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(54) Title: ANTICONVULSANT DERIVATIVES USEFUL IN TREATING AUTISM

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Anticonvulsant derivatives useful in treating autism.

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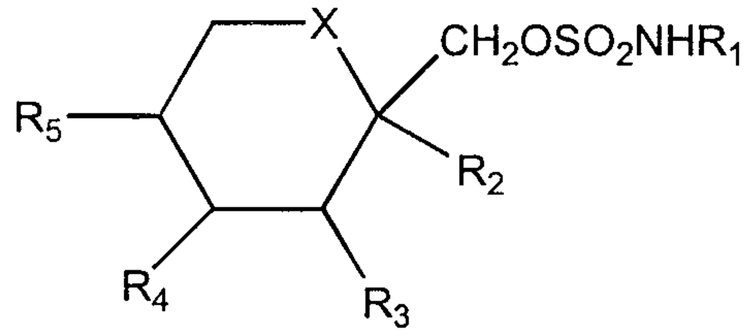
(57) Abstract

Anticonvulsant derivatives useful in treating autism.

ANTICONVULSANT DERIVATIVES USEFUL IN TREATING AUTISM

BACKGROUND OF THE INVENTION

Compounds of Formula I:



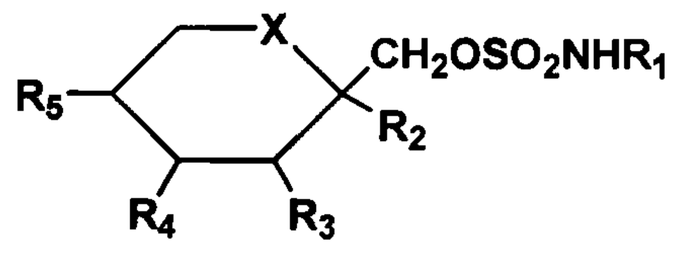
are structurally novel antiepileptic compounds that are highly effective anticonvulsants in animal tests (Maryanoff, B.E, Nortey, S.O., Gardocki, J.F., Shank, R.P. and Dodgson, S.P. *J. Med. Chem.* 30, 880-887, 1987; Maryanoff, B.E., Costanzo, M.J., Shank, R.P., Schupsky, J.J., Ortegon, M.E., and Vaught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

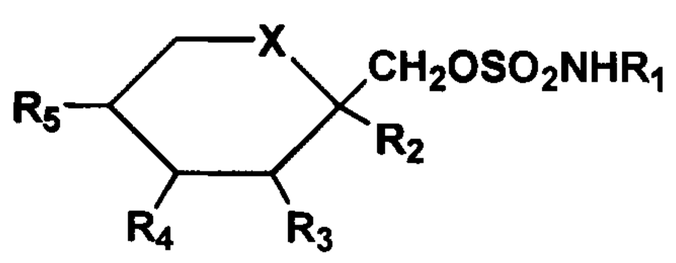
Clinical studies on topiramate have revealed previously unrecognized pharmacological properties which suggest that topiramate will be effective in treating autism.

Accordingly, it has been found that compounds of the following Formula (I):



wherein X is O or CH_2, and R_1, R_2, R_3, R_4 and R_5 are as defined hereinafter are useful in treating autism.

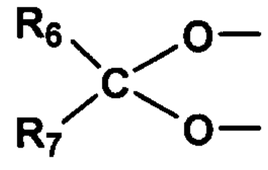
More particularly, the present invention discloses the use of compounds of Formula (I):



wherein

X is oxygen;

R_1 is hydrogen or C_1-C_4 alkyl, where alkyl includes straight and branched chain alkyl; and R_2 and R_3, and R_4 and R_5, together are a methylenedioxy group of the following Formula (II):

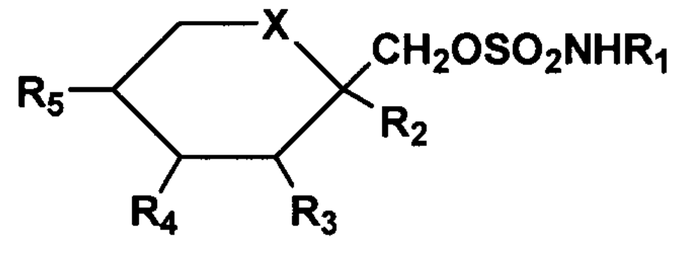


wherein

R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl, where alkyl includes straight and branched chain alkyl, or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring, in the treatment of autism.

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

The sulfamates of the Invention are of the following Formula (I):

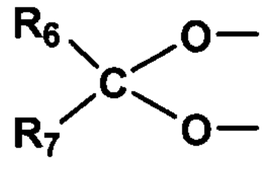


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

R_2, R_3, R_4 and R_5 are independently hydrogen or alkyl, and when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring, and when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following Formula (II):



wherein

R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

R_1 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_2, R_3, R_4, R_5, R_6 and R_7 are of about 1 to 3 carbons and include methyl, ethyl, iso-propyl and n-propyl. When X is CH_2, R_4 and R_5 may combine to form a benzene ring fused to the 6-membered X-containing ring, i.e., R_4 and R_5 are defined by the alkatrienyl group =C-CH=CH-CH=.

