



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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<table style="width: 100%; border: none;"> <tr> <td style="width: 50%; vertical-align: top; padding: 5px;"> (21) International Application Number: PCT/US00/08338 (22) International Filing Date: 30 March 2000 (30.03.00) (30) Priority Data: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>60/128,401 09/538,185</div> <div>8 April 1999 (08.04.99) 30 March 2000 (30.03.00)</div> <div>US US</div> </div> (71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventor: COTTRELL, Sandra, C.; 2 Granite Circle, Doylestown, PA 18901 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US). </td> <td style="width: 50%; vertical-align: top; padding: 5px;"> (81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, 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 <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i> </td> </tr> </table>			(21) International Application Number: PCT/US00/08338 (22) International Filing Date: 30 March 2000 (30.03.00) (30) Priority Data: <div style="display: flex; justify-content: space-between; margin-top: 10px;"> <div>60/128,401 09/538,185</div> <div>8 April 1999 (08.04.99) 30 March 2000 (30.03.00)</div> <div>US US</div> </div> (71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventor: COTTRELL, Sandra, C.; 2 Granite Circle, Doylestown, PA 18901 (US). (74) Agents: CIAMPORCERO, Audley, A., Jr. et al.; Johnson & Johnson, One Johnson & Johnson Plaza, New Brunswick, NJ 08933 (US).	(81) Designated States: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, 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, MA, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, TZ, 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 <i>With international search report.</i> <i>Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.</i>
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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN LOWERING LIPIDS				
<div style="display: flex; justify-content: space-around; align-items: center;"> <div style="text-align: center;"> <p>(I)</p> </div> <div style="text-align: center;"> <p>(II)</p> </div> </div>				
(57) Abstract <p>Use of anticonvulsant derivatives of formula (I) for lowering lipids, wherein X is CH₂ or oxygen; R₁ is hydrogen or alkyl; and R₂, R₃, R₄ and R₅ are independently hydrogen or 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 together may be a methylenedioxy group of formula (II); wherein R₆ and R₇ are the same or different and are hydrogen, or alkyl and are joined to form a cyclopentyl or cyclohexyl ring.</p>				

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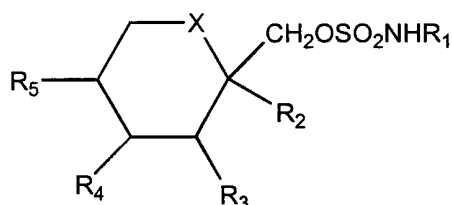
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ANTICONVULSANT DERIVATIVES USEFUL IN LOWERING LIPIDS

BACKGROUND OF THE INVENTION

5 Compounds of Formula I:



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
 10 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. *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
 15 of human epilepsy to be effective as adjunctive therapy or as monotherapy in treating simple and complex partial seizures and 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
 20 marketed for the treatment of simple and complex partial seizure epilepsy with or without secondary generalized seizures in approximately twenty countries including the United States, and applications for regulatory approval are presently pending in several additional countries throughout the world.

Compounds of Formula I were initially found to possess anticonvulsant activity
 25 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 effectively

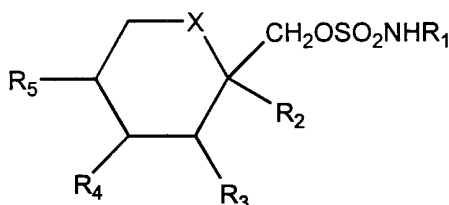
block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

- 5 Clinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate will be effective in lowering lipids in humans, particularly in overweight individuals.

DISCLOSURE OF THE INVENTION

10

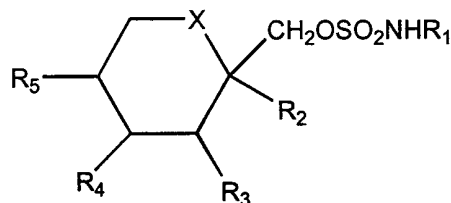
Accordingly, it has been found that compounds of the following formula I:



- 15 wherein X is O or CH₂, and R₁, R₂, R₃, R₄ and R₅ are as defined hereinafter are useful in maintaining weight loss.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

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



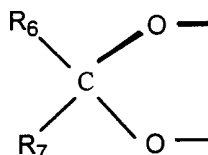
wherein

X is CH₂ or oxygen;

- 25 R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or 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):

5



wherein

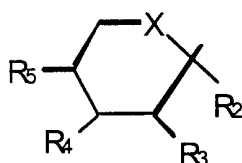
R₆ and R₇ are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

- 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
20 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 (I) is that wherein both R₂ and R₃ are hydrogen.

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

- (a) Reaction of an alcohol of the formula RCH₂OH with a chlorosulfamate of the
25 formula ClSO₂NH₂ or ClSO₂NHR₁ in the presence of a base such as potassium a-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):



(b) Reaction of an alcohol of the formula RCH_2OH with sulfurylchloride of the formula SO_2Cl_2 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 .

