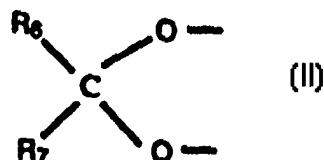
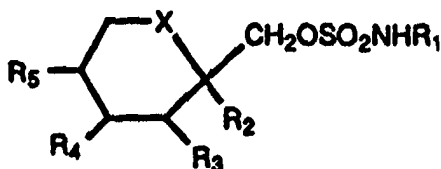




INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(21) International Application Number: PCT/US97/12350 (22) International Filing Date: 16 July 1997 (16.07.97) (30) Priority Data: 60/027,687 8 October 1996 (08.10.96) US (71) Applicant: ORTHO PHARMACEUTICAL CORPORATION [US/US]; Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventors: SHANK, Richard, P.; 551 Village Circle, Blue Bell, PA 19422-1636 (US). WILD, Kenneth; 186 Municipal Road, Pipersville, PA 18947 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).		(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, 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, TJ, TM, TR, TT, UA, UG, UZ, VN, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>

(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING NEUROPATHIC PAIN

**(57) Abstract**

The present invention describes a method for treating neuropathic pain comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of formula (I), wherein: X is CH₂ or oxygen; R₁ is hydrogen or alkyl; and R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of formula (II), wherein R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring, particularly topiramate.

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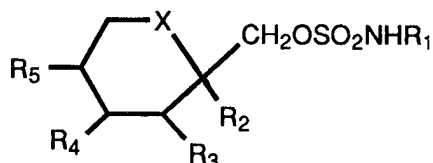
Codes used to identify States party to the PCT on the front pages of pamphlets publishing international applications under the PCT.

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ANTICONVULSANT DERIVATIVES USEFUL IN TREATING NEUROPATHIC PAIN

5 BACKGROUND OF THE INVENTION

Compounds of Formula I:



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are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* **30**, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught J.L.

15

Bioorganic & Medicinal Chemistry Letters **3**, 2653-2656, 1993). These compounds are covered by US Patent No.4,513,006. One of these compounds 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate known as topiramate has been demonstrated in clinical trials of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and

20 secondarily generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE, L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* **36 (S4)** 33, 1995; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER, *Epilepsia* **36 (S4)** 33, 1995), and is currently marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized

25 seizures in Great Britain, Finland, Sweden and Switzerland. Applications for regulatory approval are presently pending in numerous countries throughout the world including but not limited to the United States.

25

30

Compounds of Formula I were initially found to possess anticonvulsant activity in the traditional maximal electroshock seizure (MES) test in mice (SHANK, R.P., GARDOCKI, J.F., VAUGHT, J.L., DAVIS, C.B., SCHUPSKY, J.J., RAFFA, R.B., DODGSON, S.J., NORTEY, S.O., and MARYANOFF, B.E., *Epilepsia* **35** 450-460, 1994). Subsequent studies revealed that Compounds of Formula I were also highly effective in the MES test in rats. More recently topiramate was found to

35 effectively block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M.

35

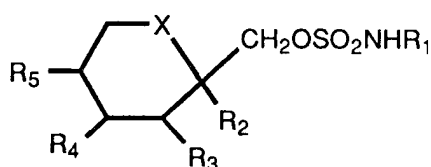
SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24 73-77, 1996).

Recent preclinical studies on topiramate have revealed previously
 5 unrecognized pharmacological properties which suggest that topiramate is effective in treating some other disorders. One of these is neuropathic pain.

