

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. _____ S. _____

MINISTERIO DE INDUSTRIA Y COMERCIO



6069700000

2020 NUECRLACIONE
100.074 PASLNACIONALII
Folios: 2

Re: P1.-WYETH.-Solicitud de Patente de Invención para
"DERIVADOS DE ACIDO [[2-(AMINO-3,4-DIOXO-1-
CICLOBUTEN-1-IL)AMINO]ALQUILO] PARA EL
TRATAMIENTO DEL DOLOR".-Clase A61K 31/662.-
Expediente número 04-032.577.-

1. Me refiero al auto dictado por ese Despacho notificado por fijación en lista de 21 de Diciembre de 2007.
2. Atentamente ruego a usted concederme un plazo de treinta (30) días para dar respuesta al auto antes mencionado, cuyo término vence el próximo **18 de Marzo de 2008**.
3. Anexo acompaño recibo número 08-19.435, que acredita el pago de los derechos que dicho plazo causa.
4. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,

ALICIA LLOREDA RICAURTE

T.P. 53.215

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 000176007-2

RECIBO OFICIAL DE CAJA : 00 - 19,435
FECHA : MARZO 5 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-032577-00005-0000

C/ 14 DE NOVIEMBRE DE 2007
C/ 14 DE NOVIEMBRE DE 2007

**** CONSIGNACION ****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LLOREDA Y CIA S. A	CONSIGNACION	BANCO DE BOGOTA	062734307	137474	05/03/2008	2,482,000.00

**** CONCEPTO ****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-08	PRORROGA DE TERMINOS	75,000.00
31		PRORROGA DE TERMINOS	75,000.00
TOTAL :			\$ 75,000.00

SON: SETENTA Y CINCO MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.



(11) Publication number: **0 496 561 A2**

(12) **EUROPEAN PATENT APPLICATION**

(21) Application number: **92300472.5**

(22) Date of filing: **20.01.92**

(51) Int. Cl.⁵: **C07C 229/16, C07D 271/07, C07F 9/38, C07D 243/10, C07D 403/06, C07D 405/04, C07D 241/38, A61K 31/195, A61K 31/66, A61K 31/675, A61K 31/495**

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29.07.92 Bulletin 92/31

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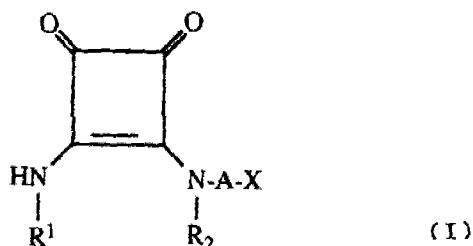
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(54) **[[[(2-Amino-3,4-dioxo-1-cyclo-buten-1-yl)amino]alkyl]-acid derivatives.**

(57) The invention concerns processes for preparing compounds of the formula



in which

R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms ;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms ;

or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁶)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, where R⁶, R⁹ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms,

A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms ;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl ;

or a pharmaceutically acceptable salt thereof which compounds are NMDA antagonists useful as anticonvulsant and neuroprotectants in situations involving excessive release of excitatory amino acids.

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Table (Continued)

	Compound of Example	CPP Binding IC ₅₀ (μM)	NMDA Induced Lethality ED ₅₀ (mg/kg)
5	8	0.030	2.1
10	9	0.019	1.8
	9(a)	0.28	50% (5)
	9(b)	>1	>10
15	9(c)	>10	>5
	10	0.55	>20
	10(a)	0.34	>20
	11	0.038	>10
20	11(a)	40% (10)	>5
	12	0.041	80% (5)

25 Where the displacement of CPP binding is expressed as a percentage, it is at the μM concentration given at the concentration in the parenthesis. Similarly, where percent inhibition of lethality at dose in parenthesis.

Thus, the compounds of this invention demonstrate the ability to antagonize NMDA-induced lethality *in vivo* in mice. They compete with 3-(2-carboxypiperazinyl-4-yl)-propyl-1-phosphonic acid (CPP), a known competitive NMDA-antagonist, for its binding site. The compounds of the present invention are, therefore, competitive
30 NMDA antagonists.

The compounds of the present invention are active against NMDA-induced lethality and are useful in the treatment of CNS disorders such as convulsions, brain cell damage and related neurodegenerative disorders, including senile dementia, Alzheimer's disease, Huntingdon's chorea, stroke, hypoglycemia, cerebral palsy, cerebral ischemia, epilepsy, and olivo-ponto cerebellar atrophy.

35 Hence, there is herewith provided in addition to the novel compounds, *supra*, a method for preventing neurodegenerative disorders induced by overstimulation of NMDA receptors in brain and spinal cord by excitatory amino acids, which comprises administering to a mammal suffering from such degenerative disease states, an anticonvulsant, neuroprotective amount of an NMDA antagonist of this invention.

As such, the compounds of this invention may be administered neat or with a pharmaceutical carrier to a
40 patient in need thereof. The pharmaceutical carrier may be solid or liquid.

Accordingly, this invention also provides a pharmaceutical composition comprising a compound of formula I as shown and defined hereinabove or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable carrier.

A solid carrier can include one or more substances which may also act as flavoring agents, lubricants solubilizers, suspending agents, fillers, glidants, compression aids, binders or tablet-disintegrating agents; it can also be an encapsulating material. In powders, the carrier is a finely divided solid which is in admixture with the finely divided active ingredient. In tablets, the active ingredient is mixed with a carrier having the necessary compression properties in suitable proportions and compacted in the shape and size desired. The powders and tablets preferably contain up to 99% of the active ingredient. Suitable solid carriers include, for example, calcium phosphate, magnesium stearate, talc, sugars, lactose, dextrin, starch, gelatin, cellulose, methyl cellulose,
50 sodium carboxymethyl cellulose, polyvinylpyrrolidone, low melting waxes and ion exchange resins.

Liquid carriers are used in preparing solutions, suspensions, emulsions, syrups, elixirs and pressurized compositions. The active ingredient can be dissolved or suspended in a pharmaceutically acceptable liquid carrier such as water, an organic solvent, a mixture of both or pharmaceutically acceptable oils or fats. The liquid
55 carrier can contain other suitable pharmaceutical additives such as solubilizers, emulsifiers, buffers, preservatives, sweeteners, flavoring agents, suspending agents, thickening agents, colors, viscosity regulators, stabilizers or osmo-regulators. Suitable examples of liquid carriers for oral and parenteral administration include water (partially containing additives as above, e.g. cellulose derivatives, preferably sodium carboxymethyl cel-

lucose solution), alcohols (including monohydric alcohols and polyhydric alcohols e.g. glycols) and their derivatives, and oils (e.g. fractionated coconut oil and arachis oil). For parenteral administration, the carrier can also be an oily ester such as ethyl oleate and isopropyl myristate. Sterile liquid carriers are used in sterile liquid form compositions for parenteral administration. The liquid carrier for pressurized compositions can be halogenated hydrocarbon or other pharmaceutically acceptable propellant.

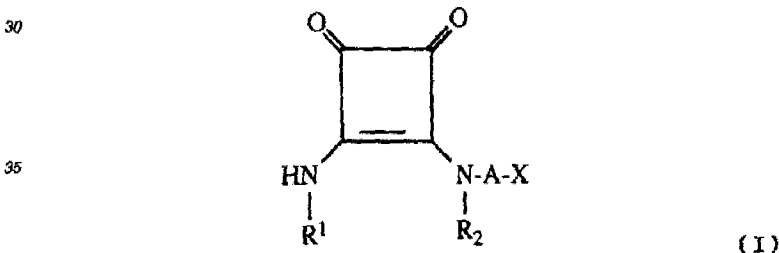
Liquid pharmaceutical compositions which are sterile solutions or suspensions can be utilized by, for example, intramuscular, intraperitoneal or subcutaneous injection. Sterile solutions can also be administered intravenously. The compounds can also be administered orally either in liquid or solid composition form.

Preferably, the pharmaceutical composition is in unit dosage form, e.g. as tablets or capsules. In such form, the composition is sub-divided in unit dose containing appropriate quantities of the active ingredient; the unit dosage forms can be packaged compositions, for example, packeted powders, vials, ampoules, prefilled syringes or sachets containing liquids. The unit dosage form can be, for example, a capsule or tablet itself, or it can be the appropriate number of any such compositions in package form.

To determine the effective amount of compound to be administered in alleviation of CNS degenerative dysfunctions, the physician need only evaluate the effects of a given NMDA antagonist in the patient by incrementally increasing the oral dosage from about 1 mg/kg to about 20 mg/kg until the desired symptomatic relief level is achieved. The continuing dose regimen may then be modified to achieve the desired result, with the range of about 1 to 100 mg/day. Similar techniques are followed by determining the effective dose range upon i.v. or i.m. administration. When using the compounds prophylactically to arrest declining cognitive function as in Alzheimer's dementia, a more subjective approach is taken such as by relating the drug dosage to improved memory responses or analogous desired responses which can be related to relief of overstimulation of the excitatory amino acid receptors.

