) under nitrogen and the resulting suspension is treated dropwise with a solution of boron trifluoride etherate (29.5 mL) in 100 mL of tetrahydrofuran. The reaction mixture is stirred at room temperature overnight. A solution of glacial acetic acid (10.3 mL) in 100 mL of tetrahydrofuran is
added dropwise, and the mixture stirred at room
temperature for 2 hours. The solvent is evaporated in
vacuo and the residue refluxed with 250 mL of a 10% solution of hydrochloric acid and 250 mL of acetone
for 2 hours. The mixture is concentrated in vacuo to
about one-half of the original volume. The remaining aqueous solution is washed twice with ethyl acetate
and made basic with ammonium hydroxide. The crude product is extracted into ethyl acetate (2 x 300 mL).
The organic extract is dried over magnesium sulfate
and concentrated in vacuo. The reaction mixture is purified by MPLC (silica; 2% methanol, 98% chloroform)
to give 9.73 g of the title compound as a colorless solid; mp 104-106°C.
1. A compound of Formula I:

![Chemical Structure](attachment:image.png)

wherein R is

- \( \text{N} - \text{N} - \text{R}^4 \) or \( \text{N} - \text{R}^4 \)

wherein \( \text{R}^4 \) is aryl, unsubstituted or substituted by one to four substituents selected from
- lower alkyl,
- lower alkoxy,
- lower thiaoalkoxy,
- hydroxy,
- lower acyloxy,
- amino,
- \( \text{O} \)
- \( \text{NH} - \text{C} - \text{R}^5 \), wherein \( \text{R}^5 \) is
  - lower alkyl,
  - halogen, or
  - trifluoromethyl,
- 2-, 3-, or 4-pyridinyl, unsubstituted or substituted by
  - halogen,
- lower alkyl,
hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{NH-C-R}^5 \]

wherein \( R^5 \) is as defined above,

2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{NH-C-R}^5 \]

wherein \( R^5 \) is as defined above,

2-pyrazinyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{NH-C-R}^5 \]

wherein \( R^5 \) is as defined above,

2- or 3-furanyl, unsubstituted or substituted by

halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy,
amino, or

\[
\begin{align*}
\text{O} \\
\text{-NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,}
\end{align*}
\]

2-, or 3-thienyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

\[
\begin{align*}
\text{O} \\
\text{-NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,}
\end{align*}
\]

2-, 4-, or 5-imidazolyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

\[
\begin{align*}
\text{O} \\
\text{-NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,}
\end{align*}
\]

2-, 4-, or 5-thiazolyl, unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or
90 \[
\begin{align*}
-\text{NH-C-R}^5, \text{ wherein R}^5 \text{ is as defined above, or}
\end{align*}
\]
2-, 3-, 4-, 5-, 6-, or 7-indolyl,
unsubstituted or substituted by
\[
\begin{align*}
\text{halogen,} \\
\text{lower alkyl,} \\
\text{hydroxy,} \\
\text{lower acyloxy,} \\
\text{lower alkoxy,} \\
\text{amino, or}
\end{align*}
\]
\[
\begin{align*}
-\text{NH-C-R}^5, \text{ wherein R}^5 \text{ is as defined above;}
\end{align*}
\]
R\(^1\) is hydrogen,
\[
\begin{align*}
-\text{CN, or} \\
-\text{CO}_2\text{H;}
\end{align*}
\]
R\(^2\) is hydrogen,
\[
\begin{align*}
\text{lower alkyl, or} \\
\text{cycloalkyl;}
\end{align*}
\]
R\(^3\) is hydrogen,
\[
\begin{align*}
\text{halogen,} \\
\text{hydroxyl,} \\
\text{lower alkoxy,} \\
\text{lower alkyl,}
\end{align*}
\]
\[
\begin{align*}
-\text{C-OR}^6, \text{ wherein R}^6 \text{ is hydrogen or lower}
\text{alkyl,}
\end{align*}
\]
\[
\begin{align*}
\text{NH-C-R}^7, \text{ wherein R}^7 \text{ is}
\end{align*}
\]
120 hydrogen,
\[
\begin{align*}
\text{lower alkyl,} \\
\text{cycloalkyl, or}
\end{align*}
\]
aryl, unsubstituted or substituted by one to four substituents selected from
lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,

amino,
\[ -\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above}, \]
halogen, or
trifluoromethyl,

\[ -\text{NH-S-R}^8 \text{ wherein } R^8 \text{ is} \]
lower alkyl,
cycloalkyl or
aryl, unsubstituted or substituted by one to four substituents selected from
lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
amino,
\[ -\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above}, \]
halogen, or
trifluoromethyl, or
\[ -\text{NH}_2; \]

\( n \) is zero or an integer of 1, 2, or 3;
\[ \ldots \] is a single or double bond; and
the corresponding geometric isomers thereof; or a
pharmaceutically acceptable acid or base addition salt thereof.

