Pyrrolidinone derivatives, their preparation and pharmaceutical compositions containing them.

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Description

This invention relates to a compound useful in medicine, to the synthesis of the compound, to pharmaceutical formulations containing the compound and the preparation of such formulations, and to the use of the compounds in medicine.

Some pyrrolidine compounds are described in the EP—A0 003 602. These derivatives are said to be capable of counteracting cerebral insufficiency.

We have found that the compound of Formula (I),

![Chemical structure](image)

which is chemically named 1-(1,3-benzodioxol-5-yl)-2-pyrrolidinone is of value in medicine in the treatment or prophylaxis of pain, inflammation or fever.

The compound of formula (I) hereinafter known as “compound (I)”; “active ingredient”, or “active compound”, has been found to have mild to moderately strong analgesic activity. As an analgesic agent, compound (I) is like morphine and codeine but superior to aspirin or acetaminophen as shown in the trypsin assay and the hot plate assay. However, the analgesic mode of action of the compound (I) is believed to be unlike that of morphine or codeine since its analgesic activity is not inhibited by naloxone, and it does not bind to the morphine receptor. Thus, compound (I) is considered non-narcotic. The duration of analgesic action is significantly greater for compound (I) than for codeine or morphine.

Compound (I) has also been found to have potent, long-lasting acute anti-inflammatory activity in the rat as shown in the carrageenan pleurisy assay (Vinegar et al., Proc. Soc. Exp. Biol. Med. 151, 686, (1976)). Compound (I) resembles acetaminophen in its acute anti-inflammatory action but it has been found to be more potent and to have a longer lasting anti-inflammatory effect at comparable dose levels.

Compound (I), like acetaminophen, has also been found to have antipyretic and hypothermic activity as shown by the yeast-induced hyperthermia assay in the rat (Khalili-Varasteh et al., Arch. Int. Pharmacodyn., 219, 149—159 (1976)). This is to say, the compound of formula (I) combats fever in the rat as does aspirin and acetaminophen.

Compound (I) may be used in the relief, treatment or prophylaxis of pain (moderate to severe), inflammation or fever, in a mammal, including man, such as: that resulting from headache, toothache, pain following general dental procedures, oral and general surgery, dysmenorrhea, myalgia, pain of unresectable cancer, joint and peripheral nerve disorders, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions, pyrexa and other conditions associated with pain, inflammation and fever.

The amount of the active compound, i.e. compound (I), required for use in the above conditions will, of course, vary with both the route of administration, the condition under treatment, and the mammal undergoing treatment, but is ultimately at the discretion of the physician. However, a suitable analgesic, anti-inflammatory and/or anti-pyretic dose of the active compound for a mammal is in the range of from 3 to 120 mg per kilogram body weight per day; a typical dose for a human recipient being 15 mg/kg body weight per day.

The desired dose is preferably presented as in the range of from two to four subdoses administered at appropriate intervals throughout the day. Thus where three sub-doses are employed each will lie in the range of from 1 to 20 mg (base)/kg body weight, a typical dose for a human recipient being 3 mg (base)/kg body weight.

While it is possible for the active compound to be administered alone as the raw chemical, it is preferable to present the active compound as a pharmaceutical formulation. Formulations of the present invention, both for veterinary and for human medical use, comprise the active compound together with one or more pharmaceutically acceptable carriers thereof and optionally any other therapeutic ingredients.

The carrier(s) must be pharmaceutically acceptable in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof. The other therapeutic ingredient(s) may include other analgesics (such as codeine) anti-inflammatory drugs or anti-pyretics.

The formulations include those suitable for oral, rectal or parenteral (including subcutaneous, intramuscular and intravenous) administration.

The formulations may conveniently be presented in unit dosage form and may be prepared by any of
the methods well known in the art of pharmacy. All methods include the step of bringing the active compound into association with a carrier which constitutes one or more accessory ingredients. In general, the formulations are prepared by uniformly and intimately bringing the active compound into association with a liquid carrier or a finely divided solid carrier or both and then, if necessary, shaping the product into the desired formulation.

Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules, cachets, tablets or lozenges, each containing a predetermined amount of the active compound; as a powder or granules; or a suspension in an aqueous liquid or non-aqueous liquid such as a syrup, an elixir, an emulsion or a draught. The active compound may also be presented as a bolus, electuary or paste.