Claims

1. A compound of the formula:



in which

R¹ is hydrogen, alkyl of 1 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

R² is hydrogen, alkyl of 1 to 6 carbon atoms, alkenyl of 2 to 6 carbon atoms or phenylalkyl of 7 to 12 carbon atoms;

or

R¹ and R² taken together are Z where Z is -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are, independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms.

A is alkylene of 1 to 6 carbon atoms or alkenylene of 2 to 6 carbon atoms;

X is CO₂R³ in which R³ is hydrogen or alkyl of 1 to 6 carbon atoms, P(O)(OR⁴)(OR⁵) in which R⁴ and R⁵ are, independently, hydrogen or alkyl of 1 to carbon atoms, 3,5-dioxo-1,2,4-oxadiazolidin-2-yl or 5-tetrazolyl; or a pharmaceutically acceptable salt thereof.

2. A compound as claimed in Claim 1 in which R¹ and R² are, independently, hydrogen, methyl, allyl, methallyl or benzyl or R¹ and R² taken together are -CH₂CH₂-, -CH₂C(R⁶)(R⁷)CH₂- or -CH₂C(R⁸)(R⁹)-C(R¹⁰)(R¹¹)CH₂-, where R⁶, R⁸ and R¹⁰ are independently, hydrogen, alkyl of 1 to 6 carbon atoms or hydroxyl and R⁷, R⁹ and R¹¹ are, independently, hydrogen or alkyl of 1 to 6 carbon atoms.

3. A compound as claimed in Claim 1 or Claim 2 where A is alkylene of 1 to 4 carbon atoms or trans-2-bu-

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tenylene.

4. A compound as claimed in any one of Claims 1 to 3 wherein X is carboxyl, phosphonyl or 5-tetrazolyl.
5. A compound as claimed in Claim 1 which is one of the following:
 - N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)beta alanine,
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine ethyl ester;
 - 2-[2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]-1,2,4-oxadiazolidine-3,5-dione;
 - N-[2-(methylamino)-3,4-dioxo-1-cyclobutenyl]beta-alanine;
 - 10 N-(2-amino-3,4-dioxo-1-cyclobuten-1-yl)-N-(2-propenyl)glycine;
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(2-methyl-2-propenyl)glycine;
 - [(2-amino-3,4-dioxo-1-cyclobutenyl)amino]methyl]phosphonic acid;
 - [3-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl]phosphonic acid;
 - [4-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]butyl]phosphonic acid;
 - 15 [(E)-4-[(2-amino-3,4-dioxo-1-cyclobutenyl-1-yl)amino]-2-butenyl]phosphonic acid;
 - [(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]methyl]phosphonic acid;
 - [(E)-3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)-1-propenyl]-phosphonic acid;
 - 2-[2-(1H-tetrazo1-5-yl)ethyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione;
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)glycine;
 - 20 4-[2-amino-3,4-dioxo-1-cyclobutenyl]amino]butanoic acid;
 - 3-[[3,4-dioxo-2-[(phenylmethyl)amino]-1-cyclobutenyl]amino]propanoic acid; or
 - N-(2-amino-3,4-dioxo-1-cyclobutenyl)-N-(phenylmethyl)glycine; or a pharmaceutically acceptable salt thereof.
- 25 6. A compound as claimed in Claim 1 which is:
 - [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)amino]ethyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - [2-[(2-amino-3,4-dioxo-1-cyclobuten-1-yl)methylamino]ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - 30 [2-(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - [2-(4-hydroxy-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - 35 [2-(4,4-dimethyl-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof;
 - 2[3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl) propyl]phosphonic acid or a pharmaceutically acceptable salt thereof;
 - 40 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-ene-2-acetic acid, or a pharmaceutically acceptable salt thereof;
 - 3-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)propanoic acid, or a pharmaceutically acceptable salt thereof;
 - 2-[(1H-tetrazo1-5-yl)methyl]-2,6-diazabicyclo[5.2.0]non-1(7)-ene-8,9-dione, or a pharmaceutically acceptable salt thereof; or
 - 45 [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-yl)ethyl]phosphonic acid, or a pharmaceutically acceptable salt thereof.
7. A compound as claimed in any one of Claims 1 to 6 when in the form of alkali metal, alkaline earth metal or ammonium salt.
8. A process for preparing a compound of formula I as defined in Claim 1 which comprises
 - a) reacting a compound of formula (II)

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WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁷ : A61K 31/485, 31/4468, 31/4535, 38/33, A61P 23/00, A61L 29/00, A61P 29/00 // (A61K 31/485, 31:138) (A61K 31/485, 31:13) (A61K 31/485, 31:445) (A61K 31/485, 31:485)	A1	(11) International Publication Number: WO 00/03716 (43) International Publication Date: 27 January 2000 (27.01.00)
(21) International Application Number: PCT/US99/16049 (22) International Filing Date: 15 July 1999 (15.07.99) (30) Priority Data: 60/092,982 16 July 1998 (16.07.98) US (63) Related by Continuation (CON) or Continuation-in-Part (CIP) to Earlier Application US 60/092,982 (CIP) Filed on 16 July 1998 (16.07.98) (71) Applicant (for all designated States except US): MEMORIAL SLOAN-KETTERING CANCER CENTER [US/US]; 1275 York Avenue, New York, NY 10021 (US). (72) Inventors; and (75) Inventors/Applicants (for US only): KOLESNIKOV, Yuri [RU/US]; 38 Ridge Road, Cresskill, NJ 07626 (US). PASTERNAK, Gavril, W. [US/US]; Apartment 21M, 500 E 83rd Street, New York, NY 10021 (US).	(74) Agents: SONNENFELD, Kenneth, H. et al.; Morgan & Finnegan, L.L.P., 345 Park Avenue, New York, NY 10154 (US). (81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG). Published With international search report. Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.	
(54) Title: TOPICAL COMPOSITIONS COMPRISING AN OPIOID ANALGESIC AND AN NMDA ANTAGONIST (57) Abstract A topical opioid paradigm was developed to determine analgesic peripheral effects of morphine. Topical morphine as well as peptides such as [D-Ala², MePhe⁴, Gly(ol)⁵]enkephalin (DAMGO) produced a potent, dose-dependent analgesia using the radiant heat tailflick assay. The topical drugs potentiated systemic agents, similar to the previously established synergy between peripheral and central sites of action. Local tolerance was rapidly produced by repeated daily topical exposure to morphine. Topical morphine tolerance was effectively blocked by the N-Methyl-D-Aspartate (NMDA) receptors antagonist MK801 and ketamine given either systemically or topically. NMDA receptor antagonists reversed pre-existing morphine tolerance. The activity of topical NMDA antagonists to block local morphine tolerance suggests that peripheral NMDA receptors mediate topical morphine tolerance. Morphine was cross tolerant to [D-Ala², MePhe⁴, Gly(ol)⁵]enkephalin (DAMGO), but not to morphine-6β-glucuronide, implying different mechanisms of action. These observations have great importance in the design and use of opioids clinically. Topical pharmaceutical compositions comprising an analgesic that functions through an opiate receptor and an NMDA receptor antagonist for producing analgesia without inducing tolerance are described.		

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WE CLAIM:

1. A topical pharmaceutical composition comprising at least one
5 N-methyl-D-aspartate (NMDA) receptor antagonist and at least one analgesic that
functions through an opiate receptor and a pharmaceutically acceptable topical
excipient.
2. The topical pharmaceutical composition according to claim 1
10 comprising at least one analgesic and wherein the analgesic is selected from the
group consisting of an opiate, an opiate derivative, an opioid, enkephalins,
endorphins and synthetic opioid peptides.
3. The topical pharmaceutical composition according to claim 2,
15 wherein the opioid is selected from the group consisting of ethylmorphine,
hydromorphone, morphine, oxymorphone, codeine, levorphanol, oxycodone,
pentazocine, propoxyphene, fentanyl, sufentanil, lofentanil, morphine-6-glucuronide
and buprenorphine.
4. The topical pharmaceutical composition according to claim 2,
20 wherein the enkephalin is selected from the group consisting of [D-Ala², MePhe⁴,
Gly (ol)⁵] enkephalin, and endomorphines.
5. The topical pharmaceutical composition according to claim 1,
wherein the analgesic is morphine.
- 25 6. The topical pharmaceutical composition according to claim 1,
wherein the NMDA receptor antagonist is selected from the group consisting of
dextromethorphan, dextrorphan, ketamine, pyroloquinoline quinone, cis-4-
(phosphonomethyl)-2-piperidine carboxylic acid, MK801, memantine, and their
30 mixtures and pharmaceutically acceptable salts thereof.
7. The topical pharmaceutical composition according to claim 1
further comprising a local anesthetic.

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US006011168A

United States Patent [19]

Asselin et al.

