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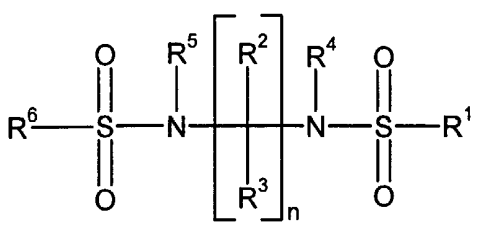
(54) Title: (BIS)SULFONAMIDE DERIVATIVES



(I)

(57) Abstract: The present invention provides (bis)sulfonamide derivatives of formula (I) useful for potentiating glutamate receptor function in a mammal and therefore, useful for treating a wide variety of conditions, such as psychiatric and neurological disorders.

(BIS)SULFONAMIDE DERIVATIVES

In the mammalian central nervous system (CNS), the transmission of nerve impulses is controlled by the interaction between a neurotransmitter, that is released by a sending neuron, and a surface receptor on a receiving neuron, which causes excitation of this receiving neuron. L-Glutamate, which is the most abundant neurotransmitter in the CNS, mediates the major excitatory pathway in mammals, and is referred to as an excitatory amino acid (EAA). The receptors that respond to glutamate are called excitatory amino acid receptors (EAA receptors). See Watkins & Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges, and Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen, and Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). The excitatory amino acids are of great physiological importance, playing a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, and sensory perception.

Excitatory amino acid receptors are classified into two general types. Receptors that are directly coupled to the opening of cation channels in the cell membrane of the neurons are termed "ionotropic". This type of receptor has been subdivided into at least three subtypes, which are defined by the depolarizing actions of the selective agonists *N*-methyl-D-aspartate (NMDA), alpha-amino-3-hydroxy-5-methylisoxazole-4-propionic acid (AMPA), and kainic acid (KA). The second general type of receptor is the G-protein or second messenger-linked "metabotropic" excitatory amino acid receptor. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increases or decreases in c-AMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Both types of receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also participate in the modification of synaptic connections during development and throughout life. Schoepp, Bockaert, and Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald and Johnson, *Brain Research Reviews*, 15, 41 (1990).

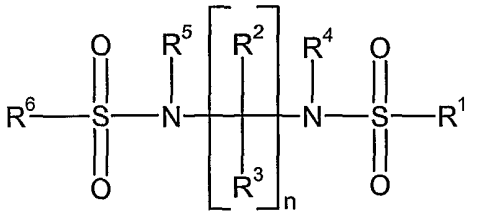
AMPA receptors are assembled from four protein sub-units known as GluR1 to GluR4, while kainic acid receptors are assembled from the sub-units GluR5 to GluR7, and KA-1 and KA-2. Wong and Mayer, *Molecular Pharmacology* 44: 505-510, 1993. It is not yet known how these sub-units are combined in the natural state. However, the structures of certain human variants of each sub-unit have been elucidated, and cell lines expressing individual sub-unit variants have been cloned and incorporated into test systems designed to identify compounds which bind to or interact with them, and hence which may modulate their function. Thus, European patent application, publication number EP-A2-0574257 discloses the human sub-unit variants GluR1B, GluR2B, GluR3A and GluR3B. European patent application, publication number EP-A1-0583917 discloses the human sub-unit variant GluR4B.

One distinctive property of AMPA and kainic acid receptors is their rapid deactivation and desensitization to glutamate. Yamada and Tang, *The Journal of Neuroscience*, September 1993, 13(9): 3904-3915 and Kathryn M. Partin, *J. Neuroscience*, November 1, 1996, 16(21): 6634-6647.

It is known that the rapid desensitization and deactivation of AMPA and/or kainic acid receptors to glutamate may be inhibited using certain compounds. This action of these compounds is often referred to in the alternative as "potentiation" of the receptors. One such compound, which selectively potentiates AMPA receptor function, is cyclothiazide. Partin et al., *Neuron*. Vol. 11, 1069-1082, 1993.

International Patent Application Publication WO 98/33496 published August 6, 1998 discloses certain sulfonamide derivatives which are useful, for example, for treating psychiatric and neurological disorders, for example cognitive disorders; neuro-degenerative disorders such as Alzheimer's disease; age-related dementias; age-induced memory impairment; movement disorders such as tardive dyskinesia, Huntington's chorea, myoclonus, and Parkinson's disease; reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states); depression; attention deficit disorder; attention deficit hyperactivity disorder; psychosis; cognitive deficits associated with psychosis, and drug-induced psychosis.

The present invention provides a method of potentiating glutamate receptor function in a patient, which comprises administering to said patient an effective amount of a compound of formula I



formula I

wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each independently represent hydrogen, (1-4C)alkyl, F, aryl, or (1-6C)alkylaryl;

R^4 and R^5 each independently represent hydrogen, (1-6C)alkyl, (1-6C)alkylcycloalkyl, aryl, or (1-6C)alkylaryl;

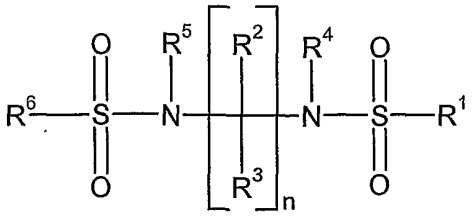
R^6 represents (1-6C)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaromatic group, cycloalkyl, or alkylcycloalkyl;

n is an integer 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof.

The present invention further provides compounds of formula IA



formula IA

wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each independently represent hydrogen, (1-4C)alkyl, F, aryl, or (1-6C)alkylaryl;

R^4 and R^5 each independently represent hydrogen, (1-6C)alkyl, (1-6C)alkylcycloalkyl, aryl, or (1-6C)alkylaryl;

R^6 represents (1-6C)alkyl, unsubstituted or substituted aryl, unsubstituted or substituted heteroaromatic group, cycloalkyl, or alkylcycloalkyl;
n is an integer 7, 8, 9, 10, 11, 12, 13, or 14; and
R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;
or a pharmaceutically acceptable salt thereof.

