The present invention relates to compounds of formula (I-1) wherein X is -O- or -CH₂-; Y is -C(O)-, -(CH₂)₂- or -(N(CH₃))₂-; n is 1 or 2 or X and Y taken together are -CH=CH₂-; Z is -NH₂-, -CH₂-, -O- or -CH₂-; A¹ is a group (a) or (b); B is -(CH₂)m-; m is 0, 1 or 2; R¹ and R² are each independently hydrogen or lower alkyl; R³ is hydrogen or halogen; R⁴ is hydrogen or hydroxy and the dotted line is an optional -CH₂-CH₂-group and to pharmaceutically acceptable acid addition salts thereof. The compounds of the present invention are antagonists of the OFQ receptor. Consequently they will be useful in the treatment of memory and attention deficits, psychiatric, neurological and physiological disorders, especially, but not limited to, amelioration of symptoms of anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias, epilepsy and convulsions, acute and/or chronic pain conditions, symptoms of addictive drug withdrawal, control of water balance, Na⁺ excretion and arterial blood pressure disorders and metabolic disorders such as obesity.
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Piperidine derivatives

The present invention relates to novel compounds of the formula

![Chemical Structure](image)

wherein
- \( X \) is \(-O-\) or \(-CH_2-\);
- \( Y \) is \(-C(O)-\), \(-(CH_2)_n-\) or \(-N(CH_3)-\);
- \( n \) is 1 or 2 or
- \( X \) and \( Y \) taken together are \(-CH=CH-\);
- \( Z \) is \(-NH-, -CH_2-, -O-, or =CH-\);
- \( A^1 \) is a group

![Chemical Structure](image)

- \( B \) is \(-(CH_2)_m-\);
- \( m \) is 0, 1 or 2;
- \( R^1 \) and \( R^2 \) are each independently hydrogen or lower alkyl;
- \( R^3 \) is hydrogen or halogen;
- \( R^4 \) is hydrogen or hydroxy and
- the dotted line is an optional \(-CH_2-CH_2-\) group

The compounds of formula I-1 and their salts are distinguished by valuable therapeutic properties. It has surprisingly been found that the compounds of the present invention are antagonists of the OFQ receptor. Consequently they will be useful in the treatment of memory and attention deficits, psychiatric, neurological and physiological disorders, especially, but not limited to, amelioration of symptoms of anxiety and stress disorders, depression, memory loss due to Alzheimer’s disease or other dementias, epilepsy and convulsions, acute and/or chronic pain conditions, symptoms of
addictive drug withdrawal, control of water balance, Na⁺ excretion and arterial blood pressure disorders and metabolic disorders such as obesity.

Orphanin FQ (OFQ), a seventeen amino-acid-long peptide (F-G-F-T-G-A-R-K-S-A-R-K-L-A-N-Q), has been isolated from rat brain and is a natural ligand for a G-protein coupled receptor (OFQ-R), found at high levels in brain tissue.

OFQ exhibits agonistic activity at the OFQ-R both in vitro and in vivo.

Julius (Nature 377,476, [1995]) discusses the discovery of OFQ noting that this peptide shares greatest sequence similarity with dynorphin A, an established endogenous ligand for opioid receptors. OFQ inhibits adenylate cyclase in CHO(LC 132⁺) cells in culture and induces hyperalgesia when administered intra-cerebroventricularly to mice. The pattern of results indicate that this heptadecapeptide is an endogenous agonist of the LC 132 receptor and it appears to have pro-nociceptive properties. It has been described that when injected intra-cerebroventricularly in mice, OFQ slows down locomotive activity and induces hyperalgesia and it has been concluded that OFQ may act as a brain neurotransmitter to modulate nociceptive and locomotive behavior.

Objects of the present invention are the novel compounds of formula I-1 per se and pharmaceutically acceptable addition salts thereof, racemic mixtures and their corresponding enantiomers, the preparation of the above-mentioned compounds, medicaments containing them and their manufacture as well as the use of the above-mentioned compounds in the control or prevention of illnesses, especially of illnesses and disorders of the kind referred to earlier.

A further object of the present invention is the use of compounds of general formula

![Chemical Structure](image)

I-2

wherein A² is diphenylmethyl and all other substituents are as defined above and of their pharmaceutically usable salts for the treatment or prevention of
memory and attention deficits, psychiatric, neurological and physiological disorders, especially, but not limited to, amelioration of symptoms, stress disorders, memory loss due to Alzheimer's disease or other dementias, epilepsy and convulsions, symptoms of addictive drug withdrawal, control of water balance, Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity or for the manufacture of corresponding medicaments.

Compounds of formula I-2, in which X is O and A² is the group diphenylmethyl, are generically described in US 3,985,889 and DE 24 58 176 and their use as tranquilizer, antidepressive and analgetic agents.

The following definitions of the general terms used in the present description apply irrespective of whether the terms in question appear alone or in combination.

As used herein, the term "lower alkyl" denotes a straight- or branched-chain alkyl group containing from 1 to 6 carbon atoms, for example, methyl, ethyl, propyl, isopropyl, n-butyl, i-butyl, 2-butyl, t-butyl.

The term "halogen" denotes chlorine, iodine, fluorine and bromine.

"Leaving group" means a labile group that is replaced in a chemical reaction by another group. Examples of leaving groups are chlorine, bromine, iodine, trifluoromethylsulfonate, methanesulfonate or tosylate.