2. A compound according to Claim 1, in which $R^4$ is aryl, unsubstituted or substituted by one to four substituents selected from
   lower alkyl,
   lower alkoxy,
   lower thioalkoxy,
   hydroxy,
   lower acyloxy,
   amino,
   \[ \text{O} \]
   \[ \text{NH-C-R}^5 \]
   wherein $R^5$ is lower alkyl, halogen, or trifluoromethyl,
   2-, 3-, or 4-pyridinyl,
   2-, 4-, or 5-pyrimidinyl,
   2-, or 3-furanyl,
   2-, or 3-thienyl,
   2-, 4-, or 5-thiazolyl, or
   2-, 3-, 4-, 5-, 6-, or 7-indolyl.

3. A compound according to Claim 2, in which $R^4$ is aryl,
   2-, 3-, or 4-pyridinyl,
   2-, 4-, or 5-pyrimidinyl,
   2-, or 3-furanyl,
   2-, or 3-thienyl,
   2-, 4-, or 5-thiazolyl, or
   2-, 3-, 4-, 5-, 6-, or 7-indolyl.

4. A compound according to Claim 1 selected from the group consisting of:
Trans 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Trans 3-[4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole,
hydrochloride;
Cis 3-[4-[2-[4-(2-pyrimidinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole,
hydrochloride;
Trans 3-[4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[2-(3,6-dihydro-4-phenyl-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 3-[4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[2-(3,6-dihydro-4-(2-thienyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 3-[4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[2-(3,6-dihydro-4-(2-pyridinyl)-1(2H)-pyridinyl)ethyl]cyclohexyl]-1H-indole;
Trans 5-methoxy-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 5-methoxy-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Trans 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Cis 5-fluoro-3-[4-[2-[4-(2-pyridinyl)-1-piperazinyl]ethyl]cyclohexyl]-1H-indole;
Trans 3-[4-[4-(2-pyridinyl)-1-piperazinylmethyl]cyclohexyl]-1H-indole;
Cis 3-[4-[4-(2-pyridinyl)-1-piperazinyl-methyl]cyclohexyl]-1H-indole;
3-[4-[2-[4-[(2-Pyridinyl)-1-piperazinyl]-ethyl]cyclohexen-1-yl]-1H-indole;
Trans 3-[4-[2-[4-((2-pyridinyl)-1-piperazinyl)ethyl]cyclohexyl]-1H-indol-5-ol;
Cis 3-[4-[2-[4-((2-pyridinyl)-1-piperazinyl)ethyl]cyclohexyl]-1H-indol-5-ol;
Trans 1-methyl-3-[4-[2-[4-((2-pyridinyl)-1-piperazinyl)ethyl]cyclohexyl]-1H-indole; and
Cis 1-methyl-3-[4-[2-[4-((2-pyridinyl)-1-piperazinyl)ethyl]cyclohexyl]-1H-indole.

5. A method of treating psychoses, depression, hypertension, galactorrhea, amenorrhea, menstrual disorders, sexual dysfunction, Parkinson's disease, or Huntington's chorea comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

6. A method of treating schizophrenia comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

7. A method of treating depression comprising administering to a host suffering therefrom a therapeutic effective amount of a compound according to Claim 1 in unit dosage form.

