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(56) Related Art
FRIEDMAN ET AL ANN. N.Y. ACAD. SCI. (97) JUN 21, 821, 359-71
DAVIDSON ET AL J.CLIN. PSYCHIATRY (97) 58 SUPPL. 9, 29-72

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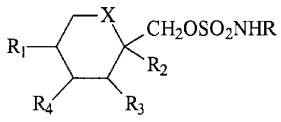
(57) Abstract

Anticonvulsant derivatives useful in treating post traumatic stress disorder, are disclosed.

ANTICONVULSANT DERIVATIVES USEFUL IN TREATING POST TRAUMATIC STRESS DISORDER

BACKGROUND OF THE INVENTION

Compounds of Formula 1:



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)-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. 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 1 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 1 were also highly effective in the MES test in rats. More recently topiramate was found to effectively

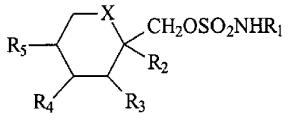
block seizures in several rodent models of epilepsy (J. NAKAMURA, S. TAMURA, T. KANDA, A. ISHII, K. ISHIHARA, T. SERIKAWA, J. YAMADA, and M. SASA, Eur. J. Pharmacol. 254 83-89, 1994), and in an animal model of kindled epilepsy (A. WAUQUIER and S. ZHOU, Epilepsy Res. 24, 73-77, 1996).

Preclinical studies on topiramate have revealed previously unrecognised pharmacological properties which suggest that topiramate will be effective in treating post traumatic stress disorder.

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

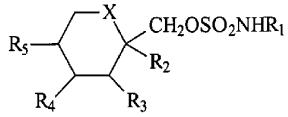
DISCLOSURE OF THE INVENTION

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



wherein X is O or CH_2 and R1, R2, R3, R4 and R5 are as defined herein after are useful in treating alcohol addiction and abuse.

According to a first aspect, the present invention provides a method for treating post traumatic stress disorder, comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

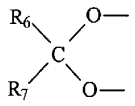


wherein

X is CH_2 or oxygen;

R_1 is hydrogen or alkyl; and

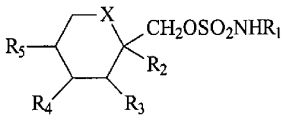
R_2, R_3, R_4 and R_5 are independently hydrogen or lower alkyl and, when X is CH_2, R_4 and R_5 may be alkene groups joined to form a benzene ring and, when X is oxygen, R_2 and R_3 and/or R_4 and R_5 together may be a methylenedioxy group of the following formula (II):



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.

According to a second aspect, the present invention provides use of a compound of the formula I:

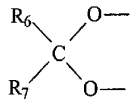


wherein

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 lower 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):



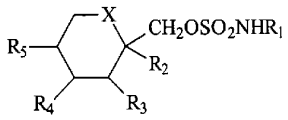
wherein

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 in the manufacture of a medicament for treating post traumatic stress disorder.

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".