The present invention relates to a group of novel compounds of the following formula:

![formula](image)

wherein

- **X** is -O- or -CH₂-;
- **Y** is -C(O)-, -(CH₃)ₙ or -N(CH₃)ₙ;
- **n** is 1 or 2 or
- **X and Y** taken together may be -CH=CH-;
- **Z** is -NH-, -CH₂-, -O- or =CH-.
B is \(-(CH_2)_m;\)
m is 0, 1 or 2;
\(R^1\) and \(R^2\) are each independently hydrogen or lower alkyl;
\(R^3\) is hydrogen or halogen;
\(R^4\) is hydrogen or hydroxy and
the dotted line is an optional \(-CH_2-CH_2\)-group;
and to their pharmaceutically acceptable acid addition salts and to a group of formula

![Chemical structure](image)

wherein
\(X\) is \(-O-\) or \(-CH_2-\);
\(Y\) is \(-C(O)-\), \(-(CH_2)_n\) or \(-N(CH_3)-\);
n is 1 or 2 or
\(X\) and \(Y\) taken together may be \(-CH=CH-\);
\(Z\) is \(-\text{NH}_2\), \(-\text{CH}_2\), \(-\text{O-}\) or \=-\text{CH}-;
\(B\) is \(-(CH_2)_m;\)
m is 0, 1 or 2;
\(R^1\) and \(R^2\) are each independently hydrogen or lower alkyl;
\(R^3\) is hydrogen or halogen;
\(R^4\) is hydrogen or hydroxy and
the dotted line is an optional \(-CH_2-CH_2\)-group;
and to their pharmaceutically acceptable addition salts.

Exemplary preferred are compounds of the formula

![Chemical structure](image)

wherein
\(X\) is O or \(-CH_2-\);
\(Y\) is \(-C(O)\) or \(-CH_2;\)
\(Z\) is NH or \(-CH_2-\);
\(B\) is \(-(CH_2)_m\)
m is 0 or 2
for example the following compounds:

1'-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-spiro-
(isobenzofuran-1,4'-piperidin)-3-one,

(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(3H-spiro(isobenzofur-
aran-1,4'-piperidin)-1'-yl)-ethyl]-amine,

(9H-fluoren-9-yl)-[2-(3H-spiro(isobenzofuran-1,4'-piperidin)-1'-yl)-ethyl]-
amine,

1'-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3H-spiro-
(isobenzofuran-1,4'-piperidine),

1'-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-2,3-dihydro-
spiro[indene-1,4'-piperidine].

The present compounds of formula I-1 and their pharmaceutically
acceptable salts can be prepared by methods known in the art, for example by
processes described below, which comprise

a) alkylating a compound of formula

\[ \text{R}^1 \quad \text{X} \quad \text{Y} \quad \text{R}^2 \]

with an alkylating agent of formula

\[ \text{A}^1 \quad \text{Z} \quad \text{L} \]

to give a compound of formula I-1,

wherein \( X, Y, R^1, R^2, Z \) and \( A^1 \) are as described as above and \( L \) is a
leaving group, or

b) reductively aminating a compound of formula II with an aldehyde of

\[ \text{A}^1 \quad \text{Z} \quad \text{CHO} \]

wherein \( A^1 \) and \( Z \) are as defined above,

or

c) reducing a compound of formula I-1, wherein \( Y \) is -C(O)- to a compound

of formula I-1, wherein \( Y \) is -CH$_2$- and,
d) if desired, converting the compound of formula I-1 obtained into a pharmaceutically acceptable acid addition salt.

The alkylation in accordance with process step a) is carried out in the presence of a base, such as triethylamine, morpholine, lithium carbonate, sodium carbonate or potassium carbonate in an inert solvent, for example acetonitrile, isobutylmethylketone, dimethylformamide or dimethylsulfoxide.

The alkylation reagent can be prepared by known methods, for example from the corresponding alcohol,

\[
\text{HO} \xrightarrow{A^1} \text{Z} \xrightarrow{\text{Cl-SO}_2\text{CH}_3} \text{A}^1 \text{Z} \xrightarrow{\text{SO}_2\text{CH}_3}
\]

or from the corresponding amines with an a-halogenated acetic acid derivative such as chloroacetyl chloride or chloroacetyl bromide, followed by reduction of the formed amide to give the corresponding 2-halogen-ethylamine. As reducing agent borane or complexes thereof can be applied.

\[
\text{A}^1 \xrightarrow{\text{NH}_2} \text{A}^1 \xrightarrow{\text{L}} \xrightarrow{\text{L}} \text{A}^1 \xrightarrow{\text{NH}} \xrightarrow{\text{L}}
\]

The reductive amination in accordance with process variant b) is carried out in conventional manner in a solvent, such as tetrahydrofurane, 1,2-dichloroethane, methanol or ethanol, and in the presence of a reducing agent, such as sodium cyanoborohydride or sodium triacetoxyborohydride.

Another method is the formation of an enamine from the reaction of II with IV with loss of water as the first step followed by reduction of this enamine to yield a compound of formula I-1 as the second step. Possible reducing agents in this case are borohydride, sodium cyanoborohydride and hydrogen in the presence of at least one hydrogenating catalyst, such as palladium on carbon, platinum or ruthenium.

