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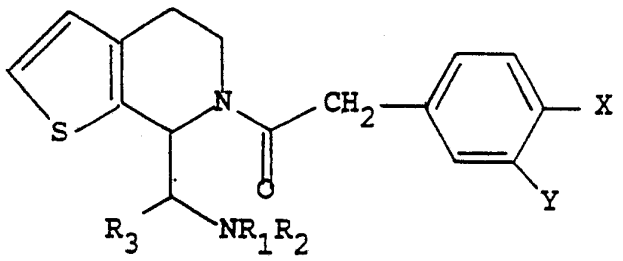
(54) Title: TETRAHYDROTHIENO(2,3-c)PYRIDINE DERIVATIVES, PROCESS FOR THEIR PREPARATION AND THEIR PHARMACEUTICAL APPLICATION



(I)

(57) Abstract

Tetrahydrothionopyridine derivatives of formula (I) with kappa-receptor agonist activity are potentially useful in the treatment of *inter alia* pain and cerebral ischaemia. X and Y, which may be the same or different, are each hydrogen, halogen, trifluoromethyl or together form a $-CO(CH_2)_3-$ or $-(CH_2)_n-$ group, in which n is 3 or 4; R_1 and R_2 are each independently hydrogen, linear or branched C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkyl alkyl or together form a C_{2-8} polymethylene group; and R_3 is hydrogen or methyl.

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Tetrahydrothieno(2,3-c)pyridine derivatives, process for their preparation and their pharmaceutical application.

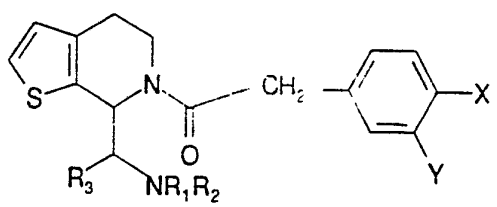
This invention is concerned with novel heterocyclic derivatives, processes for their preparation, and their use in medicine.

Compounds which are kappa-receptor agonists act as analgesics through interaction with kappa opioid receptors. The advantage of kappa-receptor agonists over the classical μ-receptor agonists, such as morphine, lies in their ability to cause analgesia while being devoid of morphine-like behavioural effects and addiction liability.

EP-A-333427 and 370732 disclose groups of heterocyclic derivatives which exhibit kappa-receptor agonism without some of the behavioural effects of morphine and morphine analogues, and which are thus of potential therapeutic utility as analgesics.

A small class of heterocyclic derivatives falling within the scope of one or other of the above European Applications, but not specifically disclosed therein, has now been discovered which also exhibit potent kappa receptor agonism without some of the undesirable behavioural effects of morphine and morphine analogues, and are therefore of potential use in the treatment of pain. This novel class of derivatives also possess diuretic activity which indicates that they are of potential use in the treatment of hyponatraemic disease states in mammals. The novel class of derivatives are also of potential use in the treatment of other conditions which respond to administration of kappa agonists, in particular convulsions, cough, asthma, inflammation (including inflammation pain), pancreatitis, arrhythmias and cerebral ischaemia.

According to the present invention there is provided a compound, or a solvate or salt thereof, of formula (I):



(I)

in which:

in which:

X and Y, which may be the same or different, are each hydrogen, halogen, trifluoromethyl or together form a $-CO(CH_2)_3-$ or $-(CH_2)_n-$ group, in which n is 3 or 4;
R_1 and R_2 are each independently hydrogen, linear or branched C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkyl alkyl or together form a C_{2-8} polymethylene group;
and R_3 is hydrogen or methyl.

Examples of X and Y are, respectively, chlorine and chlorine, trifluoromethyl and hydrogen, and $-CO(CH_2)_3-$.

Examples of R_1 and R_2 are $-(CH_2)_4-$ and methyl.

The compounds of formula (I) or their salts or solvates are preferably in pharmaceutically acceptable or substantially pure form. By pharmaceutically acceptable form is meant, inter alia, of a pharmaceutically acceptable level of purity excluding normal pharmaceutical additives such as diluents and carriers, and including no material considered toxic at normal dosage levels.

A substantially pure form will generally contain at least 50% (excluding normal pharmaceutical additives), preferably 75%, more preferably 90% and still more preferably 95% of the compound of formula I or its salt or solvate.