A tablet may be made by compression or moulding, optionally with one or more accessory ingredients. Compressed tablets may be prepared by compressing, in a suitable machine, the active compound being in a free-flowing form such as a powder or granules, optionally mixed with a binder, lubricant, inert diluent, surface active or dispersing agent. Moulded tablets may be made by moulding in a suitable machine, comprising a mixture of the powdered active compound with any suitable carrier.

A syrup may be made by adding the active compound to a concentrated, aqueous solution of a sugar, for example sucrose, to which may also be added any accessory ingredient. Such accessory ingredient(s) may include flavourings, an agent to retard crystallization of the sugar or an agent to increase the solubility of any other ingredient, such as polyhydric alcohol for example glycerol or sorbitol.

Formulations for rectal administration may be presented as a suppository with a usual carrier such as cocoa butter.

Formulations suitable for parenteral administration conveniently comprise a sterile aqueous preparation of the active compound which is preferably isotonic with the blood of the recipient.

In addition to the aforementioned ingredients, the formulations of this invention may further include one or more accessory ingredient(s) selected from diluents, buffers, flavouring agents, binders, surface active agents, thickeners, lubricants, preservatives (including antioxidants) and the like.

Compound (I) may be prepared by any method known in the art for the preparation of compound of analogous structure.

(1) A method of preparing compound (I) comprises cyclisation, as hereinafter described, of a compound of formula (II) or a compound of formula (III):

\[
\begin{align*}
\text{(I)} & \quad X-(CH_2)_3 \quad \text{NH} \\
\text{(II)} & \quad X-(CH_2)_3 \\
\text{(III)} & \quad \text{NH}
\end{align*}
\]

wherein X is a standard leaving group (J. March, Advanced Organic Chemistry, 2nd Ed., page 187, New York (1977)) such as halide for example chloride or bromide, hydroxide, —OR¹, imidazolyl, sulphonoxonium or tosyl; and R¹ is hydrogen or alkyl of 1 to 4 carbon atoms, preferably ethyl. Preferred compounds of formula (II) are those wherein the leaving group is a halide (such as chloride or bromide), hydroxide or toslyoxy, and preferred compounds of formula (III) are those wherein the leaving group is —OR¹ as defined. A particularly preferred method comprises cyclisation of a compound of formula (II) as hereinbefore defined, especially wherein X is chloride.

Cyclisation may be effected at room temperature or with heating for example at a temperature of 155°C—220°C, optionally in an oxygen-free atmosphere for example in nitrogen, optionally in an inert solvent such as tetrahydrofuran, dichloromethane, diethyl ether, tert-butanol, xylene, or toluene, and optionally with a catalyst. The catalyst chosen will depend on the compound of formula (II) or (III) to be cyclised, for example, where the reaction involves elimination of an acid such as hydrochloric, a basic catalyst may be used with or without a solvent such as water or an alcohol such as butanol optionally, but preferably, in the presence of a phase transfer catalyst such as triethylbenzyl ammonium chloride with or without a solvent such as dichloromethane, diethyl ether, xylene or toluene, but preferably dichloromethane. Examples of suitable basic catalysts are: an alkali metal hydride, hydroxide or alkoxide such as potassium or sodium hydride, potassium or sodium hydroxide, potassium tert-butoxide or lithium di-isopropylamid. The most preferred method of cyclisation is effected by using aqueous sodium
hydroxide in the presence of triethylbenzyl ammonium chloride at room temperature.
Where X is a slow or poor leaving group cyclisation may take place by conversion in situ to a further or better leaving group. For example where X is hydroxide, tosyl chloride may be present in the reaction mixture in order that the tosylxy group (a better leaving group) is substituted for the hydroxide group thereby causing cyclisation to proceed faster and more completely.

(2) A further method comprises reduction of a corresponding oxidised precursor of a compound of formula (I). For example reduction of N(1,3-benzodioxol-5-yl)succinimide (formula (IV)):

\[ O \begin{array}{c} \text{N} \\ \text{O} \end{array} \]

(IV)

The reducing agent employed may be selected from those known to persons skilled in the art, such as lithium aluminium hydride, di-iso-butyl aluminium hydride, diborane or a lithium trialkyl hydride (wherein the alkyl moiety has from one to four carbon atoms) in an inert solvent such as tetrahydrofuran and sodium borohydride in dilute mineral acid for example hydrochloric acid.

