A compound of general formula (I) wherein A is hydrocarbon containing 2-6 C-atoms; R₂ is (a) wherein R₁, R₄, R₅, R₆ and R₇ are H, halogen, alkyl, cycloalkyl, cyano, nitro or perhalomethyl; or R₁ is (b) wherein R₄, R₅, R₁₀ and R₁¹ are H, halogen, alkyl, cycloalkyl, cyano, nitro or perhalomethyl; or R₁ represents phenyl optionally substituted, or R₁ is naphthyl, azanaphthyl or diazanaphthyl either of which may be substituted; B is O, S or NH; W is N or CH; X is CH or N; R₂ is a sporanen® or pharmaceutically acceptable salts thereof are useful in the treatment of indications related to the CNS-system, cardiovascular system or gastrointestinal disorders.
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Psoralen Derivatives, their Preparation and Use

The present invention relates to novel compounds which are useful for treating CNS-system, cardiovascular system and/or gastrointestinal disorders, methods for preparing such compounds and pharmaceutical compositions containing them.

Much evidence has accumulated to suggest that neuroleptics exert their antipsychotic action by blocking dopamine (DA) receptors in the brain. In recent years, it has become clear that some neuroleptics (e.g. clozapine) show an atypical profile: the compounds are not only beneficial in treating patients, who respond poorly to classical neuroleptic therapy, but the compounds are also relatively devoid of extrapyramidal side effects (EPS) commonly seen with classical neuroleptics (Ereshefsky et al., Clin. Pharm. 8, 691-709, 1989). In this respect it has been speculated that atypical neuroleptics are working mainly by blocking so called A10 mesolimbic DA systems (areas which are thought to be affected in psychosis), while the side effects of classical neuroleptics are produced by blockade of DA receptors in the motor areas of the brain (A9 DA system (Gudelsky, Psychopharmacology (Berl) 99: S13-S17, 1989)). The antipsychotic effect of clozapine and related compounds might be due to its blockade of not only DA-receptors (D-1, D-2, D-3, D-4, D-5) but also 5HT-receptor subtypes (5HT_{2^*}, 5HT_{3^*}, 5HT_{1C^*}, 5HT_{1A^*}), NA-α₁-receptors, histamine and possibly other receptors.

Furthermore, 5HT_{2^*}-blockade may also be important (Meltzer, Schiz. Bull. 17: 263-87, 1991) to counteract the so called negative symptoms of psychosis (delusions and social withdrawal) which are otherwise difficult to treat
with conventional neuroleptics.

Compounds reducing 5-HT neurotransmission have been suggested to be useful for the treatment of various neurological and psychiatric diseases.

More specifically, the present invention relates to novel compounds of the general formula (I):

\[
R^1 - X - N - A - O - R^2
\]

wherein \( A \) is a saturated or unsaturated, straight or branched hydrocarbon containing from 2 to 6 carbon atoms;

\( R^1 \) is

\[
\begin{array}{c}
\includegraphics{structure1.png}
\end{array}
\]

wherein \( R^3, R^4, R^5, R^6 \) and \( R^7 \) independently are hydrogen, halogen, \( C_{1-6}\)-alkyl, \( C_{3-8}\)-cycloalkyl, cyano, nitro or perhalomethyl; or \( R^1 \) is

\[
\begin{array}{c}
\includegraphics{structure2.png}
\end{array}
\]

wherein \( R^8, R^9, R^{10} \) and \( R^{11} \) independently are hydrogen, halogen, \( C_{1-6}\)-alkyl, \( C_{3-8}\)-cycloalkyl, cyano, nitro and perhalomethyl; or
R¹ is phenyl, pyridyl, pyrimidyl or pyrazyl optionally mono- or disubstituted with C₁₋₆-alkoxy, halogen, cyano, nitro, acetyl or perhalomethyl, or R¹ is 1-naphthyl, 2-naphthyl, azanaphthyl or diazanaphthyl, either of which may be substituted with C₁₋₆-alkyl, C₃₋₆-cycloalkyl, C₁₋₆-alkoxy, halogen, cyano, nitro or perhalomethyl;

B is O, S or NH;

W is N or CH;

X is CH or N;

R² is a group

wherein R₁₂, R₁₃, R₁₄, R₁₅ and R₁₆ independently are hydrogen, halogen, C₁₋₆-alkyl, cyano, nitro or perhalomethyl.

Physiologically and pharmaceutically acceptable salts of the compounds of the invention include acid addition salts formed with inorganic or organic acids, for example hydrochlorides, hydrobromides, sulphates, nitrates, oxalates, phosphates, tartrates, citrates, fumarates, maleates, succinates, and sulphonates e.g. mesylates. If desirable, selected salts may be subjected to further purification by recrystallization.
The invention includes within its scope all optical isomers of compounds of the general formula I and their mixtures including racemic mixtures thereof.

The term "saturated or unsaturated, straight or branched hydrocarbon containing 2-6 carbon atoms" denotes straight or branched acyclic hydrocarbons of 2-6 carbon atoms having no double or triple bonds or one or more double bonds or one or more triple bonds, e.g. ethyl, propyl, isopropyl, tert. butyl, n-pentyl, n-hexyl, vinyl, allyl, isopropenyl, 2-propynyl, 2-butenyl, 2-pentenyl.

The term "alkoxy" as used herein, alone or in combination, refers to a monovalent substituent comprising a C_{1-6}-alkyl group linked through an ether oxygen having its free valence bond from the ether oxygen, e.g. methoxy, ethoxy, propoxy, butoxy, pentoxy.

The term "C_{1-6}-alkyl" as used herein, alone or in combination, refers to a straight or branched, saturated hydrocarbon chain having 1-6 carbon atoms such as methyl, ethyl, n-propyl, isopropyl, n-butyl, tert.butyl, n-pentyl, neopentyl, n-hexyl and 2,2-dimethylpropyl.

The term "C_{3-8}-cycloalkyl" as used herein denotes a saturated monocyclic hydrocarbon having 3-8 carbon atoms such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclooctyl.