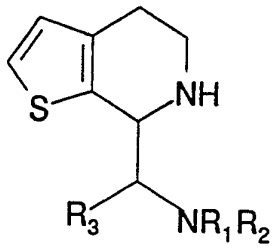
One preferred pharmaceutically acceptable form is the crystalline form, including such form in a pharmaceutical composition. In the case of salts and solvates the additional ionic and solvent moieties must also be non-toxic.

Examples of pharmaceutically acceptable salt of a compound of formula (I) include the acid addition salts with the conventional pharmaceutical acids, for example, maleic, hydrochloric, hydrobromic, phosphoric, acetic, fumaric, salicylic, citric, lactic, mandelic, tartaric, succinic, benzoic, ascorbic and methanesulphonic.

Examples of pharmaceutically acceptable solvates of a compound of formula (I) include hydrates.

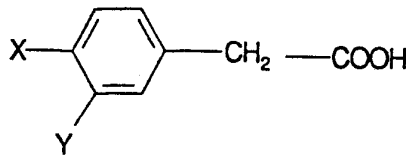
The compounds of formula (I) have an asymmetric centre and therefore exist in more than one stereoisomeric form. The invention extends to all such forms and to mixtures thereof, including racemates.

The present invention also provides a process for the preparation of a compound of formula (I) which comprises reacting a compound of formula (II):



(II)

in which R_1, R_2 and R_3 are as defined for formula (I), with a compound of formula (III):



(III)

or an active derivative thereof, in which X and Y are as defined for formula (I), and then optionally forming a salt and/or solvate of the obtained compound of formula (I).

Suitable active derivatives of the compound of formula (III) are the acid chloride or acid anhydride. Another suitable derivative is a mixed anhydride formed between the acid and an alkyl chloroformate.

For example, in standard methods well known to those skilled in the art,

the compound of formula (II) may be coupled:

a) with an acid chloride in the presence of an inorganic or organic base,

b) with the acid in the presence of dicyclohexyl carbodiimide, N-dimethylaminopropyl-N'-ethyl carbodiimide or carbonyl diimidazole,

c) with a mixed anhydride generated in situ from the acid and an alkyl (for example ethyl)chloroformate.

The compounds of formula (I) may be converted into their pharmaceutically acceptable acid addition salts by reaction with the appropriate organic or mineral acids.

Solvates of the compounds of formula (I) may be formed by crystallization or recrystallization from the appropriate solvent. For example hydrates may be formed by crystallization or recrystallization from aqueous solutions, or solutions in organic solvents containing water.

Also salts or solvates of the compounds of formula (I) which are not pharmaceutically acceptable may be useful as intermediates in the production of pharmaceutically acceptable salts or solvates. Accordingly such salts or solvates also form part of this invention.

As mentioned before, the compounds of formula (I) exist in more than one stereoisomeric form and the processes of the invention produces mixtures thereof. The individual isomers may be separated one from another by resolution using an optically active acid such as tartaric acid. Alternatively, an asymmetric synthesis would offer a route to the individual form.

Compounds of formula (II) may themselves be prepared according to methods disclosed in the aforementioned EP-A-333427.

Compounds of formula (III) are known compounds, or can be prepared from known compounds by known methods (see for example, J.O.C. 27 (1960), 70-76; Chem. Lett.(1981), 367-370).

The activity of the compounds of formula (I) in standard tests indicates

that they are of potential therapeutic utility in the treatment of pain, cerebral ischaemia, hyponatraemic disease states, convulsions, cough, asthma, inflammation (including inflammation pain) pancreatitis and arrythmias (hereinafter referred to as the Conditions).

Accordingly the present invention also provides a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

The present invention further provides a pharmaceutical composition comprising a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

The present invention also provides the use of a compound of formula (I), or a pharmaceutically acceptable salt or solvate thereof, (hereinafter referred to as the Compounds) in the manufacture of a medicament for the treatment of the Conditions.

The present invention also provides a method for the treatment and/or prophylaxis of the Conditions in mammals, particularly humans, which comprises administering to the mammal in need of such treatment and/or prophylaxis an effective amount of the Compound.