8. A pharmaceutical composition adapted for administration as a dopaminergic, antipsychotic, antihypertensive, or antidepressant agent comprising a therapeutic effective amount of a compound according to Claim 1 in admixture with a
9. A method for the preparation of a compound of Formula Ia-1

wherein R is

\[ -N-R^4 \quad \text{or} \quad -N-R^4 \]

wherein R^4 is aryl, unsubstituted or substituted by one to four substituents selected from

- lower alkyl,
- lower alkoxy,
- lower thioalkoxy,
- hydroxy,
- lower acyloxy,
- amino,
- \(-\text{NH-}C-R^5\), wherein R^5 is
  - lower alkyl,
  - halogen, or
  - trifluoromethyl,

2-, 3-, or 4-pyridiny1, unsubstituted or substituted by

- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,
lower alkoxy,
amino, or

\[ \text{NH-C-R}^2 \text{, wherein R}^2 \text{ is as defined above,} \]

2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,

lower alkoxy,
amino, or

\[ \text{NH-C-R}^5 \text{, wherein R}^5 \text{ is as defined above,} \]

2-pyrazinyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,

lower alkoxy,
amino, or

\[ \text{NH-C-R}^5 \text{, wherein R}^5 \text{ is as defined above,} \]

2- or 3-furanyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
-NH-C-R^5$, wherein R^5 is as defined above,

2-, or 3-thienyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-O-
-NH-C-R^5$, wherein R^5 is as defined above,

2-, 4-, or 5-imidazolyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-O-
-NH-C-R^5$, wherein R^5 is as defined above,

2-, 4-, or 5-thiazolyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

-O-
-NH-C-R^5$, wherein R^5 is as defined above, or
2-, 3-, 4-, 5-, 6-, or 7-indolyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{N} \]

\[-\text{NH-C-R}^5, \text{wherein R}^5 \text{ is as defined above;} \]

\[ \text{R}^1 \text{ is hydrogen,} \]

\[-\text{CN, or} \]

\[-\text{CO}_2\text{H;} \]

\[ \text{R}^3 \text{ is hydrogen, halogen,} \]

\[ \text{hydroxyl,} \]

\[ \text{lower alkoxy, lower alkyl,} \]

\[ \text{O} \]

\[-\text{C-OR}^6, \text{wherein R}^6 \text{ is hydrogen or lower} \]

\[ \text{alkyl,} \]

\[ \text{O} \]

\[-\text{NH-C-R}^7, \text{wherein R}^7 \text{ is hydrogen,} \]

\[ \text{lower alkyl,} \]

\[ \text{cycloalkyl, or} \]

\[ \text{aryl, unsubstituted or substituted by} \]

\[ \text{one to four substituents selected from} \]

\[ \text{lower alkyl,} \]

\[ \text{lower alkoxy,} \]

\[ \text{lower thioalkoxy,} \]

\[ \text{hydroxy,} \]

\[ \text{lower acyloxy,} \]

\[ \text{amino,} \]
-62-

\[ \text{N} - \text{NH-C-R}^{5}, \text{wherein R}^{5} \text{ is as defined above,} \]

halogen, or trifluoromethyl,

\[ \text{S} - \text{NH-S-R}^{8} \text{ wherein R}^{8} \text{ is} \]

lower alkyl,
cycloalkyl or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
amino,

\[ \text{N} - \text{NH-C-R}^{5}, \text{wherein R}^{5} \text{ is as defined above,} \]

halogen, or trifluoromethyl, or

\[ \text{NH}_{2} \]

n is zero or an integer of 1; and corresponding geometric isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof comprises a compound of Formula II
wherein R, R¹, R³, and n are as defined above with a hydride reagent in the presence of a solvent to afford a compound of Formula Ia-1 and, if desired, converting a compound of Formula Ia-1 to a corresponding pharmaceutically acceptable acid or base addition salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable acid or base addition salt to a compound of Formula Ia-1 by conventional means.

10. A method for the preparation of a compound of Formula Ic

wherein R is

\[ -N\bigg\{\bigg\{N-R^4\bigg\} or \bigg\{N-R^4\bigg\} \]
wherein $R^4$ is aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy, amino, 

\[ \text{O} \quad \text{II} \quad -\text{NH-C-R}^5, \text{ wherein } R^5 \text{ is} \]

lower alkyl, halogen, or trifluoromethyl,

2-, 3-, or 4-pyridinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy,

25 amino, or 

\[ \text{O} \quad \text{II} \quad -\text{NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above}, \]

2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or 

\[ \text{O} \quad \text{II} \quad -\text{NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above}, \]
40  2-pyrazinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{or} \]

\[ -\text{NH} - \text{C} - R^5, \text{wherein R}^5 \text{ is as defined above,} \]

50  2- or 3-furanyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{or} \]

\[ -\text{NH} - \text{C} - R^5, \text{wherein R}^5 \text{ is as defined above,} \]

60  2-, or 3-thienyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or

\[ \text{or} \]

\[ -\text{NH} - \text{C} - R^5, \text{wherein R}^5 \text{ is as defined above,} \]

