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**Anticonvulsant derivatives useful in treating autism**

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(71) Applicant(s)  
**Ortho-McNeil Pharmaceutical, Inc.**

(72) Inventor(s)  
**Daniel P. Van Kammen**

(74) Agent/Attorney  
**BALDWIN SHELSTON WATERS, Level 21, 60 Margaret Street, SYDNEY NSW 2000**

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**PCT**

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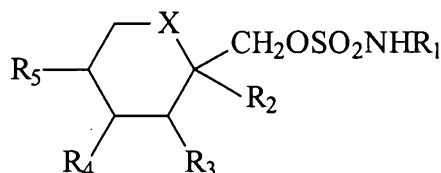
<p>(51) International Patent Classification <sup>7</sup> : A61K 31/35, 31/70, A61P 25/00</p>	<p>A1</p>	<p>(11) International Publication Number: <b>WO 00/45812</b> (43) International Publication Date: 10 August 2000 (10.08.00)</p>
<p>(21) International Application Number: PCT/US00/01127 (22) International Filing Date: 18 January 2000 (18.01.00) (30) Priority Data: 60/119,104 8 February 1999 (08.02.99) US (71) Applicant: ORTHO-MCNEIL PHARMACEUTICAL, INC. [US/US]; U.S. Route #202, P.O. Box 300, Raritan, NJ 08869-0602 (US). (72) Inventor: VAN KAMMEN, Daniel, P.; 22 Edgewood Road, Neshanic Station, NJ 08853 (US).</p>		<p>(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CR, CU, CZ, DE, DK, DM, 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).</p> <p><b>Published</b> <i>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.</i></p>
<p>(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING AUTISM (57) Abstract Anticonvulsant derivatives useful in treating autism.</p>		

## ANTICONVULSANT DERIVATIVES USEFUL IN TREATING AUTISM

### BACKGROUND OF INVENTION

Any discussion of the prior art throughout the specification should in no way be  
5 considered as an admission that such prior art is widely known or forms part of common  
general knowledge in the field.

Compounds of Formula I:



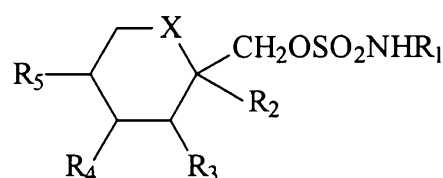
- 10 are structurally novel antiepileptic compounds that are highly effective anticonvulsants  
in animal tests (Maryanoff, B.E., Nortey, S.O., Gardocki, J.F., Shank, R.P and Dodgson,  
S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P.,  
Schupsky, J.J., Ortegon, M.E., and Vaught J.L. *Bioorganic & Medicinal Chemistry*  
Letters 3, 2653-2656, 1993). These compounds are covered by US Patent No. 4,513,006.
- 15 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 secondarily generalized seizures (E. FAUGHT, B.J.  
WILDER, R.E. RAMSAY, R.A. REIFE, L.D. KRAMER, G.W. PLEDGER, R.M.
- 20 KARIM et. al., *Epilepsia* 36 (S4) 33, 1995; S.K. SACHDEO, R.C. SACHEDO, 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 seizures in approximately twenty countries including the  
United States, and applications for regulatory approval are presently pending in several
- 25 additional countries throughout the world.

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,  
30 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. ISHI, 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).

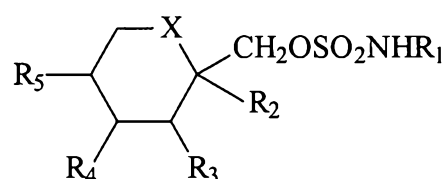
- 5        Clinical studies on topiramate have revealed previously unrecognised pharmacological properties which suggest that topiramate will be effective in treating autism.

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



- 10        wherein X is O or CH<sub>2</sub>, and R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are as defined hereinafter are useful in maintaining weight loss.

According to the first aspect of the invention, a method for treating autism in mammals, comprising administering to such a mammal a therapeutically effective amount for treating such condition of compound of the formula I:



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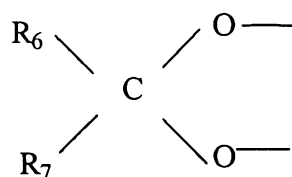
wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub>

- 20        may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):

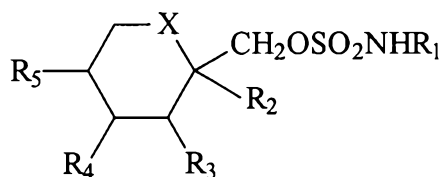


wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, or alkyl and are joined to form a

- 25        cyclopentyl or cyclohexyl ring.