Medicaments and compositions containing the Compounds may be prepared by admixture of a Compound with an appropriate carrier, which may contain a diluent, binder, filler, disintegrant, flavouring agent, colouring agent, lubricant or preservative in conventional manner.

These conventional excipients may be employed for example as in the preparation of compositions of known agents for the treatment of the Conditions.

Preferably, a medicament or pharmaceutical composition of the invention is in unit dosage form and in a form adapted for use in the medical or veterinarial fields. For example, such preparations may be in a pack form accompanied by written or printed instructions for use as an agent for the treatment of each of the Conditions.

The suitable dosage range for a Compound depends on the Compound to be employed, the Condition to be treated, and on the condition of the patient. It will also depend, inter alia, upon the relation of potency to absorbability and the frequency and route of administration.

The Compound may be formulated for administration by any route, and is preferably in unit dosage form or in a form that a human patient may administer to himself in a single dosage. Advantageously, the composition is suitable for oral, rectal, topical, parenteral, intravenous or intramuscular administration. Preparations may be designed to give slow release of the active ingredient.

Compositions may, for example, be in the form of tablets, capsules, sachets, vials, powders, granules, lozenges, reconstitutable powders, or liquid preparations, for example solutions or suspensions, or suppositories.

The compositions, for example those suitable for oral administration, may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tabletting lubricants, for example magnesium stearate; disintegrants, for example starch, polyvinylpyrrolidone, sodium starch glycollate or microcrystalline cellulose; or pharmaceutically acceptable setting agents such as sodium lauryl sulphate.

Solid compositions may be obtained by conventional methods of blending, filling, tabletting or the like. Repeated blending operations may be used to distribute the active agent throughout those compositions employing large quantities of fillers. When the composition is in the form of a tablet, powder, or lozenge, any carrier suitable for formulating solid pharmaceutical compositions may be used, examples being magnesium stearate, starch, glucose, lactose, sucrose, rice flour and chalk. Tablets may be coated according to methods well known in normal pharmaceutical practice, in particular with an enteric coating. The composition may also be in the form of an ingestible capsule, for example of gelatin containing the compound, if desired with a carrier or other excipients.

Compositions for oral administration as liquids may be in the form of, for example, emulsions, syrups, or elixirs, or may be presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid compositions may contain conventional additives such as suspending agents, for example sorbitol, syrup, methyl cellulose, gelatin, hydroxyethylcellulose, carboxymethylcellulose, aluminium stearate gel, hydrogenated edible fats; emulsifying agents, for example lecithin, sorbitan monooleate, or acacia; aqueous or non-aqueous vehicles, which include edible oils, for example almond oil, fractionated coconut oil, oily esters, for example esters of glycerine, or propylene glycol, or ethyl alcohol, glycerine, water or normal saline; preservatives, for example methyl or propyl p-hydroxybenzoate or sorbic acid; and if desired conventional flavouring or colouring agents.

The Compounds may also be administered by a non-oral route. In accordance with routine pharmaceutical procedure, the compositions may be formulated, for example, for rectal administration as a suppository or for topical administration as a cream or lotion. They may also be formulated for presentation in an injectable form in an aqueous or non-aqueous solution, suspension or emulsion in a pharmaceutically acceptable liquid, e.g. sterile pyrogen-free water or a parenterally acceptable oil or a mixture of liquids. The liquid may contain bacteriostatic agents, anti-oxidants or other preservatives, buffers or solutes to render the solution isotonic with the blood, thickening agents, suspending agents or other pharmaceutically acceptable additives. Such forms will be presented in unit dose form such as ampoules or disposable injection devices or in multi- dose forms such as a bottle from which the appropriate dose may be withdrawn or a solid form or concentrate which can be used to prepare an injectable formulation.

The Compounds may also be administered by inhalation, via the nasal or oral routes. Such administration can be carried out with a spray formulation comprising a Compound and a suitable carrier, optionally suspended in, for example, a hydrocarbon propellant.

Preferred spray formulations comprise micronised Compound particles in combination with a surfactant, solvent or a dispersing agent to prevent the sedimentation of suspended particles. Preferably, the Compound

particle size is from about 2 to 10 microns.

A further mode of administration of the Compounds comprises transdermal delivery utilising a skin-patch formulation. A preferred formulation comprises a Compound dispersed in a pressure sensitive adhesive which adheres to the skin, thereby permitting the Compound to diffuse from the adhesive through the skin for delivery to the patient. For a constant rate of percutaneous absorption, pressure sensitive adhesives known in the art such as natural rubber or silicone can be used.