The present invention provides a method of treating cognitive disorders in a patient, which comprises administering to said patient an effective amount of a compound of formula I.

In addition, the present invention further provides a method of treating cognitive deficits associated with psychosis in a patient, which comprises administering to said patient an effective amount of a compound of formula I.

According to another aspect, the present invention provides the use of a compound of formula I, or a pharmaceutically acceptable salt thereof for the manufacture of a medicament for potentiating glutamate receptor function.

In addition, the present invention provides the use of a compound of formula I or a pharmaceutically acceptable salt thereof for potentiating glutamate receptor function.

The invention further provides pharmaceutical compositions comprising, a compound of formula I and a pharmaceutically acceptable diluent or carrier.

This invention also encompasses novel compounds within the scope of formula I, and novel intermediates, and processes for the synthesis of the compounds of formula I.

The present invention further provides an article of manufacture comprising packaging material and a compound of formula I or a pharmaceutically acceptable salt thereof contained within said packaging material, wherein said packaging material comprises a label which indicates that said compound of formula I can be used for treating at least one of the following; Alzheimer's disease, schizophrenia, cognitive deficits associated with schizophrenia, depression, and cognitive disorders.

Figure 1 discloses the effect of 512511 in the forced swim test in mice. Impiramine (IM, 15 mg/Kg, i.p.) was administered 15 minutes prior to testing.

Values represent X +/- SEM of 6-8 animals. The doses of 512511 were 1, 2.5, and 5 μg/kg (p.o.,1 hour). The minimum effective dose (MED) of 512511 was 5 μg/kg in mice.

In this specification, the term "potentiating glutamate receptor function" refers to any increased responsiveness of glutamate receptors, for example AMPA receptors, to glutamate or an agonist, and includes but is not limited to inhibition of rapid desensitization or deactivation of AMPA receptors to glutamate.

A wide variety of conditions may be treated or prevented by the compounds of formulas I and IA, and their pharmaceutically acceptable salts through their action as potentiators of glutamate receptor function. Such conditions include those associated with glutamate hypofunction, such as psychiatric and neurological disorders, for example cognitive disorders; neurodegenerative disorders such as Alzheimer's disease; age-related dementias; age-induced memory impairment; movement disorders such as tardive dyskinesia, Hungtington's chorea, myoclonus, dystonia, and Parkinson's disease; reversal of drug-induced states (such as cocaine, amphetamines, alcohol-induced states); depression; attention deficit disorder; attention deficit hyperactivity disorder; psychosis; cognitive deficits associated with psychosis, drug-induced psychosis; stroke; and sexual dysfunction. The compounds of formulas I and IA may also be useful for improving memory (both short term and long term) and learning ability. The present invention provides the use of compounds of formulas I and IA for the treatment of each of these conditions.

The present invention includes the pharmaceutically acceptable salts of the compounds defined by formulas I and IA. A compound of this invention can possess a sufficiently acidic group, a sufficiently basic group, or both functional groups, and accordingly react with any of a number of organic and inorganic bases, and inorganic and organic acids, to form a pharmaceutically acceptable salt.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds of the above formula which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts prepared by reaction of the compounds of the present invention with a pharmaceutically acceptable mineral or organic acid or an organic or inorganic

base. Such salts are known as acid addition and base addition salts. Such salts include the pharmaceutically acceptable salts listed in Journal of Pharmaceutical Science, 66, 2-19 (1977) which are known to the skilled artisan.

Acids commonly employed to form acid addition salts are inorganic acids such as hydrochloric acid, hydrobromic acid, hydroiodic acid, sulfuric acid, phosphoric acid, and the like, and organic acids such as *p*-toluenesulfonic, methanesulfonic acid, benzenesulfonic acid, oxalic acid, *p*-bromophenylsulfonic acid, carbonic acid, succinic acid, citric acid, benzoic acid, acetic acid, and the like. Examples of such pharmaceutically acceptable salts are the sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, monohydrogenphosphate, dihydrogenphosphate, metaphosphate, pyrophosphate, bromide, iodide, acetate, propionate, decanoate, caprate, caprylate, acrylate, ascorbate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, propionate, phenylpropionate, salicylate, oxalate, malonate, succinate, suberate, sebacate, fumarate, malate, maleate, hydroxymaleate, mandelate, nicotinate, isonicotinate, cinnamate, hippurate, nitrate, phthalate, teraphthalate, butyne-1,4-dioate, butyne-1,4-dicarboxylate, hexyne-1,4-dicarboxylate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, dinitrobenzoate, *o*-acetoxybenzoate, naphthalene-2-benzoate, phthalate, *p*-toluenesulfonate, *p*-bromobenzenesulfonate, p-chlorobenzenesulfonate, xylenesulfonate, phenylacetate, trifluoroacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, tartrate, benzenesulfonate, methanesulfonate, ethanesulfonate, propanesulfonate, hydroxyethanesulfonate, 1-naphthalenesulfonate, 2-napththalenesulfonate, 1,5-naphthalenedisulfonate, mandelate, tartarate, and the like. Preferred pharmaceutically acceptable acid addition salts are those formed with mineral acids such as hydrochloric acid and hydrobromic acid, and those formed with organic acids such as maleic acid, oxalic acid and methanesulfonic acid.

Base addition salts include those derived from inorganic bases, such as ammonium or alkali or alkaline earth metal hydroxides, carbonates, bicarbonates, and the like. Such bases useful in preparing the salts of this invention thus include sodium hydroxide, potassium hydroxide, ammonium hydroxide,

potassium carbonate, sodium carbonate, sodium bicarbonate, potassium bicarbonate, calcium hydroxide, calcium carbonate, and the like. The potassium and sodium salt forms are particularly preferred.

It should be recognized that the particular counterion forming a part of any salt of this invention is usually not of a critical nature, so long as the salt as a whole is pharmacologically acceptable and as long as the counterion does not contribute undesired qualities to the salt as a whole. It is further understood that the above salts may form hydrates or exist in a substantially anhydrous form.

