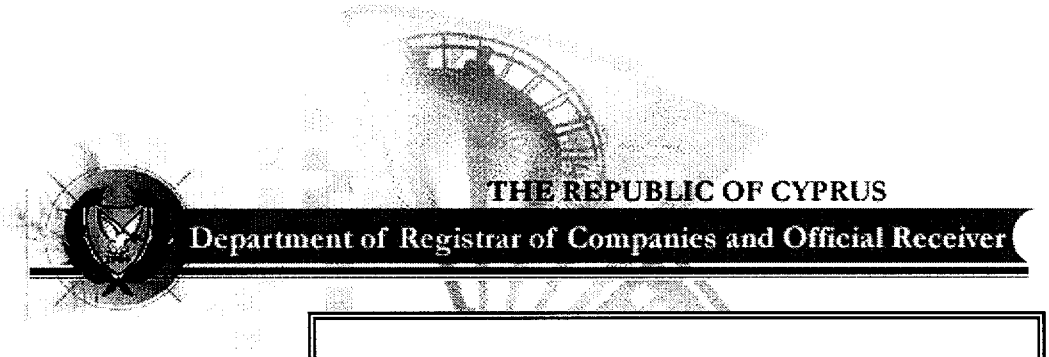

ΚΥΠΡΙΑΚΟ ΓΡΑΦΕΙΟ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
THE PATENT OFFICE OF CYPRUS

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ CY1739
PUBLICATION NUMBER

ΑΡΙΘΜΟΣ ΔΗΜΟΣΙΕΥΣΗΣ
ΓΡΑΦΕΙΟΥ ΔΙΠΛΩΜΑΤΩΝ ΕΥΡΕΣΙΤΕΧΝΙΑΣ
ΗΝΩΜΕΝΟΥ ΒΑΣΙΛΕΙΟΥ
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Το έγγραφο που παρουσιάζεται πιο κάτω καταχωρήθηκε στο «Γραφείο Διπλωμάτων Ευρεσιτεχνίας» στην Αγγλία σύμφωνα με το Νόμο Κεφ. 266 πριν την 1η Απριλίου 1998. Δημοσίευση έγινε μετέπειτα από το Γραφείο Διπλωμάτων Ευρεσιτεχνίας του Ηνωμένου Βασιλείου μόνο στην Αγγλική γλώσσα.

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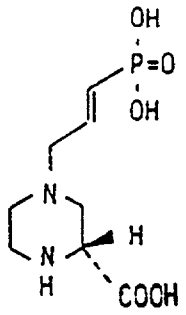
(58) Field of search
C2P

(54) Piperazinecarboxylic acid, its preparation and pharmaceutical compositions containing it

(57) A piperazinecarboxylic acid useful in the treatment of disorders associated with *LH secretion, increased muscle tone, conditions associated with cerebral ischaemia, anxiety, depression, CNS degenerative disorders, tinnitus, epilepsy* or in *relieving pain*, has the formula:-



or is a salt thereof.

GB 2 201 676 A

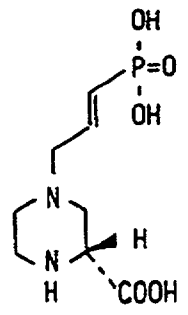
Case 500-5719

PIPERAZINECARBOXYLIC ACID, ITS PREPARATION AND PHARMACEUTICAL COMPOSITIONS CONTAINING IT

UK-Patent Application 2 157 685 describes 4-substituted 2-piperazine-carboxylic acids which have activity on the central nervous system.

It has been found that one compound of this class, which has not up until now been disclosed, has particularly strong activity on the central nervous system, is well tolerated and has long-lasting activity.

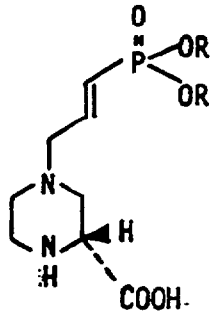
The present invention relates to [R-(E)]-4-(3-phosphono-2-propenyl)-2-piperazinecarboxylic acid of formula I,



I

its pharmaceutically acceptable salts, a process for its production, pharmaceutical compositions containing it and its use as a pharmaceutical.