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

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

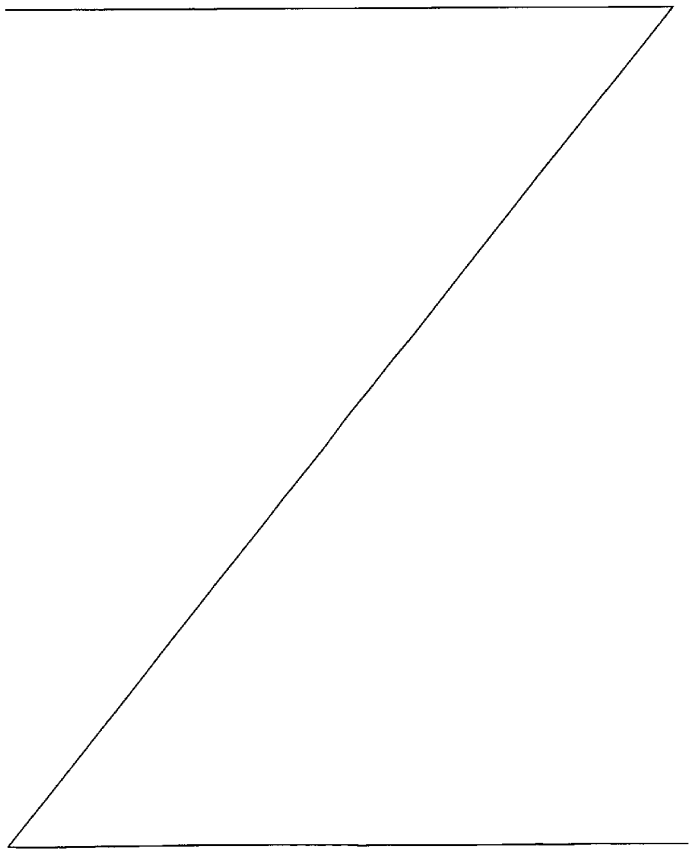


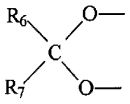
wherein

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 lower 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

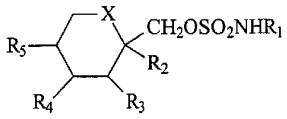
R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

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 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.

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):



(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 abut 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_2OSO2N_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 RCH2OH 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.

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

Post Traumatic Stress Disorder (PTSD) is a complicated neurobehavioral disorder involving multiple neurobiological systems that mediate cognitive, emotional and behavior processes, which maybe dyregulated in PTSD (Neurobiological and Clinical consequences of Stress: From normal adaptation to PTSD. Edited by M.J. Friedman, D.S. Charney and A.Y. Deutch. Lippincott Raven Publishers, Philadelphia, 1995). While most traumatic events lose their impact over time, symptoms of PTSD seem to increase over time and can be elicited by minor psychological trauma. A kindling animal paradigm has been proposed with reference to emotional memory in PTSD symptomatology. Kindling has thus been hypothesized as a possible mechanism in PTSD (Robert M. Post, Susan R.B. Weiss, Mark Smith, HE LI and Una McCann. Implications for the evolution and treatment of Post Traumatic Stress Disorder. Annals of the New York Academy of Sciences Volume 821, 1997).

Topiramate has been shown to be effective in rodent models of kindling seizures, (A. Wauquier and S. Zhov, Epilepsy Res. 24 73-77, 1996 in press).

For treating post traumatic stress disorder, a compound of formula (I) may be employed at a daily dosage in the range of about 32 to 512 mg, usually in two divided doses, for an average adult human. A unit dose would contain about 16 to 128 mg of the active ingredient.

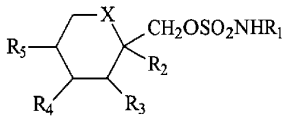
To prepare the pharmaceutical compositions of this invention, one or more sulfamate compounds of formula (I) are intimately admixed with a pharmaceutical carrier according to conventional pharmaceutical compounding techniques, which carrier may take a wide variety of forms depending on the form of preparation 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 CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:-

1. A method for treating post traumatic stress disorder, comprising administering to a mammal afflicted with such condition a therapeutically effective amount for treating such condition of a compound of the formula I:

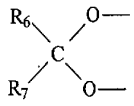


wherein

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 lower 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

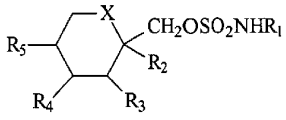
R_6 and R_7 are the same or different and are hydrogen, lower alkyl or are alkyl and are joined to form a cyclopentyl or cyclohexyl ring.

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 32 to 512 mg.

4. The method of claim 1, wherein the amount is from about 16 to 128 mg.

5. Use of a compound of the formula I:

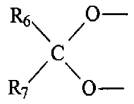


wherein

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 lower 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 in the manufacture of a medicament for treating post traumatic stress disorder.

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

7. Use according to claim 5, wherein the medicament comprises of from about 32 to 512 mg of a compound of the formula I.

8. Use according to claim 5, wherein the medicament comprises of from about 16 to 128 mg of a compound of the formula I.

9. A method for treating post traumatic stress disorder, substantially as herein described with reference to any one of the examples but excluding comparative examples.

10. Use of a compound of formula I or a pharmaceutically acceptable salt thereof in the manufacture of a medicament, substantially as herein described with reference to any one of the examples but excluding comparative examples.

DATED this 25th Day of February 2002

ORTHO-MCNEIL PHARMACEUTICAL, INC.

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