As used herein the term "512511" refers to [(methylethyl)sulfonyl](10-{[(methylethyl)sulfonyl]amino}decyl)amine.

As used herein, the term "stereoisomer" refers to a compound made up of the same atoms bonded by the same bonds but having different three-dimensional structures which are not interchangeable. The three-dimensional structures are called configurations. As used herein, the term "enantiomer" refers to two stereoisomers whose molecules are nonsuperimposable mirror images of one another. The term "chiral center" refers to a carbon atom to which four different groups are attached. As used herein, the term "diastereomers" refers to stereoisomers which are not enantiomers. In addition, two diastereomers which have a different configuration at only one chiral center are referred to herein as "epimers". The terms "racemate", "racemic mixture" or "racemic modification" refer to a mixture of equal parts of enantiomers.

The term "enantiomeric enrichment" as used herein refers to the increase in the amount of one enantiomer as compared to the other. A convenient method of expressing the enantiomeric enrichment achieved is the concept of enantiomeric excess, or "ee", which is found using the following equation:

$$ee = \frac{E^1 - E^2}{E^1 + E^2} X\ 100$$

wherein E^1 is the amount of the first enantiomer and E^2 is the amount of the second enantiomer. Thus, if the initial ratio of the two enantiomers is 50:50, such as is present in a racemic mixture, and an enantiomeric enrichment sufficient to produce a final ratio of 70:30 is achieved, the ee with respect to the first

enantiomer is 40%. However, if the final ratio is 90:10, the ee with respect to the first enantiomer is 80%. An ee of greater than 90% is preferred, an ee of greater than 95% is most preferred and an ee of greater than 99% is most especially preferred. Enantiomeric enrichment is readily determined by one of ordinary skill in the art using standard techniques and procedures, such as gas or high performance liquid chromatography with a chiral column. Choice of the appropriate chiral column, eluent and conditions necessary to effect separation of the enantiomeric pair is well within the knowledge of one of ordinary skill in the art. In addition, the specific stereoisomers and enantiomers of compounds of formulas I and IA can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981, and E.L. Eliel and S.H. Wilen," Stereochemistry of Organic Compounds", (Wiley-Interscience 1994), and European Patent Application No. EP-A-838448, published April 29, 1998. Examples of resolutions include recrystallization techniques or chiral chromatography.

Some of the compounds of the present invention have one or more chiral centers and may exist in a variety of stereoisomeric configurations. As a consequence of these chiral centers, the compounds of the present invention occur as racemates, mixtures of enantiomers and as individual enantiomers, as well as diastereomers and mixtures of diastereomers. All such racemates, enantiomers, and diastereomers are within the scope of the present invention.

The terms "R" and "S" are used herein as commonly used in organic chemistry to denote specific configuration of a chiral center. The term "R" (rectus) refers to that configuration of a chiral center with a clockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The term "S" (sinister) refers to that configuration of a chiral center with a counterclockwise relationship of group priorities (highest to second lowest) when viewed along the bond toward the lowest priority group. The priority of groups is based upon their atomic number (in order of decreasing atomic number). A partial list of priorities and a discussion of stereochemistry is contained in "Nomenclature of Organic Compounds: Principles and Practice", (J.H. Fletcher, et al., eds., 1974) at pages 103-120.

As used herein, the term "aromatic group" means the same as aryl, and includes phenyl and a polycyclic aromatic carbocyclic ring such as 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

The term "heteroaromatic group" includes an aromatic 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen, and a bicyclic group consisting of a 5-6 membered ring containing from one to four heteroatoms selected from oxygen, sulfur and nitrogen fused with a benzene ring or another 5-6 membered ring containing one to four atoms selected from oxygen, sulfur and nitrogen. Examples of heteroaromatic groups are thienyl, furyl, oxazolyl, isoxazolyl, oxadiazoyl, pyrazolyl, thiazolyl, thiadiazolyl, isothiazolyl, imidazolyl, triazolyl, tetrazolyl, pyridyl, pyridazinyl, pyrimidyl, benzofuryl, benzothienyl, benzimidazolyl, benzoxazolyl, benzothiazolyl, indolyl, and quinolyl.

The term "substituted" as used in the term "substituted aromatic or heteroaromatic group" herein signifies that one or more (for example one or two) substituents may be present, said substituents being selected from atoms and groups which, when present in the compound of formulas I or IA, do not prevent the compound of formulas I or IA from functioning as a potentiator of glutamate receptor function.

Examples of substituents which may be present in a substituted aromatic or heteroaromatic group include I, Br, Cl, F, NH_2, NO_2, cyano; hydroxy, (1-6C) alkyl, (1-6C)alkoxy, (2-6C)alkenyl; (2-6C)alkynyl; (3-8C)cycloalkyl; or halo(1-6C)alkyl.

The term (1-6C)alkyl includes (1-4C)alkyl. Particular values are methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, hexyl, heptyl, octyl, nonyl and decyl.

The term (2-6C)alkenyl includes (2-4C)alkenyl. Particular values are vinyl and prop-2-enyl.

The term (2-6C)alkynyl includes (3-4C)alkynyl. A particular value is prop-2-ynyl.

The term cycloalkyl, includes monocyclic and polycyclic groups. Particular values are (3-8C)cycloalkyl, (5-8C)cycloalkyl, and (4-6C)cycloalkyl, such as

cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, and bicyclo[2.2.2]octane.

The terms "halogen", "Hal" or "halide" include fluorine, chlorine, bromine and iodine unless otherwise specified.

The term halo(1-6C)alkyl includes fluoro(1-6C)alkyl, such as trifluoromethyl and 2,2,2-trifluoroethyl, and chloro(1-6C)alkyl such as chloromethyl.

The term (1-6C)alkoxy, refers to a straight or branched alkyl chain having from one to six carbon atoms attached to an oxygen atom and includes (1-4C)alkoxy. Examples of (1-6C)alkoxy are methoxy, ethoxy, propoxy, isopropoxy, isobutoxy, tert-butoxy, pentoxy, and the like.

The term thienyl includes thien-2-yl and thien-3-yl.