According to the second aspect of the invention, use of a compound of the formula 1:



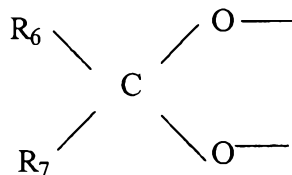
wherein

5 X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):

10



wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, or alkyl and are joined to form a cyclopentyl or cyclohexyl ring

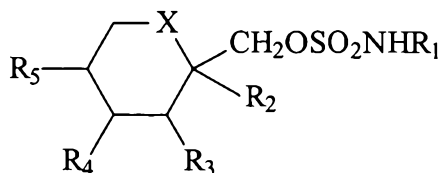
15 for the manufacture of a medicament for treating autism in mammals.

Unless the context clearly requires otherwise, throughout the description and the claims, the words 'comprise', 'comprising', and the like are to be construed in an inclusive sense as opposed to an exclusive or exhaustive sense; that is to say, in the sense of "including, but not limited to".

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## DETAILED DESCRIPTION OF THE PREFERRED EMBODIEMENTS

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



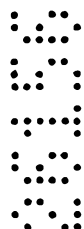
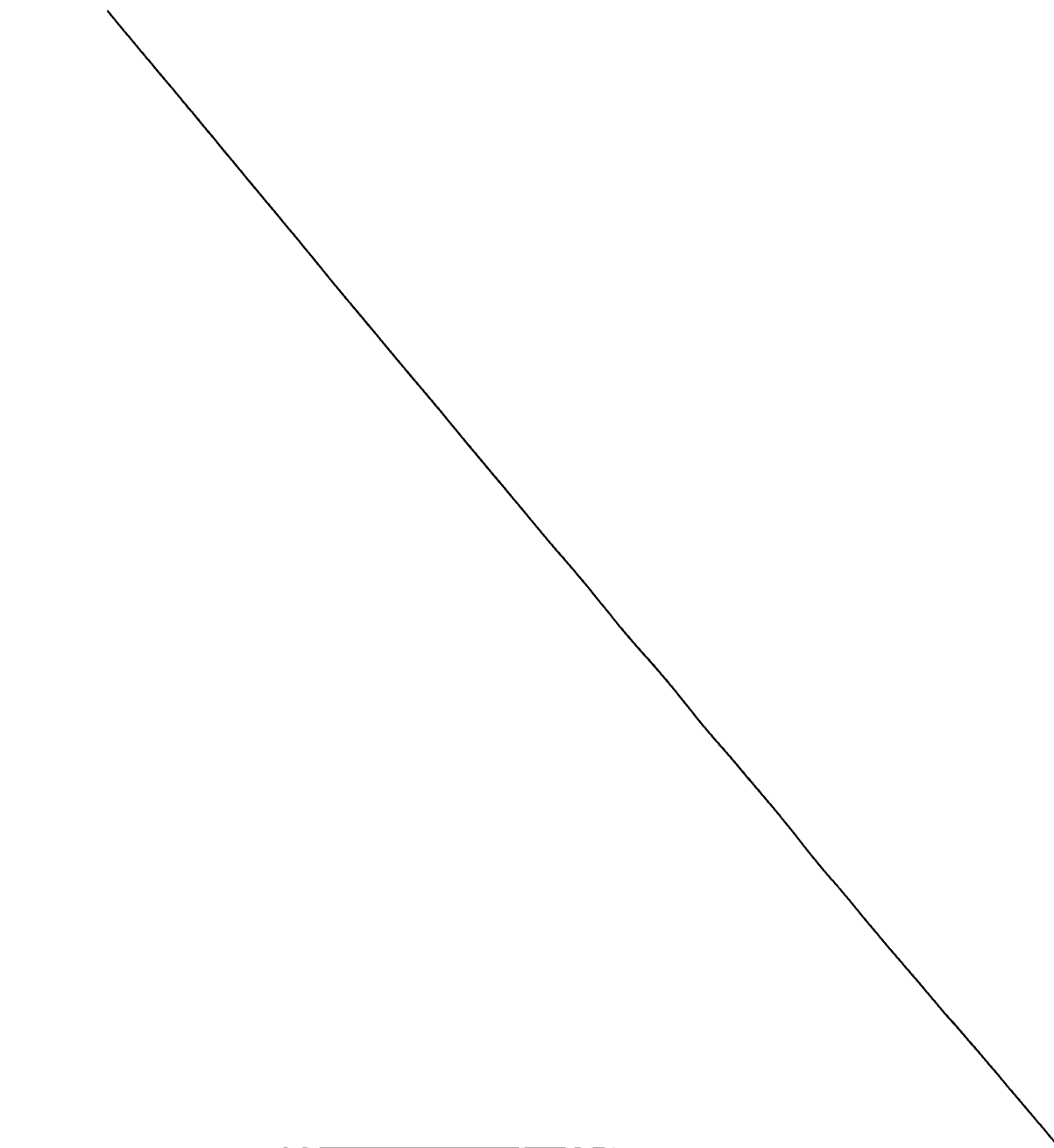
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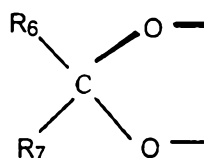
wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