The compound of formula I may be prepared by dealkylating a compound of formula II,



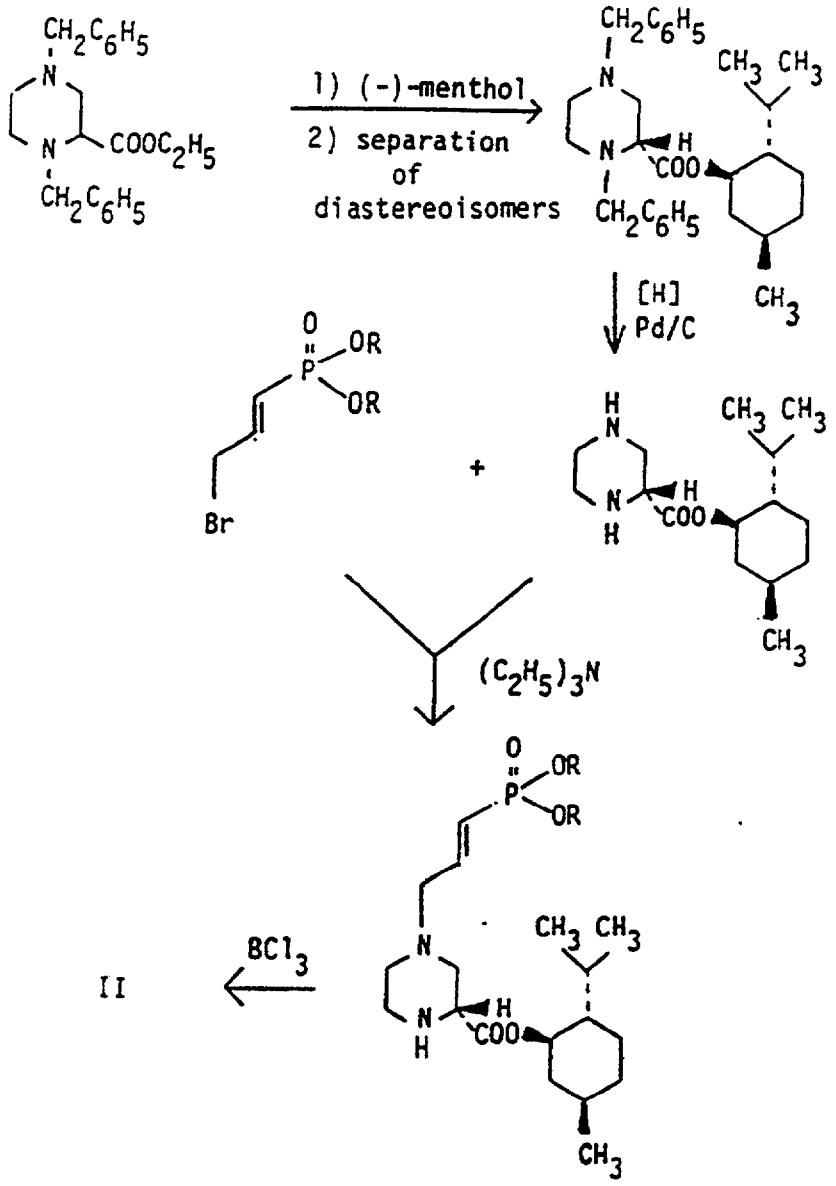
II

wherein R is (C_{1-4})alkyl or aryl(C_{1-4})alkyl.

The process can be carried out in known manner. For example the dealkylation can be effected by silylation followed by hydrolysis of the resulting silyl ester. Silylation can be performed with e.g. bromotrimethylsilane in an organic solvent such as dichloromethane or chloroform at room temperature. The subsequent hydrolysis can be effected under mild conditions.
When R is aryl(C_{1-4})alkyl, aryl is suitably an optionally substituted phenyl group, wherein suitable substituents include lower alkyl or lower alkoxy groups.

The compound of formula I including its salts, can also be obtained in the form of its hydrates, particularly the monohydrate. The hydrates, particularly the monohydrate, also form part of the invention.

The compound of formula II can be prepared as shown in the following reaction scheme:



The compound of formula I may form cationic and acid addition salts. Such salts are readily prepared by standard methods. Cationic salts include, but are not limited to, ammonium, sodium, potassium, calcium, piperidinium, morpholinium or pyrrolidinium salts. Acid addition salts include, but are not limited to, those formed with hydrochloric, hydrobromic, sulfuric, methanesulfonic, benzenesulfonic, p-toluenesulfonic and trifluoroacetic acid.