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).

(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 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 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 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 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).

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

5 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 oxygene of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

10 In those subjects with weight in excess of 100 kg who had triglycerides measured (n=14), a 20.2% reduction in triglycerides was observed. In the five subjects with high triglyceride levels at baseline (> 143 mg/dl), the reduction in triglycerides was between 24.8% and 54.8%. A mean decrease in total cholesterol of 4.4% was noted in all subject who had baseline cholesterol levels measured (n=562). The
15 decrease was more marked, 8.8%, in those subjects weighing in excess of 100 kg (n=52).

For lowering lipids, a compound of formula (I) may be employed at a daily dose in the range of about 100 mg to 400 mg, usually in two daily divided doses, for an average adult human. A unit dose would contain about 15 to 200 mg of the active
20 ingredient.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired
25 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, elixirs and solutions, suitable carriers and additives include water, glycols, oils, alcohols, flavoring agents, preservatives, coloring agents and the like; for solid oral preparations
30 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, 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 ingredients, for example, for purposes such as

5 aiding solubility or for preservation, may be included. Injectable solutions may also be prepared in which case appropriate stabilizing agents 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,

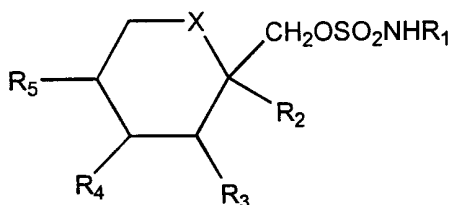
10 magnesium stearate, purified water, carnauba wax, hydroxypropyl methylcellulose, titanium dioxide, polyethylene glycol, synthetic iron oxide, and polysorbate 80.

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.

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WHAT IS CLAIMED IS:

1. A method for lowering lipids in overweight mammals, comprising administering to
 5 such a mammal a therapeutically effective amount for treating such condition of a compound of the formula I:



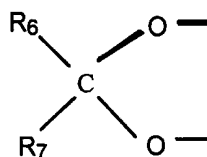
wherein

X is CH₂ or oxygen;

- 10 R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or 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):

15



wherein

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

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 100 to 400 mg/day.

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/08338

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/255 A61K31/35 A61K31/7048 A61P3/06

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 7 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)

EPO-Internal, CHEM ABS Data, MEDLINE, BIOSIS, EMBASE, SCISEARCH

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, X	YORK D A (REPRINT) ET AL: "Effects of topiramate on high fat diet-induced obesity" FASEB JOURNAL, (15 MAR 2000) VOL. 14, NO. 4, PP. A431-A431. PUBLISHER: FEDERATION AMER SOC EXP BIOL, 9650 ROCKVILLE PIKE, BETHESDA, MD 20814-3998. ISSN: 0892-6638., XP000915192 PENNINGTON BIOMED RES CTR, BATON ROUGE, LA 70808 the whole document	1-3
A	WO 98 00130 A (ORTHO PHARMA CORP) 8 January 1998 (1998-01-08) the whole document --- -/--	1-3

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

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Hoff, P

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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A	US 4 513 006 A (MARYANOFF BRUCE E ET AL) 23 April 1985 (1985-04-23) cited in the application the whole document ---	1-3
A	KYOWA HAKKO: "TOPIRAMATE" DRUGS OF THE FUTURE, ES, BARCELONA, vol. 21, no. 4, 1996, pages 463-465, XP002043895 ISSN: 0377-8282 the whole document -----	1-3

INTERNATIONAL SEARCH REPORT

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Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9800130 A	08-01-1998	AU 3957897 A CA 2258893 A CZ 9804278 A EP 0915697 A NO 986052 A ZA 9705772 A	21-01-1998 08-01-1998 11-08-1999 19-05-1999 23-02-1999 28-12-1998
US 4513006 A	23-04-1985	AT 36149 T AU 564842 B AU 3350484 A CA 1241951 A DE 3473143 D DK 198191 A,B, DK 198291 A DK 457784 A,B, EP 0138441 A ES 536225 D ES 8602634 A FI 843765 A,B, HU 36784 A,B IE 57684 B JP 1804249 C JP 5005824 B JP 60109558 A JP 5331132 A KR 9201775 B MX 9202630 A NO 843836 A,B, NZ 209494 A US 4582916 A ZA 8407550 A	15-08-1988 27-08-1987 04-04-1985 13-09-1988 08-09-1988 09-12-1991 09-12-1991 27-03-1985 24-04-1985 16-11-1985 16-03-1986 27-03-1985 28-10-1985 24-02-1993 26-11-1993 25-01-1993 15-06-1985 14-12-1993 02-03-1992 30-06-1992 27-03-1985 06-03-1987 15-04-1986 28-05-1986