The term furyl includes fur-2-yl and fur-3-yl.

The term oxazolyl includes oxazol-2-yl, oxazol-4-yl and oxazol-5-yl.

The term isoxazolyl includes isoxazol-3-yl, isoxazol-4-yl and isoxazol-5-yl.

The term oxadiazolyl includes [1,2,4]oxadiazol-3-yl and [1,2,4]oxadiazol-5-yl.

The term pyrazolyl includes pyrazol-3-yl, pyrazol-4-yl and pyrazol-5-yl.

The term thiazolyl includes thiazol-2-yl, thiazol-4-yl and thiazol-5-yl.

The term thiadiazolyl includes [1,2,4]thiadiazol-3-yl, and [1,2,4]thiadiazol-5-yl.

The term isothiazolyl includes isothiazol-3-yl, isothiazol-4-yl and isothiazol-5-yl.

The term imidazolyl includes imidazol-2-yl, imidazolyl-4-yl and imidazolyl-5-yl.

The term triazolyl includes [1,2,4]triazol-3-yl and [1,2,4]triazol-5-yl.

The term tetrazolyl includes tetrazol-5-yl.

The term pyridyl includes pyrid-2-yl, pyrid-3-yl and pyrid-4-yl.

The term pyridazinyl includes pyridazin-3-yl, pyridazin-4-yl, pyridazin-5-yl and pyridazin-6-yl.

The term pyrimidyl includes pyrimidin-2-yl, pyrimidin-4-yl, pyrimidin-5-yl and pyrimidin-6-yl.

The term benzofuryl includes benzofur-2-yl and benzofur-3-yl.

The term benzothienyl includes benzothien-2-yl and benzothien-3-yl.

The term benzimidazolyl includes benzimidazol-2-yl.

The term benzoxazolyl includes benzoxazol-2-yl.

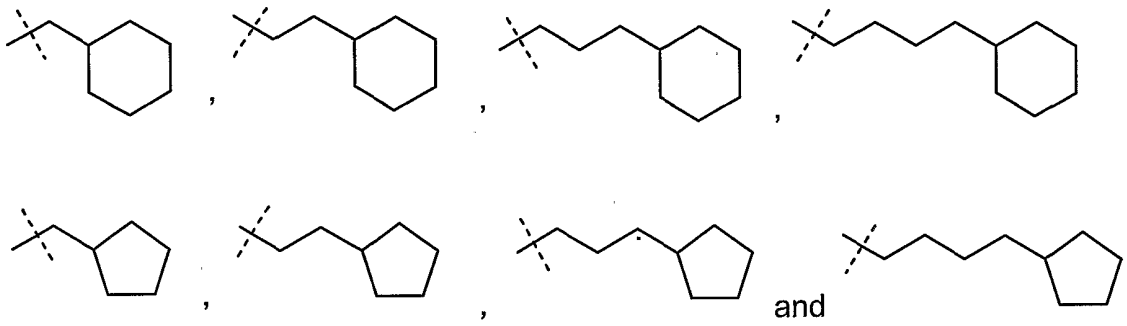
The term benzothiazolyl includes benzothiazol-2-yl.

The term indolyl includes indol-2-yl and indol-3-yl.

The term quinolyl includes quinol-2-yl.

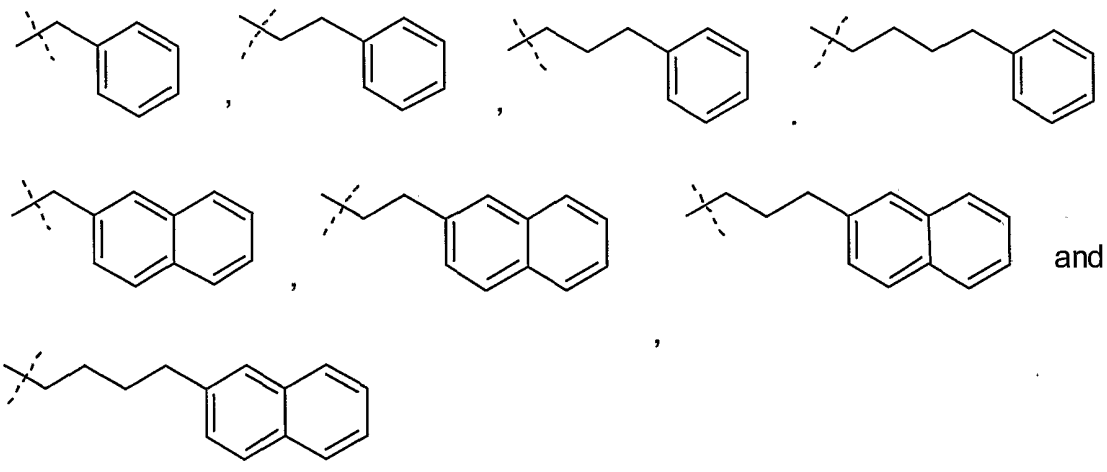
The term dihydrothiazolyl includes 4,5-dihydrothiazol-2-yl, and the term (1-4C)alkoxycarbonyldihydrothiazolyl includes 4-methoxycarbonyl-4,5-dihydrothiazol-2-yl.