The hydrate, especially the monohydrate of the compound of formula I has particularly interesting physico-chemical and other properties, e,g. as regards solubility, easy purification and stability. The hydrate may be obtained by crystallising the compound of formula I from an aqueous medium, e.g. as described in Example e), e.g. from water/methanol.

In the following examples all temperatures are given in degrees centigrade and are uncorrected. The $[\alpha]_D^{20}$ values are also uncorrected.

Example: [R-(E)]-4-(3-Phosphono-2-propenyl)-2-piperazinecarboxylic acid

a) (R)-1,4-Bis(phenylmethyl)-2-piperazinecarboxylic acid (1R, 2S, 5R)-5-methyl-2-(1-methylethyl)cyclohexyl ester

To a solution of 761 g 1,4-dibenzyl-2-piperazinecarboxylic acid ethyl ester (prepared according to E. Jucker and E. Rissi, Helv. Chim. Acta 45 (1962) 2383) and 458 g (-)-menthol are added at 45° 15 g NaH (55%-60% dispersion) and 1 l toluene. About 700 ml of the solvent are then slowly removed by destillation and continuously replaced by new portions of toluene (the reaction is monitored by TLC, ethylacetate/hexane 1:3). The mixture is cooled to room temperature, treated with 1.25 l 2N aq. HCl and 6 l diethyl ether and stirred thoroughly for 1 hour. The cristalline precipitate is filtered off and washed with diethyl ether and 0.1N aq. HCl. The crude product is recrystallised from ethanol/0.2N aq. HCl, whereby the hydrochloride hydrate of the title compound, $[\alpha]_D^{20}$ = +18.5° (c = 1.2 in $CHCl_3$) is obtained, which is used without further purification in the next step.

b) (R)-2-Piperazinecarboxylic acid (1R, 2S, 5R)-5-methyl-2-(1-methylethyl)cyclohexyl ester

210 g of the product of step a) in 2 l ethanol and 10.5 g Pd/C (10%) are hydrogenated 7 hours at room temperature and normal pressure, then filtered and evaporated in vacuum. The residue is treated with ethanolic HCl, the precipitate filtered and washed with ethanol/diethyl ether (1:1). The product is recrystallised from water/methanol/ethylacetate to give the dihydrochloride of the title compound, m.p. 225-226°, $[\alpha]_D^{20}$ = -52.0° (c = 1.34 in water). The dihydrochloride is treated with diethylether/ aq. ammonia, the organic phase is evaporated to dryness to give

the title compound, m.p. 50-52°, $[\alpha]_D^{20}$ = -56.7° (c = 1.05 in $CHCl_3$).

c) [R-(E)]-4-(3-Diethoxyphosphinyl-2-propenyl)-2-piperazinecarboxylic acid (1R, 2S, 5R)-5-methyl-2-(1-methylethyl)cyclohexyl ester

To a stirred solution of 11.3 g of the free base of step b) and 5.9 ml triethylamine in 90 ml tetrahydrofuran are added at -30° within 30 minutes 10.7 g 3-bromo-propen-2-yl-phosphonic acid diethyl ester (prepared according to K. Hemmi, H. Takeno, M. Hashimoto and T. Kamiya, Chem. Pharm. Bull 30 (1982), 111) in 45 ml tetrahydrofuran. Stirring is continued at -25° for 20 hours. After filtration of the precipitate, the solution is concentrated at reduced pressure and the resulting syrup is chromatographed on silica gel using dichloromethane with addition of an increasing concentration of a 1:19 conc. aq. ammonia/ethanol mixture reaching 10% after 2 hours. The fraction eluted with dichloromethane/conc. aq. ammonia/ethanol 200:1:19 (rf = 0.35) is isolated and concentrated in vacuum to give the title compound as an oil, $[\alpha]_D^{20}$ = -56.0° (c = 1.3 in 2N aq. HCl). By treating the product with ethanolic HCl/ether, the dihydrochloride is obtained, m.p. 157-163°, $[\alpha]_D^{20}$ = -48.2° (c = 1.4 in 2N HCl).