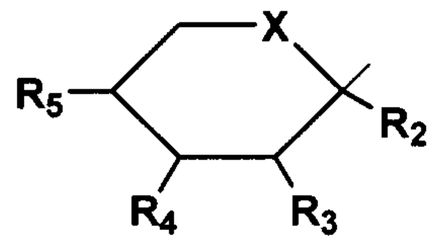
A particular group of compounds of Formula (I) is that wherein X is oxygen and both R_2 and R_3, and R_4 and R_5 together are methylenedioxy groups of the Formula (II), wherein R_6 and R_7 are both hydrogen, both alkyl, or combine to form a spiro cyclopentyl or cyclohexyl ring, in particular where R_6 and R_7 are both alkyl such as methyl. A second group of compounds is that wherein X is CH_2 and R_4 and R_5 are joined to form a benzene ring. A third group of compounds of Formula (I) is that wherein both R_2 and R_3 are hydrogen.

A particularly preferred embodiment of the present invention is a group of compounds of Formula (I) wherein X is oxygen, R_1 is hydrogen or C_1-C_4 alkyl, and R_2 and R_3, and R_4 and R_5, together are a methylenedioxy group of Formula (II), wherein R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl, or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

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

(a) Reaction of an alcohol of the formula RCH_2OH with a chlorosulfamate of the formula $ClSO_2NH_2$ or $ClSO_2NHR_1$ 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):



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(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 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. 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 formula I may also be made by the known process disclosed in U.S. Patent No. 5,387,700.

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_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.

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 $GABA_A$ 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 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.

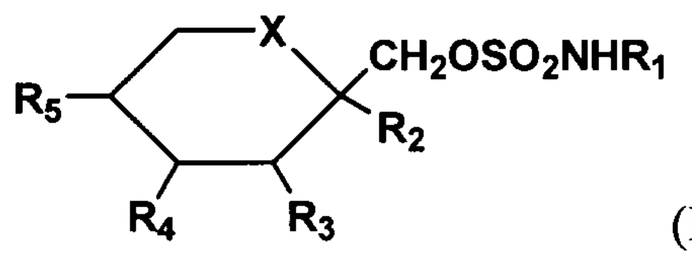
For treating autism, a compound of formula (I) may be employed at a daily dosage in the range of about 50 to 600 mg, usually in two divided doses, for an average adult human. A unit dose would contain about 25 to 200 mg of the active ingredient.

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 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 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 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, 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 embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. The use of a compound of the Formula (I):



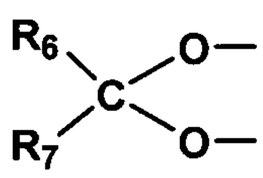
(I)

wherein

X is oxygen;

R_1 is hydrogen or C_1-C_4 alkyl, where alkyl includes straight and branched chain alkyl; and

R_2 and R_3, and R_4 and R_5, together are a methylenedioxy group of the following Formula (II):



(II)

wherein

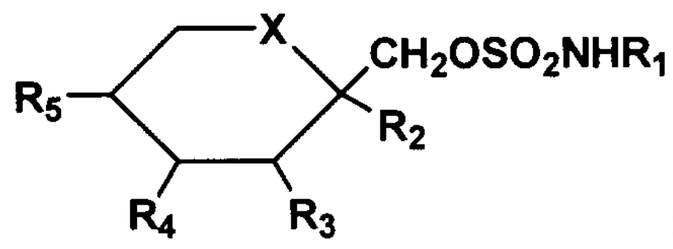
R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl, where alkyl includes straight and branched chain alkyl, or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring; in a therapeutically effective amount for treating autism in mammals.

2. The use of claim 1, wherein the compound of Formula (I) is topiramate.

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

4. The use of claim 1 or 2, wherein the therapeutically effective amount is from about 25 mg to about 200 mg per unit dose.

5. The use of a therapeutically effective amount of a compound of the Formula (I):



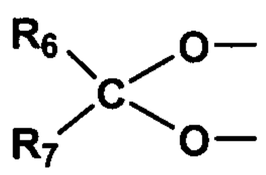
(I)

wherein

X is oxygen;

R_1 is hydrogen or C_1-C_4 alkyl, where alkyl includes straight and branched chain alkyl; and

R_2 and R_3, and R_4 and R_5, together are a methylenedioxy group of the following Formula (II):



(II)

wherein

R_6 and R_7 are the same or different and are hydrogen, C_1-C_3 alkyl, where alkyl includes straight and branched chain alkyl, or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring; in the preparation of a medicament for treating autism in mammals.

6. The use of claim 5, wherein the compound of Formula (I) is topiramate.

7. The use of claim 5 or 6, wherein the therapeutically effective amount is from about 50 mg to about 600 mg per day.

8. The use of claim 5 or 6, wherein the therapeutically effective amount is from about 25 mg to about 200 mg per unit dose.

9. The use of any of claims 5 to 8, wherein the medicament comprises a pharmaceutical composition, comprising a therapeutically effective amount of a compound of Formula (I) together with a pharmaceutically acceptable carrier.