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**UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF NEW JERSEY**

ORTHO-McNEIL)	
PHARMACEUTICAL, INC.,)	
)	Civil Action No. 06-5166 (SRC)(CCC)
Plaintiff,)	
)	
v.)	
)	FIRST AMENDED COMPLAINT
MYLAN LABORATORIES INC., and)	
MYLAN PHARMACEUTICALS INC.,)	
)	
Defendants.)	
_____)	

Plaintiff, Ortho-McNeil Pharmaceutical, Inc. ("Ortho-McNeil"), by its undersigned attorneys, brings this action against defendants, Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc., for patent infringement and alleges as follows:

Parties

1. Plaintiff, Ortho-McNeil, is a corporation organized and existing under the laws of the State of Delaware, with its principal place of business at 1000 U.S. Route 202, Raritan, New Jersey 08869. Ortho-McNeil is engaged in the business of marketing prescription pharmaceutical products in the United States.

2. On information and belief, defendant Mylan Laboratories Inc. is a corporation organized and existing under the laws of the State of Pennsylvania, having its

principal place of business at 1500 Corporate Drive, Suite 400, Canonsburg, Pennsylvania 15317.

3. On information and belief, defendant Mylan Pharmaceuticals Inc. is a corporation organized and existing under the laws of the State of West Virginia, having a principal place of business at 781 Chestnut Ridge Road, Morgantown, West Virginia 26505.

4. On information and belief, defendant Mylan Pharmaceuticals Inc. is a subsidiary of defendant Mylan Laboratories Inc.

5. On information and belief, Mylan Pharmaceuticals Inc. is registered to do business in New Jersey. Further, on information and belief, Mylan Pharmaceuticals Inc. has registered its generic drugs in the *New Jersey Generic Formulary* of the New Jersey Department of Health and Senior Services, and sells a substantial volume of such drugs and otherwise transacts business within the District of New Jersey.

6. On information and belief, the acts of Mylan Pharmaceuticals Inc. complained of herein, were done at the direction of, with the authorization of, or with the cooperation, participation, the assistance of, or at least in part for the benefit of, Mylan Laboratories Inc.

7. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. are referred to hereinafter, collectively, as “Mylan.”

Jurisdiction and Venue

8. This action for patent infringement arises under the patent laws of the United States, Title 35, United States Code, Section 271(e)(2) and Title 21, United States Code, Section 355. This Court has subject matter jurisdiction over this dispute pursuant to Title 28, United States Code, Sections 1331 and 1338(a).

9. Venue is proper in this Court pursuant to Title 28, United States Code, Sections 1391(c) and 1400(b).

Ortho-McNeil's Patent

10. On April 23, 1985, the United States Patent and Trademark Office (“USPTO”) duly and lawfully issued United States Patent No. 4,513,006 (“the ‘006 patent,” a copy of which is attached as Exhibit A), entitled ANTICONVULSANT SULFAMATE DERIVATIVES, to McNeilab, Inc., as assignee of the inventors Bruce E. Maryanoff and Joseph F. Gardocki. McNeilab, Inc. is a corporate predecessor of plaintiff, Ortho-McNeil. At all times subsequent to issuance of the ‘006 patent, Ortho-McNeil or its corporate predecessors have been the owner of the entire right, title and interest in and to the ‘006 patent, including the right to sue and recover for infringement.

11. Ortho-McNeil is the holder of approved New Drug Applications (“NDAs”) under Section 505(a) of the Federal Food Drug and Cosmetic Act (“FFDCA”), 21 U.S.C. § 335(a) for topiramate tablets (NDA 20-505) and topiramate capsules (NDA 20-844), both of which are marketed in the United States under the trade name TOPAMAX[®]. The claims of the ‘006 patent cover the drug topiramate, pharmaceutical compositions containing topiramate, and a method of using topiramate for treatment of convulsions in a mammal.