- 5 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub> and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):





wherein

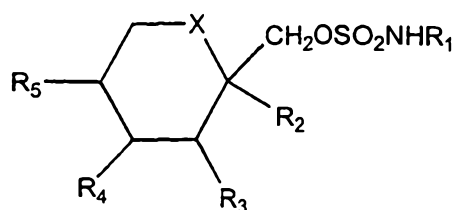
- R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, lower alkyl or are alkyl and are  
 5 joined to form a cyclopentyl or cyclohexyl ring.

- R<sub>1</sub> 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 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, R<sub>6</sub> and R<sub>7</sub> are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may  
 10 combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R<sub>4</sub> and R<sub>5</sub> are defined by the alkatrienyl group =C-CH=CH-CH=.

- A particular group of compounds of formula (I) is that wherein X is oxygen and both R<sub>2</sub> and R<sub>3</sub> and R<sub>4</sub> and R<sub>5</sub> together are methylenedioxy groups of the formula (II), wherein R<sub>6</sub> and R<sub>7</sub> are both hydrogen both alkyl or combine to form a spiro  
 15 cyclopentyl or cyclohexyl ring, in particular where R<sub>6</sub> and R<sub>7</sub> are both alkyl such as methyl. A second group of compounds is that wherein X is CH<sub>2</sub> and R<sub>4</sub> and R<sub>5</sub> are joined to form a benzene ring. A third group of compounds of formula (I) is that wherein both R<sub>2</sub> and R<sub>3</sub> are hydrogen.

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

- 20 (a) Reaction of an alcohol of the formula RCH<sub>2</sub>OH with a chlorosulfamate of the formula ClSO<sub>2</sub>NH<sub>2</sub> or ClSO<sub>2</sub>NHR<sub>1</sub> 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):



(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  $-40^\circ$  to  $25^\circ$  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  $40^\circ$  to  $25^\circ$  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 metal and  $H_2$  or by heating with  
15       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  
20       (1970) or by reaction of the trimethylsilyl enol ether of a  $R_6COR_7$  ketone or aldehyde with fructose at a temperature of about  $25^\circ$  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).

25       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  $0^\circ$  to  $100^\circ$  C, e.g. as described by H.O. House in "Modern  
30       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.



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 R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> on the 6-membered ring. Preferably, the oxygens of the methylenedioxy group (II) are attached on the same side of the 6-membered ring.

Autism is observed in a group of disorders called the pervasive developmental disorders (e.g., Autistic Disorder, Rett's Disorder, Asperger's Disorder, Pervasive Developmental Disorder Not Otherwise Specified (Including Atypical Autism). Such disorders are behaviorally defined disorders featuring qualitative impaired social interaction, language, communication and range of interests and activities. As used herein "autism" is used to cover all such disorders. Perseveration, stereotypy, concreteness, affective blunting, failure to develop peer relationships appropriate to developmental level and lack of insight into other person's thinking may be conspicuous along with motor stereotypies. In a proportion of cases, autism is associated with epilepsy, (eg., conditions such as a paroxysmal EEG or even status epilepticus in slow wave sleep). Beaumanoir A, Bureau M, Deonna T, et al. Eds. Continuous spikes and waves during slow wave sleep-electrical status epilepticus during slow wave sleep-Acquired epileptic aphasia and related conditions. John Libbey, 1995. Autistic regression also overlaps with acquired epileptic aphasia (Landau-Kleffner Syndrome). Landau WM, Kleffner FR. Syndrome of Acquired Aphasia with convulsive disorder in children. Neurology 1957; 523-530. Therefore, the treatment of underlying seizure disorder has a direct relationship to the treatment of autism.

Abnormal plasma levels of glutamate may be found in some autistic children Moreno-Fuenmayor H. Borjas L. Arrieta A. Valera V. Socorro-Candanoza L. Plasma excitatory amino acids in autism. Investigacion Clinica.37(2) : 113-28,1996 Jun. Genes for the three GABA<sub>A</sub> receptor subunits on chromosome 15q have been shown to have aberrations in autism. Schroer RJ, Phelan MC, Michaelis RC, Crawford EC, Skinner SA, Cuccaro M, Simensen RJ, Bishop J, Skinner C, Fender D, Stevensen RE. Autism and mathematically derived aberrations of chromosome 15q. American Journal of Medical Genetics. 76(4) : 327-36, 1998 Apr 1. There are also serotonin abnormalities in autism (Cook EH, Leventhal BL. The serotonin system in autism.