[11] **Patent Number:** **6,011,168**[45] **Date of Patent:** **Jan. 4, 2000**206
201[54] **PROCESS FOR THE PREPARATION**[2-((8,9)-
DIOXO-2,6-DIAZABICYCLO[5.2.0]-NON-1(7)-
EN-2-YL)ETHYL]PHOSPHONIC ACID[75] **Inventors:** **Andre A. Asselin**, Mahwah, N.J.;
William A. Kinney, Richboro, Pa.;
Jean Schmid, Chester, N.Y.[73] **Assignee:** **American Home Products**
Corporation, Madison, N.J.[21] **Appl. No.:** **09/375,345**[22] **Filed:** **Aug. 16, 1999****Related U.S. Application Data**[62] **Division of application No.** 09/127,202, Jul. 31, 1998
[60] **Provisional application No.** 60/054,553, Aug. 1, 1997.[51] **Int. Cl.** **C07F 9/40**[52] **U.S. Cl.** **558/172**[58] **Field of Search** **558/172**[56] **References Cited****U.S. PATENT DOCUMENTS**

5,168,103	12/1992	Kinney et al. .
5,212,291	5/1993	Murdock et al. .
5,583,123	12/1996	De Lombaert .
5,593,659	1/1997	Winchell et al. .
5,595,983	1/1997	Watkins et al. .
5,602,115	2/1997	Nugent .
5,708,152	1/1998	Lohmann et al. .

FOREIGN PATENT DOCUMENTS

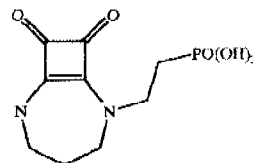
0496561	7/1992	European Pat. Off. .
1518660	7/1965	Germany .

OTHER PUBLICATIONS

Tetrahedron, vol. 38, No. 15, 2225-2277 (1982).

Primary Examiner—Michael G Ambrose
Attorney, Agent, or Firm—Steven R. Eck[57] **ABSTRACT**

This invention relates to a process for the preparation of the formula 1 compound [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]phosphonic acid, a NMDA antagonist useful as an anticonvulsant and neuroprotectant in situations involving excess release of excitatory amino acids.



In the process of the present invention, 3-aminopropyl carbamic acid 1,1-dimethyl-ethyl ester is reacted with a dialkyl vinylphosphonate to obtain N-[3-(t-butyloxycarbonyl-amino)propyl]-2-aminoethylphosphonic acid dialkyl ester (d) in 80% yield. Reaction of (d) with a 3,4-dialkoxycyclobut-3-en-1,2-dione gives [3-[[2-(dialkoxylphosphoryl)ethyl]-(2-alkoxy-3,4-dioxo-1,2-cyclobuten-1-yl)amino]propyl] carbamic acid 1,1-dimethylethyl ester (e) in 96% yield. Deprotection and cyclization of (e) in trifluoroacetic acid gives [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]phosphonic acid dialkyl ester (c) in 58% yield. The phosphonic acid diethyl ester (c) was treated with bromotrimethylsilane to give compound 1.

4 Claims, No Drawings

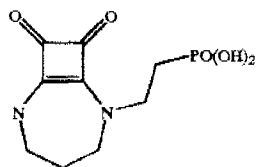
1

PROCESS FOR THE PREPARATION OF 2-((8,9)-DIOXO-2,6-DIAZABICYCLO[5.2.0]NON-1(7)-EN-2-YL)ETHYLPHOSPHONIC ACID

This application is a division of Ser. No. 09/127,202 filed Jul. 31, 1998.

This application claims the benefit of U.S. Provisional Application No. 60/054,553, filed Aug. 1, 1997.

This invention relates to a process for the preparation of the formula I compound [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid, a NMDA antagonist useful as an anticonvulsant and neuroprotectant in situations involving excess release of excitatory amino acids.



The formula I compound and a process for its preparation are disclosed in U.S. Pat. No. 5,168,103. In the disclosed process, 3-aminopropyl carbamic acid phenylmethyl ester is reacted with 2-oxoethylphosphoric acid dialkyl ester and sodium cyanoborohydride to obtain the intermediate 3-[[2-(dialkoxyphosphinyl)ethyl]amino]propyl carbamic acid phenylmethyl ester (a) in 36% yield. Reaction of (a) with a 3,4-dialkoxy (or 3,4-diaryloxy)-cyclobut-3-en-1,2-3-[[2-(dialkoxyphosphoryl)ethyl]-(2-alkoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl carbamic acid phenylmethyl ester (b) in 89% yield. Removal of the benzyloxycarbonyl protecting group and cyclization of (b) to [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid dialkyl ester (c) is accomplished in 62% yield by treating (b) with 10% palladium on carbon and 1,4-cyclohexadiene. Treatment of the bicyclic diester (c) with bromotrimethylsilane affords [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid (I) in 78% yield. The overall yield for the sequence of reactions is 15.5%.

In the processes of the present invention, as illustrated in Step II of Scheme 1 below, a 3-aminopropyl carbamic acid dialkyl ester (IV) is, instead, reacted with a dialkyl vinylphosphonate (V) to obtain the N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid dialkyl ester (VI). Further improvements provided by the present invention over the process of U.S. Pat. No. 5,168,103 as noted below, increase the overall yield to produce I to 38.8%.

One aspect of this invention is a process for the preparation of [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid which comprises the following steps:

- reacting a 3,4-di-C₁-C₆alkoxycyclobut-3-en-1,2-dione with a di-C₁-C₆alkyl ester of N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid to give 3-[[2-(di-C₁-C₆alkoxyphosphoryl)ethyl]-(2-C₁-C₆alkoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl carbamic acid tert-butyl ester;
- protecting the 3-amino group of the product of step (a);

2

c) cyclizing the product of step (b) to form the bicyclic intermediate [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid di-C₁-C₆alkyl ester; and

d) converting the di-C₁-C₆alkyl ester of step (c) to the phosphonic acid product. Step (a) is preferably carried out in anhydrous methanol or ethanol at ambient temperatures (25-30° C). Steps (a), (b) and (c) are preferably run in situ. Step (b) is preferably carried out in methylene chloride at -5° C. to 25° C. Step (d) is preferably carried out in methylene chloride or acetonitrile at about 20° C. The preferred 3,4-di-C₁-C₄alkoxycyclobut-3-en-1,2-dione in step (a) is 3,4-diethoxycyclobut-3-en-1,2-dione.

In another aspect of the invention, the di-C₁-C₆alkyl ester of N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid of step (a) is prepared by a process which comprises reacting a vinylphosphonate di-C₁-C₆alkyl ester with 3-aminopropyl carbamic acid 1,1-dimethylethyl ester. The preferred vinylphosphonate di-C₁-C₆alkyl ester is dimethyl vinylphosphonate or is diethyl vinylphosphonate, of which dimethyl vinylphosphonate is most preferred.

In another aspect, the invention provides the following compounds:

- a compound which is an N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid di-C₁-C₆alkyl ester;
- a compound which is N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid dimethyl ester or N-[3-(t-butyloxycarbonylamino)propyl]-2-aminomethylphosphonic acid diethyl ester;
- a compound which is a 3-[[2-(di-C₁-C₆alkoxyphosphoryl)ethyl]-(2-C₁-C₄alkoxy-3,4-dioxocyclobut-1-enyl)amino]propyl carbamic acid tert-butyl ester; and
- a compound which is 3-[[2-(diethoxyphosphoryl)ethyl]-(2ethoxy-3,4-dioxocyclobut-1-enyl)amino]propyl carbamic acid tert-butyl ester or is 3-[[2-(diethoxyphosphoryl)ethyl]-(2-methoxy-3,4-dioxocyclobut-1-enyl)amino]propyl carbamic acid tert-butyl ester.

The process of the present invention is illustrated in Scheme 1 below, where "alkyl" is represented by the ethyl group and "alkoxy" is represented by the ethoxy group, and is further described as follows:

In Step 1, 1,3-diaminopropane (II) is reacted with a di-t-butylcarbonate (III) to give 3-aminopropyl carbamic acid 1,1-dimethylethyl ester (IV).

In Step 2, the carbamic acid ester IV is reacted with a di-C₁-C₆alkyl vinylphosphonate (V), to give N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid di-C₁-C₆alkyl ester (VI). In the illustrated case where V is diethyl vinylphosphonate, this step provides an 80% yield. However, dimethyl vinylphosphonate provides comparable yields and is preferred commercially because it is more readily available in larger quantities.

In Step 3, aminophosphonic acid di-C₁-C₆alkyl ester (VI) is reacted with a 3,4-di-C₁-C₄alkoxycyclobut-3-en-1,2-dione (VII) to give a 3-[[2-(di-C₁-C₆alkoxyphosphoryl)ethyl]-(2-C₁-C₄alkoxy-3,4-dioxo-1-cyclobuten-1-yl)amino]propyl carbamic acid 1,1-dimethylethyl ester (VIII). In the illustrated case where alkyl refers to ethyl in both instances, this step provides a 96% yield. This step is preferably carried out in anhydrous methanol or ethanol at ambient temperatures.