DISCLOSURE OF THE INVENTION

10

Accordingly, it has been found that compounds of the following formula I:



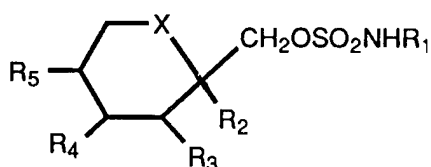
15

wherein X is O or CH₂, and R₁, R₂, R₃, R₄ and R₅ are as defined hereinafter are useful in treating neuropathic pain.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

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The sulfamates of the invention are of the following formula (I):

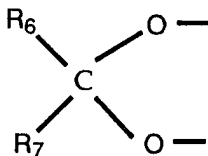


25 wherein

X is CH₂ or oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and, when X is
 30 CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):



wherein

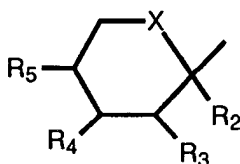
5 R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

10 R₁ in particular is hydrogen or alkyl of about 1 to 4 carbons, such as methyl, ethyl and iso-propyl. Alkyl throughout this specification includes straight and branched chain alkyl. Alkyl groups for R₂, R₃, R₄, R₅, R₆ and R₇ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH₂, R₄ and R₅ may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R₄ and R₅ are defined by the alkatrienyl group =C-CH=CH-CH=.

15 A particular group of compounds of formula (I) is that wherein X is oxygen and both R₂ and R₃ and R₄ and R₅ together are methylenedioxy groups of the formula (II), wherein R₆ and R₇ are both hydrogen both alkyl or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R₆ and R₇ are both alkyl such as methyl. A second group of compounds is that wherein X is CH₂ and R₄ and R₅ are joined to form a benzene ring. A third group of compounds of formula
20 (I) is that wherein both R₂ and R₃ are hydrogen.

The compounds of formula (I) may be synthesized by the following methods:

25 (a) Reaction of an alcohol of the formula RCH₂OH with a chlorosulfamate of the formula ClSO₂NH₂ or ClSO₂NHR₁ in the presence of a base such as potassium *n*-butoxide or sodium hydride at a temperature of about -20° to 25° C and in a solvent such as toluene, THF or dimethylformamide wherein R is a moiety of the following formula (III):



30

(b) Reaction of an alcohol of the formula RCH₂OH with sulfurylchloride of the formula SO₂Cl₂ in the presence of a base such as triethylamine or pyridine at a

temperature of about -40° to 25° C in a solvent such as diethyl ether or methylene chloride to produce a chlorosulfate of the formula RCH_2OSO_2Cl .

5 The chlorosulfate of the formula RCH_2OSO_2Cl may then be reacted with an amine of the formula R_1NH_2 at a temperature of about 40° to 25° C in a solvent such as methylene chloride or acetonitrile to produce a compound of formula (I). The reaction conditions for (b) are also described by T. Tsuchiya et al. in Tet. Letters, No. 36, p. 3365 to 3368 (1978).

10 (c) Reaction of the chlorosulfate RCH_2OSO_2Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula $RCH_2OSO_2N_3$ as described by M. Hedayatullah in Tet. Lett. p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R_1 is hydrogen by catalytic hydrogenation, e.g. with a noble
15 metal and H_2 or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH_2OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH_2OH wherein both R_2 and R_3 and R_4 and R_5 are identical and are of the
20 formula (II) may be obtained by the method of R. F. Brady in Carbohydrate Research, Vol. 14, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R_6COR_7 ketone or aldehyde with fructose at a temperature of about 25° C, in a solvent such a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid such as zinc chloride. The trimethylsilyl
25 enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Volaa 38, No. 22, p. 3935 (1973).

Further, carboxylic acids and aldehydes of the formulae $RCOOH$ and $RCHO$ may be reduced to compounds of the formula RCH_2OH by standard reduction
30 techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such a diglyme, THF or toluene at a temperature of about 0° to 100° C, e.g. as described by H.O. House in "Modern Synthetic Reactions", 2nd Ed., pages 45 to 144 (1972).

35 The compounds of formula I: may also be made by the process disclosed in 5,387,700, which is incorporated by reference herein.