The term "halogen" means fluorine, chlorine, bromine and iodine, preferably fluorine.

The term "perhalomethyl" means -CF₃, -CCl₃, -CBr₃ and -Cl₃.

Preferred compounds of the invention are:

9-(3-(4-(2-Chlorophenyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(1-Naphthyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)propoxy)psoralen,
9-(3-(4-(2-Pyridyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(4-Fluorobenzoyl)piperidino)propoxy)psoralen,
9-(3-(4-(4-Chlorophenyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(4-Acetylphenyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(3,4-Dichlorophenyl)piperazin-1-yl)propoxy)psoralen,
9-(3-(4-(8-Quinolinyl)piperazin-1-yl)propoxy)psoralen,
9-(4-(4-(4-Fluorobenzoyl)piperidino)butyloxy)psoralen,

9-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyloxy)psoralen,
9-(4-(4-Fluorobenzoyl)piperidino)butyloxy)-6,7-dihydropсорален,
9-(2-(4-(4-Fluorobenzoyl)piperidino)ethoxy)psoralen,
9-(2-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)ethoxy)psoralen,
9-(2-(4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl)ethoxy)psoralen,

5-Chloro-9-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)-psoralen,
5-Bromo-9-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)psoralen,
9-(2-(4-(2-Pyrimidyl)piperazin-1-yl)ethoxy)psoralen,
9-(2-(4-(2-Pyridyl)piperazin-1-yl)-ethoxy)psoralen,

9-(2-(4-(2-Chlorophenyl)piperazin-1-yl)ethoxy)psoralen,
9-{3-[4-(6-Fluoro-1H-indazol-3-yl)piperdin-1-yl]propoxy}psoralen

or pharmaceutically acceptable acid addition salts of these compounds.

The compounds of this invention demonstrate high affinity for various receptor subtypes including the 5HT2, the NA-α1, the dopamine D1- and D2- receptors or a combination of these.

Accordingly, in another aspect the invention relates to a compound of the general formula (I) or a pharmaceutically acceptable acid addition salt thereof for use as a therapeutically acceptable substance, preferably for use as a therapeutically acceptable substance in the treatment of CNS-system
disorders, cardiovascular disorders or gastrointestinal disorders.

Furthermore, the invention also relates to the use of the inventive compounds of formula (I) as medicaments useful for treating CNS-system, cardiovascular system and gastrointestinal disorders, such as treatment of anxiety, sleep disorders, depression, psychosis, schizophrenia, migraine, ischemic neuronal damage, asthma, hypertension, urticaria, analgesia and emesis.

The compound of this invention and physiologically acceptable salts thereof may be prepared by a variety of synthetic routes, which includes reacting a compound of formula (V)

\[
\begin{align*}
\text{R} & - \text{X} \\
& \text{NH} \\
\end{align*}
\]

(V)

wherein \( R^1 \) and \( X \) have the meanings set forth above, with a compound of formula (VI)

\[
\text{Y-A-O-R}^2
\]

(VI)

wherein \( A \) and \( R^2 \) have the meanings set forth above and \( Y \) is a suitable leaving group such as halogen, tosylate or mesylate.

A compound of formula VI can be synthesized by a procedure described in C. Antonello et al: II Farmaco-Ed. Sci. 34, 193 (1979).

Compounds of the formula (I), wherein \( R^2 \) is either the group (III) or the group (IV) can be prepared by catalytic reduction of compounds of the
formula (I), wherein R² is the group (II), or by reduction of a compound of
the formula (VI) wherein R² is the group (II), or by catalytical reduction of 9-
methoxypsoralen, followed by demethylation and reaction with a compound
of formula Y-A-Y, wherein Y and A have the meaning set forth above, by a
procedure described in C. Antonello et al: II Farmaco, Ed.Sci. 34, 193
(1979).

In yet another aspect, the invention relates to a method of preparing the
compounds of formula (I) as described above.

Compounds of the general formula I were tested for binding to various CNS
receptor subtypes.

Detailed conditions for the in vitro assays are described below:

IN-VITRO inhibition of DOPAMINE D2 receptor binding.

Method description

Principle:

Radioactive-labelled ligand ³H-Spiroperidol is incubated with isolated cell-
membrane fragments at 37°C for a given period of time. Following complet-
ed incubation, the incubate is filtered through GF/B filters which are rinsed
following filtration to remove unspecifically adhered radioactivity. As
opposed to low-molecular compounds, membrane fragments are not rinsed
through the filters, the radioactivity bound to the filters is indicative of the
amount of ligand bound specifically as well as nonspecifically to the mem-
branes.

Tissue preparation:

The procedure is performed in ice bath. Polytron kinematica is rinsed with
milli-Q-H₂O before and after use. Male Wistar rats, 150-200 g are decapitated, striatum is removed quickly and weighed (approx. 50 mg). Striatum is transferred to a centrifuging vial containing 10 ml ice-cold D2 buffer. Homogenization is performed applying polytron kinematica (homogenizer) setting 6 for 20 sec. The homogenizer is rinsed with 10 ml D2 buffer in another centrifuging vial. The 10 ml rinsing buffer is added to the tissue vial. Centrifugation at 18,000 rpm for 10 min. at 4°C. Final pellet is transferred to 1,000 x vol. of same buffer. (Ex. 50 mg striatum in 50 ml D2 buffer). Can be stored at 0°C for at least 4 hours. Note that the tissue must be monogeneous (uniform) before use. If not, brief homogenization is performed.

**Assay:**

2,500 µl tissue (homogeneous)

- 25 µl ³H-Spiroperidol (0.05 nM)
- 25 µl test substance/H₂O/blind (Domperidone 0.2 µM)

Incubation for 20 min. at 37°C - 10 min. on ice bath.

10 ml ice-cold 0.9% NaCl is added to the tubes and filtered through GF/B filters (use gloves). This procedure is repeated. The filters are placed in counting vials and 4 ml opti-flour is added (perform in fume cupboard, use gloves). Counting is performed at window 0-19 of the beta-counter (Pachard). Note that receptor box and lid are rinsed thoroughly in H₂O after use to avoid contamination. Further, the analytical site is cleaned carefully every day after use.