The term alkylcycloalkyl includes -(1-4C)alkyl(4-6C)cycloalkyl and -(1-4C)alkyl(3-8C)cycloalkyl such as the following:



and

The term -(1-4C)alkylaromatic includes the following:

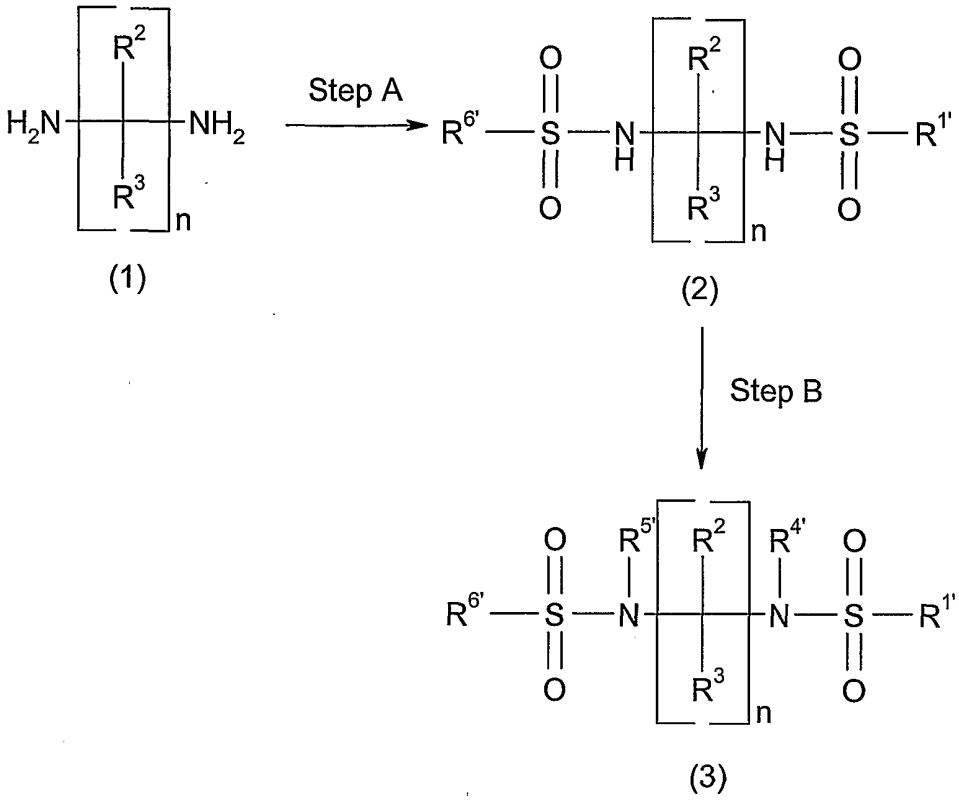


and

The compounds of formulas I and IA can be prepared by one of ordinary skill in the art, for example, following the procedures set forth below. The

reagents and starting materials are readily available to one of ordinary skill in the art. All substituents, unless otherwise specified are as previously defined.