The effective dose of Compound depends on the particular Compound employed, the Condition to be treated, the condition of the patient and on the frequency and route of administration. A unit dose will generally contain from 20 to 1000 mg and preferably will contain from 30 to 500 mg, in particular 50, 100, 150, 200, 250, 300, 350, 400, 450, or 500 mg. The composition may be administered once or more times a day for example 2, 3 or 4 times daily, and the total daily dose for a 70 kg adult will normally be in the range 100 to 3000 mg. Alternatively the unit dose will contain from 2 to 20mg of active ingredient and be administered in multiples, if desired, to give the preceding daily dose.

No unacceptable toxicological effects are expected when the Compounds are administered in accordance with the invention.

Compounds of this invention and their preparation are illustrated in the following Examples and compounds of the Examples are summarised in Table I. The pharmacological data are summarised in Table II.

Example 1

6-(3,4-dichlorophenyl)acetyl-7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride

1.5 g (6.76 mmoles) of 7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine were dissolved in 40 ml of dry chloroform.
1.9 g (13.76 mmoles) of anhydrous potassium carbonate were added and the slurry cooled at -5°C.
1.7 g (7.60 mmoles) of distilled 3,4-dichlorophenylacetyl chloride, dissolved in 10 ml of dry chloroform, were added dropwise. The reaction mixture was kept at +5°C 1 hour and then allowed to reach room temperature.
20 ml of water were added, the organic layer was separated, washed twice with water, dried over Na_2SO_4 and evaporated in vacuo to dryness.
The residue was flash chromatographed on silica gel, eluting with a mixture of n-hexane/AcOEt, 35:15 respectively, containing 0.3% of 28% NH_4OH, to afford 2.0 g of the free base, which was dissolved in 40 ml of ethyl acetate containing 10% of acetone and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried, to yield 1.7 g of the title compound.

$C_{20}H_{22}Cl_2N_2OS$ .HCl

M.P. = 206-208°C
M.W. = 445.837

Elemental analysis: Calcd.: C, 53.87; H, 5.20; N, 6.28; Cl, 23.86; S, 7.19;
Found : C, 53.74; H, 5.21; N, 6.25; Cl, 23.74; S, 7.16.

I.R. (KBr) : 3450, 2980, 1630, 1420 cm^{-1}

N.M.R. ($CDCl_3$): 80 MHz δ 11.80 (s broad, 1H); 7.15-7.45 (m, 4H); 6.79 (d, J=5 Hz, 1H); 6.20 (dd, 1H); 3.40-4.45 (m, 7H); 2.40-3.15 (m, 5H); 1.90-2.30 (m, 4H).

Example 2

6-(4-trifluoromethylphenyl)acetyl-7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride monohydrate

Prepared as described in Example No. 1, from 1.7 g (7.65 mmoles) of 7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno [2,3-c]pyridine, 2.12 g (15.36 mmoles) of anhydrous potassium carbonate and 1.88 g (8.40 mmoles) of distilled 4-trifluoromethylphenylacetyl chloride in 50 ml of dry chloroform. The crude product was dissolved in 30 ml of ethyl acetate and the solution brought to acidic pH with HCl/Et_2O.
The precipitate was filtered and recrystallized from 70 ml of ethyl acetate to yield 1.81 g of the title compound.

$C_{21}H_{23}F_3N_2OS \cdot HCl \cdot H_2O$

M.P. = 140-145°C
M.W. = 462.953

Elemental analysis: Calcd.: C, 54.48; H, 5.66; N, 6.05; Cl, 7.66; F, 12.31; S, 6.93;
Found : C, 54.07; H, 5.60; N, 5.97; Cl, 7.58; F, 12.18; S, 6.93.