**Test substances:**

Dissolved in H₂O, EtOH, MeOH or DMSO and further diluted in H₂O. The D2 binding will stand concentrations of up to approx. 20% of these solvents without affecting the binding. Most stock solutions are stable at 4°C,
attention is, however, paid to any precipitation, change in colour etc. Test-substance dilutions are always made fresh every day. When weighing out test substances, it is attempted to weigh out approx. 1 mg of substance. Less than 0.8 mg must never be weighed out and only infrequently more than 2 mg (for economy reasons), dependent, however, on conc./assay.

Results:

The test value is given as IC₅₀, indicating the concentration inhibiting specific binding by 50%.

\[
\frac{\text{Conc.}}{100 - \text{"% Control"}} = \text{IC}_{50} \ (\text{nM})
\]

IN-VITRO inhibition of Alpha₁-receptor binding.

Method description

Principle:

Radioactive-labelled ligand ³H-Prazosin is incubated with isolated cell-membrane fragments at 25°C for a given period of time. Following completed incubation, the incubate is filtered through GF/B filters, which are rinsed following filtration to remove unspecifically adhered radioactivity. As opposed to low-molecular compounds, membrane fragments are not rinsed through the filters, the radioactivity bound to the filters indicates the amount of ligand bound specifically as well as nonspecifically to the membranes.
Tissue preparation:

The procedure is performed in ice bath. Polytron kinematica is rinsed with milli-Q-H₂O before and after use. Male Wistar rats, 150-200 g are decapitated, cortex is removed quickly and weighed (approx. 500 mg). Cortex is transferred to a centrifuging vial containing 10 ml ice-cold D2 buffer. Homogenization applying polytron kinematica (homogenizer) setting 6 for 20 sec. The homogenizer is rinsed with 10 ml D2 buffer in another centrifuging vial. The 10 ml rinsing buffer is added to the tissue vial. Centrifugation at 18,000 rpm for 12 min. at 4°C. This is repeated once. Final pellet is added to 400 x vol. of same buffer. (ex. 500 mg cortex in 200 ml D2 buffer). Can be stored for 30 min. at 0°C.

Assay:

2,000 μl tissue

  25 μl ³H-Prazosin (0.5 nM)
  25 μl test substance/H₂O/blind Phentolamine (10 μM)

Incubation for 30 min. at 25°C.

10 ml of ice-cold 0.9% NaCl is added to the tubes and filtered through GF/B filters (use gloves). This procedure is repeated. Filters are placed in counting vials and 4 ml opti-flour is added (perform in fume cupboard, use gloves). Counting is performed at window 0-19 of the beta-counter (Pachard). Note that receptor box and cover are rinsed thoroughly in H₂O after use to avoid contamination. Further, the analytical site is cleaned carefully every day after use.

Test substances:

Dissolved in H₂O, EtOH, MeOH or DMSO and further diluted in H₂O. The
binding will stand concentrations of up to approx. 5% of these solvents without affecting the binding. Most stock solutions are stable at 4°C. Attention is, however, paid to any precipitation, change in colour etc. Test-substance dilutions are always made fresh every day. When weighing out test substances, it is attempted to weigh out approx. 1 mg of substance. Less than 0.8 mg must never be weighed out and only infrequently more than 2 mg (for economy reasons), dependent, however, on conc./assay.

Results:

The test value is given as IC₅₀ indicating the concentration inhibiting specific binding by 50%.

\[
\frac{\text{Conc.}}{\frac{100}{1\text{ "}\%\text{ Control}} - 1} = IC_{50} \text{ (nM)}
\]

IN-VITRO inhibition of DOPAMINE D1 receptor binding.

Method description

Principle:

Radioactive-labelled ligand \(^3\text{H}\)-SCH 23390 is incubated with isolated cell-membrane fragments in incubation buffer at 30°C for a given period of time. Following completed incubation, the incubate is filtered through GF/B filters, which are rinsed following filtration to remove unspecifically adhered radioactivity. As opposed to low-molecular compounds, membrane fragments are not rinsed through the filters, the radioactivity bound to the filters indicates the amount of ligand bound specifically as well as nonspecifically
to the membranes.

**Tissue preparation:**

5 Male Wistar rats, 150-200 g are decapitated. Striatum is removed quickly, weighed (approx. 50 mg) and carefully homogenized in 100 x vol. of buffer I applying glass/teflon homogenizer 10 up/down strokes. Ex. 50 mg striatum is homogenized in 5,000 µl buffer I. The homogenate is centrifuged at 18,000 rpm for 20 min. at 4°C, and the supernate is decanted. This step is performed three times, and each time the pellet is resuspended and homogenized in 100 x vol. of buffer I. Following the third centrifugation, the pellet is suspended in 100 x vol. of resuspension buffer and homogenized. The tissue is now ready for use. The tissue is stable at 0°C for 8 hours.

15 **Assay:**

600 µl incubation buffer  
100 µl ³H-SCH 23390 (0.2 nM)  
100 µl tissue  
20 200 µl test substance/H₂O/blind (cis-flupentixol 2 µM)

Incubation for 60 min. at 30°C.

10 ml of ice-cold 0.9% NaCl is added to the tubes. Filtration is performed through GF/B filters (use gloves). This procedure is repeated. Filters are placed in counting vials and 4 ml opti-flour is added (perform in fume cupboard, use gloves) and counting is performed at window 0-19 of the beta-counter (Pachard). Note that receptor box and lid are rinsed thoroughly in H₂O after use to avoid contamination. Further, the analytical site is cleaned carefully every day after use.
**Test substances:**

Dissolved in H₂O, EtOH, MeOH or DMSO and further diluted in H₂O. The D1 binding will stand concentrations of up to approx. 20% of these solvents without affecting the binding. Most stock solutions are stable at 4°C. Attention should, however, be paid to any precipitation, change in colour etc. Test-substance dilutions are always made fresh every day. When weighing out test substances, it is attempted to weigh out approx. 1 mg of substance. Less than 0.8 mg must never be weighed out and only infrequently more than 2 mg (for economy reasons), dependent, however, on conc./assay.

