Inventors: Niels Mork, Virum (DK); Heidi Lopez de Diego, Kokkedal (DK); Ole Nielsen, Valby (DK)

Correspondence Address:
DARBY & DARBY P.C.
P. O. BOX 5257
NEW YORK, NY 10150-5257 (US)

Assignee: H. Lundbeck A/S, Valby-Copenhagen (DK)

Filed: Dec. 13, 2004

The present invention relates to a hydrohalogenide of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]spiro[isobenzofuran-1(3H),4'-piperidine] hydrohalogenides containing the acid addition salts and the use thereof for the treatment of psychic and neurological disorders.
The present invention relates to hydrohalogenides of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-butyl]spiro[isobenzofuran-1(3H), 4'-piperidine] and their use as anxiolytics. These compounds have been shown to be useful in the treatment of anxiety, depression, and other related disorders.

Also, some guanidine derivatives having sigma receptor activity have been disclosed to be useful as anxiolytics. These compounds were found to show anti-amnesic effects in animal models.

The free base of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-butyl]spiro[isobenzofuran-1(3H), 4'-piperidine] was disclosed for the first time in International Patent Publication No. WO 92/22544 as a suitable salt.

Another acid addition salt of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-butyl]spiro[isobenzofuran-1(3H), 4'-piperidine] has been disclosed. This fumarate has been shown to be effective in reducing anxiety and depression in animal models.

The aqueous solubility of both the free base and the fumarate is very low, a property which is known to possibly compromise the bioavailability of the drug. The free base has been found to show a three times larger bioavailability than that of the fumarate salt.

The hydrochloride of the invention also have improved water solubility, making it potentially easier to deliver the drug to the patient.

According to the present invention new hydrohalogenides of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-butyl]spiro[isobenzofuran-1(3H), 4'-piperidine] have been disclosed for their use as anxiolytics.
butyl-spiro[isobenzofuran-1(3H),4'-piperidine] with improved bioavailability has been provided.

0018 In a particularly preferred embodiment of the invention the acid addition salt according to the invention is the hydrochloride of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine].

0019 In another embodiment of the invention relates to the hydrobromide of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine].

0020 The invention also relates to pharmaceutical compositions containing the hydrogenogalnic salts of the invention and the use of the salts for the preparation of pharmaceutical compositions and the use thereof for the treatment of anxiety, psychoses, epilepsy, convulsion, movement disorders, motor disturbances, amnesia, cerebrovascular diseases, senile dementia of Alzheimer type and Parkinson’s disease.

0021 As used herein, a hydrogenogalnic of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] means the hydrochloride, the hydrobromide or the hydroiodide of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] and includes the anhydrate, the hemi-, mono- and dihydrate thereof as well as solvents thereof.

0022 The hydrogenogalnicos according to the invention may be obtained by treatment of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] with hydrochloric, hydrobromic or hydroiodic acid in an inert solvent followed by precipitation, isolation and optionally recrystallization by known methods and if desired micronisation of the crystalline product by wet or dry milling or another convenient process, or preparation of particles from a solvent-emulsification process.

0023 Precipitation of the hydrogenogalnic addition salt is preferably carried out in an inert solvent, e.g. an inert polar solvent such as an alcohol (e.g. ethanol, 2-propanol and n-propanol).

0024 According to the invention, hydrogenogalic of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] may be administered in any suitable way e.g. orally or parenterally, and the salt may be presented in any suitable form for such administration, e.g. in the form of tablets, capsules, powders, syrups or solutions or dispersions for injection. Preferably, and in accordance with the purpose of the present invention, the salt of the invention is administered in the form of a solid pharmaceutical entity, suitably as a tablet or a capsule.

0025 Methods for the preparation of solid pharmaceutical preparations are well known in the art. Tablets may thus be prepared by mixing the active ingredients with ordinary adjuvants and/or diluents and subsequently compressing the mixture in a convenient tablettting machine. Examples of adjuvants or diluents comprise: corn starch, lactose, talc, magnesium stearate, gelatine, lactose, gums, and the like. Any other adjuvant or additive such as colourings, aroma, preservatives, etc. may also be used provided that they are compatible with the active ingredients.

0026 The salts of the invention are most conveniently administered orally in unit dosage forms such as tablets or capsules, containing the active ingredient in an amount from about 10 µg/day/kg to 25 mg/day/kg body weight, or between 25 µg/day/kg to 10 mg/day/kg body weight. A suitable daily dose is between 1.0 and 160 mg/day.