d) [R-(E)]-4-(3-Diethoxyphosphinyl-2-propenyl)-2-piperazinecarboxylic acid

To a stirred solution of 5.79 g of the product of step c) in 58 ml abs. CH_2Cl_2 are added at -30° within 30 minutes 22.8 ml of a solution of boron trichloride in 1,2-dichloroethane (about 2.2 M). The reaction mixture is stirred 1 hour at -25° and 3½ hours at 0°. At 0° 50 ml water are added and the mixture is neutralized by addition of 2N aq. NaOH and partitioned between H_2O

and CH_2Cl_2. The aqueous phase is evaporated to dryness in vacuum, the residue taken up in $CHCl_3$, filtered, dried (Na_2SO_4) and evaporated to dryness in vacuum to give the title compound, which is used without further purification in the next step.

An analytical sample is purified by HPLC (Nucleosil RP-8, H_2O/CH_3OH 3 : 2) to give a foam $[\alpha]_D^{20}$ = - 18.0 ° (c = 1.1 in 0.5 N HCl).

360 MHz ^{1}H-NMR (DMSO, 150 °C):
1.24 (6H, t, J = 7.0 Hz), 2.26 (1H, dxdxd, J = 11.3 x 9.0 x 3.3 Hz), 2.35 (1H, dxd, J = 11.3 x 8.6 Hz), 2.52 - 2.58 (1H, m), 2.77 (1H, dxdxd, J = 12.1 x 9.0 x 3.3 Hz), 2.83 (1H, dxdxd, J = 11.3 x 3.3 x 1.7 Hz), 2.99 (1H, dxt, J = 12.1 x 3.9 Hz), 3.10 - 3.15 (2H, m), 3.33 (1H, dxd, J = 8.6 x 3.3 Hz), 3.97 (4H, dxq, J = 8.6 x 7.0 Hz), 5.50 (2H, broad), 5.88 (1H, dxdxt, J = 21.5 x 17.1 x 2.1 Hz), 6.52 (1H, dxdxt, J = 22.0 x 17.1 x 5.6 Hz).

e) [R-(E)]-4-(3-Phosphono-2-propenyl)-2-piperazinecarboxylic acid

3.9 g of the crude compound of step d) are dissolved in 300 ml abs. CH_2Cl_2, treated at room temperature with 9.6 ml bromotrimethylsilane and stirred for 16 hours. The reaction mixture is evaporated, the residue taken up in H_2O, stirred for 1 hour and filtered. The pH of the solution is adjusted to 6 by addition of Dowex 1x4 (OH-form) and the mixture is placed on the top of a column containing Dowex 1x4 (acetate form). Elution with a gradient of aqueous acetic acid (0.05 to 0.25 N) gives a foam on concentration to dryness in vacuum. The foam is crystallized from H_2O/CH_3OH and recrystallized from H_2O/C_2H_5OH to give the title compound as the monohydrate, m.p. 206° (decomposition). $[\alpha]_D^{20}$ = -21.6° (c = 1.1 in 2N HCl). The absolute configuration is deduced by a chemical correlation with D-asparagine and confirmed by an X-ray structure analysis.

The compound of formula I exhibits valuable pharmacological activity and is, therefore, indicated for use as a pharmaceutical, e.g. for therapy. In particular, the compound possess luteinising hormone (LH) and testosterone secretion inhibiting activity in the following test:

Adult male rats of the Wistar strain (SIV, Kissleg, West Germany, 200-300 g) receive the test compound intraperitoneally. 2 hours later the rats are killed by decapitation and blood samples are taken. Serum LH is measured using a bioassay based on the production of testosterone by disperse, collagenase treated rat interstitial Leydig cells exposed to LH containing serum or rat LH-standard; serum testosterone is measured by radioimmunoassay (125-J-T, cis, Medipro Teufen, Switzerland) [cf. E. del Pozo, A. Podestà, A. Solano, J. Calaf, M. Markò, in : Biorhythms and Stress in the Physiopathology of Reproduction, P. Pancheri and L. Zichella (Eds), Hemisphere Publishing Co. Washington, 389-398 (1988)].

The compound of formula I inhibits LH- and testosterone-secretion at the dose of 3.2 mg/kg i.p. significantly. (±)-4-(3-Phosphono-2-propenyl)-2-piperazinecarboxylic acid (hereinafter called CPP-ene), the corresponding racemate of the compound of formula I, at 3.2 mg/kg i.p. has no effect on LH-secretion and only weakly inhibits testosterone-secretion.