I.R. (KBr) : 3480, 3350, 1645, 1632, 1322 cm^{-1}

N.M.R. ($CDCl_3$): δ 11.85 (s broad, 1H); 7.40-7.70 (m, 4H); 7.21 (d, 1H); 6.78 (d, 1H); 6.20 (dd, 1H); 3.30-4.45 (m, 7H); 1.85-3.20 (m, 9H); 1.80 (s, H_2O).
80 MHz

Example 3

6-(3,4-dichlorophenyl)acetyl-7-dimethylaminomethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride

Prepared as described in Example No. 1, from 1.1 g (5.60 mmoles) of 7-dimethylaminomethyl-4,5,6,7-tetrahydrothieno[2,3-c] pyridine, 1.8 g (13.04 mmoles) of anhydrous potassium carbonate and 1.6 g (7.19 mmoles) of distilled 3,4-dichlorophenylacetyl chloride in 30 ml of dry chloroform.
The crude product was purified by silica gel flash column

chromatography, eluting with a mixture of CH_2Cl_2 , MeOH, 28% NH_4OH , 95:5:0.5 respectively, to afford the pure free base which was dissolved in 40 ml of ethyl acetate and the solution was brought to acidic pH with HCl/Et_2O.
The precipitate was filtered, washed and dried, to yield 1.60 g of the title compound.

$C_{18}H_{20}Cl_2N_2OS$ .HCl

M.P. = 249-251°C
M.W. = 419.801

Elemental analysis: Calcd.: C, 51.50; H, 5.04; N, 6.67; Cl,25.34; S, 7.64;
Found : C, 51.48; H, 5.03; N, 6.64; Cl,25.28; S, 7.68.

I.R. (KBr) : 3430, 2960, 1625, 1420 cm^{-1}

Example 4

6-[1-oxo-3,4-dihydro-(2H)-napht-6-yl]acetyl-7-dimethylaminomethyl -4,5,6,7-tetrahydrothieno[2,3-c]pyridine

Prepared as described in Example No. 1, from 1.1 g (5.60 mmoles) of 7-dimethylaminomethyl-4,5,6,7-tetrahydrothieno[2,3-c] pyridine, 1.0 g (7.24 mmoles) of anhydrous potassium carbonate and 1.48 g (6.61 mmoles) of crude 1-oxo-3,4-dihydro-(2H)-napht-6-yl acetyl chloride in 35 ml of dry chloroform.
The crude product was purified by silica gel flash column chromatography, eluting with ethyl acetate containing 1.5% of methanol and 0.5% of 28% NH_4OH.
The pure free base was recrystallized from 50 ml of ethyl acetate to yield 1.52 g of the title compound.

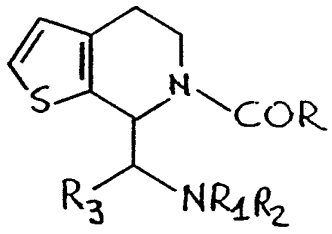
$C_{22}H_{26}N_2O_2S$

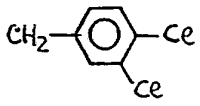
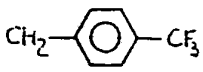
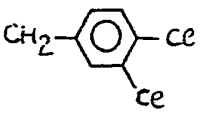
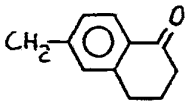
M.P. = 129-130°C
M.W. = 382.510

Elemental analysis: Calcd.: C,69.08; H,6.85; N,7.32; S,8.38;
Found : C,68.88; H,6.87; N,7.19; S,8.22.

I.R. (KBr) : 3540, 2940, 1685, 1675, 1645, 1605, 1430 cm^{-1}

TABLE I



Example No.	R	R1 R2	R3	MOLECULAR FORMULA	MELTING POINT (°C)
1		-(CH2)4-	H	$C_{20}H_{22}Cl_2N_2OS$ .HCl	206-208
2		-(CH2)4-	H	$C_{21}H_{23}F_3N_2OS.HCl.H_2O$	140-145
3		Me Me	H	$C_{18}H_{20}Cl_2N_2OS$ .HCl	249-251
4		Me Me	H	$C_{22}H_{26}N_2O_2S$	129-130

The pharmacological activity of the compounds of this invention is illustrated by various in vitro and in vivo models, using the following test procedures.

PHARMACOLOGICAL TESTS

A) P-phenylquinone-induced abdominal writhing test in mice

The methodology employed is based on that described by Sigmund et al, Proc. Soc. Exptl. Biol. 95, 729/1957, modified by Milne and Twomey, Agents and Actions, 10, 31/1980.