12. Pursuant to 21 U.S.C. § 355(b)(1), the ‘006 patent is identified in the Food and Drug Administration publication entitled “Approved Drug Products with Therapeutic Equivalence Evaluations” (the “Orange Book”), as covering TOPAMAX[®] products.

13. The ‘006 patent was the subject of an application under 35 U.S.C. § 156, requesting a patent term restoration of five years, or until September 26, 2008. On March 11, 2003, the USPTO issued an Order Granting Interim Extension, indicating that the ‘006 patent

was eligible for restoration of the patent term and extending the original expiration date of the '006 patent for one year, until September 26, 2004. On July 23, 2004, the USPTO granted for the '006 patent a term restoration of five years. On July 4, 2006, the USPTO issued a Certificate of Correction stating that the expiration date of the '006 patent shall be five years from September 26, 2003. Accordingly, the term of the '006 patent expires on September 26, 2008.

Mylan's Actions

14. Pursuant to Section 505 of the FFDCA, Mylan filed an Abbreviated New Drug Application ("ANDA") for topiramate capsules, seeking approval to engage in the commercial manufacture, use, offer for sale and sale of topiramate capsules, 15 and 25 mg ("ANDA products"), before the '006 patent expires. The Mylan ANDA number is 78-418.

15. In connection with the filing of its ANDA as described in the preceding paragraph, Mylan has provided written certification to the Food and Drug Administration, as called for by § 505 of the FFDCA, alleging that the claims of the '006 patent are invalid, unenforceable, and/or will not be infringed by the activities described in Mylan's ANDA. Thus, Mylan has alleged that no valid claim of the '006 patent will be infringed by the ANDA products it proposes to manufacture, use, offer for sale and sell.

16. Mylan sent written notice of its filing to Ortho-McNeil, which notice was received by Ortho-McNeil. The notice alleged that the claims of the '006 patents are invalid, unenforceable, and/or will not be infringed by Mylan and further alleged that, as a result, no valid claim of the '006 patent will be infringed by Mylan's proposed manufacture, use, offer for sale, and sale of the ANDA products. Mylan's notice also informed Ortho-McNeil that Mylan seeks approval to market the ANDA products before the '006 patent expires. This action is being filed within 45 days after Ortho-McNeil received Mylan's notice.

COUNT ONE

(Infringement of the '006 patent against Mylan)

17. Ortho-McNeil restates and incorporates by reference the allegations of the foregoing paragraphs 1-16 as though fully set forth herein.

18. Because Mylan seeks approval of its ANDA to engage in the commercial manufacture, use or sale of a drug or drug formulation claimed in the '006 patent before it expires, Mylan has infringed the '006 patent pursuant to 35 U.S.C. § 271(e)(2)(A).

19. Ortho-McNeil is entitled to relief provided by 35 U.S.C. § 271(e)(4), including an order of this Court that the effective date of the approval of Mylan's ANDA be a date that is not earlier than the present expiration date of the '006 patent, or any later expiration of exclusivity to which Ortho-McNeil is or becomes entitled.

20. Upon information and belief, Mylan was aware of the existence of the '006 patent and was aware that the filing of its ANDA and certification with respect to the '006 patent constituted an act of infringement of that patent.

21. Mylan's statement of the factual and legal bases for its opinion regarding the alleged invalidity of the '006 patent is devoid of an objective good faith basis in either the facts or the law.

22. Ortho-McNeil will be irreparably harmed if Mylan is not enjoined from infringing or actively inducing or contributing to infringement of the '006 patent.

23. Ortho-McNeil does not have an adequate remedy at law for Mylan's infringement of the '006 patent.

24. This case is an exceptional one, and Ortho-McNeil is entitled to an award of its reasonable attorneys' fees under 35 U.S.C. § 285.