The compound of formula (II), (III) or (IV) may itself be prepared by analogous methods known to those skilled in the art, for example, by reacting 3,4-methylene dioxyaniline (formula (V)):

\[ \begin{array}{c} \text{NH}_2 \\ \text{O} \\ \text{O} \\ \text{CH}_2 \end{array} \]

(V)

or a salt thereof such as an acid addition salt thereof for example the hydrochloride or an alkali metal or alkaline earth metal salt thereof for example the lithium salt, with an internal ester, acid halide for example acid chloride, or acid anhydride. For example, the compound of formula (V) may be reacted with CI-(CH\textsubscript{3})\textsubscript{3}-COCI to produce a compound of formula (II) wherein X in chlorine in the presence of triethylamine in dimethoxyethane or dichloromethane.

The reaction may be carried out under the same or similar conditions as described hereinabove for cyclisation since the compound of formula (II) or (III), or the corresponding open-chain precursor of the compound of formula (IV), need not be isolated but may be cyclised in situ, for example by a method analogous those described by A. Pernot and A. Willemart in Mmoires Presentes a La Soc. Chim. 324 (1953); W. R. Schlegl, A. Catala and F. D. Popp in J. Het. Chem., 2, 379 (1965); or I Badlescu in Tetrahedron, 26 4207 (1970).

(3) A further method comprises hydrolysis of 1-(1,3-benzodioxol-5-yl)-2-iminoppyrrolidine (formula (VI)):

\[ \begin{array}{c} \text{N} \\ \text{NH} \\ \text{O} \\ \text{CH}_2 \end{array} \]

(VI)

The hydrolysis may be effected by standard hydrolysing agents known to those skilled in the art, for example, by adding a few drops of water or dilute aqueous acid to the compound.
The compound of formula (VI) may itself be prepared according to the method described by Kwok et al. in J. Org. Chem. (1967) 32, 738.

(4) A further method comprises a displacement reaction between a compound of formula (VII) and the pyrrolidinone anion formula (VIII):

wherein $X$ is a standard leaving group such as those hereinbefore described and $M^+$ is an alkali metal or alkaline earth metal cation such as Na$^+$.

(5) Another method comprises reacting 3,4-(methylenedioxy)aniline with y-butyrolactone.

(6) Another method of preparation of compound (I) comprises the conversion of the compound of formula (IX) by standard literature methods such as treatment with methylene sulphate or a dihalomethane (such as diiodomethane) with a suitable base such as potassium carbonate. The compound of formula (IX) can be prepared by reacting 3,4-dihydroxyaniline (with the hydroxy groups protected) by the method described in method (1) or (5) above (followed by deprotection of the hydroxy groups) to form the pyrrolidinone.

(7) Yet another preparation of compound I consists of subjecting a compound of formula (X) (where in $X$ as defined in method (1) above) to ring closure conditions similar to those described in method (1) above. Compounds of formula (X) can be prepared by reacting 3,4-(methylenedioxy)aniline with a compound of formula (XI), wherein $X_1$ and $X_2$ may be the same or different and as defined as $X$ in method (1) above, followed by acylation of the nitrogen by standard methods.

It will be understood from the foregoing description that what we shall claim in accordance with this invention may comprise any novel feature described herein, principally but not exclusively, for example:

(a) The compound of formula (I), chemically named 1-(1,3-benzodioxol-5-yl)-2-pyrrolidinone;

(b) A method as hereinbefore described for the preparation of the compound of formula (I), together with the compound when so prepared:

(c) A method for the preparation of a compound of formula (II), (III), (IV), (V), (VI), (VII), (IX) or (X);

(d) A pharmaceutical formulation, comprising the compound of formula (I) together with a pharmaceutically acceptable carrier therefor;

(e) A method for the preparation of a formulation of the compound of formula (I) comprising admixture of the active compound as hereinbefore defined with a pharmaceutically acceptable carrier therefor;

(f) A method for the treatment or prophylaxis of pain in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective analgesic amount of the compound of formula (I);

(g) A method for the treatment or prophylaxis of inflammation in a mammal, including man, comprising the administration to said mammal of a non-toxic, effective anti-inflammatory amount of the compound of formula (I);

(h) A method for the treatment or prophylaxis of pyrexia in a mammal, including man, comprising the
administration to said mammal of a non-toxic, effective anti-pyretic amount of compound of formula (I); or
(i) The compound of formula (I) for use in the treatment or prophylaxis of pain, inflammation or pyrexis
in a mammal, including man.