Male Charles River mice (Swiss Strain), 25-36g body weight, were used. Animals were allowed food and water ad libitum and were randomized into groups of 10 prior to experimentation. Test compounds were dissolved in either distilled water or distilled water plus 0.1 M AMS, and administered by the subcutaneous route in a final volume of 10 ml/Kg. Control animals received 10 ml/Kg of the appropriate vehicle alone. Following a pretreatment period of 20 min., mice were injected intraperitoneally with p-phenylquinone, 2 mg/Kg at 37°C in a final volume of 10 mg/Kg. Next, the mice were placed, in groups of 3, in a compartmented perspex box maintained at room temperature and were observed for a period of 8 min. During this period the number of abdominal writhing responses per animal were recorded where writhing consists of an intermittent contraction of the abdomen associated with hind leg extension.

The degree of antinociceptive protection afforded by the test compound was determined as the mean number of writhing responses observed in the treated group (T) expressed as a percentage of the mean number of writhing responses in the

control group (C) according to the following formula:

[1-(T/C]x100% = % graded protection

B) Tail-flick test in mice

The methodology employed is based on that described by D'Amour and Smith, J. Pharmacol. Exp. Ther. 72, 74/1941.

Male Charles River mice (Swiss Strain), 22-34g body weight were used. Animals were allowed food and water ad libitum and were randomized into groups of 10 prior to experimentation. Before administration of the test compound, the reaction time of each animal was determined by focusing a beam of light onto the tail, eliciting a reflex withdrawal after a certain latency; only mice exhibiting a latency between 3-8 sec. were used subsequently in the evaluation of drug effects.

Test compounds were dissolved in either distilled water or distilled water plus 0.1 M AMS and administered by the subcutaneous route in a final volume of 10 ml/Kg. Control animals received 10 ml/kg of the appropriate vehicle alone. Following a pretreatment period of 30 min., the mice were again placed under the heat source and the reaction tine re-determined.

Percentage quantal protection was determined as the number of mice in which the reaction time was doubled compared to pretreatment values, expressed as a percentage of the total number of mice in the group.

RECEPTOR AFFINITY STUDY

Tissue Preparation

Radio receptor binding to kappa site is performed on fresh guinea pig brain homogenates prepared according to Kosterlitz (1981).

Whole brain without cerebellum is homogenized in 50 mM Tris-buffer (pH 7.4 at 0°C) and centrifuged at 49,000 xg for 10 min.

The pellet is then resuspended in the same buffer, incubated at 37°C for 45 min and centrifuged again.

1.9 ml of the final homogenate (1:100 in Tris pH 7.4, 0°C) is used for the binding assay.

Binding to kappa sites

The binding to the kappa sites is performed using a tritiated kappa selective compound. Final homogenate with solutions of the cold ligand and of the labelled ligand is incubated for 40 min at 25°C, filtered through Whatman GF/C glass filter discs and washed.
The radioactivity bound to the filters is counted by liquid scintillation spectrophotometry.

The non-specific binding is determined in the presence of 500 nM of the benzomorphan non-selective compound Mr 2266.

Binding to mu sites (Magnan J., 1982)

^{3}H[D-Ala^{2}, MePhe^{4}, Gly-ol^{5}] Enkephalin (^{3}H-DAGO), an enkephalin analogue that binds selectively to mu receptor, is added to the biological substrate and incubated at 25°C for 40 min, filtered through Whatman GF-C and washed with ice-cold Tris-buffer.

The filters are then dried, solubilized in Filtercount and the radioactivity monitored. Non-specific binding is determined in the presence of 10^{-6} M naloxone.

Binding to delta sites (Magnan J., 1982)

For binding experiments, ^{3}H-DADLE, which binds to mu and delta sites, is used in the presence of 30 nM of unlabelled DAGO to prevent mu binding. A concentration of radioligand near KD is used in the binding assays evaluating compounds of the invention. Non-specific binding is determined by addition of Mr 2266 2.5 µM.

The tubes are incubated for 40 min at 25°C and bound ligand is separated from free by filtration through Whatman GF/C filters. The level of bound radioactivity of the filters is measured by liquid scintillation after solubilization in Filtercount.