**Results:**

The test value is given as IC₅₀ indicating the concentration inhibiting specific binding by 50%.

\[
\frac{\text{Conc.}}{100 - \% \text{ Control}} = \text{IC}_{50} \text{ (nM)}
\]

**IN VITRO inhibition of 5HT₂-receptor binding**

**Method description**

**Principle:**

Radioactive-labelled ligand ³H-Ketanserine is incubated with isolated cell membrane fragments at 37°C for a given period of time. Following completed incubation, the incubate is filtered through GF/B filters, which are rinsed
following filtration to remove unspecifically adhered radioactivity. As opposed to low-molecular compounds, membrane fragments are not rinsed through the filters, the radioactivity bound to the filters indicates the amount of ligand bound specifically as well as nonspecifically to the membranes.

**Tissue preparation:**

The preparation is made in ice bath. Polytron kinematica is rinsed with milli-Q-H$_2$O before and after use. Male Wistar rats, 150-200 g are decapitated. Frontal cortex is removed quickly and weighed (approx. 200 mg). Frontal cortex is added to centrifuging vial containing 10 ml ice-cold D2 buffer. Homogenization applying polytron kinematica (homogenizer) setting 6 for 20 sec. The homogenizer is rinsed with 10 ml D2 buffer in another centrifuging vial. Centrifuged at 18,000 rpm for 10 min. at 4°C. Final pellet is transferred to 125 x vol. of same buffer. (Ex 200 mg in 25 ml D2 buffer). Can be stored for approx. 30 min. at 0°C.

**Assay:**

1250 µl tissue

25 µl $^3$H-Ketanserine (0.4 nM)

25 µl test substance/H$_2$O/blind cyproheptadine (2 µM)

Incubation for 15 min. at 37°C.

10 ml ice-cold 0.9% NaCl is added to the tubes. Filtration is performed through GF/B filters (use gloves). This procedure is repeated. The filters are placed in counting vials and 4 ml opti-flour is added (prepare in fume cupboard, use gloves). Counting at window 0-19 of the beta-counter (Pachard). Note that receptor box and lid are rinsed thoroughly in H$_2$O after use to avoid contamination. Further, the analytical site is cleaned carefully every day.
Test substances:

Dissolved in H₂O, EtOH, MeOH or DMSO and further diluted in H₂O. The 5HT₂ binding will stand concentrations of up to approx. 5% of these solvents without affecting the binding. Most stock solutions are stable at 4°C. Attention should, however, be paid to any precipitation, change in colour etc. Test-substance dilutions are always made fresh every day. When weighing out test substances, it is attempted to weigh out approx. 1 mg of substance. Less than 0.8 mg must never be weighed out and only infrequently more than 2 mg (for economy reasons), dependent, however, on conc./assay.

Results:

The test value is given as IC₅₀ i.e. the concentration inhibiting specific binding by 50%.

\[
\begin{align*}
\text{Conc.} & = \text{IC}_{50} \text{ (nM)} \\
\frac{100}{\% \text{ Control}} - 1
\end{align*}
\]

The compounds of this invention typically binds to NA-α₁, 5HT₂, DA-D₁, and DA-D₂ receptors, with IC₅₀ values in the order of 0.1 nM to 1 μM. Furthermore the compounds are able to antagonize the acetic acid induced writhing in mice with ED₅₀-values typically in the order of 0.1 mg/kg to 100 mg/kg.

The compounds of the invention, together with a conventional adjuvant, carrier, or diluent, and if desired a pharmaceutically acceptable acid addition salt thereof, may be placed into the form of pharmaceutical composi-
tions and unit dosages thereof, and in such form may be employed as solids, such as tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use, in the form of suppositories for rectal administration; or in the form of sterile injectable solutions for parenteral (including subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective central nervous system ailment alleviating amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing one (1) milligram of active ingredient or, more broadly, one (1) to thirty (30) milligrams, per tablet, are accordingly suitable representative unit dosage forms.

The compounds of this invention can thus be used for the formulation of pharmaceutical preparations, e.g. for oral and parenteral administration to mammals including humans, in accordance with conventional methods of galenic pharmacy.

Conventional excipients are such pharmaceutically acceptable organic or inorganic carrier substances suitable for parenteral or oral application which do not deleteriously react with the active compound.

Examples of such carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, gelatine, lactose, amylose, magnesium stearate, talc, silicic acid, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, hydroxymethylcellulose and polyvinylpyrrolidone.

The pharmaceutical preparations can be sterilized and mixed, if desired, with auxiliary agents, such as lubricants, preservatives, stabilizers, wetting agents, emulsifiers, salt for influencing osmotic pressure, buffers and/or
colouring substances and the like, which do not deleteriously react with the active compounds.

For parenteral application, particularly suitable are injectable solutions or suspensions, preferably aqueous solutions with the active compound dissolved in polyhyroxylated castor oil.

Ampoules are convenient unit dosage forms.

For oral application, particularly suitable are tablets, dragees, or capsules having talc and/or a carbohydrate carrier or binder or the like, the carrier preferably being lactose and/or corn starch and/or potato starch. A syrup, elixir or like can be used when a sweetened vehicle can be employed. Generally, as to broader ranges, the compound of the invention is dispensed in unit dosage form comprising 0.05-100 mg in a pharmaceutically acceptable carrier per unit dosage.

A typical tablet which may be prepared by conventional tablettng techniques contains:

<table>
<thead>
<tr>
<th>Active compound</th>
<th>1.0 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lactosum</td>
<td>67.8 mg Ph.Eur.</td>
</tr>
<tr>
<td>Avicel®</td>
<td>31.4 mg</td>
</tr>
<tr>
<td>Amberlite®</td>
<td>1.0 mg</td>
</tr>
<tr>
<td>Magnesii stearas</td>
<td>0.25 mg Ph.Eur.</td>
</tr>
</tbody>
</table>

The following examples illustrate the specific methods employed in production of a representative number of compounds embraced by this invention.