In female rats the compound of formula I inhibits LH-dependent spontaneous ovulation in the following test [cf. M. Markò and E. Flückiger, Neuroendocrinology 30, 228-231 (1980)]:

Female rats of the Wistar strain (SIV, Kissleg, West Germany, 200-300 g) with regular 4 day cycles receive the test substance during proestrus at 13.00 and 15.00 hrs. intraperitoneally. The next day at 9.00 h, when the rats are in estrus, they are sacrified, the oviducts examined

microscopically and the ova counted. Ovulation is deemed to be inhibited only if no ova counted. The compound of formula I (tested as the monohydrate) inhibits spontaneous ovulation significantly when administered at dosages of 2 x 3.2 mg/kg i.p. (at 13.00 3.2 mg/kg i.p. and at 15.00 h 3.2 mg/kg i.p.). CPP-ene inhibits spontaneous ovulation very weakly when administered at dosages of 2 x 3.2 mg/kg i.p. under the same experimental conditions.

The compound of formula I is, therefore, indicated for use in the treatment of disorders having an aetiology associated with or modulated by LH secretion or having an aetiology in which the physiological regulation of LH secretion is implicated, for example in the treatment of prostate hypertrophy, in the treatment of menopausal syndrome, as well as the treatment of mammary- and prostate-carcinoma. For this use an indicated daily dosage is in the range from about 1 to about 800 mg of the compound conveniently given in divided doses 2 to 4 times a day in unit dosage form containing for example from about 0.25 to about 400 mg of the compound or in sustained release form.

The compound of formula I shows muscle relaxant activity in the conscious rabbit in dosages from 0.01 to 0.05 mg/kg i.v. [H.J. Teschendorf et al., Arch. Exp. Pharmacol. 266, 467-468 (1970)]. In this test the monohydrate of the compound of formula I causes a 50% inhibition of reflex muscle tone after administration of 0.02 mg/kg i.v., whereas CPP-ene inhibits reflex muscle tone by 47% after administration of 0.5 mg/kg i.v.; the compound of formula I being about 25 times more active than the corresponding racemate.

The compound of formula I is, therefore, indicated for use in the treatment of increased muscle tone, for example in the treatment of painful muscle spasms attributable to static and functional

disorders of the lumbar or cervical spine or after surgery or in the treatment of spasticity, e.g. due to multiple sclerosis, diseases of the spinal cord, cerebrovascular accidents, cerebral trauma or cerebral palsy. For this use an indicated daily dosage is in the range from about 1 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 0.25 to about 400 mg of the compound or in sustained release form.

Furthermore, the compound of formula I reduces ischaemia-induced neuronal damage and ensuing symptoms in the middle cerebral artery (MCA) occlusion model in rats at a dosage of 1-30 mg/kg s.c. and particularly at 3 x 10 mg/kg i.p. [cf. A.Tamura et al., J. Cereb. Blood Flow Metabol. 1, 53-60 (1981), A. Sauter, M. Rudin, Stroke 17, 1228-1234 (1986)]. The area of infarcted tissue is measured using MCID image analysis software (developed by Imaging Research Inc.) in 5 horizontal 20 µm thick slices sectioned at multiple levels and stained by cresyl violett. The total volume of brain showing ischaemic damage is estimated by adding the 5 areas obtained from the 5 slices. The infarct size determined histologically 5 days after occlusion of MCA is reduced by more than 20% after treatment with 3 x 10 mg/kg i.p. of the monohydrate of compound of formula I (first injection immediately after MCA occlusion, second and third after 8 respectively 16 hours).

The compound is therefore indicated for use in the prophylaxis and therapy of conditions associated with cerebral ischaemia e.g. stroke. For this use an indicated daily dosage is in the range from about 25 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 6 to about 400 mg of the compound or in sustained release form.