Scheme I

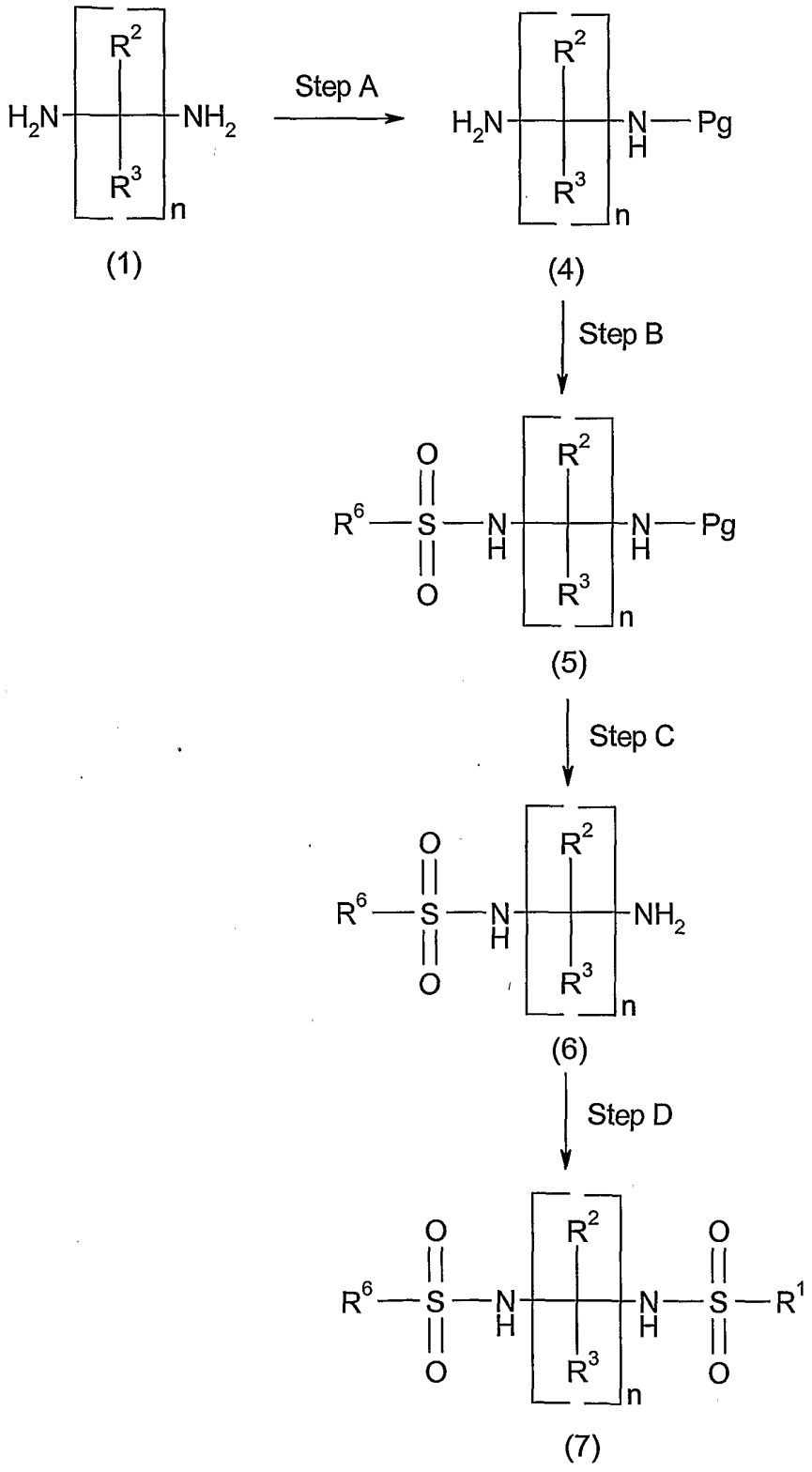


In Scheme I, step A, the diamino compound of structure (1) is sulfonylated under standard conditions to provide sulfonamide of structure (2). Examples of diamino compound (1) include but are not limited to 1,2-diaminoethane, 1,3-diaminopropane, 2,2-dimethyl-1,3-propanediamine, 1,4-butane, 1,5-diaminopentane, 1,6-diaminohexane, 1,7-diaminoheptane, 1,8-diaminooctane, 1,9-diaminononane, 1,10-diaminodecane. For example, the diamino compound (1) is dissolved in a suitable organic solvent or mixtures thereof. Examples of suitable organic solvents include methylene chloride, tetrahydrofuran, and the like. Solvent mixtures include, for example, THF/methylene chloride. The solution is treated with a slight excess of a suitable base. Examples of suitable bases include triethylamine, pyridine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and the like. To the stirring solution is added about 2 equivalents of a compound of either formula $LgSO_2R^{1'}$ or $LgSO_2R^{6'}$. It is understood that under these reaction conditions, $R^{1'}$ and $R^{6'}$ will be equivalent in the sulfonamide (2). In addition, under these

conditions, $R^{1'}$ and $R^{6'}$ each represent (1-6C)alkyl. The term "Lg" as used herein refers to a suitable leaving group. Examples of suitable leaving groups include, Cl, Br, and the like. Cl is the preferred leaving group. The reaction mixture is stirred for about 0.5 hours to about 16 hours. The sulfonamide (2) is then isolated and purified by techniques well known in the art, such as extraction techniques and chromatography. For example, the mixture is washed with 10% sodium bisulfate, the layers separated and the aqueous extracted with several times with a suitable organic solvent, such as methylene chloride. The organic extracts are combined, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The residue is then purified either by chromatography on silica gel with a suitable eluent such as ethyl acetate/hexane or methanol/methylene chloride, or by trituration with ethyl acetate to provide the sulfonamide (2).

In Scheme I, step B, the sulfonamide (2) is alkylated under standard conditions to provide the N-alkylated derivative of structure (3). For example, sulfonamide (2) is dissolved in a suitable organic solvent, such as tetrahydrofuran and treated with an equivalent of a suitable base, such as sodium bis(trimethylsilyl)amide. The reaction mixture is then treated with about 1.0 to about 1.1 equivalents of compound of formula Hal-$R^{4'}$ or of formula Hal-$R^{5'}$, wherein Hal represents Cl, Br, or I. $R^{4'}$ and $R^{5'}$ are equivalent and represent (1-6C)alkyl, (1-6C)alkylcycloalkyl, aryl, or (1-6C)alkylaryl. Examples of Hal-$R^{4'}$ or Hal-$R^{5'}$ include iodomethane, iodoethane, and the like. The reaction is stirred at a temperature of about 0°C to about 100°C for about one hour to about 48 hours. The product is then isolated by procedures well known in the art, such as extraction techniques and chromatography. For example, the reaction is diluted with a suitable organic solvent, such as ethyl acetate, washed with water, dried over anhydrous magnesium sulfate, filtered and concentrated under vacuum. The crude product is then purified by flash chromatography on silica gel with a suitable eluent, such as ethyl acetate/hexane to provide the purified N-alkylated derivative (3).

Scheme II



(1) (4) (5) (6) (7)

In Scheme II, step A, diamino compound (1) is protected with a suitable protecting group "Pg" under standard conditions to provide the mono-protected

compound of structure (4). As used herein the term "Pg" refers to suitable protecting groups on the amine which are commonly employed to block or protect the amine while reacting other functional groups on the compound. Examples of suitable protecting groups used to protect the amino group and their preparation are disclosed by T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, 1981, pages 218-287. Choice of the suitable protecting group used will depend upon the conditions that will be employed in subsequent reaction steps wherein protection is required, and is well within the knowledge of one of ordinary skill in the art. Preferred protecting groups are t-butoxycarbonyl also known as a BOC protecting group, and benzyloxycarbonyl, also known as CBz. For example, the diamino compound (1) is dissolved in a suitable organic solvent, such as methylene chloride and treated with about 1.2 equivalents of triethylamine. The solution is then cooled to about –5 °C and treated with one equivalent of as suitable protecting group, such as benzylchloroformate. The reaction mixture was warmed up to room temperature while stirring overnight. The reaction is then diluted with a suitable organic solvent, such as ethyl acetate, rinsed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to provide the crude mono-protected compound (4) wherein Pg represents a CBz protecting group. The crude material can then be purified by techniques well known in the art, such as flash chromatography on silica gel with a suitable eluent, such as methanol/methylene chloride.

In Scheme II, step B, the protected compound (4) is sulfonylated with a compound of formula $LgSO_2R^6$ to provide sulfonamide (5) in a manner analogous to the procedure described in Scheme I, step A.

In Scheme II, step C, sulfonamide (5) is deprotected under conditions well known in the art as disclosed by T. W. Greene, "Protective Groups in Organic Synthesis," John Wiley & Sons, 1981, pages 218-287 to provide the amino derivative of structure (6). The conditions employed for deprotection will depend upon the protecting group that needs to be removed and the substituents present on the compound itself which must remain unaffected by the deprotection reaction conditions, the conditions of which are well within the knowledge of one of ordinary skill in the art. For example, sulfonamide (5)

wherein Pg represents a CBz protecting group is dissolved in a suitable organic solvent, such as ethanol and treated with a catalytic amount of 10% palladium on carbon. The reaction mixture is placed under an atmosphere of hydrogen for 2 to 12 hours and then filtered through Celite®. The filtrate is concentrated under vacuum and the crude amino derivative (6) is purified using standard techniques well known in the art, such as chromatography on silica gel with a suitable eluent, such as methanol/methylene chloride.

In Scheme II, step D, the amino compound (6) is sulfonylated with a compound of formula $LgSO_2R^1$ to provide sulfonamide (7) in a manner analogous to the procedure described in Scheme I, step A.