The following Examples are provided by the way of illustration of the present invention. All
temperatures indicated are in degrees Celsius.

Example 1
Preparation of 1-(1,3-Benzodioxol-5-yl)-2-pyrrolidinone

Method A

A mixture of 3,4-(methylenedioxy)aniline (200 g, 1.46 mole) and y-butyrolactone (225 ml) was heated
(in a dry nitrogen atmosphere) with stirring in a 200° oil bath for 2 days. Product was isolated from the
reaction mixture by distillation under reduced pressure (b.p. 156°, 33 u). Product was filtered over Silica Gel
60 (Trade Name) eluting with ethyl acetate. The eluant was concentrated and the crystalline product was
collected and washed with ether and petroleum ether affording 1-(1,3-benzodioxol-5-yl)-2-pyrrolidinone
(153.4 g; 51%), m.p. 89—91° which was one spot on TLC analysis.

Elemental Analysis: Calculated for C_{11}H_{12}NO_{2}: C, 64.38%; H, 5.40%; N, 6.83%. Found: C, 64.30%; H,
5.33%; N, 6.81%.

Method B

4-Chlorobutryl chloride (1095.5g, 7.77 mole) was added at 10—25°C to a mixture of 3,4-
(methylenedioxy)aniline (1000.0 g, 7.29 mole), triethylamine (748.0 g, 7.40 mole) and methylene chloride
(2500 mL). After stirring for 18 hours at ambient temperature ether was added and the butyramide
intermediate was filtered then reslurred in water. The damp butyramide was wased with methylene
chloride (10 L), 50% w/w aqueous sodium hydroxide (2000.0 g, 25.0 mole) and benzyltriethylammonium
chloride (50.0 g, 0.22 mole). After stirring 2.5 hours at ambient temperature the mixture was diluted with
water and the aqueous layer was then separated. The methylene chloride layer was washed with water,
decolourized with Darco G-60 and Filtral 19, then vacuum concentrated. Ether was added to the concentrate.
The mixture was chilled and the solids were collected and recrystallized from methylene chloride/ether
giving 2245.0 g (75%).

Example II

Analgesic Activity

A. Acetic Acid Writing Test (AAWT)

Using the procedure described by Koster et al. in Fed. Proc. 18, 412 (1959) and Vinegar et al., in
Handbook of Experimental Pharmacology, 50-2, ch. 28, Anti-Inflammatory Drugs, Ed J R Vane and S H Ferreira
(1978), the acetic acid writing test was performed, using both the mouse and the rat, to
demonstrate the mild analgesic activity of the compound (I). Comparative results are given in Table I.

<table>
<thead>
<tr>
<th>TABLE I</th>
</tr>
</thead>
<tbody>
<tr>
<td>Results of the Acetic Acid Writing Assay in the Rat</td>
</tr>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>---------------</td>
</tr>
<tr>
<td>Compound</td>
</tr>
<tr>
<td>Acetaminophen</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
<tr>
<td>Codeine Phosphate</td>
</tr>
</tbody>
</table>

B. Modified Trypsin Hyperalgesic Assay (THA)

This assay quantitatively measures analgesia and is designed to be unaffected by compounds
possessing anti-inflammatory activity. The procedure described by Vinegar et al. in Eur. J. Pharmacol. 37,
23, (1976) was used to demonstrate the analgesic activity of the compound (I) and of certain known
analgesics. The analgesic agents were administered 30 minutes after the administration of trypsin. In
addition, a modification of Vinegar's published assay was carried out, comprising the administration of the
analgesic agent preceding subplantar injection of trypsin, (0.10 ml) of 10% solution of trypsin in pyrogen-
free water) by 15 minutes. In both THA's, pain scores were determined 60 minutes after trypsin injection.
The results of the modification was to increase the sensitivity of the THA to the mild analgesic action of the
agents. The comparative results are given in Table II. Compound I is observed to be active against the 7.5 kg
force as well as the 6.0 kg force while acetaminophen was essentially inactive at 7.5 kg.
TABLE II
Results of the Modified Trypsin Hyperalgesic Assay in the Rat