Furthermore, compounds bearing the 3H-spiro[isobenzofuran-1,4'-piperidine] moiety can be prepared from the corresponding spiro[isobenzofuran-1,4'-piperidine]-3-ones by reduction. Suitable reducing agents are for example borane, lithium-aluminium hydride, mixtures of boron trifluoride and complex hydrides such as sodium borohydride or lithium-aluminium hydride, sodium
borohydride in acidic solution, lithium, phenyl silane or trichlorosilane and hydrogen in the presence of at least one catalyst such as platinum dioxide or Raney nickel.

If desired, compounds of formula I can be converted into a pharmaceutically acceptable acid addition salt. The salt formation is effected at room temperature with methods which are known per se and which are familiar to any person skilled in the art. Not only salts with inorganic acids, but also salts with organic acids come into consideration. Hydrochlorides, hydrobromides, sulphates, nitrates, citrates, acetates, maleates, succinates, methanesulphonates, p-toluenesulphonates and the like are examples of such salts.

The amines of formula II which are used as starting materials are known compounds or were prepared according to J. Org. Chem. 41 (1976), 2628 by lithiation of 2-bromobenzoic acid and reaction with the corresponding 1-benzyl-piperid-4-ones and subsequent debenzylation as follows:

Scheme 1

As mentioned earlier, the compounds of formula I and their pharmaceutically usable addition salts possess valuable pharmacodynamic properties. It has been found that the compounds of the present invention are antagonists of the OFQ receptor and have effects in animal models of memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety, stress disorders, depression, memory loss due to Alzheimer's
disease or other dementias, epilepsy and convulsions, acute and/or chronic pain conditions, symptoms of addictive drug withdrawal, control of water balance, Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

5 The compounds were investigated in accordance with the tests given hereinafter:

**Methods of OFQ-R Binding Assay**

**Cell Culture**

HEK-293 cells adapted to suspension growth (293s) were cultured in HL medium plus 2% FBS. The cells were transfected with the rat OFQ receptor cDNA (LC132), FEBS Lett. 347, 284-288, 1994, cloned in the expression vector pCEP4 (Invitrogen, SanDiego, CA, USA) using lipofectin (Life Technologies, Bethesda, MD, USA). Transfected cells were selected in the presence of hygromycin (1000 U/ml) (Calbiochem, SanDiego, CA, USA). A pool of resistant cells was tested for OFQ-R expression by binding of [³H]-OFQ (Amersham PLC, Buckinghamshire, England). These cells (293s-OFQ-R) were expanded for large scale culture and membrane preparation.

**Membrane preparation**

293s-OFQ-R cells were harvested by centrifugation, washed 3 times with phosphate buffered saline (PBS) before resuspension in buffer A (50 mM Tris-HCl, pH 7.8, 5 mM MgCl₂, 1 mM EGTA) and disruption with a tissue homogenizer (30 seconds, setting 4, Pt 20, Kinematica, Kriens-Lucern, Switzerland). A total membrane fraction was obtained by centrifugation at 49,000 x g at 4°C. This procedure was repeated twice and the pellet was resuspended in buffer A. Aliquots were stored at -70°C and protein concentrations were determined using the BCA™ Protein Assay Reagent (Pierce, Rockford, IL) following the manufacturer's recommendations.

**Binding Assays**

[³H]-OFQ competition studies were carried out with 77 µg membrane protein in a final assay volume of 0.5 ml buffer A plus 0.1% BSA and 0.01% bacitracin (Boehringer-Mannheim, Mannheim, Germany) for one hour at room temperature. 50 nM unlabeled OFQ was used to define the non-specific binding. The assays were terminated by filtration through Whatman GF/C
filters (Unifilter-96, Canberra Packard S.A., Zurich, Switzerland) pretreated with 0.3% polyethylenimine (Sigma, St. Louis, MO, USA) and 0.1% BSA (Sigma) for 1 hour. The filters were washed 6 times with 1 ml of ice cold 50 mM Tris-HCl pH 7.5. The retained radioactivity was counted on a Packard Top-Count microplate scintillation counter after addition of 40 μl of Microscint 40 (Canberra Packard). The effects of compounds were determined using at least 6 concentrations in triplicate, and determined twice. IC₅₀ values were determined by curve fitting and these values were converted to Kᵢ values by the method of Cheng and Prusoff, Biochem. Pharmacol., 22, 3099, 1973.

The affinity to the OFQ-receptor, given as pKi, is in the range of 6.7 to 8.2, for example the pKi for the compounds mentioned below is as follows:

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<tr>
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A/1 1'-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-spiro[isobenzofuran-1,4'-piperidine]-3-one methanesulfonate (1:2)

B/5 2-(3H-Spiro[isobenzofuran-1,4'-piperidine]-1'yl)-ethyl)-(5,6,7,8-tetrahydro-4H-benzocyclohepten-4-yl)-amine hydrochloride (1:2)

C 1'-[2-Benzhydryloxy-ethyl]-3H-spiro[isobenzofuran-1,4'-piperidine] hydrochloride (1:1)

The compounds of formula I as well as their pharmaceutically usable acid addition salts can be used as medicaments, e.g. in the form of pharmaceutical preparations. The pharmaceutical preparations can be administered orally,
e.g. in the form of tablets, coated tablets, dragées, hard and soft gelatine capsules, solutions, emulsions or suspensions. The administration can, however, also be effected rectally, e.g. in the form of suppositories, or parenterally, e.g. in the form of injection solutions.