65  2-, 4-, or 5-imidazolyl, unsubstituted or substituted by halogen,
5 lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
aminoo, or

\[ \mathrm{O} \]
\[ \text{\(-\text{NH}\-\text{C\-R}^5,\)} \]
wherein \( R^5 \) is as defined above,
2-, 4-, or 5-thiazolyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
aminoo, or

\[ \mathrm{O} \]
\[ \text{\(-\text{NH\-C\-R}^5,\)} \]
wherein \( R^5 \) is as defined above, or
2-, 3-, 4-, 5-, 6-, or 7-indolyl,
unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,

\[ \text{\(-\text{NH\-C\-R}^5,\)} \]
wherein \( R^5 \) is as defined above;

\[ R^1 \text{ is hydrogen,} \]
\[ \text{-CN, or} \]
\[ \text{-CO}_2\text{H;} \]

\[ R^3 \text{ is hydrogen,} \]
halogen,
hydroxyl,
lower alkoxy,
lower alkyl,
\(-C\text{-OR}^6\), wherein \(R^6\) is hydrogen or lower alkyl,
\(-\text{NH-C-R}^7\), wherein \(R^7\) is hydrogen, lower alkyl, cycloalkyl, or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy, amino,
\(-\text{NH-C-R}^5\), wherein \(R^5\) is as defined above, halogen, or trifluoromethyl,
\(-\text{NH-S-R}^8\) wherein \(R^8\) is lower alkyl, cycloalkyl or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy,
lower acyloxy, amino,
\[ \text{O} \quad \text{II} \quad \text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above}, \]
halogen, or trifluoromethyl, or
\[ \text{NH}_2; \]
n is zero or an integer of 1, 2, or 3; or a pharmacologically acceptable acid or base addition salt thereof comprises reacting a compound of Formula VIII

\[ \text{VIII} \]

wherein \( R^1 \) and \( R^2 \) are as defined above with a compound of Formula XI

\[ \text{XI} \]

wherein R and n are as defined above in the presence of a base and a solvent to afford a compound of Formula Ic and, if desired, converting a compound of Formula Ic to a corresponding pharmacologically acceptable acid or base addition salt by conventional means and, if
so desired, converting the corresponding 
pharmaceutically acceptable acid or base addition 
salt to a compound of Formula Ic by conventional 
means.

11. A method for the preparation of a compound of 
Formula Id

\[ \text{Id} \]

wherein \( R^4 \) is aryl, unsubstituted or substituted 
by one to four substituents selected from 
- lower alkyl, 
- lower alkoxy, 
- lower thioalkoxy, 
- hydroxy, 
- lower acyloxy, 
- amino, 
- \(-\text{NH-C-R}^5, \) wherein \( R^5 \) is 
  - lower alkyl, 
  - halogen, or 
  - trifluoromethyl, 
- 2-, 3-, or 4-pyridinyl, unsubstituted or 
substituted by 
- halogen, 
- lower alkyl, 
- hydroxy, 
- lower acyloxy, 
- lower alkoxy,
amino, or

\[-\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above,}\]

2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,

amino, or

\[-\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above,}\]

2-pyrazinyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,

amino, or

\[-\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above,}\]

2- or 3-furanyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,

amino, or
-NH-C-R⁵, wherein R⁵ is as defined above,

2-, or 3-thienyl, unsubstituted or substituted by
- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,
- lower alkoxy,
- amino, or

-NH-C-R⁵, wherein R⁵ is as defined above,

2-, 4-, or 5-imidazolyl, unsubstituted or substituted by
- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,
- lower alkoxy,
- amino, or

-NH-C-R⁵, wherein R⁵ is as defined above,

2-, 4-, or 5-thiazolyl, unsubstituted or substituted by
- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,
- lower alkoxy,
- amino, or
\[ -\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above, or} \]
\[ 2-, 3-, 4-, 5-, 6-, \text{or } 7\text{-indolyl,} \]
unsubstituted or substituted by