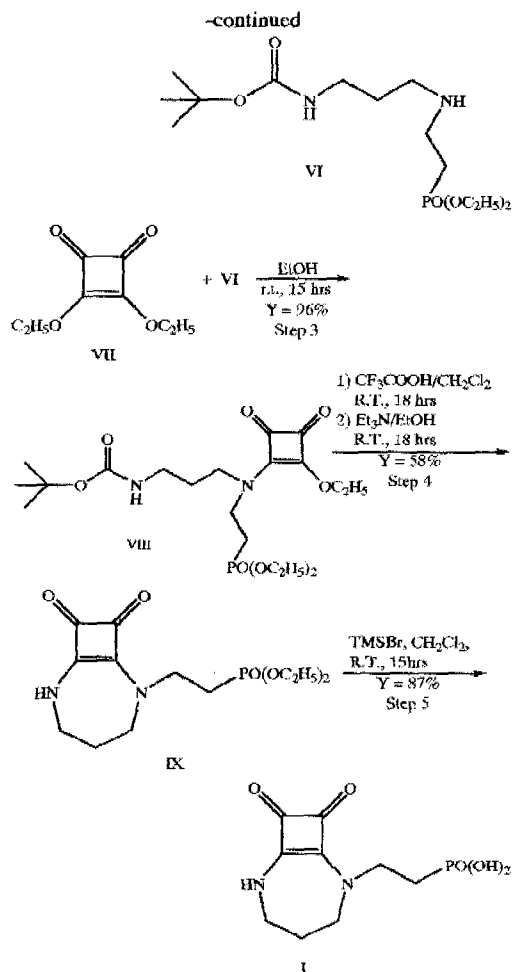
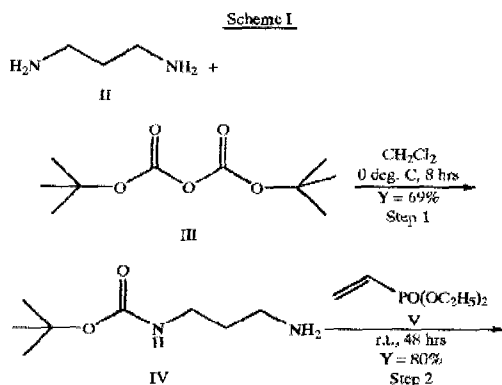
In step 4, deprotection of (VIH) in trifluoro-acetic acid followed by cyclization with triethylamine as a cyclizing agent gives [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]-phosphonic acid di-C₁-C₆alkyl ester (IX). In the illustrated case the yield of the product IX is 58% yield. The deprotection is preferably carried out in methylene chloride at -5° C. to 25° C. The cyclization is preferably carried out in methylene chloride or acetonitrile, with methylene chloride being particularly preferred, at about 20° C.

In Step 5, the phosphonic acid diethyl ester (IX) is treated with bromotrimethylsilane to give compound I in 87% yield. The overall yield for preparing [2-((8,9)-dioxo-2,6-diazabicyclo[5.2.0]-non-1(7)-en-2-yl)ethyl]phosphonic acid (I) according to the process of this invention is 38.8%, a considerable improvement over the 15.5% yield disclosed in U.S. Pat. No. 5,168,103.

Steps 2, 3 and 4 are preferably done in situ.

In the reaction sequence above, the term "alkyl" means a C₁-C₆ alkyl, straight or branched, and the term "alkoxy" means a C₁-C₆ alkoxy group, except with respect to the squarate compounds VII where alkyl means methyl, ethyl or butyl. The yields refer to specific instances where "alkyl" is ethyl and "alkoxy" is ethoxy. Advantages of the process of this invention are several fold. First, 1,3-propanediamine is mono-protected in excellent yield with di-*t*-butyldicarbonate, a reaction that is less hazardous than using benzylchloroformate to prepare a benzyloxycarbamate protecting group. Second, the monoprotected-1,3-propanediamine is reacted with diethyl vinylphosphonate in excellent yield without employing additional reagents such as sodium cyanoborohydride and acid, each of which is not without hazard, which were required when using diethyl 2-oxoethylphosphonate as previously disclosed. Third, the *t*-butyloxy-carbonyl group is removed readily with acid whereas the removal of the benzyloxycarbonyl group required the use of palladium catalyst and a hydrogen source.

The process according to this invention is outlined in the following scheme I. In this scheme, "alkyl" is represented by the ethyl group and "alkoxy" is represented by the ethoxy group.



The following specific examples are included to illustrate the process of this invention and should not be construed as limiting to the process of this invention in any way. Those skilled in the art may be aware of still other procedures or modifications which may be used in an equivalent manner to perform the invention process.

EXAMPLE 1

3-(*t*-Butyloxycarbonylamino)propanamine

To a solution of 1,3-diaminopropane (500 g, 6.75 moles; Aldrich D2, 360-2) in tetrahydrofuran (1.6 l) at from -3° C. to +2° C. with stirring was added dropwise a solution of di-*t*-butyldicarbonate (300 g, 1.375 mole; Aldrich 19, 913-3) in tetrahydrofuran (800 mL) over a period of -8 hr. The resulting white suspension was stirred at 0° C. and let slowly warm to ambient temperature overnight. The reaction mixture was concentrated in vacuo and the residue was taken up in a mixture of ethyl acetate and saturated sodium chloride solution. The aqueous layer was extracted with ethyl acetate. The combined extracts were washed once with sat. sodium chloride, dried over magnesium sulfate and filtered to yield an oil (~245 g, quantitative). The oil was suspended in water (200 mL) and cooled to 0° C. to -5° C. An aqueous solution

of bromo cresol green (3 mL, 0.04% in water; Aldrich 31, 870-1) was added to result in a blue solution. With vigorous stirring (1N hydrochloric acid (1.4 L) was added dropwise to give a light blue to green/yellow colored solution (pH ~5-6, pH-paper). This suspension was extracted with methylene chloride (2x300 mL) and the aqueous layer made basic with 2.5 N sodium hydroxide to pH ~12. The basic aqueous layer was extracted with methylene chloride (5x300 mL) and the organic layer was washed with saturated sodium chloride solution (2x100 mL), dried over anhydrous potassium carbonate powder, filtered through Celite and concentrated to give the title compound as a faint bluish oil which crystallized on standing (165 g, 69%) (very hygroscopic solids). NMR (CDCl₃, 400 MHz): 1.43 (s, 9H), 1.61 (p, 2H), 1.59 (s, 2H), 2.76 (t, 2H), 3.20 (q, 2H), 4.95 (br, 1H).

EXAMPLE 2

N-[3-(t-Butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid diethyl ester

To a solution of 3-(t-butyloxycarbonylamino) propanamine (77 g, 0.44 mole) in methanol (500 mL) was added diethyl vinylphosphonate 97% (75 g, 0.44 mole; Aldrich 11, 613-0) under nitrogen and kept in a water bath at -20° C. for 48 hr. The reaction mixture was concentrated in vacuo and the residue (~160 g) was put on a pad of "Florisil" (3"x6") and eluted with methylene chloride/hexane 1:1, methylene chloride and finally 10% methanol/methylene chloride to give the title compound as a colorless oil (121 g, 80%).

NMR (CDCl₃, 400 MHz): 1.32 (t, 6H), 1.43 (s, 9H), 1.65 (t, 2H), 1.80 (br, 1H), 1.97 (dt, 2H), 2.67 (t, 2H), 2.85 (dt, 2H), 3.20 (q, 2H), 4.09 (m, 4H), 5.08 (br, 1H).

EXAMPLE 3

[3-[[2-(Diethoxy-phosphoryl)-ethyl]-(2-ethoxy-3,4-dioxocyclobut-1-enyl)amino]propyl]carbamic acid tert-butyl ester

To a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione (45 g, 0.265 mole; Aldrich 31,077-8) in absolute ethanol (1.2 L) under nitrogen was added dropwise a solution of N-[3-(1-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid diethyl ester (80 g, 0.24 mole) in absolute ethanol (600 mL) and the reaction mixture was stirred at ambient temperature 15 hr. The reaction mixture was concentrated in vacuo and the residue was put on a pad of silica gel (6"x4") and eluted first with a mixture of methylene chloride/hexane 1:1 to remove excessive 3,4-diethoxy-3-cyclobutene-1,2-dione and finally with 10% methanol/methylene chloride to yield the title compound after evaporation as a viscous oil (107 g, 96%). NMR: (CDCl₃, 400 MHz): 1.34 (t, 6H), 1.43 (s, 9H), 1.46 (t, 3H), 1.80 (m, 2H), 2.12 (m, 2H), 3.14 (m, 2H), 3.49 (t, 1H), 3.66 (m, 1H), 3.73 (t, 1H), 3.90 (m, 1H), 4.10 (m, 4H), 4.74 (m, 4H), 5.05 (br, H).