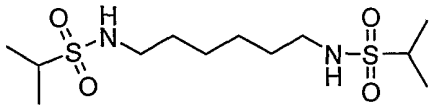
Sulfonamide (7) can then be N-alkylated with a compound of formula Hal-$R^{4'}$ or of formula Hal-$R^{5'}$ in a manner analogous to the procedure described in Scheme I, step B.

The following examples further illustrate the invention and represent typical syntheses of the compounds of formulas I and IA as described generally above. The reagents and starting materials are readily available to one of ordinary skill in the art. As used herein, the following terms have the meanings indicated: "eq" refers to equivalents; "g" refers to grams; "mg" refers to milligrams; "kPa" refers to kilopascals; "L" refers to liters; "mL" refers to milliliters; "μL" refers to microliters; "mol" refers to moles; "mmol" refers to millimoles; "psi" refers to pounds per square inch; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ"refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to methyl sulfoxide; "LDA" refers to lithium diisopropylamide; "EtOAc" refers to ethyl acetate; "aq" refers to aqueous; "iPrOAc" refers to isopropyl acetate; "$PdCl_2$(dppf)" refers to [1,1' bis(diphenylphosphino)-ferrocene] dichloropalladium (II); "methyl DAST" refers to dimethylaminosulfur trifluoride, "DAST" refers to diethylaminosulfur trifluoride, "DBU" refers to 1,8-diazabicyclo[5.4.0]undec-7-ene; "TFA" refers to

trifluoroacetic acid; "DME" refers to dimethoxyethane; "9-BBN" refers 9-borabicyclo[3.3.1]nonane; and "RT" refers to room temperature.

Example 1

Preparation of [(methylethyl)sulfonyl](6-{[(methylethyl)sulfonyl]amino}hexyl)amine.



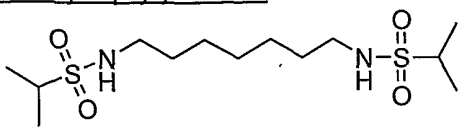
Into a 50 mL single neck flask was placed 1,6-diaminohexane (1 g, 8.61 mmol), DBU, (3.1 mL, 20.66 mmol), and isopropylsulfonyl chloride (2.13 mL, 18.94 mmol) in THF : methylene chloride (10:10 mL), and the mixture was warmed from 0 °C to RT while stirring for 12 hours. The reaction was poured into 1M HCl. The product was extracted with methylene chloride (50 mL) and the organic layer was separated and washed with water (2 X 50 mL), dried over anhydrous sodium sulfate, filtered, and concentrated under reduced vacuum. The resulting semi-solid was purified via trituration with Hexanes/EtOAc 1:2 to provide the title compound (2.21 g, 78%) as a white crystalline solid. Electron spray M.S. 327 (M*-1).

Analysis for $C_{12}H_{28}N_2O_4S_2$:

Theory:	C, 43.87	H, 8.59	N, 8.53
Found:	C, 43.48	H, 8.02	N, 8.35

Example 2

Preparation of [(methylethyl)sulfonyl](7-{[(methylethyl)sulfonyl]amino}heptyl)amine.

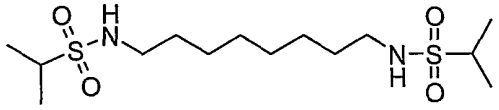


In a manner analogous to the procedure set forth in example 1, 1,7-diaminoheptane (1 g, 7.68 mmol), DBU (2.76 mL, 18.43 mmol), and isopropylsulfonyl chloride (1.9 mL, 16.9 mmol) were combined to provide the title compound (2.05 g, 78%) as a white crystalline solid. Electron spray M.S. 341 (M*-1).

Analysis for $C_{13}H_{30}N_2O_4S_2$:
Theory: C, 45.58 H, 8.82 N, 8.17
Found: C, 45.30 H, 8.60 N, 8.08

Example 3

Preparation of [(methylethyl)sulfonyl](8-{[(methylethyl)sulfonyl]amino}octyl)amine.

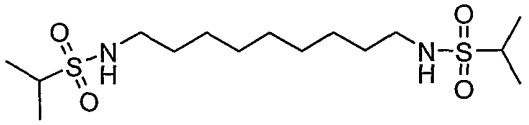


In a manner analogous to the procedure set forth in example 1, 1,8-diaminooctane (1 g, 6.93 mmol), DBU (2.5 mL, 16.63 mmol), and isopropylsulfonyl chloride (1.7 mL, 15.25 mmol) were combined to provide the title compound (1.5 g, 60%) as a white crystalline solid. Electron spray M.S. 355 (M*-1).

Analysis for $C_{14}H_{32}N_2O_4S_2$:
Theory: C, 47.16 H, 9.05 N, 7.86
Found: C, 47.10 H, 9.23 N, 7.88

Example 4

Preparation of [(methylethyl)sulfonyl](9-{[(methylethyl)sulfonyl]amino}nonyl)amine.

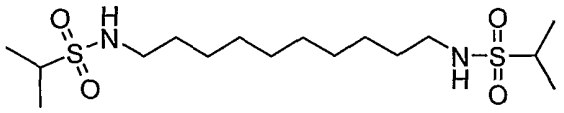


In a manner analogous to the procedure set forth in example 1, 1,9-diaminononane (1 g, 6.32 mmol), DBU (2.27 mL, 15.17 mmol), and isopropylsulfonyl chloride (1.56 mL, 13.9 mmol) were combined to provide the title compound (1.9 g, 84%) as a white crystalline solid. Electron spray M.S. 369(M*-1).

Analysis for $C_{15}H_{34}N_2O_4S_2$:
Theory: C, 48.61 H, 9.25 N, 7.56
Found: C, 48.00 H, 8.75 N, 7.43

Example 5

Preparation of [(methylethyl)sulfonyl](10-{[(methylethyl)sulfonyl]amino}decyl)amine [512511].



In a manner analogous to the procedure set forth in example 1, 10-diaminodecane (1 g, 5.81 mmol), DBU (2.1 mL, 13.94 mmol), and isopropylsulfonyl chloride (1.44 mL, 12.78 mmol) were combined to provide the title compound (1.47 g, 68%) as a white crystalline solid. Electron spray M.S. 383(M*-1).