Current Opinion in Pediatrics.8(4):348-354,1996 Aug.), which will be treated through GABA and glutamate alterations induced by compounds of formula I.

Placebo controlled, add on trials of topiramate in adults and children with partial onset seizures have shown a statistically significant reduction of seizure rate greater for  
5 Topiramate than placebo. There is also known enhancement of GABA activity in the brain along with reduced glutamate receptor activity. Accordingly, compounds of formula I are useful in the treatment of autism.

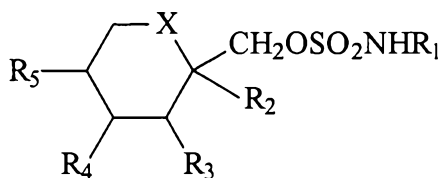
For treating autism, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 600 mg, usually in two divided doses, for an average  
10 adult human. A unit dose would contain about 25 to 200 mg of the active ingredient.

To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation desired  
15 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  
20 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  
25 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 solutions may also be prepared in which case appropriate stabilizing agents may be employed. Topiramate is  
30 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.

**THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-**

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



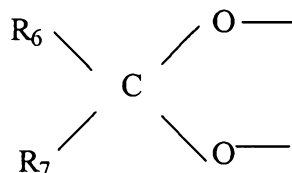
wherein

X is  $\text{CH}_2$  or oxygen;

$\text{R}_1$  is hydrogen or alkyl; and

$\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$  and  $\text{R}_5$  are independently hydrogen or alkyl and, when X is  $\text{CH}_2$ ,  $\text{R}_4$  and  $\text{R}_5$

may be alkene groups joined to form a benzene ring and, when X is oxygen,  $\text{R}_2$  and  $\text{R}_3$  and/or  $\text{R}_4$  and  $\text{R}_5$  together may be a methylenedioxy group of the following formula (II):



wherein

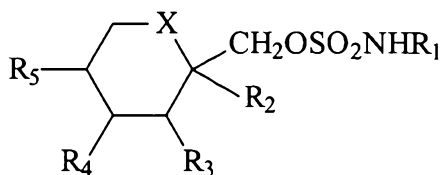
$\text{R}_6$  and  $\text{R}_7$  are the same or different and are hydrogen, or alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

2. The method of claim 1 wherein the compound of formula I is topiramate.

3. The method of claim 1 or claim 2, wherein the therapeutically effective amount is of from about 50 to 600 mg/day.

4. The method of claim 1 or claim 2, wherein the amount is of from about 25 to 200mg/day.

5. Use of a compound of the formula 1:



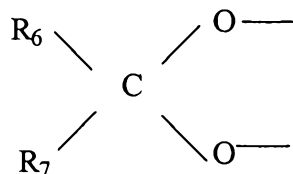
wherein

X is CH<sub>2</sub> or oxygen;

R<sub>1</sub> is hydrogen or alkyl; and

R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub> and R<sub>5</sub> are independently hydrogen or alkyl and, when X is CH<sub>2</sub>, R<sub>4</sub> and R<sub>5</sub> may be alkene groups joined to form a benzene ring and, when X is oxygen, R<sub>2</sub> and R<sub>3</sub>

5 and/or R<sub>4</sub> and R<sub>5</sub> together may be a methylenedioxy group of the following formula (II):



wherein

R<sub>6</sub> and R<sub>7</sub> are the same or different and are hydrogen, or alkyl and are joined to form a  
10 cyclopentyl or cyclohexyl ring, for the manufacture of a medicament for treating autism  
in mammals.

6. Use of a compound according to claim 5, wherein the compound of formula I is  
topiramate.

7. Use of a compound according to claim 5 or claim 6, wherein the medicament is  
15 administered from about 50 to 600mg/day.

8. Use of a compound according to claim 5 or 6, wherein the medicament is  
administered from about 25 to 200mg/day.

9. A method for treating autism in mammals, substantially as herein described with  
reference to any one of the examples but excluding comparative examples.

20 10. Use of a compound for the manufacture of a medicament for treating autism in  
mammals substantially as herein described with reference to any one of the examples but  
excluding comparative examples.

DATED this 6<sup>th</sup> day of June 2003

25 BALDWIN SHELSTON WATERS

Attorneys for: ORTHO-MCNEIL PHARMACEUTICAL, INC.