EXAMPLE 4

[2-(8,9-Dioxo-2,6-diazabicyclo 5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic Acid Diethyl Ester

A solution of N-[3-(t-butyloxycarbonylamino)propyl]-N-[4-ethoxy-2,3-dioxocyclobut-1-en-1-yl]-2-aminoethylphosphonic acid diethyl ester (100 g, 0.22 mole) in methylene chloride (600 mL) was cooled in ice and treated with trifluoroacetic acid (300 mL). The reaction mixture was left to warm to ambient temperature overnight. The solution was concentrated in vacuo at max. 40° C. and

co-evaporated with toluene (2x500 mL) to yield a viscous oil (159.5g) which was dissolved in absolute ethanol (1.5 L) and added dropwise over eight hours to a solution of triethylamine (350 mL) in ethanol (1.5 L) and stirred for 8 hr. at room temperature. The reaction mixture was concentrated in vacuo to an oil which was taken up in ethyl acetate (1 L). Compound crystallized and was cooled in ice, filtered and washed with ethyl acetate and finally hexane to give the title compound as a white compound (40 g, 58%). NMR (CDCl₃, 400 MHz): 1.34 (t, 6H), 2.06 (m, 2H), 2.20 (dt, 2H), 3.50 (m, 4H), 4.05 (m, 2H), 4.15 (m, 4H), 7.87 (br, 1H). MS (DEI) M⁺m/z 316. LC analysis (column: Microsorb-MV C18, 150x4.6 mm; Eluent: 30/70 MeOH/0.01 M NH₄H₂PO₄ pH 4.7; Flow rate: 1 mL/min; UV detector at 210 nm; Analysis: Calc'd. for C₁₃H₂₁N₂O₅P: C, 49.36; H, 6.69; N, 8.85%. Found: C, 49.47; H, 6.74; N, 8.77%.

EXAMPLE 5

[2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]-phosphonic Acid

Under N₂ bromotrimethylsilane (83 mL, 96.3 g, 0.63 mole; Aldrich 19,440-9) was added dropwise at a fast rate to a solution of [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic acid diethyl ester (37.6 g, 0.12 mole) in methylene chloride (350 mL). The reaction mixture was kept in a water bath at approximately 20° C. for 15 hr. The clear solution was concentrated in vacuo and the foamy residue was taken up in acetone (600 mL) with vigorous shaking to result in a thin suspension. Water (50 mL, 2.78 moles) was added to give a gummy precipitate which solidified instantly. The suspension was shaken vigorously for 10 minutes, filtered and washed with acetone to give a yellow solid compound. The solids were taken up in boiling water (450 mL) and the hot solution was filtered through a fluted filter paper to remove a small amount of insoluble material. The clear aqueous solution was cooled in ice and crystallization began at once. The thick crystalline mass was diluted by slow addition of acetone (800 mL), kept cold for 1 hr, filtered and washed with acetone and then hexane to give the title compound as a pale yellow solid (20.2 g). A second crop from the mother liquor (100% purity by LC) yielded an additional amount (6.5 g) for a total yield of 87%. NMR (DMSO-d₆, 400 MHz): 1.90 (m, 4H), 3.25 (m, 2H), 3.36 (m, 2H), 3.84 (q, 2H), 8.45 (s, 1H). LC analysis: (Column: Nova Pak C18, 300x3.9 mm; Eluent: 20/80 MeOH/0.005 M Pic A; Flowrate: 1 mL/min; UV detectors at 210 nm). Analysis: Calc'd. for C₉H₁₃N₂O₅P.0.1H₂O: C, 41.26; H, 5.08; N, 10.69%;

Found: C, 41.17; H, 5.04; N, 10.42%; Karl-Fischer analysis: 0.55% H₂O; MS: -FAB [M-H]⁻ m/z 259.

EXAMPLE 6

Preparation of 3-(t-Butyloxycarbonylamino) propanamine ("t-BOC-Propanamine")

A solution of di-t-butylidicarbonate (0.50 Kg, 2.29 moles) in methanol was added to an excess (5 equivalents) of 1,3-diaminopropane (0.83 Kg, 11.2 moles) over a 4 hour period at 25-30° C. The product 1,3-Diaminopropane t-butyloxycarbonate was filtered off and the methanol removed by vacuum distillation. The residual oil was taken into ethyl acetate, washed with brine, water added, and the pH adjusted to 5.5. The layers were separated and the aqueous phase made strongly alkaline. The alkaline aqueous solution was extracted six times with toluene. The combined

toluene extracts were dried over sodium sulfate and concentrated to afford t-BOC-propanamine (0.365 Kg) in a 77.4 % yield, 11.5 % total impurities.

EXAMPLE 7

Preparation of [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)phosphonic acid, dimethyl ester ("Dimethyl Phosphonate Ester")

A. Formation of t-BOC-phosphonate Dimethyl Ester

A solution of t-BOC-Propanamine, 98% (0.67 Kg, 3.77 moles) and dimethylvinylphosphonate (0.59 Kg, 4.12 moles) in anhydrous methanol (2.7 L) were stirred at room temperature for 2 days to give a solution of the Dimethyl Phosphonate Ester product.

B. Formation of t-BOC-Phosphonate Dimethyl Ethyl Squarate

The Dimethyl Phosphonate Ester product solution in A was then added to a solution of 3,4-diethoxy-3-cyclobutene-1,2-dione ("Ethyl Squarate") (0.55 Kg, 3.23 moles) in anhydrous methanol (3.24 L) over a six hour period. After stirring at 0-5° C. overnight the reaction mixture was concentrated by distillation. Toluene (1 L) added and the distillation repeated to a final volume of 1.6 L 3-[[2-(Diethoxy-phosphoryl)ethyl]-(2ethoxy-3,4-dioxocyclobut-1-enyl)amino]propylcarbamate acid tert-butyl ester ("t-BOC-Phosphonate Dimethyl Ethyl Squarate").

C. Formation of Deprotected Phosphonate Dimethyl Ethyl Squarate

To the product solution of t-BOC-Phosphonate Dimethyl Ethyl Squarate from B was added toluene (5.0 L) at 0-5° C., followed by trifluoroacetic acid (4.71 Kg, 41.31 moles) over 0.25-5 hrs. while keeping the temperature under 15° C. After stirring for 4 hours at room temperature, the reaction mixture was concentrated to afford the crude deprotected Phosphonate Dimethyl Ethyl Squarate.

D. Formation of Dimethyl Phosphonate Ester

Anhydrous methanol (4.5 L) was added to the reaction product concentrate from C, and the resulting solution was added over a 6 hour period to a solution of excess triethylamine (2.9 Kg, 28.66 moles) in anhydrous methanol at room temperature. The resulting mixture was concentrated, followed by the addition of ethyl acetate which precipitated out the tided Dimethyl Phosphonate Ester product. After filtration and washing of the cake with cold ethyl acetate a 50.4 % yield of [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic Acid Diethyl Ester

("Dimethyl Phosphonate Ester") (0.56 Kg), 97.6% strength, was obtained, single impurity of 1.05 % and total impurities of 1.76%.

EXAMPLE 8

Preparation and Purification of [2-(8,9-Dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]phosphonic Acid

10 Bromotrimethylsilane, 97.6% (0.55 Kg, 3.59 moles) was added at room temperature to a stirring suspension of dimethyl phosphonate ester (0.46 Kg, 1.56 moles) in acetonitrile (4.1 L). The resulting solution is then added to stirring acetonitrile-water. The titled phosphonic acid precipitated out of solution as cream-colored solids. The slurry was cooled to 0° C. and the product collected by filtration. The wet cake was stirred in water and 30 % NaOH added to a pH of 13. A solution formed. Hydrochloric acid was added to a pH of 1.0. The titled phosphonic acid precipitated out of solution as white-colored solids. The product was collected on a Buchner and washed with ice-cold water. The titled phosphonic acid was then purified by recrystallization from water. The wet cake was dissolved in 12 parts water, filtered through paper on a Buchner, and the filtrate concentrated. Upon cooling the titled phosphonic acid crystallized out of solution. The slurry was cooled to 0° C. and collected on a Buchner. The cake was washed with water, dried in a vacuum oven at 65° C. to afford the titled phosphonic acid, purified in an 86% yield, 99.9% strength, single impurity, 0.05%, total impurities, 0.13%.

We claim:

1. A compound which is a N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid di-C₁-C₆ alkyl ester.

2. The compound N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid dimethyl ester or compound N-[3-(t-butyloxycarbonylamino)propyl]-2-aminoethylphosphonic acid diethyl ester.

3. A compound which is a 3-[[2-(di-C₁-C₆alkoxy-phosphoryl)ethyl]-(2-C₁-C₆alkoxy-3,4-dioxocyclobut-1-enyl)amino]propylcarbamate acid tert-butyl ester, where the alkoxy groups are the same or different.

4. The compound 3-[[2-(diethoxy-phosphoryl)ethyl]-(2ethoxy-3,dioxocyclobut-1-enyl)amino]propylcarbamate acid tert-butyl ester.