- halogen,
- lower alkyl,
- hydroxy,
- lower acyloxy,
- lower alkoxy,
- amino, or

\[ -\text{NH-C-R}^5, \text{wherein } R^5 \text{ is as defined above;} \]

\[ R^1 \text{ is hydrogen,} \]
\[ -\text{CN}, \text{or} \]
\[ -\text{CO}_2\text{H;} \]

\[ R^3 \text{ is hydrogen,} \]
\[ \text{halogen,} \]
\[ \text{hydroxyl,} \]
\[ \text{lower alkoxy,} \]
\[ \text{lower alkyl,} \]
\[ -\text{C-OR}^6, \text{wherein } R^6 \text{ is hydrogen or lower alkyl,} \]
\[ -\text{NH-C-R}^7, \text{wherein } R^7 \text{ is} \]
\[ \text{hydrogen,} \]
\[ \text{lower alkyl,} \]
\[ \text{cycloalkyl, or} \]
\[ \text{aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy,} \]
hydroxy,
lower acyloxy,
amino,
-\(\text{NH}-\text{C}-\text{R}^5\), wherein \(\text{R}^5\) is as defined above,
halogen, or
trifluoromethyl,
-\(\text{NH}-\text{S}-\text{R}^8\) wherein \(\text{R}^8\) is
lower alkyl,
cycloalkyl or
aryl, unsubstituted or substituted by one to four substituents selected from
lower alkyl,
lower alkoxy,
lower thioalkoxy,
hydroxy,
lower acyloxy,
amino,
-\(\text{NH}-\text{C}-\text{R}^5\), wherein \(\text{R}^5\) is as defined above,
halogen, or
trifluoromethyl, or
-\(\text{NH}_2\);
n is zero or an integer of 1, 2, or 3; and corresponding geometric isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof comprises reacting a compound of Formula Ic-1
Ic-1

wherein R^4, R^1, R^3, and n are as defined above with hydrogen in the presence of a catalyst and a solvent to afford a compound of Formula Ic and, if desired, converting a compound of Formula Ic to a corresponding pharmaceutically acceptable acid or base addition salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable acid or base addition salt to a compound of Formula Ic by conventional means.

12. A method for the preparation of a compound of Formula Ik

Ik

wherein R is

- N-N-R^4 or - N-R^4
wherein R⁴ is aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy, amino, 0 \| -NH-C-R⁵, wherein R⁵ is lower alkyl, halogen, or trifluoromethyl, 2-, 3-, or 4-pyridinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or 0 \| -NH-C-R⁵, wherein R⁵ is as defined above, 2-, 4-, or 5-pyrimidinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or 0 \| -NH-C-R⁵, wherein R⁵ is as defined above,
2-pyrazinyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{O} \]
\[ \text{NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,} \]
2- or 3-furanyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{O} \]
\[ \text{NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,} \]
2-, or 3-thienyl, unsubstituted or substituted by halogen, lower alkyl, hydroxy, lower acyloxy, lower alkoxy, amino, or
\[ \text{O} \]
\[ \text{NH-C-R}^5, \text{ wherein } R^5 \text{ is as defined above,} \]
2-, 4-, or 5-imidazoly1, unsubstituted or substituted by halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

\[
\text{-NH-C-R^5, wherein } R^5 \text{ is as defined above,}
\]
2-, 4-, or 5-thiazolyl, unsubstituted or substituted by

halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

\[
\text{-NH-C-R^5, wherein } R^5 \text{ is as defined above, or}
\]
2-, 3-, 4-, 5-, 6-, or 7-indolyl,
unsubstituted or substituted by
halogen,
lower alkyl,
hydroxy,
lower acyloxy,
lower alkoxy,
amino, or

\[
\text{-NH-C-R^5, wherein } R^5 \text{ is as defined above;}
\]

\[ R^1 \text{ is hydrogen,} \]
-\[ \text{CN, or} \]
-\[ \text{-CO}_2\text{H;} \]
\[ R^{2a} \text{ is lower alkyl, or} \]
cycloalkyl;
R³ is hydrogen, halogen, hydroxyl, lower alkoxy, lower alkyl,

-C-OR⁶, wherein R⁶ is hydrogen or lower alkyl,

-NH-C-R⁷, wherein R⁷ is hydrogen, lower alkyl, cycloalkyl, or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy, lower thioalkoxy, hydroxy, lower acyloxy, amino,