The following examples illustrate the present invention:
EXAMPLE 1

9-(3-(4-(2-Chlorophenyl)piperazin-1-yl)propoxy)psoralen, HCl

1-(2-Chlorophenyl)piperazin (400 mg; 1.5 mmol), 9-(3-bromopropoxy)psoralen, and potassium carbonate (2.5 g) in acetone (25 ml) was refluxed for 16 h. The mixture was cooled to room temperature, filtered and concentrated in vacuo. The resulting oil was triturated with water and the resulting compound dissolved in ethanol. Addition of concentrated HCl precipitated the desired product as white crystals. Recrystallization from ethanol gave 0.54 g. M.p. 242-243°C. MS (70 eV): m/z 440 (M⁺, 8%), 438 (M⁺, 23%), 272 (18), 211 (33), 209 (100), 202 (10).

EXAMPLE 2

9-(3-(4-(1-Naphthyl)piperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(1-naphthyl)piperazin (0.32 g; 1.4 mmol) and 9-(3-bromopropoxy)psoralen (0.54 g; 1.68 mmol) using the procedure described in example 1 was prepared 0.5 g of the desired product. M.p. > 255°C. MS (70 eV): m/z 454 (M⁺, 37%), 299 (9), 272 (13), 225 (72), 182 (11), 154 (25), 98 (20), 70 (100).

EXAMPLE 3

9-(3-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)propoxy)psoralen, oxalate

Starting from 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride (440 mg, 2.0 mmol), 9-(3-bromopropoxy)psoralen (680 mg, 2.1 mmol) and potassium carbonate (500 mg, 2.1 mmol) using the procedure described in example 1 was prepared 700 mg of the title compound as the free base. This product was dissolved in acetone and oxalic acid (180 mg) in acetone
(2 ml) added to precipitate 700 mg desired product as white crystals. M.p.
161-163°C. MS (70 eV): m/z 462 (M⁺, 42), 324 (28), 233 (50), 190 (16), 122
(10), 96 (100).

EXAMPLE 4

9-(3-(4-(2-Pyridylpiperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(2-pyridyl)piperazin (250 mg, 1.55 mmol) and 9-(3-bromo-
propoxy)psoralen (520 mg, 1.6 mmol) using the procedure described in
example 1 was prepared 0.54 g of the title compound. M.p. > 230°C. MS
(70 eV): m/z 405 (M⁺, 2%), 311 (10), 298 (8), 286 (22), 202 (5), 185 (15),
107 (83), 70 (100).

EXAMPLE 5

9-(3-(4-(4-Fluorobenzoyl)piperidino)propoxy)psoralen, HCl

4-(4-Fluorobenzoyl)piperidine p-toluene sulfonate (1.15 g, 3 mmol) 9-(3-
bromopropoxy)psoralen (1.08 g, 3 mmol) and potassium carbonate (anhyd)
(2 g) was stirred in acetone (75 ml) for 10 days at room temperature and at
reflux for 3 h. The mixture was conc. in vacuo and then taken up in
water/ethyl acetate. The organic phase was dried over MgSO₄ and evapo-
rated. The resulting oil was taken up in ethanol and HCl ether added to
precipitate a white compound. Recrystallization from ethanol/methanol (3:1)
afforded 0.66 g of the title compound. M.p. 237-239° (dec.). MS (70 eV) 449
(M⁺, 12%), 298 (46), 286 (3), 220 (82), 123 (37), 70 (100).
EXAMPLE 6

9-(3-(4-(4-Chlorophenyl)piperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(4-Chlorophenyl)piperazin (0.4 g, 2 mmol) and 9-(3-bromo-proproxy)psoralen (0.68 g, 2.1 mmol) using the procedure described in example 1 was prepared 0.75 g of the title compound. M.p. 220-222°C. MS (70 eV): m/z 440 (M⁺, 10%), 438 (M⁺, 30%), 298 (7), 286 (3), 272 (19), 237 (2), 211 (32), 209 (98), 70 (100).

EXAMPLE 7

9-(3-(4-(4-Acetylphenyl)piperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(4-acetylphenyl)piperazin (0.4 g, 2 mmol) and 9-(3-bromoproproxy)psoralen (0.68 g, 2.1 mmol) using the procedure described in example 1 was prepared 0.45 g of the title compound. M.p. 213-215°C. MS (70 eV): m/z 446 (M⁺, 27%), 298 (8), 286 (3), 272 (13), 217 (100), 174 (15).

EXAMPLE 8

9-(3-(4-(3,4-Dichlorophenyl)piperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(3,4-dichlorophenyl)piperazin (0.46 g, 2 mmol) and 9-(3-bromoproproxy)psoralen (0.68 g, 2.1 mmol) using the procedure described in example 1 was prepared 0.9 g of the title compound. M.p. 210-212°C. MS (70 eV): m/z 474 (M⁺, 10%), 472 (M⁺, 15%), 298 (20), 286 (3), 272 (20), 245 (45), 243 (76), 70 (100).
EXAMPLE 9

9-(3-(4-(8-Quinolinyl)piperazin-1-yl)propoxy)psoralen, HCl

Starting from 1-(8-quinolinyl)piperazin (0.533 g, 2.5 mmol), 9-(3-bromo-propanoxy)psoralen (0.85 g, 2.63 mmol) and potassium carbonate (0.414 g, 3 mmol) using the procedure described in example 1 was prepared 0.6 g of the desired product. M.p. 250-251°C. MS (70 eV): m/z 455 (M⁺, 19%), 298 (12), 254 (3), 170 (27), 157 (63), 129 (35), 70 (100).