The compounds of formula I and their pharmaceutically usable acid addition salts can be processed with pharmaceutically inert, inorganic or organic excipients for the production of tablets, coated tablets, dragées and hard gelatine capsules. Lactose, corn starch or derivatives thereof, talc, stearic acid or its salts etc can be used as such excipients e.g. for tablets, dragées and hard gelatine capsules.

Suitable excipients for soft gelatine capsules are e.g. vegetable oils, waxes, fats, semi-solid and liquid polyols etc.

Suitable excipients for the manufacture of solutions and syrups are e.g. water, polyols, saccharose, invert sugar, glucose etc.

Suitable excipients for injection solutions are e.g. water, alcohols, polyols, glycerol, vegetable oils etc.

Suitable excipients for suppositories are e.g. natural or hardened oils, waxes, fats, semi-liquid or liquid polyols etc.

Moreover, the pharmaceutical preparations can contain preservatives, solubilizers, stabilizers, wetting agents, emulsifiers, sweeteners, colorants, flavorants, salts for varying the osmotic pressure, buffers, masking agents or antioxidants. They can also contain still other therapeutically valuable substances.

The dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of general formula I should be appropriate, although the above upper limit can also be exceeded when it appears to be indicated.

The following examples illustrate the present invention, but are not intended to be limiting in any manner.
Example 1

1'-(2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-
spirol(isobenzofuran-1,4'-piperidin)-3-one methansulfonate (1:2)

5-Amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene (10 mmol) was dissolved
in acetone (25 ml) and sodium carbonate (1.6 g) was added. The mixture was
cooled (0-5 °C) and chloroacetyl chloride (15 mmol) was added slowly. After
stirring for 1 h at room temperature water (25 ml) and ethyl acetate (25 ml)
were added. The organic phase was separated, washed with saturated
NaHCO₃ solution, dried (MgSO₄) and concentrated to yield 88% of the

chloroacetamide, which was used without further purification.

Crude chloroacetamide (4 mmol) was dissolved in THF (10 ml). At 0-5 °C
borane-THF-complex (1M solution in THF, 12 ml) was added slowly under
argon. The mixture was stirred for 2 h at room temperature. After addition of
hydrochloric acid (4M, 8 ml) the mixture was stirred for 15 min and then
concentrated. The residue was partitioned between dichloromethane (10 ml)
and saturated NaHCO₃ solution (10 ml) and the pH of the aqueous phase was
adjusted to 8-9 with concentrated NaOH solution. The organic layer was
separated, the aqueous layer was extracted several times with
dichloromethane and the combined organic phases were dried (MgSO₄).

Evaporation yielded the crude 2-chloroethyl-amine.

This compound was dissolved in DMF (15 ml), then spiro(isobenzofuran-
1(3H),4'-piperidin)-3-one (4 mmol), potassium carbonate (5.5 mmol) and
potassium iodide (0.2 mmol) was added. After 3h at 140 °C the solvent was
evaporated under reduced pressure. Saturated NaHCO₃ solution was added
and the mixture was extracted with dichloromethane. The combined organic
layers were dried (MgSO₄) and concentrated. The residue was
chromatographed over silicagel (ethylacetate). Addition of methanesulfonic
acid to a solution of the product in ethylacetate/ethanol yielded 1'-(2-(10,11-
Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-spirol(isobenzofuran-
1,4'-piperidin)-3-one methansulfonate (1.06 g, 42%) as colourless solid, m.p.
196 °C.
Example 2

1'-[2-(3-Chloro-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-spiro[isobenzofuran-1,4'-piperidin]-3-one hydrochloride (1:2)

The title compound, m.p. 228 °C and MS: m/e = 473 (M+H⁺), was prepared in accordance with the general method of example 1 from 5-amino-3-chloro-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, chloroacetyl chloride, spiro[isobenzofuran-1(3H),4'-piperidin]-3-one and HCl.

Example 3

(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-yl)-ethyl]-amine hydrochloride (1:2)

The title compound, m.p. 215 °C and MS: m/e = 425.3 (M+H⁺), was prepared in accordance with the general method of example 1 from 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, chloroacetyl chloride, spiro[isobenzofuran-1(3H),4'-piperidine] and HCl.

Example 4

(9H-Fluoren-9-yl)-[2-(3H-spiro[isobenzofuran-1,4'-piperidin]-1'-yl)-ethyl]-amine hydrochloride (1:2)

The title compound, m.p. 244 °C and MS: m/e = 397.3 (M+H⁺), was prepared in accordance with the general method of example 1 from 9-amino-fluorene, chloroacetyl chloride, spiro[isobenzofuran-1(3H),4'-piperidine] and HCl.

Example 5

[2-(3H-Spiro[isobenzofuran-1,4'-piperidin]-1'yl)-ethyl]-5,6,7,8-tetrahydro-4H-benzocyclohepten-4-yl]-amine hydrochloride (1:2)

The title compound, m.p. 220 °C and MS: m/e = 377.3 (M+H⁺), was prepared in accordance with the general method of example 1 from (5,6,7,8-tetrahydro-4H-benzocyclohepten-4-yl]-amine, chloroacetyl chloride, spiro[isobenzofuran-1(3H),4'-piperidine] and HCl.