PRAYER FOR RELIEF

WHEREFORE, plaintiff Ortho-McNeil respectfully requests that:

- a. Judgment be entered that defendant Mylan has infringed the '006 patent by submitting the aforesaid ANDA;
- b. Judgment be entered that Ortho-McNeil is entitled to its reasonable attorneys' fees pursuant to 35 U.S.C. § 285;
- c. To the extent Mylan has committed any acts with respect to the compounds claimed in the '006 patent, other than those acts expressly exempted by 35 U.S.C. § 271(e)(1), Ortho-McNeil be awarded damages for such acts, which this Court should treble pursuant to 35 U.S.C. § 284;
- d. A permanent injunction be granted, pursuant to 35 U.S.C. § 271(e)(4)(B), restraining and enjoining Mylan, its officers, agents, attorneys and employees, and those acting in privity or concert with them, from engaging in the commercial manufacture, use, offer for sale, or sale within the United States, or importation into the United States, of drug compounds or formulations as claimed in the '006 patent, or from practicing any method of treatment as claimed in the '006 patent, or from actively inducing or contributing to infringement of the '006 patent;
- e. An order be issued pursuant to 35 U.S.C. § 271(e)(4)(A) that the effective date of any approval of ANDA No. 78-418 be a date that is not earlier than the present expiration date for the '006 patent, or any later expiration of exclusivity to which the '006 patent is or becomes entitled; and
- f. An order be issued for such other and further relief as the Court may deem just and proper under the circumstances.

Respectfully Submitted,

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Dated: November 3, 2006

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LOCAL CIVIL RULE 11.2 CERTIFICATION

I hereby certify that plaintiff Ortho-McNeil Pharmaceutical Inc. has filed four patent infringement actions, which are pending, in the United States District Court for the District of New Jersey.

The first such action is titled *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc.*, Civil Action No. 04 CV 1689 (SRC) (Newark vicinage) (“the *Mylan I* action”). The complaint in the *Mylan I* action alleges in part that defendants Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. infringed United States Patent No. 4,513,006 (“the ‘006 patent”) by filing Abbreviated New Drug Application (“ANDA”) No. 76-314, seeking approval to engage in the commercial manufacture, use, offer for sale and sale of topiramate tablets, 25 mg, 100 mg and 200 mg, before the ‘006 patent expires. The second such action is titled *Ortho-McNeil Pharmaceutical, Inc. v. Cobalt Pharmaceuticals Inc.*, Civil Action No. No. 05-4961 (SRC) (Newark vicinage) (“the *Cobalt I* action”). The complaint in the *Cobalt I* action alleges in part that defendant Cobalt Pharmaceuticals Inc. infringed the ‘006 patent by filing ANDA No. 77-643. The third such action is titled *Ortho-McNeil Pharmaceutical, Inc. v. Cobalt Pharmaceuticals Inc.*, Civil Action No. No. 05-5920 (SRC) (Newark vicinage) (“the *Cobalt II* action”). The complaint in the *Cobalt II* action alleges in part that defendant Cobalt Pharmaceuticals Inc. infringed the ‘006 patent by filing ANDA No. 77-868. The fourth such action is titled *Ortho-McNeil Pharmaceutical, Inc. v. Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc.*, Civil Action No. 06 CV 757 (SRC) (Newark vicinage) (“the *Mylan II* action”). The complaint in the *Mylan II* action alleges in part that defendants Mylan Laboratories Inc. and Mylan Pharmaceuticals Inc. infringed

the '006 patent by filing an amendment to ANDA No. 76-314. *Mylan I* and *Mylan II* were later consolidated pursuant to an order entered on May 17, 2006.

ANDA No. 76-314, ANDA No. 77-643, and ANDA No. 77-868 all relate to the same active drug ingredient, topiramate, which gave rise to the foregoing Complaint for Patent Infringement.

The *Mylan I* and *Mylan II* actions, the *Cobalt I* and *Cobalt II* actions, and the present action all involve the validity, enforceability, and infringement of the '006 patent.

By s/Matthew J. Atlas
Matthew J. Atlas

Dated: November 3, 2006

EXHIBIT A

United States Patent [19]

Maryanoff et al.