<table>
<thead>
<tr>
<th>Compound</th>
<th>6.0 kg Force</th>
<th>ED\textsubscript{50} mg/kg, p.o. 7.5 kg Force</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>24 ± 5.3</td>
<td>23 ± 3.5</td>
</tr>
<tr>
<td>Acetaminophen</td>
<td>95 ± 17.2</td>
<td>1 @ 200</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1 @ 180</td>
<td>—</td>
</tr>
<tr>
<td>Codeine Phosphate</td>
<td>10 ± 1.7</td>
<td>8.8 ± 2.77</td>
</tr>
</tbody>
</table>

I = inactive

There were usually 6 rats at each dose level and at least 3 dose levels were used.

C. Rat Hot Plate Assay

The rat hot plate assay incorporated 2 modifications of the mouse hot plate assay originally described by Eddy \textit{et al.}, J. Pharmacol. Exp. Ther. 98, 121—137 (1950). The first modification was enlargement of the diameter of the cylindrical (water filled) copper plate to 25.0 cm to accommodate rats instead of mice. The second modification was the use of a temperature controller to regulate a 250 watt infrared heat lamp which was activated via a thermistor probe attached to the undersurface of the top of the copper plate. The surface temperature was thus maintained at 45 ± 1.0°C (N = 28 measurements of the hot plate temperature under experimental conditions). The time in which a rat placed on the hotplate responded by lifting, shaking or licking either or its hind or forelimbs was recorded in tenths of a second.

Only animals responding in pretest within 6-13 seconds were used in the studies. Drugs were suspended in 0.5% sodium carboxymethylcellulose and administered orally, by gavage, in a volume of 1.00 ml/100 g b.wt. 60 min prior to testing. Animals which responded in less than 18.3 seconds were considered unprotected and those which did not respond within 18.3 seconds were considered protected. The reaction time of 18.3 seconds represented the sum of the mean pretest times of 40 untreated rats plus the time of 3 standard deviations of the mean. ED\textsubscript{50}'s and their standard errors were estimated from a graph of the dose-response curves using the method of Miller and Tainter (Proc. Soc. Exp. Biol. Med. 57, 261—262 (1944). Following this procedure the analgesic activity of the compound of formula (I) was compared to that of standard analgesic drugs (Table III).

TABLE III
Results of Hot Plate Assay

<table>
<thead>
<tr>
<th>Assay</th>
<th>Compound of Formula (I)</th>
<th>Aspirin</th>
<th>Acetaminophen</th>
<th>Codeine</th>
<th>Morphine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hot Plate Assay-rat</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ED\textsubscript{50}-mg/kg</td>
<td>86 ± 16.5</td>
<td>Inactive at 360</td>
<td>Inactive at 360</td>
<td>57 ± 35.3</td>
<td>17 ± 3.6</td>
</tr>
<tr>
<td>p.o.</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hot Plate Duration of Action* Hrs</td>
<td>5.0</td>
<td>(Dose-mg/kg.</td>
<td></td>
<td>3.3</td>
<td>2.5</td>
</tr>
<tr>
<td>(Dose-mg/kg. p.o.)</td>
<td></td>
<td>(120)</td>
<td></td>
<td>(90)</td>
<td>(30)</td>
</tr>
</tbody>
</table>

* Duration of Action in Rat Hot Plate assay represents the time in hrs to reduce 1.5 times the hot plate ED\textsubscript{50} to 40% inhibition.

Example III

Acute Anti-Inflammatory Activity: Carrageenin Pleurisy Assay (CPA)

Following the procedure described by Vinegar \textit{et al.} in Proc. Soc. Exp. Biol. Med. 151, 556, (1976), the acute anti-inflammatory activity of the compound (I) was compared with that of known anti-inflammatory drugs in the rat. The average 3 hour exudate volume for each drugtreated group was determined and the % inhibition related to solvent-fed control animals calculated, the ED\textsubscript{50} being the dose required to reduce the 3 hour exudate volume by 50%


**0 065 082**

**TABLE II**

Results of Acute Anti-inflammatory Activity Assay (CPA)

All Results expressed as ED$_{50}$ mg/kg, p.o.

| 5  | Aspirin      | 28 ± 3.2       |
| 10 | Acetaminophen| 172 ± 22.4     |
| 10 | Compound I   | 48 ± 10.5      |

Example IV

Antipyretic Activity

The Yeast-Induced Hyperthermia Assay was used according to the procedure described by Khalili-Varasteh et al. in Arch. Int. Pharmacodyn. 213, 149—159, (1976) to demonstrate the antipyretic activity of compound I and certain known antipyretics in the rat. The results as shown in Table III.