* * * * *

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International Nonproprietary Names for Pharmaceutical Substances (INN)

RECOMMENDED International Nonproprietary Names: List 53

Notice is hereby given that, in accordance with paragraph 7 of the Procedure for the Selection of Recommended International Nonproprietary Names for Pharmaceutical Substances [Off. Rec. *Wld Health Org.*, 1955, 60, 3 (Resolution EB15.R7); 1969, 173, 10 (Resolution EB43.R9)], the following names are selected as Recommended International Nonproprietary Names. The inclusion of a name in the lists of Recommended International Nonproprietary Names does not imply any recommendation of the use of the substance in medicine or pharmacy.

Lists of Proposed (1-91) and Recommended (1-52) International Nonproprietary Names can be found in *Cumulative List No. 11, 2004* (available in CD-ROM only).

Dénominations communes internationales des Substances pharmaceutiques (DCI)

Dénominations communes internationales RECOMMANDÉES: Liste 53

Il est notifié que, conformément aux dispositions du paragraphe 7 de la Procédure à suivre en vue du choix de Dénominations communes internationales recommandées pour les Substances pharmaceutiques [*Actes off. Org. mond. Santé*, 1955, 60, 3 (résolution EB15.R7); 1969, 173, 10 (résolution EB43.R9)] les dénominations ci-dessous sont choisies par l'Organisation mondiale de la Santé en tant que dénominations communes internationales recommandées. L'inclusion d'une dénomination dans les listes de DCI recommandées n'implique aucune recommandation en vue de l'utilisation de la substance correspondante en médecine ou en pharmacie.

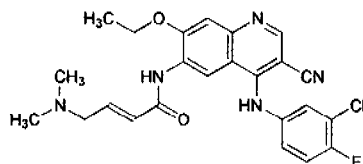
On trouvera d'autres listes de Dénominations communes internationales proposées (1-91) et recommandées (1-52) dans la *Liste récapitulative No. 11, 2004* (disponible sur CD-ROM seulement).

Denominaciones Comunes Internacionales para las Sustancias Farmacéuticas (DCI)

Denominaciones Comunes Internacionales RECOMENDADAS: Lista 53

De conformidad con lo que dispone el párrafo 7 del Procedimiento de Selección de Denominaciones Comunes Internacionales Recomendadas para las Sustancias Farmacéuticas [*Act. Of. Mund. Salud*, 1955, 60, 3 (Resolución EB15.R7); 1969, 173, 10 (Resolución EB43.R9)], se comunica por el presente anuncio que las denominaciones que a continuación se expresan han sido seleccionadas como Denominaciones Comunes Internacionales Recomendadas. La inclusión de una denominación en las listas de las Denominaciones Comunes Internacionales Recomendadas no supone recomendación alguna en favor del empleo de la sustancia respectiva en medicina o en farmacia.

Las listas de Denominaciones Comunes Internacionales Propuestas (1-91) y Recomendadas (1-52) se encuentran reunidas en *Cumulative List No. 11, 2004* (disponible sólo en CD-ROM).



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perflubutane

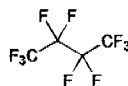
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perflubutane

décafluorobutane

perflubutano

decafluorobutano



perzinfotelum
perzinfotel

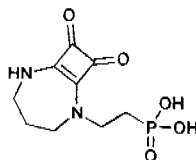
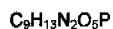
[2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-yl)ethyl]=
phosphonic acid

perzinfotel

acide [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-én-2-yl)éthyl]=
phosphonique

~~perzinfotel~~

ácido [2-(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-il)etil]=
fosfónico



prasugrelum
prasugrel

5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-
4,5,6,7-tetrahydrothieno[3,2-*c*]pyridin-2-yl acetate

prasugrel

acétate de 5-[(1*RS*)-2-cyclopropyl-1-(2-fluorophényl)-2-oxoéthyl]-
4,5,6,7-tétrahydrothiéno[3,2-*c*]pyridin-2-yle

prasugrel

acetato de 5-[(1*RS*)-2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-
4,5,6,7-tetrahidrotieno[3,2-*c*]piridin-2-ilo

Fármacos analgésicos opioides

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Introducción

El objetivo fundamental de este capítulo no es tanto presentar una descripción farmacológica sistematizada de este grupo de fármacos, que puede encontrarse en otros lugares^{1,2}, como ofrecer los datos más importantes que ayuden a utilizarlos de un modo práctico con rigor y confianza.

Es demasiado el miedo que hemos infundido a numerosas promociones de médicos, farmacéuticos y diplomados en enfermería ante la utilización de estos analgésicos, con nefastas consecuencias para la calidad de vida de demasiados pacientes, obligados a sufrir un dolor innecesario. Por consiguiente, urge esforzarse por reparar de alguna manera este distate pedagógico, de modo que los profesionales y cuidadores sanitarios recuperen la confianza en los opioides y los utilicen de manera eficiente y oportuna.

Propiedades generales

Definiciones

El término de analgésicos opiáceos u opioides sustituyó al viejo nombre de analgésicos narcóticos porque la analgesia nada tiene que ver en sí con la narcosis, término, por otra parte, bastante impreciso que crea un clima con tonalidad peyorativa que resulta falso y contraproducente. Estos analgésicos constituyen un grupo de fármacos que se caracterizan por poseer afinidad selectiva por los receptores endógenos opioides.

Convencionalmente se decidió que todo producto que alivie el dolor previa fijación a dicho receptor, sea denominado analgésico opioide. El término opiáceo queda restringido a los fármacos naturales o sintéticos que derivan estrictamente del opio, jugo extraído de la adonidiera *Papaver*

somniferum. En consecuencia, en el presente capítulo se adopta el término general de fármacos opioides que comprende toda la gama de fármacos, sintéticos en su inmensa mayoría, capaces de aliviar o suprimir el dolor tras interactuar con alguno o algunos de los tipos de receptor opioide.

Los receptores opioides

Se conoce con certeza la existencia de tres tipos de receptores opioides, μ , κ y δ , y es muy posible que de ellos existan varios subtipos, aunque a efectos prácticos bastan estos tres³. (Prescindimos del llamado receptor ORL₁ por desconocer todavía su función⁴). Estos receptores son moléculas endógenas que pertenecen al grupo de receptores celulares de membrana, constituidos por una cadena proteica con siete segmentos transmembrana, asociados a proteínas G. Se encuentran distribuidos a todo lo largo y ancho del sistema nervioso, tanto el central como el periférico y el entérico. Lógicamente, su ubicación marca la acción del fármaco opioide, ya que, si la acción de un fármaco se debe a su

interacción con su receptor y a la cascada de procesos neuronales resultantes de esa interacción, el sitio en el que se encuentre el receptor opioide condicionará la acción del fármaco que con él interactúa. Los receptores opioides reciben lógicamente las señales de sus ligandos naturales, las encefalinas, endorfinas y otros neuropéptidos opioides.

En general, las consecuencias neuronales inmediatas de la activación de estos receptores consisten en una reducción de la actividad neuronal; pierde excitabilidad y pierde capacidad para liberar sus neurotransmisores específicos. Ello se debe básicamente a la inhibición de la adenililciclase, a la apertura de canales de potasio y al cierre de canales de calcio. Queda depri-mida, pues, la transmisión nerviosa.

En la tabla 1 se exponen algunas de las respuestas opiáceas relacionadas con la activación de los receptores, las cuales lógicamente marcan los efectos terapéuticos y tóxicos de los productos. Importa, por tanto, saber qué receptor opioide es el activado por un fármaco, para deducir así sus principales efectos.

Clasificación

A efectos prácticos, es útil clasificar los fármacos opioides en: agonistas puros, agonistas/antagonistas mixtos, agonistas parciales y antagonistas puros.

En la tabla 2 se exponen los principales fármacos que pertenecen a estos grupos.

TABLA 1
Acciones de los opioides y receptores implicados

Acción	Receptores	Localización
Inhibición del dolor	μ, δ, κ	Asta posterior de la médula espinal y centros supraspinales
Depresión respiratoria	μ, δ	Tronco cerebral; centro respiratorio
Farmacodependencia	$\mu > \kappa$	SNC; sistemas "gratificantes"
Euforia y sedación	μ	SNC
Disforia y psicotomimesis	κ	SNC
Miosis	μ, κ	SNC
Rigidez muscular	μ	SNC; núcleos basales
Dependencia física	$\mu > \kappa > \delta?$	SNC y SNA
Tolerancia	μ, κ, δ	
Morbilidad gastrointestinal	$\mu, \delta?$	SNE y centros espinales
Morbilidad vesical	μ	SNA y centros espinales
Dinorexia		
Inhibición	μ	Hipotálamo/hipófisis
Estimulación	κ	¿Riñón?
Bradicardia	$\mu > \delta > \kappa$	Tronco cerebral
Hipotensión	$\delta > \kappa > \mu$	SNA y tronco cerebral
Acciones endocrinológicas		Hipotálamo/hipófisis
Liberación de prolactina	μ	
Liberación de GH	$\delta > \mu$	
Liberación de ACTH	μ, κ	
Inhibición de ADH	κ	
Inhibición de LH	μ, δ	

Agonistas puros

Son los fármacos que fundamentalmente activan receptores μ . En consecuencia, y de acuerdo con los datos de la tabla 1, producirán analgesia espinal y supraespinal, euforia, depresión respiratoria, miosis, náuseas y vómitos, estreñimiento y aumento de la presión de vías biliares. La mayoría de todos estos efectos adquieren la característica de reacciones adversas, y sus peculiaridades y formas de resolverlas se expondrán más adelante.