[11] **Patent Number:** 4,513,006[45] **Date of Patent:** Apr. 23, 1985[54] **ANTICONVULSANT SULFAMATE
DERIVATIVES**[75] **Inventors:** Bruce E. Maryanoff, New Hope;
Joseph F. Gardocki, Doylestown,
both of Pa.[73] **Assignee:** McNeil Lab., Inc., Fort Washington,
Pa.[21] **Appl. No.:** 535,475[22] **Filed:** Sep. 26, 1983[51] **Int. Cl.³** A61K 31/35; C07D 311/78;
C07D 311/94; C07D 309/06[52] **U.S. Cl.** 514/23; 549/426;
549/396; 549/387; 549/338; 549/337; 549/336;
549/427; 536/54; 260/456 A; 514/459; 514/517[58] **Field of Search** 549/387, 396, 426, 337,
549/338; 260/456 A; 424/283, 303; 536/54[56] **References Cited****U.S. PATENT DOCUMENTS**

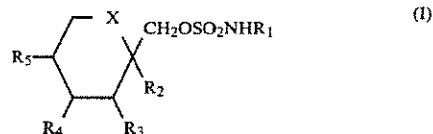
4,075,351 2/1978 Hirsch 424/303

OTHER PUBLICATIONSN. K. Kochetkov, et al., in Zhurnal Obshchei Khimii,
vol. 41, No. 8, pp. 1866-1871, (1971).N. K. Kochetkov, et al., in Journal of General Chemis-
try of the USSR 42 (12) 2755-2757 (1972).N. K. Kochetkov, et al., in Journal of General Chemis-
try of the USSR 44 (4) 871-875 (1974).N. K. Kochetkov, et al., in Doklady Akademii Nauk
SSSR, vol. 216, No. 1, pp. 97-100, (1974).Tetrahedron Letters No. 36, pp. 3365-3368, Pergamon
Press Ltd. (1978) by T. Tsuchiya.

J. Med. Chem. 1981, 24, 901-903, A. F. Hirsch.

Primary Examiner—Nicky Chan*Attorney, Agent, or Firm*—David J. Levy[57] **ABSTRACT**

Sulfamates of the following formula (I):



wherein X is O or CH₂ and R₁, R₂, R₃, R₄ and R₅ are as herein defined have been found to exhibit anticonvulsant activity and are thus useful in the treatment of conditions such as epilepsy. Further, pharmaceutical compositions containing a compound of formula (I) as well as methods for their use and intermediates form part of the present invention.

12 Claims, No Drawings

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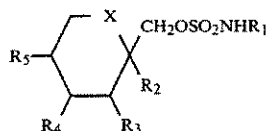
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ANTICONVULSANT SULFAMATE DERIVATIVES

Sulfamates of various structures, including those derived from monosaccharides are described in references such as N. K. Kochetkov et al in *Zhurnal Obshchei Kimii*, Vol. 41, No. 8, 1866 to 1871 (1971), Vol. 42, No. 12, 2755 to 2757 (1972) and Vol. 44, No. 4, 871 to 875 (1974) and in *Doklady Akademii Nauk SSR*, Vol. 216, No. 1, 97 to 100 (1974); T. Tsuchiya et al., in *Tetrahedron Letters*, No. 36, 3365 to 3368 (1978); and A. F. Hirsch in *Journal of Medicinal Chemistry*, 24, 901 to 903 (1981) and U.S. Pat. No. 4,075,351.

SUMMARY OF THE INVENTION

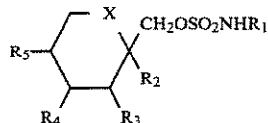
It has been found that sulfamates of the following formula (I):



wherein X is O or CH₂ and R₁, R₂, R₃, R₄ and R₅ are as hereinafter defined, possess anticonvulsant activity in mammals and are thus useful in treating disease states such as epilepsy and glaucoma. Also part of the present invention are pharmaceutical compositions containing one or more sulfamates of formula (I) as well as methods for the treatment e.g., prevention, of convulsions using such compositions.