Furthermore, the compound of formula I has a potent, selective and competitive antagonistic action on NMDA (N-Methyl-D-aspartic acid) receptors. Thus the monohydrate of the compound of formula I inhibits NMDA-induced depolarisations in the isolated frog spinal cord assay [P.L.Herrling, Neuroscience 14, 417-426 (1985)] with a pA_2 value of 6.8, CPP-ene with a pA_2 value of 6.2, thus the compound of formula I being about 4-fold as active as the corresponding racemate. CPP [(±)--3-(2-carboxypiperazin-4-yl)propyl-1-phosphonic acid], the emphasized compound of UK Patent Application 2 157 685 has a pA_2 value of 5.8.

In the NMDA-induced sodium efflux assay on rat brain slices (Luini A., Goldberg O. + Teichberg V.I., Proc. Natl. Acad. Sci. USA 78, 3250-3254 (1981)] the monohydrate of the compound of formula I has a pA_2 value of 6.5 and CPP-ene a pA_2 of 6.2, the compound of formula I being about twice as active as the corresponding racemate. CPP has a pA_2 value of 6.0.

The selectivity of the NMDA antagonistic action is indicated in that it is inactive, as well as CPP-ene and CPP,in the quisqualate- and kainate-induced sodium efflux test up to a concentration of 1 mM.

As a result of its NMDA receptor antagonism the compound of formula I is indicated for use in the treatment of anxiety, schizophrenia and depression or of CNS degenerative disorders, such as Huntington's,

Alzheimer's or Parkinson's diseases. For these uses an indicated daily dosage is in the range from about 25 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 6 to about 400 mg of the compound or in sustained release form.

As a result of its NMDA receptor antagonism the compound of formula I is further indicated for use in the treatment of tinnitus. For this use an indicated daily dosage is in the range from about 25 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 6 to about 400 mg of the compound or in sustained release form.

Additionally the compound of formula I shows anticonvulsant activity in electroshock-induced convulsions in the mouse [E.A. Swinyard, J.Am. Pharm. Assoc. Scient. Ed. 38, 201 (1949) and J. Pharmacol. Exptl. Therap. 106, 319 (1952)]. In this test, groups of 6 male mice (18-26 g, OF-1, Sandoz Basle) receive the test substance intraperitoneally. After 1, 2 and 4 hrs. a 50 mA, 200 ms long shock is applied via corneal electrodes, smeared with electrolyte jelly. This supra-maximal shock produces tonic extensor convulsions of all extremities. Inhibition of the hindlimb extension is taken as a protective action. After investigation of several dose-levels the threshold dose is estimated. The threshold dose at 1 hour, the dose required to inhibit the hindlimb extension is <1 mg/kg i.p. for the compound of formula I (monohydrate) and between 3-10 mg/kg i.p. for CPP-ene. The literature threshold dose of CPP is 10 mg/kg i.p.

In the following table, the inhibition of hindlimb extension, expressed in % is given for the compound of formula I in comparison with the corresponding racemate:

	Dose	% Inhibition of E-shock induced hindlimb extension		
	mg/kg i.p.	1h	2h	4h
Compound of formula I monohydrate	1	67*	67*	33
	2.5	83*	83*	67*
	3	100*	100*	83*
CPP-ene	1	20	50	25
	3	33	67*	17
	10	67*	80*	80*

Fisher-Test, control vs. substance group, * $p <= 0.05$.

As can be seen from the table, the compound of formula I has higher anticonvulsant activity than the corresponding racemate when tested against electroshock-induced convulsions in mice.

The compound of formula I further inhibits N-Methyl-D-aspartic acid (NMDA) induced convulsions in the mouse. In this test groups of 6 female mice (18-26 g, OF-1, Sandoz Basle) were pretreated with the test substance intraperitoneally. 30 minutes later they are challenged with 400 mg/kg s.c. NMDA in the neck region and observed for 30 minutes. The latencies for the appearance of the first signs of convulsions, for the first tonic convulsions and for the occurrence of death are noted. The significance of any differences is assessed using the Mann-Whitney U-test [S. Siegel, Non-parametric Statistics, McGraw-Hill, New York 1956]. The threshold dose is the smallest dose at which there is a significant inhibition of convulsive symptoms. The threshold dose of the compound of formula I (tested as monohydrate) is approximately 5 mg/kg i.p., of CPP 10 mg/kg i.p.

As a result of its anticonvulsant activity the compound of formula I is indicated for use in the treatment of epilepsy. For this use an indicated daily dosage is in the range from about 25 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing for example from about 6 to about 400 mg of the compound or in sustained release form.