**TABLE V**

Results of Antipyretic Activity Assay

All results are expressed as ED$_{50}$ mg/kg

<table>
<thead>
<tr>
<th>20</th>
<th>Assay</th>
<th>Compound I</th>
<th>Aspirin</th>
<th>Acetaminophen</th>
</tr>
</thead>
<tbody>
<tr>
<td>25</td>
<td>Rat Yeast Hyperthermia (p.o.)</td>
<td>67 ± 4.2</td>
<td>50 ± 8.1</td>
<td>72 ± 8.6</td>
</tr>
</tbody>
</table>

Example V

**Pharmaceutical Formulations**

**A. Capsule**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per Capsule (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>325.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>174.0</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>174.0</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>2.0</td>
</tr>
</tbody>
</table>

The finely ground active compound was mixed with the powdered excipients lactose, corn starch and stearic acid and packed into gelatin capsule.

**B. Tablet**

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per tablet (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>325.0</td>
</tr>
<tr>
<td>Lactose</td>
<td>125.0</td>
</tr>
<tr>
<td>Corn Starch</td>
<td>50.0</td>
</tr>
<tr>
<td>Polyvinylpyrrolidone</td>
<td>3.0</td>
</tr>
<tr>
<td>Stearic Acid</td>
<td>1.0</td>
</tr>
<tr>
<td>Magnesium stearate</td>
<td>1.0</td>
</tr>
</tbody>
</table>

The active compound was finely ground and intimately mixed with the powdered excipients lactose, corn starch, polyvinylpyrrolidone, magnesium stearate and stearic acid. The formulation was then compressed to afford one tablet weighing 505 mg.
C. Suppository

<table>
<thead>
<tr>
<th>Ingredient</th>
<th>Amount per suppository</th>
</tr>
</thead>
<tbody>
<tr>
<td>Compound I</td>
<td>325.0 mg</td>
</tr>
<tr>
<td>Cocoa Butter, q.s.</td>
<td>2.0 g</td>
</tr>
<tr>
<td>or Wecobee Base</td>
<td></td>
</tr>
</tbody>
</table>

Wecobee is the trade name of a hydrogenated carboxylic acid.

Example VI

Toxicity
The LD₉₀ of compound (I) in the rat (p.o.) was found to be 447 ± 22.0 mg/kg for the male and 435 ± 17.6 mg/kg for the female. This is well above the therapeutic range.

Claims

1. The compound of formula (II) chemically named 1-(1,3-benzodioxol-5-yl)-2-pyrrolidinone.

2. A pharmaceutical formulation comprising the compound of formula (II) as defined in claim 1 together with a pharmaceutically acceptable carrier therefor.

3. A pharmaceutical formulation as claimed in claim 2 in unit dosage form.

4. A pharmaceutical formulation as claimed in claim 2, characterised by being in the form of a tablet, syrup, suppository or sterile aqueous preparation.

5. A pharmaceutical formulation as claimed in either of claims 2, 3 or 4, wherein the compound of formula (I) as defined in claim 1 is combined with a therapeutic ingredient.

6. A method for the preparation of the compound of formula (I) as defined in claim 1, which method comprises:
   a) cyclisation of a compound of formula (II) or a compound of formula (III)

wherein X is a standard leaving group.
b) reduction of \( N(1,3\text{-}\text{benzodioxol-5-yl})\text{succinimide} \) (formula (IV))

![Chemical Structure](image)

(IV)

15 c) hydrolysis of 1-(1,3-benzodioxol-5-yl)-2-imino-pyrrolidine (formula (VII))

![Chemical Structure](image)

(VI)

d) reaction of a compound of formula (VII), and the pyrrolidinone anion (formula (VIII))

![Chemical Structure](image)

(VII)

(VIII)

wherein \( X \) is a standard leaving group.

e) reaction of 3,4(methylene dioxy) aniline with \( \gamma \)-butyrolactone

f) conversion of the compound of formula (IX) or

g) cyclisation of a compound of formula (X)

![Chemical Structure](image)

(IX)

(X)

7. A process according to claim 6a characterised in that the method comprises cyclisation of a compound of formula (II) or a compound of formula (III), wherein \( X \) is a standard leaving group, in the presence of an aqueous alkali, metal hydride, hydroxide or alkoxide, and a phase transfer catalyst.