DETAILED DESCRIPTION OF THE INVENTION

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

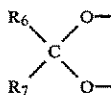


wherein

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 the following 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.

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

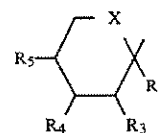
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branched chain alkyl. Alkyl groups for R₂, R₃, R₄, R₅, R₆ and R₇ are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH₂, R₄ and R₅ may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R₄ and R₅ are defined by the alkatrienyl group =CH—CH=CH—CH=.

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 (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 formula ClSO₂NHR₁ or ClSO₂NHR₁ in the presence of a base such as potassium t-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 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 RCH₂OSO₂Cl.

The chlorosulfate of the formula RCH₂OSO₂Cl may then be reacted with an amine of the formula R₁NH₂ 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 RCH₂OSO₂Cl with a metal azide such as sodium azide in a solvent such as methylene chloride or acetonitrile yields an azidosulfate of the formula RCH₂OSO₂N₃ as described by M. Hedayatullah in *Tet. Lett.* p. 2455-2458 (1975). The azidosulfate is then reduced to a compound of formula (I) wherein R₁ is hydrogen by catalytic hydrogenation, e.g. with a noble metal and H₂ or by heating with copper metal in a solvent such as methanol.

The starting materials of the formula RCH₂OH may be obtained commercially or as known in the art. For example, starting materials of the formula RCH₂OH wherein both R₂ and R₃ and R₄ and R₅ are identical and are of the formula (II) may be obtained by the method of R. F. Brady in *Carbohydrate Research*, Vol. 15, p. 35 to 40 (1970) or by reaction of the trimethylsilyl enol ether of a R₆COR₇ ketone or aldehyde with fructose at a temperature of about 25° C. in a solvent such as a halocarbon, e.g. methylene chloride in the presence of a protic acid such as hydrochloric acid or a Lewis Acid

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such as zinc chloride. The trimethylsilyl enol ether reaction is described by G. L. Larson et al in J. Org. Chem. Vol. 38, No. 22, p. 3935 (1973).

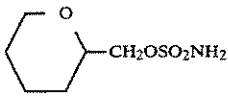
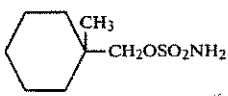
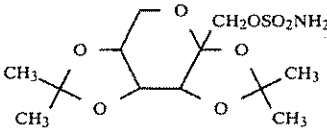
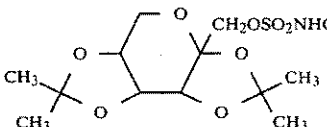
Further, carboxylic acids and aldehydes of the formulae RCOOH and RCHO may be reduced to compounds of the formula RCH_2OH by standard reduction techniques, e.g. reaction with lithium aluminum hydride, sodium borohydride or borane-THF complex in an inert solvent such as diglyme, THF or toluene at a temperature 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 the invention 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 R_2 , R_3 , R_4 and R_5 on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

The compounds of formula (I) are useful as anticonvulsant agents. The anticonvulsant activity of the subject compounds was determined using a standard "maximal electroshock test" (MES). In this test, activity is indicated by a block of the toxic extensor seizure caused by application of an electric shock to mice via corneal electrodes, as described by Swinyard et al in J. Pharmacol. Exptl. Therap. 106, 319 (1952), and recorded as % block. A more recent description of current anticonvulsant drug screening is given in Swinyard et al in Epilepsia 19, 409 (1978).

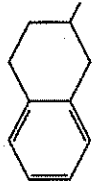
The anticonvulsant activity of compounds of this invention tested according to the Swinyard (1952) method is shown in the following Table I:

TABLE I

Ex- am- ple	Compound	MES test ED_{50}^* (mg/ kg, i.p.)
1		195
2		270
3		26
4		70% block at 200 mg/kg, i.p.