The equilibrium dissociation constant (KD) and the maximum binding capacity (Bmax) are determined from the analysis of saturation curves, while the inhibition constant (Ki) is determined from the analysis of competition experiments (Hill 1910; Scatchard 1949; Cheng and Prusoff 1973; Gillan et al 1980).

Published references are summarized as follows:

- Hill, A.V. (1910): J. Physiol. 40, IV-VIII
- Scatchard G. (1949): Ann. N.Y. Acad. Sci. 51, 660-674
- Cheng and Prusoff W.H. (1973): Biochem. Pharmac. 22, 3099-3102
- Gillan M.C.G., Kosterlitz H.W. and Paterson S.Y. (1980): Br. J. Pharmac. 70, 481-490
- Kosterlitz H.W., Paterson S.Y. and Robson L.E. (1981): Br. J. Pharmac. 73, 939-949
- Magnan J., Paterson S.Y., Tavani A. and Kosterlitz H.W. (1982): Arch. Pharmacol. 319, 197-205.

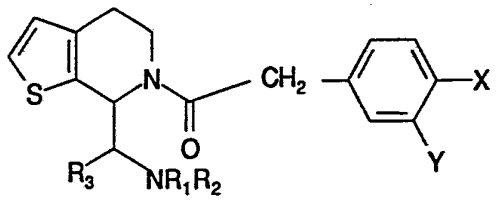
TABLE II

Pharmacological data

Example No.	ANALGESIA		RECEPTOR BINDING AFFINITY	
	MW ED_{50} mg/kg s.c.	MTF ED_{50} mg/kg s.c.	kappa K_i nM	mu K_i nM
1	0.002	0.030	0.46	47
2	0.004	0.039	0.49	21
3	0.020	0.386	0.51	316
4	0.007	0.091	0.90	ca 100

Claims

1. A compound, or salt or solvate thereof, of formula (I):



(I)

in which:
X and Y, which may be the same or different, are each hydrogen, halogen, trifluoromethyl or together form a $-CO(CH_2)_3-$ or $-(CH_2)_n-$ group, in which n is 3 or 4;
R_1 and R_2 are each independently hydrogen, linear or branched C_{1-6} alkyl, C_{3-6} cycloalkyl or C_{4-12} cycloalkyl alkyl or together form a C_{2-8} polymethylene group;
and R_3 is hydrogen or methyl.

2. A compound according to claim 1 in which X and Y are, respectively, chlorine and chlorine; trifluoromethyl and hydrogen; or together form a $-CO(CH_2)_3-$ group.

3. A compound according to claim 1 or 2, in which R_1 and R_2 are each methyl, or together form a $-(CH_2)_4-$ group.

4. A compound according to claim 1, selected from:

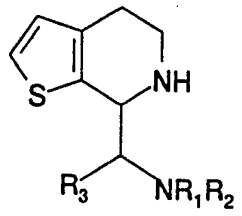
6-(3,4-dichlorophenyl)acetyl-7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride;

6-(4-trifluoromethylphenyl)acetyl-7-(pyrrolidin-1-yl)methyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine hydrochloride;

6-(3,4-dichlorophenyl)acetyl-7-dimethylaminomethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine;

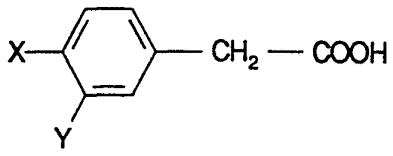
6-[1-oxo-3,4-dihydro-(2H)-naphth-6-yl]acetyl-7-dimethylaminomethyl-4,5,6,7-tetrahydrothieno[2,3-c]pyridine.

5. A process for the preparation of a compound according to any one of claims 1 to 4 which comprises reacting a compound of formula (II):



(II)

in which R_1, R_2 and R_3 are as defined for formula (I), with a compound of formula (III):



(III)

or an active derivative thereof, in which X and Y are as defined for formula (I), and then optionally forming a salt and/or solvate of the obtained compound of formula (I).

6. A pharmaceutical composition comprising a compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, and a pharmaceutically acceptable carrier.

7. A compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, for use as an active therapeutic substance.

8. The use of a compound of formula (I) according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof, in the manufacture of a medicament for the treatment of pain, cerebral ischaemia, hyponatraemic disease states, convulsions, cough, asthma, inflammation, pancreatitis or arrythmias.