Example 6

(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(2,3-dihydro-spiro[indene-1,4'-piperidin]-1'-yl)-ethyl]-amine hydrochloride (1:2)

The title compound, m.p. 170 °C and MS: m/e = 423.4 (M+H⁺), was prepared in accordance with the general method of example 1 from 5-amino-10,11-dihydro-
5H-dibenzo[a,d]cycloheptene, chloroacetyl chloride, 2,3-dihydro-spiro[1H-indene-1,4'-piperidine] and HCl.

**Example 7**

(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(spiro[indene-1,4'-piperidin]-1'-yl)-ethyl]-amine hydrochloride (1:2)

The title compound, m.p. 186 °C and MS: m/e = 421.3 (M+H+), was prepared in accordance with the general method of example 1 from 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, chloroacetyl chloride, spiro[1H-indene-1,4'-piperidine] and HCl.

**Example 8**

1'-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-spiro[isobenzofuran-1,4'-piperidin]-3-one hydrochloride (1:1)

A solution of 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol (1 mmol) and triethylamine (1.5 mmol) in dichloromethane was cooled to 0-5 °C. A solution of methanesulfonyl chloride (1.5 mmol) in dichloromethane (1.5 ml) was added dropwise. After stirring for 1 h at 0-5 °C, the mixture was concentrated under reduced pressure to yield the crude methanesulfonate as an oil. This was dissolved in acetonitrile together with spiro[isobenzofuran-1(3H),4'-piperidin]-3-one (1 mmol) and potassium carbonate (2.5 mmol) followed by reflux for 20 h. After evaporating the solvent saturated NaHCO₃ solution was added and the mixture was extracted with dichloromethane. The combined organic layers were dried (MgSO₄) and concentrated. The residue was chromatographed over silicagel (ethylacetate). Addition of HCl in ethanol to a solution of the product in ethylacetate/ethanol yielded 1'-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-spiro[isobenzofuran-1,4'-piperidin]-3-one hydrochloride (0.25 g, 53%) as colourless solid, m.p. 210°C and MS: m/e = 438.4 (M+H+).

**Example 9**

1'-[3-(5-Hydroxy-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-spiro[isobenzofuran-1,4'-piperidin]-3-one hydrochloride (1:1)

The title compound, m.p. 178 °C and MS: m/e = 454.5 (M+H+), was prepared in accordance with the general method of example 8 from 3-(5-hydroxy-10,11-
dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and spiro(isobenzofuran-1(3H),4'-piperidin)-3-one.

**Example 10**

1'-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3H-spiro(isobenzofuran-1,4'-piperidine) hydrochloride (1:1)

The title compound, m.p. 235 °C and MS: m/e = 424.3 (M+H^+), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and spiro(isobenzofuran-1(3H),4'-piperidine).

**Example 11**

5-[3-(3H-Spiro(isobenzofuran-1,4'-piperidin)-1'-yl)-propyl]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol hydrochloride (1:1)

The title compound, m.p. 201 °C and MS: m/e = 440.3 (M+H^+), was prepared in accordance with the general method of example 8 from 5-[3-hydroxypropyl]-10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ol and spiro(isobenzofuran-1(3H),4'-piperidine).

**Example 12**

1'-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propyl]-3H-spiro(isobenzofuran-1,4'-piperidin) hydrochloride (1:1)

The title compound, m.p. 231 °C and MS: m/e = 422.3 (M+H^+), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-ylidene)-propan-3-ol and spiro(isobenzofuran-1(3H),4'-piperidine).

**Example 13**

1'-[3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-2,3-dihydro-spirolindene-1,4'-piperidin) hydrochloride (1:1)

The title compound, m.p. 220 °C and MS: m/e = 422.3 (M+H^+), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and 2,3-dihydro-spirolindene-1,4'-piperidine).
Example 14

1',3'-[10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl]-propyl]-4'-piperidine] hydrochloride (1:1)

The title compound, m.p. 227 °C and MS: m/e = 420.3 (M+H⁺), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and spiro[indene-1,4'-piperidine].

Example 15

(1RS,3'SR)-1'-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3'-methyl-spiro[isobenzofuran-1,4'-piperidine]-3-one hydrochloride (1:1)

The title compound, m.p. 214 °C and MS: m/e = 452.4 (M+H⁺), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and (1RS,3'SR)-3'-methyl-spiro[isobenzofuran-1,4'-piperidine]-3-one.

Example 16

(1RS,3'SR)-1'-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3'-methyl-spiro[isobenzofuran-1,4'-piperidine] hydrochloride (1:1)

(1RS,3'SR)-1'-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3'-methyl-spiro[isobenzofuran-1,4'-piperidine]-3-one (0.5 mmol) was dissolved in tetrahydrofuran and borane-THF-complex (1M solution in THF, 3 mmol) was added under argon. The resulting mixture was heated at reflux for 18 h. It was cooled to 0 °C, and 1M HCl was added dropwise until no more gas evolution was observed. The mixture was concentrated in vacuo and HCl (1N, 5 ml) was added to the white foam obtained, and the resulting mixture was stirred at 100 °C for 1 h. The solution was then cooled and basified with concentrated aqueous ammonia solution. The product was extracted into dichloromethane and purified by column chromatography over silicagel (ethylacetate). Addition of HCl in ethanol to a solution of the product in ethylacetate/ethanol yielded (1RS,3'SR)-1'-(3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3'-methyl-spiro[isobenzofuran-1,4'-piperidine] hydrochloride (0.18 g, 82%) as colourless solid, m.p. 225 °C and MS: m/e = 438.4 (M+H⁺).
Example 17

(1R,3'R,5'S)-1'-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyll-3',5'-dimethyl-3H-spiro[isobenzofuran-1,4'-piperidine] hydrochloride (1:1)

The title compound, m.p. 237 °C and MS: m/e = 452.5 (M+H⁺), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and (1R,3'R,5'S)-3',5'-dimethyl-3H-spiro[isobenzofuran-1,4'-piperidine] followed by borane reduction according to example 16.