The compounds of formula I include the various individual isomers as well as the racemates thereof, e.g., the various alpha and beta attachments, i.e., below

and above the plane of the drawing, of R₂, R₃, R₄ and R₅ on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

5 The activity of the compounds of formula I in treating neuropathic pain was first evidenced in preclinical studies conducted to evaluate the efficacy of topiramate in an animal model of neuropathic pain. This model was developed and first described by S.H. KIM and J.M. CHUNG, Pain 50 355-363, 1992, and is termed the "Kim and Chung model".

10

 Male, Sprague-Dawley rats, weighing between 150-250 grams, have the L5 and L6 (lumbar region) spinal nerves tightly ligated (tied-off with surgical thread) between the spinal cord and entry into the sciatic nerve (in the hind leg) on one side of their body only. This procedure results in
15 allodynia (a painful response to normally innocuous stimuli) and hyperalgesia (an exaggerated response to normally painful stimuli) in the hind paw on the same side of the body as the ligation (affected paw), but does not render the paw useless. The subjects are still capable of walking and using the affected paw. Within a few days the subjects are placed in
20 elevated observation chambers (approximately 4" x 6" x 10") having wire mesh floors. Graded pressure is presented to a localized area on the bottom of the paw via the use of von Frey hairs (monofilaments which are calibrated to bend under a certain amount of pressure, ranging from 0.41 to 15.1 g). Tactile allodynia is measured by recording the various pressures at which
25 the affected paw is withdrawn from the graded stimuli according to the procedure of S.R. CHAPLAN et al. (J. Neurosci. Meth. 53 55-63, 1994). Animals respond to 12-15 grams of pressure on their non-affected paws, whereas Kim and Chung model animals respond to 1-3 grams of pressure on their affected paw. The cutoff value for a rat to be included in this study
30 was a response to 4 grams or less of pressure on the affected paw within 7 days after surgery.

 Three doses of topiramate (3, 10, and 30 mg/kg) were tested for oral activity against neuropathic pain in the Kim and Chung model; an oral dose of ULTRAM™
35 (tramadol hydrochloride, 60 mg/kg) was tested as a positive control (D. BIAN et al., Analgesia 2 57-62, 1996). As expected, tramadol hydrochloride (60 mg/kg, p.o.) decreased the sensitivity of affected paws of Chung model rats from 3.0 grams to a peak of 13.9 grams at 2 hours after dosing; sensitivity returned back to 4.6 grams

by 8 hours (n=4). Topiramate (30 mg/kg, p.o.) also decreased the sensitivity of affected paws of Chung model rats from 3.0 grams to a peak of 8.9 grams at 1 hour; sensitivity returned slowly to 6.3 grams at 8 hours and remained at 5.6 grams 24 hours after dosing (n=4). Smaller doses of topiramate had less effect, altering the
5 sensitivity to a maximum of 2.9 grams at 4 hours (3 mg/kg, p.o.) and 5.2 grams at 8 hours (10 mg/kg, p.o.), but these effects were not deemed significant in this study (n=4 each).

The long-lasting anti-allodynic effect of topiramate in this animal model of
10 neuropathic pain indicates that it may be useful for the treatment of neuropathic pain in humans.

For treating neuropathic pain, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 400 mg administered orally, usually in two
15 divided doses, for an average adult human. A unit dose would contain about 25 to 200 mg of the active ingredient.

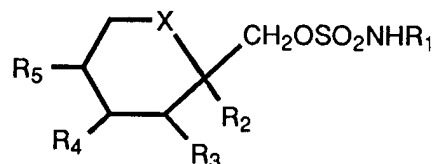
To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical
20 carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired for administration, e.g., oral, by suppository, or parenteral. In preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed. Thus, for liquid oral preparations, such as for example, suspensions,
25 elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations such as, for example, powders, capsules and tablets, suitable carriers and additives include starches, sugars, diluents, granulating agents, lubricants, binders, disintegrating agents and the like. Because of their ease in administration,
30 tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. If desired, tablets may be sugar coated or enteric coated by standard techniques. Suppositories may be prepared, in which case cocoa butter could be used as the carrier. For parenterals, the carrier will usually comprise sterile water, though other
35 ingredients, for example, for purposes such as aiding solubility or for preservation, may be included. Injectable suspensions may also be prepared in which case appropriate liquid carriers, suspending agents and the like may be employed.