EXAMPLE 10

9-(4-(4-(4-Fluorobenzoyl)piperidino)butyloxy)psoralen, oxalate

4-(4-(Fluorobenzoyl)piperidine, p-toluene sulfonate (0.75 g, 2.0 mmol), 9-(3-bromompropoxy)psoralen (0.71 g, 2.1 mmol) and potassium carbonate (0.6 g, 4.2 mmol) in dry DMF (10 ml) was stirred at 70°C for 16 h and then taken up in water at ethyl acetate. The organic phase was washed with saturated sodium chloride, dried over magnesium sulfate and concentrated in vacuo. The resulting oil was purified by column chromatography (silica gel 60, eluted with ethyl acetate, methanol; 4:1 (v/v)). The product was dissolved in acetone (5 ml) and oxalic acid (150 mg) in 2 ml acetone added to give 320 mg of the title compound. M.p. 115-118°C. MS (70 eV): m/z 463 (M⁺, 1%), 220 (18), 202 (100), 174 (52).

EXAMPLE 11

9-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyloxy)psoralen, oxalate

Starting with 6-fluoro-3-(4-piperidinyl)-1,2-benzisoxazol, HCl (450 mg, 2.0 mmol), 9-(4-bromobutyl)psoralen (710 mg, 2.1 mmol) and potassium carbonate (600 mg, 4.2 mmol) in 10 ml dry DMF using the procedure
described in example 10, 0.36 g of the title compound was prepared. M.p. 127-131°C. MS (70 eV): m/z 476 (M⁺, 5%), 233 (8%), 202 (100), 174 (72%).

**EXAMPLE 12**

9-(4-(4-Fluorobenzoyl)piperidino)butyloxy)-6,7-dihydropsoralen, oxalate

9-(4-(4-(6-Fluo-1,2-benzisoxazol-3-yl)piperidino)butyloxy)psoralen of example 10 (240 mg, 0.52 mmol) was reduced catalytically in 50 ml abs. ethanol (2 atm., room temperature, 50 mg 10% Pd/C). The mixture was filtered and concentrated in vacuo. The product was dissolved in acetone (5 ml) and oxalic acid (25 mg) in 2 ml acetone added to give 42 mg of the title compound. M.p. 114-115°C. MS (70 eV): m/z 465 (M⁺, 3%), 220 (100).

**EXAMPLE 13**

9-(2-(4-(4-Fluorobenzoyl)piperidino)ethoxy)psoralen, oxalate

Starting from 4-(4-Fluorobenzoyl)piperidine, p-toluene sulfonate (330 mg, 1.5 mmol), 9-(2-bromoethoxy)psoralen (500 mg, 1.6 mmol) and potassium carbonate (220 mg, 1.6 mmol) using the procedure described in example 10, 300 mg of the title compound was prepared. M.p. 114-115°C. MS (70 eV): m/z 435 (M⁺, 5%), 284 (23), 234 (3), 220 (100), 202 (1), 123 (43).

**EXAMPLE 14**

9-(2-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)ethoxy)psoralen, oxalate

Starting with 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, HCl (450 mg, 2.0 mmol), 9-(2-bromoethoxy)psoralen (400 mg, 1.3 mmol) and potassium carbonate (180 mg, 1.3 mmol) in dry DMF (3 ml) using the procedure described in example 10, 280 mg of the title compound was prepared. M.p.
178-179°C. MS (70 eV) 448 (M⁺, 29%), 310 (18), 233 (76), 202 (6), 190 (19), 96 (100).

**EXAMPLE 15**

9-(2-(4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl)ethoxy)psoralen, oxalate

Starting from 1-(1,2-benzisothiazol-1-yl)piperazin (0.25 g, 1 mmol) and 9-(2-bromoethoxy)psoralen (0.36 g, 1.2 mmol) using the procedure described in example 10, 0.2 g of the desired product was prepared. M.p. 157-162°C. MS (70 eV): m/z 447 (M⁺, 7%), 432 (5), 246 (38), 232 (25), 202 (12), 177 (30), 56 (100).

**EXAMPLE 16**

5-Chloro-9-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)-psoralen, HCl

A. To 9-(4-Bromobutyloxy)psoralene (510 mg; 1.5 mmol) in 10 ml dry CH₂Cl₂, stirred at 0°C, was added dropwise Cl₂ (1.5 ml of a 1.2 M solution in CCl₄, 1.8 mM). The solution was stirred for additionally 30 min., washed with H₂O and saturated NaCl, dried over MgSO₄ and concentrated in vacuo to give 600 mg 5-chloro-9-(4-bromobutyloxy)psoralene as an oil, which was used in step B without further purification.

MS (70 eV): m/z 372 (M⁺, 10%), 370 (M⁺, 85%), 236 (86), 208 (40), 137 (100).

B. 4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride (640 mg, 2.5 mmol), 5-chloro-9-(4-bromobutyloxy)psoralene (550 mg, 1.5 mmol) and K₂Cl₃ (420 mg, 3 mmol) in 5 ml dry DMF was stirred at 90°C for 1.5 h. The mixture was cooled to room temperature and taken up in water and ether.
The organic phase was washed with water and saturated NaCl, dried over MgSO₄ and concentrated in vacuo to give 650 mg oil. The product was purified by column chromatography (silica gel 60, eluted with methylene chloride, methanol, 9:1 (v/v)). The resulting oil was crystallized by trituration with acetone and subsequently dissolved in 1 ml absolute ethanol. Addition of HCl in ether precipitated 350 mg of the title compound as white crystals. M.p. 138-140°C. MS (FAB): 511 (M⁺ 1).

EXAMPLE 17

5-Bromo-9-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)psoralen, HCl

A. To 9-(4-bromobutyloxy)psoralene (850 mg, 2.5 mmol) in 5 ml glacial acetic acid was added slowly Br₂ (480 mg, 3 mmol) dissolved in 3 ml glacial acetic acid. The mixture was stirred at room temperature for 1 h, neutralized by addition of 4N NaOH and extracted with ethyl acetate. The organic phase was washed with water and saturated NaCl, dried over MgSO₄ and concentrated in vacuo. The resulting crystals was washed with ether and ethyl acetate and dried to give 0.5 g of 5-bromo-9-(4-bromobutyloxy)psoralene. M.p. 101-102°C.