Example 18

1'-(3-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyll-1-methyl-1,2-dihydro-spiro[indole-3,4'-piperidine] hydrochloride (1:1)

For the synthesis of the title compound, m.p. 222 °C and MS: m/e = 437.4 (M+H⁺), 1-methyl-spiro[3H-indole-3,4'-piperidin]-2(1H)-one is reduced with borane according to example 16 to yield 1-methyl-1,2-dihydro-spiro[indole-3,4'-piperidine], which was further reacted with 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol in accordance with the general method of example 8.

Example 19

(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(spiros[isochroman-1,4'-piperidin]-1'-yl)ethyl]-amine hydrochloride (1:2)

The title compound, m.p. 190 °C and MS: m/e = 439.4 (M+H⁺), was prepared in accordance with the general method of example 1 from 5-amino-10,11-dihydro-5H-dibenzo[a,d]cycloheptene, chloroacetyl chloride, spiro[isochroman-1,4'-piperidine] and HCl.

Example 20

1'-(3-(9,10-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyll-spiro[isochroman-1,4'-piperidine] hydrochloride (1:1)

The title compound, m.p. 243 °C and MS: m/e = 438.4 (M+H⁺), was prepared in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and spiro[isochroman-1,4'-piperidine].
Example 21

(1RS,5SR)-8-[3-(9,10-Dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-
spiro[8-aza-bicyclo[3.2.1]octane-3,1'-isobenzofuran]-3'-one hydrogen chloride (1:1)

The title compound, m.p. 284 °C and MS: m/e = 464.3 (M+H+) , was prepared
in accordance with the general method of example 8 from 3-(10,11-dihydro-5H-
dibenzo[a,d]cyclohepten-5-yl)-propan-3-ol and (1RS,5SR)-spiro[8-aza-
bicyclo[3.2.1]octane-3,1'-isobenzofuran]-3'-one, 1RS,3'SR)-3'-methyl-
spiro[isobenzofuran-1,4'-piperidin]-3-one.

Synthesis of new intermediates

Beispiel 22

(1RS,3'SR)-3'-Methyl-spiro[isobenzofuran-1,4'-piperidin]-3-one

2-Bromobenzoic acid (70 mmol) was added to a dry three-necked flask
equipped with an addition funnel, low temperature thermometer, inert gas
inlet, and mechanical stirrer. Dry tetrahydrofurane (250 ml) was added and
the solution was cooled to -78 °C. n-Butyl-lithium was added slowly (2 h) while
maintaining the mixture below -70 °C and the resulting solution was stirred
for an additional 1 h. 1-Benzyl-3-methyl-piperid-4-one (98 mmol) in a mixture
of hexane and tetrahydrofurane (25 ml/25 ml) was added over 30 min while
maintaining the mixture below -70 °C (within 1 h) and the mixture was
allowed to warm to room temperature. After stirring overnight the mixture
was poured into water (300 ml), extracted with ether and was acidified with
concentrated HCl (to pH 2-3) and extracted with ether. The acidic solution was
boiled for 1 h and was then cooled (0-5 °C) and made alkaline (to pH 9-10) with
aqueous NaOH. The cold solution was extracted with dichloromethane. The
combined organic extracts were dried (MgSO₄) and concentrated to give a
yellow oil (7.0 g). This was chromatographed over silicagel (ethylacetate) to
yield 6.35 g of (1RS,3'SR)-1'-benzyl-3'-methyl-spiro[isobenzofuran-1,4'-
piperidin]-3-one a colourless oil (20.6 mmol, 30 %).

For debenzylation this compound was dissolved in ethanol (250 ml) and
palladium on charcoal (10%, 0.64 g) was added. The suspension was stirred
and hydrogenated (1 bar) overnight. After filtering off the catalyst the solution
was concentrated. The remaining solid was recrystallized from ethyl acetate to
yield (1RS,3'SR)-3'-methyl-spiro[isobenzofuran-1,4'-piperidin]-3-one as
colourless solid (2.7 g, 60%), m.p. 131°C and MS: m/e = 218.3 (M+H⁺).

**Beispiel 23**

(1R,3'R,5'S)-3',5'-Dimethyl-3H-spiro[isobenzofuran-1,4'-piperidin]-3-one

The title compound, m.p. 125 °C and MS: m/e = 231 (M⁺), was prepared in
accordance with the method for the synthesis of (1RS,3'SR)-3'-methyl-
spiro[isobenzofuran-1,4'-piperidin]-3-one using 1-benzyl-3,5-dimethyl-piperid-
4-one.