0027 The invention will be illustrated in the following examples. The examples may not be construed as limiting.

0028 The fumarate of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] can be prepared as described in Perregaard, J. et al., J. Med. Chem. 1995, 38, 11, p. 1998-2008 (compound 14f).

EXAMPLE 1

1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine]

0029 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine], fumarate (69 g) was suspended in water (350 ml) and ethylacetate (350 ml). The mixture was made alkaline (pH 10-12) by the addition of concentrated aqueous sodium hydroxide and stirred until all solids were dissolved. The aqueous layer was extracted with ethylacetate (2×100 ml) and the combined organic extracts were dried over sodium sulphate and evaporated in vacuo.

EXAMPLE 2

1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine], hydrochloride

0030 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] (10.3 g) and 2-propanol (100 ml) were heated to reflux. The solution was allowed to cool to 45°C. Aqueous hydrochloric acid (2.2 ml, 56%) was added dropwise and a precipitate of the title compound was formed. The suspension was heated to reflux and allowed to cool to ambient temperature. The suspension was cooled in ice, filtered off and dried. Yield: 10.1 g (90%). The salt is a mono salt and according to our investigations an anhydrate.

0031 KF: 0.51%; HPLC 100.8%; DSC (onset/peak_max) 222.5°C/C.223.8°C.

0032 CHN (calculated/measured): C, 73.38/73.13; H, 6.57/6.56; N, 5.70/5.80.

EXAMPLE 3

1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] hydrobromide

0033 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] (1.05 g, oil) and 2-propanol (10 ml) was stirred and heated until the oil was dissolved. Aqueous hydrobromic acid (2.5 ml, 47% HBr) was added dropwise and a precipitate of the title compound was formed. More 2-propanol (5 ml) and hydrobromic acid (2.5 ml, 47% HBr) was added to the suspension. The suspension was cooled on ice and the precipitate was filtered off and dried.

EXAMPLE 4

1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] hydroiodide

0034 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] (1.0 g, oil)
and 2-propanol (15 ml) was stirred and heated until the oil was dissolved. Aqueous hydroiodic acid (1 ml, 57% HI) was added dropwise and crystals of the title compound was formed. More 2-propanol (10 ml) and hydrobromic acid (4 ml, 57% HI) was added to the suspension. The suspension was cooled on ice and the precipitate was filtered off and dried.

[0035] Bioavailability Study

[0036] After multiple administration in Beagle dogs, the bioavailability of the salts of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] was investigated as described in the following study:

[0037] Two groups, each consisting of four Beagle dogs (2 males and 2 females) were used in the study.

[0038] The dogs in the individual groups were given single daily doses of 10 mg/kg/day (calculated as free base) of the fumarate of the hydrochloride of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] for seven days.

[0039] Blood samples for serum preparation were drawn from the test animals at specific nominal time points before and after dosing on each day and analyzed using HPLC.

[0040] Test Animals

[0041] Four male and four female purpose-bred Beagle dogs all from Interfauna, Ltd., Huntingdon, UK were allocated at random in pairs to one of the two study groups.

[0042] At the start of the treatment, the dogs were approximately 12-38 months old and weighed 9.8-13.0 kg.

[0043] Dose and Formulation

[0044] Single doses of the different salts corresponding to 10.0 mg (~21997 nmol) of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] per kg body weight were accurately weighed into gelatine capsules. The calculated amounts of test compound for each dog were based on body weights measured at study start.

[0045] Dosing

[0046] The test animals were dosed once daily between 08:00 and 09:00 (24-hour clock) for 7 days.

[0047] Blood Sampling and Serum Preparation

[0048] Blood samples (approx. 3 ml) for serum preparation were drawn from the jugular vein of the test animals at the following nominal time points before and after dosing on each day:

| Day 1: | Before, 1, 2, 3, 4, 6, 8 and 12 hours after dosing. |
| Day 2-6: | Before and 3 hours after dosing. |
| Day 7: | Before, 1, 2, 3, 4, 6, 8, 12, 24, 48, 72 and 96 hours after dosing. |

[0049] The time points above corresponds to: before, 1, 2, 3, 4, 6, 8, 12, 24, 27, 48, 51, 72, 75, 96, 99, 120, 123, 144, 145, 146, 147, 148, 150, 152, 156, 168, 192, 216 and 240 hours after the first dosing on day 1.

[0050] The exact blood sampling times for each dog relative to the first dose were recorded.