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TABLE I-continued

Ex- am- ple	Compound	MES test ED_{50}^* (mg/ kg, i.p.)
5		55

*Unless otherwise noted.

For treating epilepsy, a compound of formula (I) may be employed at a daily dosage in the range of about 30 to 2000 mg, usually in 2 to 4 divided doses, for an average adult human. A unit dose would contain about 10 to 500 mg of the active ingredient.

In general, compounds of formula (I) may be used in treating epilepsy in a manner similar to that used for phenytoin. Medical aspects of the treatment of epilepsy are described by L. S. Goodman et al in "The Pharmacological Basis of Therapeutics", 5th Ed. pages 201 to 226, Macmillan (1975).

Further, compounds of formula (I) are inhibitors of carbonic anhydrase, as determined by the methods described by S. J. Dodgson et al in the Proc. Natl. Acad. Sci., U.S.A., 77, pages 5562 to 5566 (1980) or by N. Itada et al in the Journal Biol. Chem., 252, pages 3881 to 3890 (1977) and as such, are useful in the treatment of glaucoma. The relationship between the treatment of glaucoma and carbonic anhydrase inhibition is described by A. Stein et al in the American Journal of Ophthalmology, 95:222-228 (1983). For the treatment of glaucoma, a compound of formula (I) may be administered systemically, e.g. by oral or parenteral routes as described below, or topically in the eye in a mineral oil solution or suspension, or aqueous suspension. When used systemically, the compound would be administered in an amount of about 50 to 500 mg per day for an average adult human, while the topical dosage would be about 1 to 3 drops (per eye) of a solution or suspension containing about 1 to 5% by weight of a compound of formula (I) with the dosage being administered about 1 to 4 times per day.

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 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 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

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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 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.

The pharmaceutical compositions herein will contain, per dosage unit, e.g., tablet, capsule, powder, injection, teaspoonful, suppository and the like, from about 10 to about 500 mg of the active ingredient.

The foregoing compositions are particularly suitable for use in the treatment of epilepsy or the symptoms of epilepsy by a method comprising internally administering to a subject suffering from the symptoms of epilepsy compositions comprising an effective epilepsy inhibiting amount of a compound of formula (I).

Also part of the present invention are intermediates of the formulae RCH_2OSO_2Cl and $RCH_2OSO_2N_3$.

In the following Examples and throughout the specification the following abbreviations may be used: g (grams); ml (milliliters); min (minutes); hr (hours); mol (moles); cm (centimeters); v/v (volume to volume); mp (melting point); TLC (thin layer chromatography); NMR (nuclear magnetic resonance); IR (infrared); DMF (dimethylformamide); THF (tetrahydrofuran); and C, H, N, etc. (the chemical symbols for the elements).

EXAMPLE 1

(Tetrahydro-2H-pyran-2-yl)methane sulfamate

To a cold solution (-5°C) of tetrahydropyran-2-methanol (2.33 g, 0.02 mol) in DMF (40 ml) was added 50% oily sodium hydride (1.17 g, 0.024 mol as NaH). After stirring for 45 min, sulfamoyl chloride (3.42 g, 0.03 mol) was added and the stirring continued for an additional 45 min, at -5°C . The reaction mixture was poured into cold water and extracted with chloroform. The organic layer was dried (Na_2SO_4) and the solvents were removed under vacuum to give a syrup which was dry column chromatographed (eluted with ethyl acetate:hexane, 4:1 v/v) to give pure (tetrahydro-2H-pyran-2-yl) methanesulfamate as a pale yellow syrup, IR: $(CHCl_3)$ 1180 cm^{-1} and 1370 cm^{-1} (OSO_2NH_2).