**Example A**

Tablets of the following composition are manufactured in the usual
manner:

<table>
<thead>
<tr>
<th>Component</th>
<th>mg/tablet</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td>5</td>
</tr>
<tr>
<td>Lactose</td>
<td>45</td>
</tr>
<tr>
<td>Corn starch</td>
<td>15</td>
</tr>
<tr>
<td>Microcrystalline cellulose</td>
<td>34</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1</td>
</tr>
<tr>
<td><strong>Tablet weight</strong></td>
<td><strong>100</strong></td>
</tr>
</tbody>
</table>

**Example B**

Capsules of the following composition are manufactured:

<table>
<thead>
<tr>
<th>Component</th>
<th>mg/capsule</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td>10</td>
</tr>
<tr>
<td>Lactose</td>
<td>155</td>
</tr>
<tr>
<td>Corn starch</td>
<td>30</td>
</tr>
<tr>
<td>Talc</td>
<td>5</td>
</tr>
<tr>
<td><strong>Capsule fill weight</strong></td>
<td><strong>200</strong></td>
</tr>
</tbody>
</table>

The active substance, lactose and corn starch are firstly mixed in a mixer
and then in a comminuting machine. The mixture is returned to the mixer, the
talc is added thereto and mixed thoroughly. The mixture is filled by machine
into hard gelatine capsules.

**Example C**

Suppositories of the following composition are manufactured:

<table>
<thead>
<tr>
<th>Component</th>
<th>mg/supp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Active substance</td>
<td>15</td>
</tr>
<tr>
<td>Suppository mass</td>
<td>1285</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>1300</strong></td>
</tr>
</tbody>
</table>
The suppository mass is melted in a glass or steel vessel, mixed thoroughly and cooled to 45°C. Thereupon, the finely powdered active substance is added thereto and stirred until it has dispersed completely. The mixture is poured into suppository moulds of suitable size, left to cool, the suppositories are then removed from the moulds and packed individually in wax paper or metal foil.
20

Claims

1. Compounds of the general formula

\[
\begin{align*}
A' & \quad \text{wherein} \\
5 & \quad X \quad \text{is -O- or -CH}_2-; \\
Y & \quad \text{is -C(O)-, -(CH}_2)_n- \text{ or -N(CH}_3)_2-; \\
n & \quad \text{is 1 or 2 or} \\
X \text{ and } Y & \quad \text{taken together are -CH=CH-;} \\
z & \quad \text{is -NH-, -CH}_2-, -O- \text{ or =CH-;} \\
10 & \quad A^1 \quad \text{is a group} \\
\end{align*}
\]

\[
\begin{align*}
a) & \quad B \\
\text{is -(CH}_2)_{m-}; \\
m & \quad \text{is 0, 1 or 2;} \\
R^1 \text{ and } R^2 & \quad \text{are each independently hydrogen or lower alkyl;} \\
R^3 & \quad \text{is hydrogen or halogen;} \\
R^4 & \quad \text{is hydrogen or hydroxy and} \\
\text{the dotted line is an optional -CH}_2\text{-CH}_2\text{-group} \\
\text{and their pharmaceutically acceptable acid addition salts.}
\end{align*}
\]

20

2. Compounds of the formula

\[
\begin{align*}
\text{in accordance with claim 1,} \\
\text{wherein} \\
X & \quad \text{is -O- or -CH}_2-;
\end{align*}
\]
21

Y is -(C(O))-, -(CH₂)ₙ or -N(CH₃)⁺;

n is 1 or 2 or

X and Y taken together are -CH=CH⁺;

Z is -NH⁺, -CH₂-, -O- or =CH⁺;

5 B is -(CH₂)ₘ;

m is 0, 1 or 2;

R¹ and R² are each independently hydrogen or lower alkyl;

R³ is hydrogen or halogen;

R⁴ is hydrogen or hydroxy and

10 the dotted line is an optional -CH₂-CH₂-group;

and their pharmaceutically acceptable acid addition salts.

3. Compounds of the formula

![Chemical Structure]

15 in accordance with claims 1 to 2,

wherein

X is O or -CH₂⁺;

Y is -(C(O)) or -CH₂⁺;

Z is NH or -CH₂⁺;

20 B is -(CH₂)ₘ

m is 0 or 2

and their pharmaceutically acceptable acid addition salts.

4. Compounds in accordance with claims 1-3, wherein the compounds are

25 1’-[2-(10,11-Dihydro-5H-dibenzo[a,d]cyclohepten-5-ylamino)-ethyl]-spiro-
[isobenzofuran-1,4’-piperidin]-3-one,

(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-[2-(3H-spiro[isobenzofuran-1,4’-piperidin]-1’-yl)-ethyl]-amine,

(9H-fluoren-9-yl)-[2-(3H-spiro[isobenzofuran-1,4’-piperidin]-1’-yl)-ethyl]-amine,

1’-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3H-spiro-
[isobenzofuran-1,4’-piperidine],

1’-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-3H-spiro-
[isobenzofuran-1,4’-piperidine],
1′-[3-(10,11-dihydro-5H-dibenzo[a,d]cyclohepten-5-yl)-propyl]-2,3-dihydro-spiro[indene-1,4′-piperidine].