The compound of formula I further shows analgesic activity in the isolated rat spinal cord-tail in vitro using capsaicin (0.8-1 µM) as a chemical noxious stimulus eliciting depolarising ventral root responses [M. Yanagisawa et al., European J. Pharmacol. 106,231-239 (1984)]. The monohydrate of the compound of formula I reduces the chemical stimulus by 75-80% at a concentration of 10 µM.

The compound of formula I is, therefore,indicated for use for relieving pain. For this use an indicated daily dosage is in the range from about 25 to about 800 mg of the compound conveniently administered in divided doses 2 to 4 times a day in unit dosage form containing

for example from about 6 to about 400 mg of the compound or in sustained release form.

Moreover, the compound of formula I as well as the corresponding racemate have no effects on blood pressure and heart rate in the anaesthetised cat in a dose up to 10 mg/kg i.v. In pilot toxicity tests with dogs over 4 weeks 3 mg/kg/day i.v. of the compound of formula I are well tolerated.

As can be seen from the above test results, the strong LH secretion inhibiting activity, the marked (25 fold) increase of the muscle relaxant activity as well as the two- to four-fold NMDA receptor antagonistic activity of the compound of formula I as compared to the corresponding racemate is not accompanied by a similar increase in the side effects, e.g. cardiovascular effects.

The compound of formula I may be administered as such or as its pharmaceutically acceptable salts. Such salts exhibits the same order of activity as the compound of formula I.

The present invention further provides pharmaceutical compositions comprising the compound of formula I or a pharmaceutically acceptable salt thereof in association with a pharmaceutically acceptable carrier or diluent.

The compound of formula I may be administered by any conventional route, in particular enterally, preferably orally or parenterally. The compound of formula I may be administered as such or admixed with conventional pharmaceutical carriers. For example, for oral administration e.g. in the form of tablets or capsules, the compound of formula I may be admixed with conventional pharmaceutically acceptable excipients, e.g. inert diluents, such as lactose, mannitol, calcium sulfate, microcristalline cellulose; disintegrating agents, e.g. starch, sodium carboxymethyl cellulose, sodium carboxymethyl starch, alginic acid, crospovidone; binding agents such as cellulose derivates (methyl-, hydroxymethyl-, hydroxypropylmethyl-), povidone, gelatine; lubricating agents e.g. siliciumdioxide, stearic acid, magnesium or calcium stearate; hydrogenated oils such as castor oil, glycerolesters e.g. palmitostearate and/or flavouring, colouring and sweetening agents. The tablets may be uncoated or coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. Parenteral compositions are preferably in the form of a sterile injectable aqueous solution. Such aqueous solutions should be suitably buffered if necessary and rendered isotonic with sufficient saline. Optionally a preservative, such as benzyl alcohol, can be added.

A unit dosage may contain from about 0.25 to about 400 mg of the compound of formula I or a pharmaceutically acceptable salt thereof.

The pharmaceutical compositions can be prepared according to conventional techniques.

For the manufacture of tablets, the compound of formula I can be mixed with lactose and granulated with water, 0.5% sodium alginate or 5% hydroxypropylmethylcellulose solution. The dried granulate is compressed into tablets in the presence of about 20% of corn starch and 1% of magnesium stearate. In this way, there are obtained, e.g. tablets of the following composition:

Ingredients	Tablet Weight (mg)
Compound of formula I monohydrate	50
Lactose	97
Corn Starch	40
Hydroxypropylmethylcellulose	10
Magnesium stearate	2
Siliciumdioxide	1
	200

These tablets, which are provided with a crackline, can be administered orally in a dosage of one half to one tablet one to four times per day.

Capsules may contain the active agent alone or admixed with an inert solid excipient, for example as mentioned above.

Capsules containing the ingredients indicated below may be prepared by conventional techniques and are administered at a dose of one capsule 1 to 4 times a day.

Ingredients	Capsule Weight (mg)
Compound of formula I monohydrate	50
Inert solid excipient (corn starch, lactose, aerosil, magnesium stearate)	250

Similarly tablets and capsules containing 25 mg and 100 mg of the compound of formula I may be prepared.

The following injectable solution is formulated with the indicated amount of active agent using conventional techniques. The injectable solution is suitable for administration once a day.