Los efectos son dependientes de la dosis; es decir, el grado de analgesia crece casi ilimitadamente con la dosis y podría alcanzar un *techo* muy alto si no fuera por las limitaciones impuestas por sus efectos adversos (somnolencia y perturbación cognitiva/estupor/coma, depresión respiratoria grave, mioclonías). La analgesia del opioide se debe a una depresión de los mecanismos de transmisión *aférente* del dolor, propios del asta posterior de la médula espinal, del tronco cerebral y del cerebro límbico, de modo que no sólo perturba la transmisión nerviosa específica de la sensibilidad nociceptiva sino también la tonalidad afectiva del dolor. A su vez, potencia la acción *eférente* endógena, controlante de la transmisión nociceptiva. Ésta es la razón de que la analgesia opioide sea tan poderosa, si bien es importante conocer que hay dolores, fundamentalmente de carácter neuropático, que son más resistentes a la acción del opiáceo, como más adelante se verá. Todos ellos muestran potencialidad para inducir farmacodependencia, tanto en su expresión física como psíquica, si bien su aparición dependerá notablemente del modo de utilización y de las circunstancias que lo acompañan.

A la intensidad de la analgesia conseguida solemos llamar *eficacia* o *techo analgésico* y a la cantidad de producto necesario para conseguirla llamamos *potencia*, de forma que es más potente quien menos dosis requiera y no quien más grado de analgesia consiga. Los agonistas puros μ que tienen un techo analgésico más bajo son frecuentemente llamados opioides menores (tabla 2) y se utilizan en dolores leves o moderados, solos o en asociación con analgésicos no opioides. En contraposición, los denominados mayores sirven para dolores de fuerte intensidad. Algunos más modernos como el tramadol se encuentran en posición intermedia.

TABLA 2
Clasificación funcional de analgésicos opioides

Agonistas puros
<i>Para dolor moderado-intenso</i>
De semivida corta
Morfina
Petidina
Heroína
Fenando
Hidromorfona
Sufentanilo
Tramadol
Oxycodona
Oximorfona
De semivida larga
Metadona
Levorfanol
L- α -acilmetadol
<i>Para dolor ligero-moderado</i>
Codeína
Dihidrocodeína
Dextropropoxifeno
Tramadol
Oxycodona
Ulidina
Agonistas/antagonistas mixtos
Pentazocina
Nalbuphina
Butorfanol
Dezocina
Agonistas parciales
Buprenorfina
Antagonistas puros
Naloxona
Naltrexona

Agonistas/antagonistas mixtos

Se caracterizan por activar preferentemente el receptor opioide κ , y por comportarse como agonistas débiles o incluso como antagonistas de receptores μ . Su representante más conocido es la pentazocina. De acuerdo con estas acciones, producen analgesia (tabla 1), pero de calidad diferente: su techo antiálgico es inferior al de los agonistas puros μ , no se acompaña de sensación euforizante que, por el contrario, puede ser disfórica. El aumento de dosis fácilmente provoca efectos psicotomiméticos. Aventajan a los agonistas puros μ en que inducen menor grado de depresión respiratoria cuando se administran dosis acumulativas, no producen estreñimiento ni aumentan la presión en vías biliares, y tienen menor potencialidad para producir farmacodependencia. Pero la disforia y la psicotomimesis limitan su utilización, como se verá en su momento.

Agonistas parciales

Su principal representante es la buprenorfina. Su eficacia intrínseca al interactuar con los receptores μ es inferior a la de los agonistas puros, por lo que será también menor su eficacia o techo antiálgico. Su

modo de utilización se expondrá más adelante.

Antagonistas puros

Son fármacos con alta afinidad por los tres tipos de receptores opioides, en el orden $\mu > \delta > \kappa$, pero con nula eficacia intrínseca. Por tanto, compiten con los agonistas en su capacidad de unirse a los receptores, los desplazan, y sirven así para suprimir o evitar los efectos de cualquiera de los agonistas (con alguna excepción, como después se verá). Los principales representantes son la naloxona, de semivida muy rápida y sólo administrable por vía parenteral, y la naltrexona de semivida más lenta y absorbible por vía oral.

Características diferenciales

En la tabla 3 se resumen los datos farmacocinéticos diferenciales de mayor interés práctico para la correcta dosificación de los opioides. A efectos clínicos conviene distinguir los que se emplean para tratar el dolor de intensidad débil a moderada, de aquellos que sirven para el dolor moderado a intenso.

Agonistas opioides utilizados en el dolor débil o moderado

En España disponemos de los siguientes: codeína, dihidrocodeína, dextropropoxifeno, ulidina y tramadol. Se dispone de ellos en diversas formulaciones: a) como preparados de formulación única y simple; b) como preparados de liberación controlada en el caso de la codeína y dihidrocodeína; c) en combinación fija con analgésicos antiinflamatorios no esteroideos (AINE) o antipiréticos (AAP) o antiinflamatorios no esteroideos (AINE). Todos ellos en su formulación ordinaria se caracterizan por tener una semivida que oscila entre las 2 y 4 horas, por lo que en caso de tratarse de un dolor persistente han de ser administrados cada 4 o, como mucho, cada 6 horas si se quiere conseguir un control permanente del dolor. Cuando se administran en forma combinada con AAP/AINE, es conveniente que estos últimos tengan una semivida de duración similar, como suele ser el caso del ácido acetilsalicílico o del paracetamol. En las formulaciones de liberación controlada, la duración del efecto antiálgico se prolonga hasta 12 horas.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020
Bogotá, D.C., 10/04/2009

Abogado
Alicia Lloreda Ricaurte
(Apoderado)

ASUNTO	Radicación	04 32577
	Trámite	002
	Evento	001
	Actuación	430
	Oficio	Nº 4475
	Folios	006

Patente de Invención	☒	Patente de Modelo de Utilidad	☐
Vía Nacional	☐		
Vía PCT (fase nacional)	☒	Cap. I	☐
		Cap. II	☒

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

1. Documentos estudiados

- 1.1 Descripción: Folios: 87 a 119
- 1.2 Reivindicaciones: Folios: 120 a 129
Folios: 187 a 192 Memorial 02/05/2008
- 1.3 Datos PCT:

Solicitud Internacional:	PCT/US02/32252
Capítulo II	
Fecha Sol. Internacional:	09/10/2002
Publicación. Internacional:	WO03/031416
Fecha Pub. Internacional:	17/04/2003
Fecha Inicio Fase Nacional:	10/05/2004
Solicitud Nacional:	CO 04 32577
Fecha Sol. Nacional:	06/04/2004
- 1.4 Prioridad: US60/328,245 de 10/10/2001
- 1.5 Respuesta del solicitante: Folios: 176 a 192 Memorial de 02/05/2008

2. Objeto de la invención

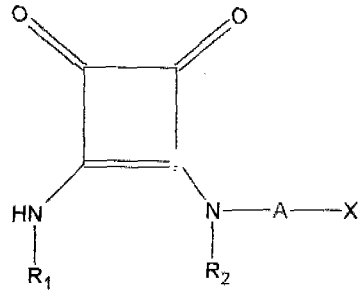
Título de la solicitud

***Derivados de ácido [[2-(amino-3,4-dioxo-1-ciclobuten-1-il)amino]alquilo]
para el tratamiento del dolor***

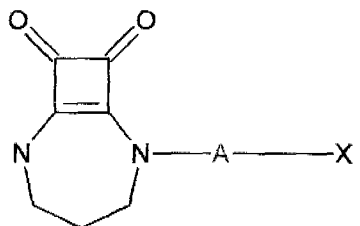
Reivindicaciones (Folios 187 a 192)

Reivindicaciones 1 a 4, 7, 8, 9, 14 y 15: Se reivindica una composición para el tratamiento del dolor que comprende:

a) Una cantidad efectiva para tratar el dolor de al menos un compuesto de fórmula (I) o una sal farmacéuticamente aceptable, en donde la cantidad efectiva es de al menos 150mg/día para una dosis oral, y de al menos 3mg/día para dosis IV, y



En especial, el compuesto de fórmula (I) presenta la fórmula (III):



O se elige entre:

- Ácido [2-[(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-il)etil]fosfónico
- Ácido [2-[(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2il)etil]fosfónico

b) Una cantidad farmacéuticamente aceptable de al menos un agente aliviador del dolor, tal es el caso de un analgésico opiode.

Reivindicaciones 5 y 6, 10, 11, 12, 13: Se reivindica una composición que contiene como principio activo el compuesto de fórmula (I) y al menos un vehículo farmacéuticamente aceptable.