B. Starting from 4-(6-fluoro-1,2-benzisoxazol-3-yl)piperidine, hydrochloride (1.0 g, 4 mmol) and 5-bromo-9-(4-bromobutyloxy)psoralene (420 mg, 1 mmol) and potassium carbonate (140 mg, 1 mmol) using the procedure described in example 16 was prepared 370 mg of the title compound as white crystals. M.p. 181-182°C. MS (FAB): 255 (M+1).
EXAMPLE 18

9-[(2-(4-(2-Pyrimidyl)piperazin-1-yl)ethoxy)]psoralen, oxalate

Starting with 1-(2-pyrimidyl)piperazin, dihydrochloride (470 mg, 2.0 mmol), 9-(2-bromoethoxy)psoralene (310 mg, 1 mmol) and potassium carbonate (410 mg, 3 mmol) using the procedure described in example 10 was prepared 300 mg of the title compound as white crystals. M.p. 199-200°C. MS (70 eV): m/z 392 (M⁺, 18%), 284 (19), 272 (13), 191 (48), 177 (100).

EXAMPLE 19

9-[(2-(4-(2-Pyridyl)piperazin-1-yl)-ethoxy)]psoralen, HCl

Starting with 1-(2-pyridyl)piperazin, (250 mg, 1.5 mmol), 9-(2-bromoethoxy)psoralene (310 mg, 1 mmol) and potassium carbonate (410 mg, 3 mmol) in dry DMF using the procedure described in example 16 was prepared 250 mg of the title compound as white crystals. M.p. 213-213°C.

MS (70 eV): 391 (M⁺, 3%), 284 (10), 272 (7), 228 (18), 190 (100).

EXAMPLE 20

9-[(2-(4-(2-Chlorophenyl)piperazin-1-yl)ethoxy)]psoralen, hydrochloride

Starting with 9-(2-bromoethoxy)psoralene (0.3 g, 1 mmol), 1-(2-chlorophenyl)piperazin, hydrochloride and potassium carbonate in 50 ml acetone, using the procedure described in example 1 was prepared 140 mg of the title compound as white crystals. M.p. 137-138°C.
NMR (400 MHz, DMSO-d$_6$) $\delta$ (ppm): 3.3-3.5 (m, 6H); 3.7-3.8 (m, 4H); 4.85 (bs, 2H); 6.5 (d, J=9Hz, 1H); 7.10-7.5 (t, J=8Hz, 1H); 7.16 (bs, 1H); 7.25 (d, J=8Hz, 1H); 7.35 (t, J=8Hz, 1H); 7.46 (d, J=8Hz, 1H); 7.8 (s, 1H); 8.16 (s, 1H); 8.2 (d, J=9Hz, 1H); 11.25 (bs, 1H).

**EXAMPLE 21**

9-{3-[4-(6-Fluoro-1H-indazol-3-yl)-piperidin-1-yl]-propoxy}psoralen, dihydrochloride

Starting from 6-fluoro-3-(4-piperidinyl)-1H-indazole (270 mg; 1.23 mmol), 9-(3-bromopropoxy)psoralen (484.5 mg; 1.5 mmol) and potassium carbonate (500 mg; 2.66 mmol) using the procedure described in example 1 was prepared 150 mg (22.8%) of the title compound.

NMR DMSO-d$_6$ (ppm): 2.15 (br d, 2H), 2.32 (m, 5H), 3.18 (m, 2H), 3.37 (m, 2H), 3.62 (br. d, 2H), 4.5 (t, 2H), 6.45 (d, 1H), 6.98 (t, 1H), 7.15 (s, 1H), 7.30 (d, 1H), 7.78 (s, 1H), 7.98 (q, 1H), 8.15 (m, 2H), 10.9 (s, 1H), 13.0 (br., 1H).
CLAIMS

1. A compound of the general formula I

\[ R^1 - X - N - A - O - R^2 \]

wherein A is a saturated or unsaturated, straight or branched hydrocarbon containing 2-6 carbon atoms;

\[ R^1 \]

wherein \( R^3, R^4, R^5, R^6 \) and \( R^7 \) independently are hydrogen, halogen, \( C_{1-6} \)-alkyl, \( C_{3-8} \)-cycloalkyl, cyano, nitro or perhalomethyl; or \( R^1 \) is

\[ \]

wherein \( R^8, R^9, R^{10} \) and \( R^{11} \) independently are hydrogen, halogen, \( C_{1-6} \)-alkyl, \( C_{3-8} \)-cycloalkyl, cyano, nitro or perhalomethyl; or

\( R^1 \) represents phenyl, pyridyl, pyrimidyl or pyrazinyl optionally mono- or disubstituted with \( C_{1-6} \)-alkoxy, halogen, cyano, nitro or perhalomethyl, or

\( R^1 \) is 1-naphtyl, 2-naphtyl, azanaphtyl or diazanaphtyl either of which may be substituted with \( C_{1-6} \)-alkyl, \( C_{3-8} \)-cycloalkyl, \( C_{1-6} \)-alkoxy, halogen, cyano,
nitro, acetyl or perhalomethyl;

B is O, S or NH;

W is N or CH;

X is CH or N;

$R^2$ is a group

![Chemical Structures](image)

wherein $R_{12}$, $R_{13}$, $R_{14}$, $R_{15}$ and $R_{16}$ independently are hydrogen, halogen, C$_{1-6}$-alkyl, cyano, nitro and perhalomethyl;

or pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 which is

9-(3-(4-(2-Chlorophenyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(1-Naphthyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)propoxy)psoralen, oxalate

9-(3-(4-(2-Pyridyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(4-Fluorobenzoyl)piperidino)propoxy)psoralen, HCl

9-(3-(4-(4-Chlorobenzoyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(4-Acetylphenyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(3,4-Dichlorophenyl)piperazin-1-yl)propoxy)psoralen, HCl