[0051] Blood samples were allowed to clot at room temperature for 30-90 minutes after sampling. The clotted samples were centrifuged at 1000 g for 15 minutes and separated serum transferred to clean test tubes. Serum samples were stored at approx. –20° C. until analysis.

[0052] Drug Assay

[0053] The serum samples obtained were analysed for content of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] by a pseudo-normal phase HPLC-method after liquid-liquid extraction. 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[5-fluoro-isobenzofuran-1(3H),4'-piperidine] was used as internal standard. Serum samples were analysed for content of 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine] using the following reference substances, extraction procedure and high performance liquid chromatographic (HPLC) method.

[0054] Reference Substances

[0055] 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[isobenzofuran-1(3H),4'-piperidine], fumarate,

[0056] 1'-[4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl]-spiro[5-fluoro-isobenzofuran-1(3H),4'-piperidine] (ISTD),

[0057] 1'-[5-phenyl-1-pentyl]-spiro[isobenzofuran-1(3H),4'-piperidine] (stabilising agent).

[0058] Extraction Procedure

[0059] Ethanol (50 µl), 100 µl 2 N NaOH and 4.0 ml n-heptane containing 1% isobutanol was added to serum samples of 500 µl. The samples were shaken for 15 minutes, centrifuged for 5 minutes at approximately 2000 g and then frozen in an ethanol/dry ice bath. The organic phase was transferred to a clean test tube and evaporated under nitrogen (N2) at 40° C. The residue was dissolved in 150 µl mobile phase for HPLC (see below) and 75 µl analysed by HPLC.

<table>
<thead>
<tr>
<th>HPLC method</th>
</tr>
</thead>
<tbody>
<tr>
<td>Column:</td>
</tr>
<tr>
<td>Column temperature:</td>
</tr>
<tr>
<td>Mobile phase composition:</td>
</tr>
<tr>
<td>Mobile phase flow:</td>
</tr>
<tr>
<td>Detection:</td>
</tr>
<tr>
<td>Injection volume:</td>
</tr>
<tr>
<td>Runtime:</td>
</tr>
<tr>
<td>Retention time:</td>
</tr>
</tbody>
</table>

[0060] All serum samples were analysed as single determinations.
The limit of quantification was 2 ng per sample for 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] corresponding to 8.80 nmol/L serum using 300 μl serum for analysis.

Calibration samples for calculation of serum concentrations of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] were prepared and analysed on each day of analysis from control dog serum spiked with known amounts of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] in the range 0-500 ng of each compound per sample.

Quality control (QC) samples were prepared and analysed on each day of analysis from control dog serum spiked with known amounts (1, 50 or 400 ng per sample) of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine].

Serum concentrations of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] (ng/ml and nmol/L) were calculated from the actual amounts (ng) found by analysis and the serum volume used for analysis.

The area under the serum concentration versus time curve from time zero to 24 hours after dosing on day 7 (AUC_{0-24,7}) was calculated by the linear trapezoidal rule.

The relative oral bioavailability of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] (F_{rel}) of the hydrochloride compared to the bioavailability of the fumarate salt was estimated as the ratio between the mean AUC_{0-24,7} values found for the group of dogs which had received the hydrochloride and the mean AUC_{0-24,7} value found for group of dogs which had received the fumarate.

Results are presented in table 1:

<table>
<thead>
<tr>
<th>Acid addition salt</th>
<th>AUC_{0-24,7} Mean</th>
<th>SD</th>
<th>F_{rel}</th>
<th>(compared to fumarate)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fumarate</td>
<td>4017</td>
<td>2403</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>Hydrochloride</td>
<td>12023</td>
<td>3999</td>
<td>2.99</td>
<td>—</td>
</tr>
</tbody>
</table>

* 1-4. (canceled)

5. A method for the treatment of a condition selected from the group consisting of anxiety, psychosis, epilepsy, convulsion, movement disorders, motor disturbances, amnesia, cerebrovascular diseases, senile dementia of Alzheimer type and Parkinson’s disease, comprising administering a therapeutically effective amount of a hydrohalogenide of 1'-4-[1-(4-fluorophenyl)-1H-indole-3-yl]-1-butyl-spiro[isobenzofuran-1(3H),4'-piperidine] orhydrate or solvate thereof to a subject suffering from such a condition.

6. The method according to claim 5 wherein anxiety is treated.

7. The method according to claim 5 wherein the hydrohalogenide is the hydrochloride.

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