8. The compound of formula (I) as defined in claim 1 for use in the treatment of mammals including man by therapy.
9. The compound of formula (I) as defined in claim 1 for use in the treatment of prophylaxis of pain, inflammation or pyrexia in a mammal, including man.

10. The compound of formula (I) as defined in claim 1 for use in treatment or prophylaxis of pain, inflammation of pyrexia in a mammal including man, such as that resulting from headache, pain following dental procedures, oral and general surgery, dysmenorrhea, myalgia, pain of unresectable cancer, joint and peripheral nerve disorders, rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other conditions associated with pain, inflammation and fever.

10 Patentansprüche

1. 1-(1,3-Benzdioxo-5-yl)-2-pyrrolidinon der Formel (I)

\[
\begin{align*}
\text{N} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CH}_2 & \\
\end{align*}
\]

(1)

2. Pharmazeutische Zubereitung, enthaltend die Verbindung der Formel (I), wie in Anspruch 1 definiert, zusammen mit einem pharmazeutisch brauchbaren Träger.

3. Pharmazeutische Zubereitung nach Anspruch 2 in Form einer Einzeldosierung.

4. Pharmazeutische Zubereitung nach Anspruch 2, dadurch gekennzeichnet, daß sie in Form einer Tablette, eines Sirups, eines Suppositoriums oder als sterile wässrige Zubereitung vorliegt.

5. Pharmazeutische Zubereitung nach Anspruch 2, 3 oder 4, in der die Verbindung der Formel (I), wie in Anspruch 1 definiert, mit einem therapeutischen Wirkstoff kombiniert ist.

6. Verfahren zur Herstellung der Verbindung der Formel (I), wie in Anspruch 1 definiert, bestehend aus

(a) Cyclisierung einer Verbindung der Formel (II) oder einer Verbindung der Formel (III)

\[
\begin{align*}
\text{X} & \quad \text{-(CH}_2\text{)}_3 & \\
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CH}_2 & \\
\end{align*}
\]

(II)

\[
\begin{align*}
\text{X} & \quad \text{-(CH}_2\text{)}_3 & \\
\text{NH} & \quad \text{O} \\
\text{O} & \quad \text{O} \\
\text{CH}_2 & \\
\end{align*}
\]

(III)

in der X eine übliche austretende Gruppe bedeutet;

55
(b) Reduzierung von N-(1,3-Benzodioxol-5-yl)-succinimid (Formel IV)

(c) Hydrolyse von 1-(1,3-Benzodioxol-5-yl)-2-iminopyrrolidin (Formel VI)

(d) Reaktion einer Verbindung der Formel (VII) mit dem Pyrrolidon-anion (Formel VIII)

in der X eine herkömmliche austretende Gruppe bedeutet;
(e) Reaktion von 3,4-(Methylenedioxy)-anilin mit γ-Butyrolacton;
(f) Umwandlung der Verbindung der Formel (IX) oder
g) Cyclisierung einer Verbindung der Formel (X).

7. Verfahren nach Anspruch 6 (a), dadurch gekennzeichnet, daß das Verfahren die Cyclisierung einer Verbindung der Formel (II) oder einer Verbindung der Formel (III), in der X eine bekannte austretende Gruppe bedeutet, in Gegenwart eines wäßrigen Alkali, Metallhydrids, Hydroxids oder Alkoxids und eines Phasentransfer-katalysators, umfaßt.
8. Verbindung der Formel (I), wie in Anspruch 1 definiert, zur Verwendung in der therapeutischen Behandlung von Säugetieren einschließlich des Menschen.