Ingredients	Sterile injectable solution Weight (mg/ml)
Compound of formula I monohydrate	25
Sodium chloride	7.0
Potassium dihydrogen phosphate	3.63
Disodium hydrogen phosphate	5.68
Benzyl alcohol	9.0
Water for injection	q.s. to 1 ml

The solutions may be filtered through a 0.2 µm sterile filter and aseptically filled in ampoules. The ampoules are gassed with carbon dioxide.

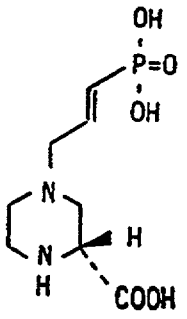
The present invention also provides the compound of formula I or a pharmaceutically acceptable salt thereof for use as a pharmaceutical, e.g. for use in the treatment of disorders associated with LH secretion; treatment of increased muscle tone; treatment of conditions associated with cerebral ischaemia; treatment of anxiety, schizophrenia, depression or CNS degenerative disorders; treatment of tinnitus; treatment of epilepsy or relieving pain.

The present invention accordingly provides a method for the treatment of disorders associated with LH secretion; treatment of increased muscle tone; treatment of conditions associated with cerebral ischaemia; treatment of anxiety, schizophrenia, depression or CNS degenerative disorders; treatment of tinnitus; treatment of epilepsy or relieving pain in a subject which comprises administering a therapeutically effective amount of the compound of formula I or a pharmaceutically acceptable salt thereof to a subject in need of such treatment.

The present invention further provides the compound of formula I or a pharmaceutically acceptable salt thereof for use in the manufacture of a pharmaceutical composition for use in the treatment of disorders associated with LH secretion, increased muscle tone, conditions associated with cerebral ischaemia, anxiety, schizophrenia, depression, CNS degenerative disorders, tinnitus or epilepsy or in relieving pain.

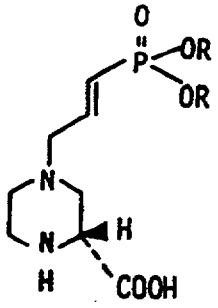
CLAIMS:

1. A process for the production of [R-(E)]-4-(3-Phosphono-2-propenyl)-2-piperazinecarboxylic acid of formula I,



I

or a salt thereof, which comprises dealkylating a compound of formula II,



II

wherein R is (C_{1-4})alkyl or aryl(C_{1-4})alkyl, and optionally forming a salt thereof.

2. A process for the production of the compound of formula I or a salt thereof as hereinbefore described with reference to any of the Examples.

3. Compound of formula I or a salt thereof whenever produced by a process according to claim 1.

4. Compound of formula I or a salt thereof.

5. Compound according to claim 4 in the form of its monohydrate or a salt thereof.

6. A compound as claimed in claim 4 or 5 or a pharmaceutically acceptable salt thereof for use as a pharmaceutical.

7. A compound according to claim 6 for use in the treatment of disorders associated with LH secretion.

8. A compound according to claim 6 for use in the treatment of increased muscle tone.

9. A compound according to claim 6 for use in the treatment of conditions associated with cerebral ischaemia.

10. A compound according to claim 6 for use in the treatment of anxiety.

11. A compound according to claim 6 for use in the treatment of schizophrenia.

12. A compound according to claim 6 for use in the treatment of depression.

13. A compound according to claim 6 for use in the treatment of CNS degenerative disorders.

14. A compound according to claim 6 for use in the treatment of tinnitus.

15. A compound according to claim 6 for use in the treatment of epilepsy.

16. A compound according to claim 6 for use in relieving pain.

17. A pharmaceutical composition comprising a compound as claimed in claim 4 or 5 or a pharmaceutically acceptable salt thereof together with a pharmaceutically acceptable diluent or carrier therefor.

18. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of disorders associated with LH secretion.

19. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of increased muscle tone.

20. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of conditions associated with cerebral ischaemia.

21. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of anxiety.

22. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of schizophrenia.

23. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of depression.

24. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of CNS degenerative disorders.

25. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of tinnitus.

26. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in the treatment of epilepsy.

27. Use of the compound of formula I or the monohydrate thereof or a pharmaceutically acceptable salt thereof for the manufacture of a pharmaceutical composition for use in relieving pain.

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