9-(3-(4-(8-Quinolinyl)piperazin-1-yl)propoxy)psoralen, HCl
9-(4-(4-(4-Fluorobenzoyl)piperidino)butyloxy)psoralen, oxalate
9-(4-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)butyloxy)psoralen, oxalate
9-(4-(4-Fluorobenzoyl)piperidino)butyloxy)-6,7-dihydrosporalen, oxalate
9-(2-(4-(4-Fluorobenzoyl)piperidino)ethoxy)psoralen, oxalate
5
9-(2-(4-(6-Fluoro-1,2-benzisoxazol-3-yl)piperidino)ethoxy)psoralen, oxalate
9-(2-(4-(1,2-Benzisothiazol-3-yl)piperazin-1-yl)ethoxy)psoralen, oxalate
5-Chloro-9-(4-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)-psoralen, HCl
5-Bromo-9-(4-(6-fluoro-1,2-benzisoxazol-3-yl)-1-piperidyl)butyloxy)psoralen,
10 HCl
9-(2-(4-(2-Pyrimidyl)piperazin-1-yl)ethoxy)psoralen, oxalate
9-(2-(4-(2-Pyridyl)piperazin-1-yl)-ethoxy)psoralen, HCl
9-(2-(4-(2-Chlorophenyl)piperazin-1-yl)ethoxy)psoralen, hydrochloride
9-{3-[4-(6-Fluoro-1H-indazol-3-yl)piperidin-1-yl]propoxy}psoralen,
15 dihydrochloride.

3. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance.

20 4. A compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for use as a therapeutically acceptable substance in the treatment of CNS-system, cardiovascular system or gastrointestinal disorders.

25 5. A method of preparing compounds of formula I according to claim 1, which comprises

a) reacting a compound of formula (V)

\[
\begin{array}{c}
\text{R} \\
\text{X} \\
\text{NH}
\end{array}
\]

(V)
wherein $R^1$ and $X$ have the meanings set forth above, with a compound of formula (VI)

\[
Y-A-O-R^2
\]

wherein $A$ has the meaning set forth above and $Y$ is a suitable leaving group, to form a compound of formula I, wherein $R^2$ is a group (II),

\[
\begin{align*}
&\text{or} \\
b) \text{catalytical reduction of a compound of formula (I), wherein } R^2 \text{ is a group (II)} \\
&\text{to form a compound of formula I, wherein } R^2 \text{ is a group (III) or a group (IV)}
\end{align*}
\]
6. A pharmaceutical composition comprising a compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient.

7. A pharmaceutical composition suitable for the treatment of CNS-system, cardiovascular disorders or gastrointestinal disorders, which comprises a compound according to claim 1 or 2 or a pharmaceutically acceptable salt thereof and a therapeutically inert excipient, carrier or diluent.

8. Use of a compound of formula (I) according to claim 1 or 2 or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for the treatment of CNS-system disorders, cardiovascular disorders or gastrointestinal disorders.

9. A method of treating CNS-system disorders, cardiovascular disorders or gastrointestinal disorders in a subject in need thereof, which comprises the step of administering to the said subject an effective amount of a compound according to claim 1 or 2.

10. A method of treating CNS-system disorders, cardiovascular disorders or gastrointestinal disorders, in a subject in need thereof comprising administering a pharmaceutical composition according to claim 6.

11. A process for the manufacture of a medicament, particularly to be used in the treatment of CNS-system disorders, cardiovascular disorders or gastrointestinal disorders which process comprises bringing a compound of formula (I) according to claim 1 or 2 or a pharmaceutically acceptable salt thereof into a galenical dosage form.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

**IPC5:** C07D 493/04, A61K 31/37

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)

**IPC5:** C07D

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

SE, DK, FI, NO classes as above

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

**REG, MEDLINE, EMBASE**

**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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<tr>
<td>A</td>
<td>GB, A, 1024385 (CHEMETRON CORPORATION), 19 December 1962 (19.12.62), see the whole document</td>
<td>1-8,11</td>
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<tr>
<td>A</td>
<td>EP, A2, 0368388 (JANSSEN PHARMACEUTICA N.V.), 16 May 1990 (16.05.90), see the whole document</td>
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<tr>
<td>A</td>
<td>EP, A1, 0377528 (LIPHA, LYONNAISE INDUSTRIELLE PHARMACEUTIQUE), 11 July 1990 (11.07.90), see the whole document</td>
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Further documents are listed in the continuation of Box C.

See patent family annex.

* Special categories of cited documents:
  "A" document defining the general state of the art which is not considered to be of particular relevance
  "E" earlier document but published on or after the international filing date of the later one
  "L" later document published prior to the international filing date but later than the priority date claimed

**X** later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

**X** document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

**Y** document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

**&** document member of the same patent family

**Date of the actual completion of the international search:** 31 August, 1994

**Date of mailing of the international search report:** 08-09-1994

**Name and mailing address of the ISA/Swedish Patent Office**

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Form PCT/ISA/210 (second sheet) (July 1992)
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<td>A</td>
<td>EP, A1, 0402644 (HOECHST-ROUSSEL PHARMACEUTICALS INCORPORATED), 19 December 1990 (19.12.90), see the whole document</td>
<td>1-8,11</td>
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<td>EP, A1, 0428437 (ADIR ET COMPAGNIE), 22 May 1991 (22.05.91), see the whole document</td>
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<tr>
<td>A</td>
<td>US, A, 5015740 (LUDO E. J. KENNIS ET AL), 14 May 1991 (14.05.91), see the whole document</td>
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<td>Category</td>
<td>Citation of document, with indication, where appropriate, of the relevant passages</td>
<td>Relevant to claim No.</td>
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<td>Chemical Abstracts, Volume 103, No 5, 5 August 1985 (05.08.85), (Columbus, Ohio, USA), Hansen, John B et al, &quot;Synthesis, pharmacological behavior, and DNA binding of 5-(aminomethyl)-8-methoxy-5({3)-aminopropyl}oxy methy]-and 8({3)-aminopropyl}oxy\psoralen derivatives&quot;, page 488, THE ABSTRACT No 37238e, J. Med. Chem. 1985, 28 (8), 1001-1010</td>
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# INTERNATIONAL SEARCH REPORT

**International application No.**

**PCT/DK 94/00200**

## 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.: 6 because they relate to subject matter not required to be searched by this Authority, namely: See PCT Rule 39.1(iv): Methods for treatment of the human or animal body by surgery or therapy, as well as diagnostic methods.

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)
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