9. A method of treatment and/or prophylaxis of pain, cerebral ischaemia, hyponatraemic disease states, convulsions, cough, asthma, inflammation, pancreatis or arrythmias in mammals, which comprises administering to a mammal in need of such treatment and/or prophylaxis an effective amount of a compound of formula (I), according to any one of claims 1 to 4, or a pharmaceutically acceptable salt or solvate thereof.

INTERNATIONAL SEARCH REPORT

International Application No PCT/EP 92/00411

I. CLASSIFICATION OF SUBJECT MATTER (if several classification symbols apply, indicate all)[6]

According to International Patent Classification (IPC) or to both National Classification and IPC

Int.Cl.5 C 07 D 495/04 A 61 K 31/445 //(C 07 D 495/04 C 07 D 333:00 C 07 D 221:00)

II. FIELDS SEARCHED

Minimum Documentation Searched[7]

Classification System	Classification Symbols
Int.Cl.5	C 07 D 495/00 A 61 K 31/00

Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched[8]

III. DOCUMENTS CONSIDERED TO BE RELEVANT[9]

Category °	Citation of Document,[11] with indication, where appropriate, of the relevant passages[12]	Relevant to Claim No.[13]
X	EP,A,0333427 (Dr. LO. ZAMBELETTI) 20 September 1989, see claims 1,16 (cited in the application)	1,8
X	EP,A,0370732 (Dr. LO. ZAMBELETTI) 30 May 1990, see claims 1,13 (cited in the application)	1,8
P,X	Journal of Medicinal Chemistry, vol. 34, no. 8, August 1991, (Washington, DC, US), V. VECCHIETTI et al.: "(1S)-1-(aminomethyl)-2-(arylacetyl)-1,2,3,4-tetrahydroisoquinoline and heterocycle-condensed tetrahydropyridine derivatives: Members of a novel class of very potent k opioid analgesics", pages 2624-2633, see abstract; page 2627, table IV, compound 51, scheme III, compound 24	1,8

-/-

° Special categories of cited documents :[10]

"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)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"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

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step

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

"&" document member of the same patent family

IV. CERTIFICATION

Date of the Actual Completion of the International Search	Date of Mailing of this International Search Report
07-05-1992	19. 06. 92
International Searching Authority	**Signature of Authorized Officer**
EUROPEAN PATENT OFFICE	Maria Peis Maria Peis

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

Category °	Citation of Document, with indication, where appropriate, of the relevant passages	Relevant to Claim No.
A	EP,A,0366327 (GLAXO GROUP) 2 May 1990, see claims 1,9	1,8

FURTHER INFORMATION CONTINUED FROM THE SECOND SHEET

V. [X] OBSERVATION WHERE CERTAIN CLAIMS WERE FOUND UNSEARCHABLE [1]

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

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

Although claim 9 is directed to a method of treatment of (diganostic method practised on) the human/animal body the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claim numbers because they relate to parts of the International application that do not comply with the prescribed requirements to such an extent that no meaningful International search can be carried out, specifically:

3. [ ] Claim numbers because they are dependent claims and are not drafted in accordance with the second and third sentences of PCT Rule 6.4(a).

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

This International Searching Authority found multiple inventions in this International application as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International search report covers all searchable claims of the International application

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

3. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International search report is restricted to the invention first mentioned in the claims; it is covered by claim numbers:

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

Remark on Protest

[ ] The additional search fees were accompanied by applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

ANNEX TO THE INTERNATIONAL SEARCH REPORT ON INTERNATIONAL PATENT APPLICATION NO. EP 9200411 SA 56576

This annex lists the patent family members relating to the patent documents cited in the above-mentioned international search report. The members are as contained in the European Patent Office EDP file on 11/06/92 The European Patent Office is in no way liable for these particulars which are merely given for the purpose of information.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
EP-A- 0333427	20-09-89	AU-A-	3131589	21-09-89
		JP-A-	2101062	12-04-90
		US-A-	4999359	12-03-91
EP-A- 0370732	30-05-90	JP-A-	2184674	19-07-90
		US-A-	5041451	20-08-91
EP-A- 0366327	02-05-90	AU-A-	4294889	26-04-90
		CA-A-	2000894	18-04-90
		JP-A-	2191278	27-07-90