Sustento Descriptivo

Los antagonistas de glutamato de receptor NMDA convencionales no presentan en mayor medida efectos secundarios psicotomiméticos en humanos o los efectos de estímulos discriminatorios del tipo PCP en no humanos, por esta razón los compuestos utilizados constituyen una alternativa efectiva dado que presentan efectos secundarios adversos reducidos y son más efectivos en el tratamiento del dolor. Por esta razón la invención (ver folio 93) provee un método para el tratamiento del dolor que incluye la administración a un mamífero en necesidad de dicho

tratamiento de una cantidad efectiva para tratar el dolor de al menos un compuesto que tenga la fórmula (I).

La invención también provee una composición farmacéutica que contiene una cantidad efectiva para tratar el dolor del compuesto de fórmula (I) o una sal farmacéuticamente aceptable de este y al menos un vehículo farmacéutico.

- Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K³¹/662** de la **Clasificación Internacional de Patentes**.

3. De la solicitud de Patente

3.1. Reivindicaciones (artículo 30 D. 486)

- El solicitante mediante memorial de fecha 02/05/2008 presenta un nuevo juego de reivindicaciones en el que modifica el contenido de las cláusulas y las convierte en reivindicaciones de composición definidas en términos de los elementos que las componen, a saber: derivados del núcleo de fórmula (I) en combinación con analgésico opioide. Además reivindica composiciones que contienen como único componente activo el compuesto de fórmula (I) y un vehículo farmacéuticamente aceptable.

Al respecto es preciso señalar que el contenido de las cláusulas 1 a 4 se repite de manera innecesaria a partir de la cláusula 7 cuando al segundo grupo de invención, es decir, al que corresponde a las composiciones que contienen exclusivamente el compuesto de fórmula (I) en la forma de derivados de diazabicyclo[4.2.0]octeno o diazabicyclo[5.2.0]noneno en un vehículo farmacéuticamente aceptable se le incorpora un segundo componente activo en la forma de analgésico opioide o como especie química.

Esta situación ocurre nuevamente con las cláusulas 10 a 15 que no plantean modalidades diferentes de la invención que no hubieran sido especificadas en las cláusulas precedentes 1 a 4, razón por la cual, esta dependencia considera que el nuevo juego de reivindicaciones presenta problemas de concisión. Y teniendo en cuenta que el número de reivindicaciones debe ser razonable y acorde con el número de alternativas de la invención a proteger, esta dependencia considera necesario que el solicitante elimine del pliego reivindicatorio aquellas cláusulas que repiten de manera innecesaria el contenido de las cláusulas 1 a 4, lo anterior, con el fin de dar cumplimiento a las disposiciones del artículo 30 de la Decisión 486.

- Por otra parte, al incluir en la definición de la materia la actividad terapéutica de los compuestos en la forma de agentes para el tratamiento del dolor, el señor solicitante está definiendo la invención en términos del resultado a alcanzar, es decir, incluyendo no solamente la alternativa terapéutica para el manejo del dolor objeto de la invención, sino todas las alternativas presentes o futuras que se relacionen con este blanco farmacológico y que puedan contener derivados de fórmula (I).

Además, el segundo componente activo lo define en términos de la categoría farmacológica en la que se han encasillado ciertos agentes por su capacidad para modular un grupo determinado de receptores endógenos denominados opioides¹, es

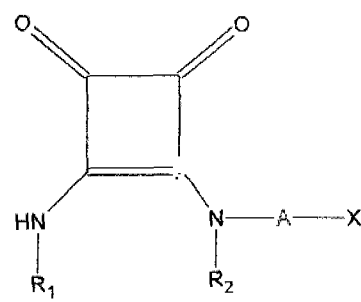
¹ Flórez Beledo, J. Fármacos analgésicos opioides. Departamento de Medicina Universidad de Santander. Medicine. 1998; 7(105): 4908-4919

decir, en la forma de un género o clasificación terapéutica, en el que se pueden agrupar un variado grupo de sustancias, tal es el caso de los agonistas puros dentro de los que se encuentran: morfina, petidina, heroína, fentanilo, hidromorfona, sufentanilo, tramadol, oxiconona, oximorfona, metadona, levorfanol, L- α -acetilmetadol, codeína, dihidrocodeína, dextropropoxifeno, timidina; los agonistas/antagonistas mixtos como pentazocina, nalbufina, butorfanol y dezocina; los agonistas parciales como buprenorfina y los antagonistas puros como naloxona y naltrexona, entre otros.

Sobre el particular es preciso recordar al señor solicitante que las composiciones de materia que contienen combinaciones de agentes farmacológicamente activos se definen en términos de las especies químicas combinadas y de las dosis subterapéuticas que se consiguen con la administración conjunta porque de lo contrario la materia continuará definiéndose en términos del resultado esperado. Por las razones expuestas se reitera la necesidad de que el solicitante defina claramente la materia objeto de su interés, a fin de dar cumplimiento a las disposiciones del artículo 30 de la Decisión 486.

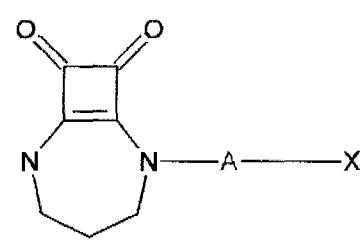
4. Unidad de Invención (artículo 25 D. 486)

Como se señaló en el aparte definición de materia, la invención hace referencia a dos objetos independientes y claramente diferenciados o grupos inventivos, a saber: el primero relacionado con composiciones farmacéuticas que contienen como agente activo un compuesto de la fórmula (I)



En conjunción con un vehículo farmacéuticamente aceptable (reivindicaciones 5 y 6).

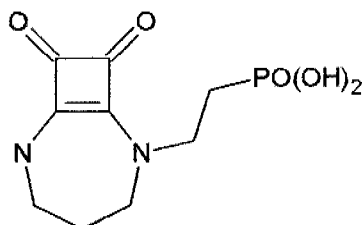
En particular, contienen derivados de la fórmula (III) o se seleccionan entre las siguientes especies químicas:



- Ácido [2-[(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-il)etil]fosfónico
- Ácido [2-[(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-il)etil]fosfónico
- Ácido [2-(4-hidroxi-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-il)etil]fosfónico
- Ácido 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-eno-2-acético
- 2-[(1H-tetrazol-5-il)metil]-2,6-diazabicyclo[5.2.0]non-1(7)-eno-8,9 diona
- Ácido [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-il)etil]fosfónico

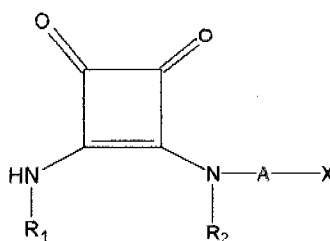
El segundo objeto relacionado con composiciones farmacéuticas que contienen como primer componente activo un compuesto derivado de la fórmula (I) en conjunción con un analgésico opioide (reivindicaciones 1 a 4).

El análisis de unidad de invención a posteriori, es decir, en virtud de las enseñanzas reveladas por el estado del arte permitió comprobar que el concepto común relacionado con la estructura de los compuestos derivados de la fórmula (I) y en particular con compuestos derivados de la fórmula (III) no es nuevo, tal y como lo evidencia el documento **US6011168** que hace referencia a derivados de fórmula estructural:



Comúnmente denominado Perzinfotel (ver Recomendaciones Denominaciones comunes internacionales INN. Lista 53 OMS)

Por otra parte, el documento **EP0496561** hace referencia a derivados de la fórmula:



Y en particular a las especies químicas:

- Ácido [2-[(7,8-dioxo-2,5-diazabicyclo[4.2.0]oct-1(6)-en-2-il)etil]fosfónico
- Ácido [2-[(8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-il)etil]fosfónico
- Ácido [2-(4-hidroxi-8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-en-2-il)etil]fosfónico
- Ácido 8,9-dioxo-2,6-diazabicyclo[5.2.0]non-1(7)-eno-2-acético
- 2-[(1H-tetrazol-5-il)metil]-2,6-diazabicyclo[5.2.0]non-1(7)-eno-8,9 diona
- Ácido [2-(9,10-dioxo-2,7-diazabicyclo[6.2.0]dec-1(8)-en-2-il)etil]fosfónico

Y además precisa que los compuestos pueden ser objeto de formulación farmacéutica y además pueden administrarse en cantidades que oscilan entre 1 y 100mg/día.

Por consiguiente, tanto el concepto común como las composiciones que contienen los compuestos no son nuevos, razón por la cual bajo su amparo no pueden reivindicarse dos grupos inventivos como son las composiciones de materia que contienen derivados de la fórmula (I) como las composiciones de materia que contiene derivados de fórmula (I) en combinación con analgésicos opioides.

Adicionalmente, la combinación efectiva que resulta de administrar conjuntamente antagonistas NMDA y analgésicos opioides fue revelada por el documento

WO0003716, razón por la cual, tampoco puede considerarse concepto común e inventivo la interacción farmacológica definida en términos de categorías terapéuticas.

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CÉSPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha
7 ABR. 2009

CONCEPTO TÉCNICO No. 1141	EXAMINADOR TÉCNICO Código No. 202044
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