5. Compounds of the formula

![Chemical Structure]

wherein

- \(X\) is -O- or -CH\(_2\)-;
- \(Y\) is -C(O)-, -(CH\(_2\))\(_n\) or -N(CH\(_3\))-;
- \(n\) is 1 or 2 or
- \(X\) and \(Y\) taken together are -CH=CH-;
- \(Z\) is -NH-, -CH\(_2\)-, -O- or =CH-;
- \(B\) is -(CH\(_2\))\(_m\);
- \(m\) is 0, 1 or 2;
- \(R^1\) and \(R^2\) are each independently hydrogen or lower alkyl;
- \(R^3\) is hydrogen or halogen;
- \(R^4\) is hydrogen or hydroxy and the dotted line is an optional -CH\(_2\)-CH\(_2\)-group; and
- their pharmaceutically acceptable addition salts.

6. A compound in accordance with claims 1 and 5, wherein the compound is

\[2-(3H-spiro[isobenzofuran-1,4′-piperidin]-1′-yl)-ethyl]-\((5,6,7,8\)-tetrahydro-4H-benzocyclohepten-4-yl)-amine.

7. A medicament containing one or more compounds of any one of claims 1 to 6 or a pharmaceutically acceptable salt thereof for the treatment of diseases.

8. A medicament according to claim 7 for the treatment of Orphanin FQ (OFQ) receptor related diseases, which include memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias, epilepsy and convulsions, acute and/or chronic pain conditions, and symptoms of addictive drug withdrawal, control of water balance, Na\(^+\)
excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

9. A process for preparing a compound as claimed in claim 1, which process comprises

5 a) alkylating a compound of formula

\[ \text{II} \]

with an alkylating agent of formula

\[ \text{III} \]

to give a compound of formula I-1,

10 wherein X, Y, R¹, R², Z and A¹ are as defined in claim 1 and L is a leaving group, or

b) reductively aminating a compound of formula II with an aldehyde of formula

\[ \text{IV} \]

wherein A¹ and Z are given in claim 1,

or
c) reducing a compound of formula I-1, wherein Y is -C(O)- to a compound of formula I-1, wherein Y is -CH₂- and
d) if desired, converting the compound of formula I-1 obtained into a

20 pharmaceutically acceptable acid addition salt.

10. A compound according to any one of claims 1-6, whenever prepared by a process as claimed in claim 9 or by an equivalent method.

11. The use of a compound as claimed in any one of claims 1 - 6 for the treatment of Orphanin FQ (OFQ) receptor related diseases, which include memory and attention deficits, psychiatric, neurological and physiological disorders, such as anxiety and stress disorders, depression, memory loss due to Alzheimer's disease or other dementias, epilepsy and convulsions, acute and/or chronic pain conditions, and symptoms of addictive drug withdrawal, control of
water balance, Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity.

12. The use of a compound of the general formula

\[
\begin{align*}
A^2 & \quad Z \\
\text{X} & \quad \text{is -O- or -CH₂-;} \\
\text{Y} & \quad \text{is -C(O)-, -CH₂⁻ or -N(CH₃)⁻;} \\
n & \quad \text{is 1 or 2; or} \\
\text{X and Y} & \quad \text{taken together are -CH=CH⁻;} \\
\text{Z} & \quad \text{is -NH⁻, CH₂⁻, O or =CH⁻;} \\
\text{A²} & \quad \text{is diphenylmethyl;} \\
m & \quad \text{is 0, 1 or 2;} \\
\text{R¹ and R²} & \quad \text{are hydrogen or lower alkyl;} \\
\text{R³} & \quad \text{is hydrogen or halogen;} \\
\text{R⁴} & \quad \text{is hydrogen or hydroxy and} \\
\end{align*}
\]

and of their pharmaceutically acceptable acid addition salts for the control or treatment of diseases such as memory and attention deficits, psychiatric, neurological and physiological disorders, especially, but not limited to, amelioration of symptoms, stress disorders, memory loss due to Alzheimer’s disease or other dementias, epilepsy and convulsions, symptoms of addictive drug withdrawal, control of water balance, Na⁺ excretion, arterial blood pressure disorders and metabolic disorders such as obesity or for the manufacture of corresponding medicaments.
**INTERNATIONAL SEARCH REPORT**

**A. CLASSIFICATION OF SUBJECT MATTER**

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

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

| IPC 6  | C07D A61K |

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

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

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

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

22 April 1999

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

03/05/1999

**Name and mailing address of the ISA**

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-3040, Tx 31 651 epo nl
Fax: (+31-70) 340-3016

**Authorized officer**

Alfaro Faus, I

Form PCT/ISA/210 (second sheet) (July 1992)
INTERNATIONAL SEARCH REPORT

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 (C07D0471/20, 307:00, 221:00, 209:00)

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)

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

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**“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
- **“L”** document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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**“T”** 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

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**“S”** document member of the same patent family

Date of the actual completion of the international search: 22 April 1999

Name and mailing address of the ISA:
European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HJ Rijswijk
Tel. (+31-70) 340-3040, Tx. 31 651 epi nl
Fax. (+31-70) 340-9016

Authorized officer: Alfaro Faus, I
INTERNATIONAL SEARCH REPORT

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

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

1. X Claims Nos.: 8,11 and 12 because they relate to subject matter not required to be searched by this Authority, namely:
   
   Remark: Although claims 8,11 and 12 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

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

3.  
   Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 8.4(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.
# INTERNATIONAL SEARCH REPORT

Information on patent family members

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