**Revendications**

1. Composé de formule (I):

![Structure de la formule (I)](image1)

dit 1-(1,3-benzodioxol-5-yl)-2-pyrroolidinone en nomenclature chimique.

2. Formulation pharmaceutique comprenant le composé de formule (I) tel que défini dans la revendication 1, conjointement avec un excipient pharmaceutiquement acceptable.

3. Formulation pharmaceutique suivant la revendication 2, sous forme dosée unitaire.

4. Formulation pharmaceutique suivant la revendication 2, caractérisée en ce qu’elle est présentée sous forme d’un comprimé, d’un sirop, d’un suppositoire ou d’une préparation aqueuse stérile.

5. Formulation pharmaceutique suivant la revendication 2, 3 ou 4, dans laquelle le composé de formule (I) tel que défini dans la revendication 1 est combiné avec un constituant thérapeutique.

6. Procédé de préparation du composé de formule (I) tel que défini dans la revendication 1, lequel procédé comprend:

   a) la cyclisation d’un composé de formule (II) ou d’un composé de formule (III):

![Structure de la formule (II)](image2)

![Structure de la formule (III)](image3)

où X représente un radical partant ordinaire.
b) la réduction du N-(1,3-benzodioxol-5-yl)-succinimide (formule (IV)):

\[
\begin{align*}
&\text{N} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2 \\
&\text{O} \\
&\text{N} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2
\end{align*}
\]

(IV)

10

15
c) l'hydrolyse de la 1-(1,3-benzodioxol-5-yl)-2-iminopyrrolidone (formule (VI)):

\[
\begin{align*}
&\text{N} \\
&\text{NH} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2 \\
&\text{O} \\
&\text{N} \\
&\text{O}
\end{align*}
\]

(VI)

20

25
d) la réaction d'un composé de formule (VII) avec l'anion pyrrolidinone (formule (VIII)):

\[
\begin{align*}
&X \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2 \\
&\text{O} \\
&\text{O} \\
&\text{N}
\end{align*}
\]

(VII)

\[
\begin{align*}
&\text{N} \\
&\text{O}
\end{align*}
\]

(VIII)

30

35

40

ou X représente un radical partant ordinaire;
e) la réaction de la 3,4-(méthylènedioxyl)aniline avec la γ-butyrolactone;
f) la conversion du composé de formule (IX), ou
g) la cyclisation d'un composé de (formule X):

\[
\begin{align*}
&\text{N} \\
&\text{O} \\
&\text{O} \\
&\text{OH} \\
&\text{OH} \\
&\text{CH}_2 \\
&\text{O} \\
&\text{N} \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2
\end{align*}
\]

(IX)

\[
\begin{align*}
&\text{N} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_3 \\
&\text{CH}_2 \\
&\text{O} \\
&\text{O} \\
&\text{O} \\
&\text{CH}_2 \\
&\text{O} \\
&\text{N} \\
&\text{O} \\
&\text{O}
\end{align*}
\]

(X)

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7. Procédé suivant la revendication 6a, caractérisé en ce que le procédé comprend la cyclisation d'un composé de formule (II) ou d'un composé de formule (III), où X représente un radical partant ordinaire, en présence d'un hydrure, hydroxyde ou alcoolate de métal alcalin aqueux et d'un catalyseur de transfert de phase.

8. Composé de formule (I) tel que défini dans la revendication 1 à utiliser pour le traitement de
mammifères y compris l'être humain à des fins thérapeutiques.

9. Composé de formule (I) tel que défini dans la revendication 1 à utiliser pour le traitement ou la prophylaxie de la douleur, de l'inflammation et de la pyrexie chez un mammifère y compris l'être humain.

10. Composé de formule (I) tel que défini dans la revendication 1 à utiliser pour le traitement ou la prophylaxie de la douleur, de l'inflammation ou de la pyrexie chez un mammifère, y compris l'être humain, souffrant, par exemple, de céphalées, de maux de dents, de douleurs consécutives à des interventions de dentisterie générale et de la chirurgie orale et générale ou à la dysménorrhée, de myalgie, de douleurs d'un cancer inopérable, d'affections articulaires et nerveuses périphériques, d'arthrite rhumatoïde, de spondylite rhumatoïde, d'ostéoarthrite, d'arthrite goutteuse et d'autres états arthritiques associés à de la douleur, de l'inflammation et de la fièvre.