EXAMPLE 2

(1-Methylcyclohexyl)methane sulfamate

To a cold solution (-4°C) of (1-methylcyclohexyl)-methanol (6.2 g, 0.048 mol) in DMF (90 ml) was added 50% oily sodium hydride (2.81 g, 0.059 mol as NaH). After stirring for 1 hr, sulfamoyl chloride (7.82 g, 0.062 mol) was added and the stirring was continued for an additional 30 min at -4°C . The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents were removed under vacuum to give a syrup which crystallized upon cooling. Recrystallization from chloroform/hexane gave pure (1-methylcyclohexyl)methane sulfamate, mp $40^\circ\text{--}42^\circ\text{C}$.

EXAMPLE 3

2,3:4,5-Bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate

To a cold solution (-4°C) of 2,3:4,5-di-O-isopropylidene- β -fructopyranose (75 g, 0.29 mol) in DMF

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(725 ml) was added 50% oily sodium hydride (16.34 g, 0.34 mol as NaH). After stirring for 90 min, sulfamoyl chloride (54.9 g, 0.48 mol) was added and the stirring continued for an additional 3.5 hr at that temperature. The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum to give a syrup which crystallized immediately. Recrystallization from ethylacetate/hexane gave pure 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose sulfamate, mp $125^\circ\text{--}126^\circ\text{C}$.

EXAMPLE 4

2,3:4,5-Bis-O-(1-methylethylidene)- β -D-fructopyranose methyl sulfamate

A solution of sulfonyl chloride (93 ml, 1.15 mol) in methylene chloride (100 ml) was added dropwise to a cold solution (-35°C) of 2,3:4,5-di-O-isopropylidene- β -D-fructopyranose (150 g, 0.58 mol) in methylene chloride (400 ml) and pyridine (150 ml). The reaction mixture was allowed to stir and warm to room temperature (25°C); it was stirred for an additional 2 hr. Solvents were removed under vacuum. The resulting semi-solid was dissolved in anhydrous acetonitrile (35 g, 150 ml) and methyl amine was bubbled in. The reaction mixture was tightly stoppered and solvents removed under vacuum. The resulting syrup was subjected to liquid chromatography (dry column ethyl acetate:hexane, 4:1) yielding a light yellow syrup, 2,3:4,5-bis-O-(1-methylethylidene)- β -D-fructopyranose methylsulfamate, which was homogeneous by TLC and ^1H NMR.

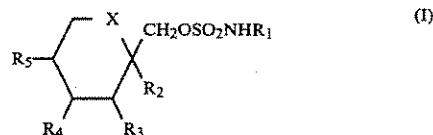
EXAMPLE 5

(1,2,3,4-Tetrahydro-2-naphthalenyl)methyl sulfamic acid ester

To a cold solution (-5°) of (1,2,3,4-tetrahydro-2-naphthalenyl)methanol (7.1 g, 0.044 mol) in DMF (80 ml) was added 50% oily sodium hydride (2.56 g, 0.054 mol as NaH). After stirring for 45 min, sulfamoyl chloride (6.6 g, 0.057 mol) was added and the stirring continued for an additional 95 min at -5°C . The reaction mixture was poured into cold water and extracted with toluene. The organic layer was dried (Na_2SO_4) and the solvents removed under vacuum to give a syrup which crystallized immediately. Recrystallization from chloroform/hexane gave pure (1,2,3,4-tetrahydro-2-naphthalenyl)methyl sulfamic acid ester, mp $108^\circ\text{--}109^\circ\text{C}$, as a white solid.

What is claimed is:

1. A sulfamate of the following formula (I):



wherein

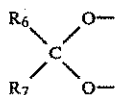
X is oxygen;

R₁ is hydrogen or alkyl; and

R₂, R₃, R₄ and R₅ are independently hydrogen or lower alkyl and R₂ and R₃ and/or R₄ and R₅ together may be a group of the following formula (II):

4,513,006

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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.

2. The sulfamate of claim 1, wherein

R₂ and R₃ and R₄ and R₅ together are groups of the formula (II).