-NH-C-R⁵, wherein R⁵ is as defined above, halogen, or trifluoromethyl,

-NH-S-R⁸, wherein R⁸ is lower alkyl, cycloalkyl or aryl, unsubstituted or substituted by one to four substituents selected from lower alkyl, lower alkoxy,
145 lower thialkoxy, hydroxy, lower acyloxy, amino, 
\[ \text{O} \]
150 \[-\text{NH-C-R}^5, \text{wherein R}^5 \text{ is as defined above, halogen, or} \]
\[-\text{NH}_2; \]
155 \[\text{n is zero or an integer of 1, 2, or 3; } \text{---- is a single or double bond; and corresponding geometric isomers thereof; or a pharmaceutically acceptable acid or base addition salt thereof comprises reacting a compound of Formula Ij} \]

\[
\begin{array}{c}
\text{R}^3 \\
\text{N} \\
\text{H} \\
\end{array}
\]
160 \[\text{Ij} \]

wherein \( \text{R} \), \( \text{R}^1 \), \( \text{R}^3 \), \( \text{n} \) and \( \text{----} \) are as defined above with a compound of Formula B

\[ \text{R}^{2a}X \]
165 \[\text{B} \]

wherein \( \text{X} \) is a halogen or a leaving group and \( \text{R}^{2a} \) is as defined above in the presence of a base and a solvent to afford a compound of Formula Ik and, if desired, converting a compound of Formula Ik
to a corresponding pharmaceutically acceptable acid or base addition salt by conventional means and, if so desired, converting the corresponding pharmaceutically acceptable acid or base addition salt to a compound of Formula I(k) by conventional means.
**INTERNATIONAL SEARCH REPORT**

**Classification of Subject Matter**
According to International Patent Classification (IPC) or to both National Classification and IPC

<table>
<thead>
<tr>
<th>Int.Cl.5</th>
<th>C 07 D 401/12</th>
<th>C 07 D 409/14</th>
<th>C 07 D 401/14</th>
</tr>
</thead>
<tbody>
<tr>
<td>A 61 K</td>
<td>31/40</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Fields Searched**

Minimum Documentation Searched

<table>
<thead>
<tr>
<th>Classification System</th>
<th>C 07 D 401/00</th>
<th>C 07 D 409/00</th>
</tr>
</thead>
</table>

Documentation Searched other than Minimum Documentation to the extent that such Documents are Included in the Fields Searched

**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</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>EP, A, 0345808 (BRISTOL-MYERS CO.) 13 December 1989, see example 23; page 8, lines 39-50 (cited in the application)</td>
<td>1, 8</td>
</tr>
<tr>
<td>A</td>
<td>EP, A, 0387603 (MERCK PATENT GmbH) 19 September 1990, see claim 1; page 11, lines 25-30</td>
<td>1, 8</td>
</tr>
<tr>
<td>A</td>
<td>EP, A, 0121716 (MERCK PATENT GmbH) 17 October 1984, see claim 1; page 24, lines 9-24</td>
<td>1, 8</td>
</tr>
</tbody>
</table>

**Certification**

Date of the Actual Completion of the International Search: 15-05-1992

Date of Mailing of this International Search Report: 24. 06. 92

International Searching Authority: EUROPEAN PATENT OFFICE

Signature of Authorized Officer: Nicole De Bie
V. [ ] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE 1

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [ ] Claim numbers because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 5-7 are directed to a method of treatment of (diagnostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers 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. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 8.4(e).

VI. [ ] OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING 2

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 of the international application

2. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims of the international application for which fees were paid, specifically claims:

3. [ ] 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 claim numbers:

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

Remark on Protest

[ ] The additional search fees were accompanied by applicant’s protest.
[ ] No protest accompanied the payment of additional search fees.
ANNEX TO THE INTERNATIONAL SEARCH REPORT
ON INTERNATIONAL PATENT APPLICATION NO. US 9200162
SA 56994

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 09/06/92. The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

<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-A- 3628289</td>
<td>14-12-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-A- 2085277</td>
<td>26-03-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU-A- 5116290</td>
<td>13-09-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA-A- 2011834</td>
<td>11-09-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-A- 2273672</td>
<td>08-11-90</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU-B- 564182</td>
<td>06-08-87</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AU-A- 2476284</td>
<td>13-09-84</td>
</tr>
<tr>
<td></td>
<td></td>
<td>CA-A- 1259999</td>
<td>26-09-89</td>
</tr>
<tr>
<td></td>
<td></td>
<td>DE-A- 3468026</td>
<td>21-01-88</td>
</tr>
<tr>
<td></td>
<td></td>
<td>JP-A- 59170090</td>
<td>26-09-84</td>
</tr>
</tbody>
</table>

For more details about this annex: see Official Journal of the European Patent Office, No. 12/82.