Topiramate is currently available for oral administration in round tablets containing 25 mg, 100 mg or 200 mg of active agent. The tablets contain the following inactive ingredients: lactose hydrous, pregelatinized starch, microcrystalline cellulose, sodium starch glycolate, magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder injection, teaspoonful, suppository and the like from about 25 to about 200 mg of the active ingredient.

WHAT IS CLAIMED IS:

1. A method for treating neuropathic pain comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

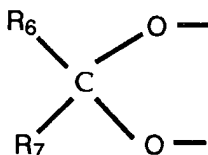


10 wherein

X is CH₂ or oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and, when X is CH₂, R₄ and R₅ may be alkene groups joined to form a benzene ring and, when X is oxygen, R₂ and R₃ and/or R₄ and R₅ together may be a methylenedioxy group of the following formula (II):



20

wherein

R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

- 25 2. The method of claim 1 wherein the compound of formula I is topiramate.
3. The method of claim 1, wherein the therapeutically effective amount is of from about 50 to 400 mg.
- 30 4. The method of claim 1, wherein the amount is of from about 25 to 200 mg.

INTERNATIONAL SEARCH REPORT

Inter. Appl. No
PCT/US 97/12350

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K31/35 //A61K31/18,A61K31/34

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 4 513 006 A (B. E. MARYANOFF) 23 April 1985 cited in the application see the whole document ---	1-4
A	SANDER: "The new anti-epileptic drugs : their current role in the management of epilepsy" EUR. J. BIOCHEM., vol. 3 suppl., no. 3, August 1996, pages 15-20, XP002043894 see page 18 ---	1-4
A	"Topiramate" DRUGS FUTURE, vol. 21, no. 4, 1996, pages 463-465, XP002043895 see the whole document ---	1-4
-/--		

Further documents are listed in the continuation of box C. Patent family members are listed in annex.

° Special categories of cited documents :

<p>*A* document defining the general state of the art which is not considered to be of particular relevance</p> <p>*E* earlier document but published on or after the international filing date</p> <p>*L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>*O* document referring to an oral disclosure, use, exhibition or other means</p> <p>*P* document published prior to the international filing date but later than the priority date claimed</p>	<p>*T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>*X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone</p> <p>*Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>*Z* document member of the same patent family</p>
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Date of the actual completion of the international search <p style="text-align: center;">17 October 1997</p>	Date of mailing of the international search report <p style="text-align: center;">31.10.97</p>
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Name and mailing address of the ISA European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer <p style="text-align: center;">Gac, G</p>
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INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 97/12350

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 97 13510 A (NEW ENGLAND MEDICAL CENTER HOSPITAL INC.) 17 April 1997 see the whole document -----	1-4

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US 97/ 12350

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

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

1. Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
**Remark: Although claim(s) 1-4
is(are) directed to a method of treatment of the human/animal
body, the search has been carried out and based on the alleged
effects of the compound/composition.**
2. Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such
an extent that no meaningful International Search can be carried out, specifically:
3. Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

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

1. As all required additional search fees were timely paid by the applicant, this International Search Report covers all
searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment
of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this International Search Report
covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is
restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
- No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Inter. .nal Application No

PCT/US 97/12350

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 4513006 A	23-04-85	AU 564842 B AU 3350484 A CA 1241951 A DE 3473143 A DK 198191 A DK 198291 A DK 457784 A EP 0138441 A JP 1804249 C JP 5005824 B JP 60109558 A JP 5331132 A MX 9202630 A US 4582916 A	27-08-87 04-04-85 13-09-88 08-09-88 09-12-91 09-12-91 27-03-85 24-04-85 26-11-93 25-01-93 15-06-85 14-12-93 30-06-92 15-04-86
WO 9713510 A	17-04-97	AU 7443496 A	30-04-97