3. The sulfamate of claim 1, wherein said alkyl group for R₁ is alkyl of about 1 to 4 carbons; said lower alkyl group for R₂, R₃, R₄ and R₅ is alkyl of about 1 to 3 carbons; and said lower alkyl for R₆ and R₇ is alkyl of about 1 to 3 carbons.

4. The sulfamate of claim 1, wherein said sulfamate of formula (I) is selected from the group consisting of:

(tetrahydro-2H-pyran-2-yl)methane sulfamate;

2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate;

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2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose methylsulfamate.

(II) 5. The sulfamate of claim 4, wherein said sulfamate is 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose sulfamate.

6. A pharmaceutical composition effective for the treatment of convulsions comprising an anticonvulsantly effective amount of a sulfamate of claim 1 and a pharmaceutically-acceptable carrier.

7. The pharmaceutical composition of claim 6, wherein said sulfamate is present in a unit dosage amount of about 10 to 500 milligrams of the sulfamate.

8. A method for the treatment of convulsions in a mammal which comprises administering to the mammal, the pharmaceutical composition of claim 6.

9. The sulfamate of claim 4, wherein said sulfamate is 2,3:4,5-bis-O-(1-methylethylidene)-β-D-fructopyranose methylsulfamate.

10. The sulfamate of claim 1, wherein the two oxygen atoms of the group of formula (II) are attached on the same side of the six-membered ring depicted in formula (I).

11. The sulfamate of claim 1, wherein the sulfamate of formula (I) is a fructopyranose.

12. The sulfamate of claim 1, wherein in formula (I), R₁ is hydrogen.

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UNITED STATES PATENT AND TRADEMARK OFFICE
CERTIFICATE OF CORRECTION

PATENT NO. : 4,513,006
APPLICATION NO. : 06/535475
DATED : April 23, 1985
INVENTOR(S) : Maryanoff et al.

Page 1 of 2

It is certified that error appears in the above-identified patent and that said Letters Patent is hereby corrected as shown below:

In the Certificate Extending the Patent Term under 35 U.S.C. 156, the original expiration date is incorrect. In the second paragraph line 1

Delete: September 23, 2003

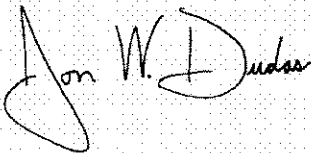
and insert therefor

--September 26, 2003--.

This certificate supersedes Certificate of Correction issued March 2, 2006.

Signed and Sealed this

Fourth Day of July, 2006

A handwritten signature in black ink, reading "Jon W. Dudas". The signature is written in a cursive style with a large, stylized "J" and "D".

JON W. DUDAS
Director of the United States Patent and Trademark Office

UNITED STATES PATENT AND TRADEMARK OFFICE

(12) CERTIFICATE EXTENDING PATENT TERM
UNDER 35 U.S.C. § 156

(68) PATENT NO. : 4,513,006
(45) ISSUED : April 23, 1985
(75) INVENTOR : Bruce E. Maryanoff, et al.
(73) PATENT OWNER : McNeil Lab, Inc.
(95) PRODUCT : TOPAMAX® (topiramate)


This is to certify that an application under 35 U.S.C. § 156 has been filed in the United States Patent and Trademark Office, requesting extension of the term of U.S. Patent No. 4,513,006 based upon the regulatory review of the product TOPAMAX® (topiramate) by the Food and Drug Administration. Since it appears that the requirements of the law have been met, this certificate extends the term of the patent for the period of

(94) Five Years

from September 23, 2003, the original expiration date of the patent, subject to the payment of maintenance fees as provided by law, with all rights pertaining thereto as provided by 35 U.S.C. § 156(b).



I have caused the seal of the United States Patent and Trademark Office to be affixed this 23rd day of July 2004.


Jon W. Dudas
Acting Under Secretary of Commerce for
Intellectual Property and Acting Director of the
United States Patent and Trademark Office