Analysis for $C_{16}H_{36}N_2O_4S_2$:

Theory:	C, 49.97	H, 9.43	N, 7.28
Found:	C, 49.61	H, 9.15	N, 7.23

The ability of compounds of formulas I and IA to potentiate glutamate receptor-mediated response may be determined using fluorescent calcium indicator dyes (Molecular Probes, Eugene, Oregon, Fluo-3) and by measuring glutamate-evoked efflux of calcium into GluR4 transfected HEK293 cells, as described in more detail below.

In one test, 96 well plates containing confluent monolayers of HEK 293 cells stably expressing human GluR4B (obtained as described in European Patent Application Publication Number EP-A1-583917) are prepared. The tissue culture medium in the wells is then discarded, and the wells are each washed once with 200 µl of buffer (glucose, 10mM, sodium chloride, 138mM, magnesium chloride, 1mM, potassium chloride, 5mM, calcium chloride, 5mM, N-[2-hydroxyethyl]-piperazine-N-[2-ethanesulfonic acid], 10mM, to pH 7.1 to 7.3). The plates are then incubated for 60 minutes in the dark with 20 µM Fluo3-AM dye (obtained from Molecular Probes Inc., Eugene, Oregon) in buffer in each well. After the incubation, each well is washed once with 100 µl buffer, 200 µl of buffer is added and the plates are incubated for 30 minutes.

Solutions for use in the test are also prepared as follows. 30 µM, 10 µM, 3 µM and 1 µM dilutions of test compound are prepared using buffer from a 10 mM solution of test compound in DMSO. 100 µM cyclothiazide solution is prepared by adding 3 µl of 100 mM cyclothiazide to 3 mL of buffer. Control buffer solution is prepared by adding 1.5 µl DMSO to 498.5 µl of buffer.

Each test is then performed as follows. 200 µl of control buffer in each well is discarded and replaced with 45 µl of control buffer solution. A baseline fluorescent measurement is taken using a FLUOROSKAN II fluorimeter (Obtained from Labsystems, Needham Heights, MA, USA, a Division of Life Sciences International Plc). The buffer is then removed and replaced with 45 µl of buffer and 45 µl of test compound in buffer in appropriate wells. A second fluorescent reading is taken after 5 minutes incubation. 15 µl of 400 µM glutamate solution is then added to each well (final glutamate concentration 100 µM), and a third reading is taken. The activities of test compounds and cyclothiazide solutions are determined by subtracting the second from the third reading (fluorescence due to addition of glutamate in the presence or absence of test compound or cyclothiazide) and are expressed relative to enhance fluorescence produced by 100 µM cyclothiazide.

In another test, HEK293 cells stably expressing human GluR4 (obtained as described in European Patent Application Publication No. EP-A1-0583917) are used in the electrophysiological characterization of AMPA receptor potentiators. The extracellular recording solution contains (in mM): 140 NaCl, 5 KCl, 10 HEPES, 1 $MgCl_2$, 2 $CaCl_2$, 10 glucose, pH = 7.4 with NaOH, 295 mOsm kg-1. The intracellular recording solution contains (in mM): 140 CsCl, 1 $MgCl_2$, 10 HEPES, (N-[2-hydroxyethyl]piperazine-N1-[2-ethanesulfonic acid]) 10 EGTA (ethylene-bis(oxyethylene-nitrilo)tetraacetic acid), pH = 7.2 with CsOH, 295 mOsm kg-1. With these solutions, recording pipettes have a resistance of 2-3 MΩ. Using the whole-cell voltage clamp technique (Hamill et al.(1981)Pflügers Arch., 391: 85-100), cells are voltage-clamped at -60mV and control current responses to 1 mM glutamate are evoked. Responses to 1 mM glutamate are then determined in the presence of test compound. Compounds are deemed active in this test if, at a test concentration of 10 µM or less, they produce a greater than 10% increase in the value of the current evoked by 1 mM glutamate.

In order to determine the potency of test compounds, the concentration of the test compound, both in the bathing solution and co-applied with glutamate, is increased in half log units until the maximum effect was seen. Data collected in this manner are fit to the Hill equation, yielding an EC_{50} value, indicative of the potency of the test compound. Reversibility of test compound activity is

determined by assessing control glutamate 1mM responses. Once the control responses to the glutamate challenge are re-established, the potentiation of these responses by 100 μM cyclothiazide is determined by its inclusion in both the bathing solution and the glutamate-containing solution. In this manner, the efficacy of the test compound relative to that of cyclothiazide can be determined.

Behavioral despair models such as the forced swim test (FST) and tail suspension test (TST) are widely used to detect antidepressant agents [see for example, Borsini and Meli, *Psychopharmacology*, 94, 147-160 (1988)]. 512511 was evaluated using the forced swim test as follows:

Animals: Male NIH-Swiss mice (Harlan Sprague-Dawley) weighing between 25-30 g were used in the FST. Group housed animals were removed from the vivarium to the testing area in their own cages and allowed to adapt to the new environment for at least 1 hour before testing. All compounds and vehicle were administered orally 1 hour before the test except as indicated. Imipramine was injected intraperitoneally.

Forced Swim Test (mice): Mice were placed in a cylinder (diameter: 10 cm; height: 25 cm) filled with 6 cm of water (22-25°C) for six min. The duration of immobility during the last four min of the six min period test was scored. A mouse was recorded as immobile when floating motionless or making only those movements necessary to keep its head above water.

Statistical analysis: Data were analyzed by ANOVA followed by Dunnett's two tailed test for comparison of treated groups to vehicle controls. An asterisk (*) indicat statistical significance ($p < 0.05$).

Results: 512511 significantly reduced the duration of immobility in the FST. The minimum effective dose (MED) was 5 μg/kg in mice when administered 60 minutes prior to testing (p.o.) (Fig. 1).

According to another aspect, the present invention provides a pharmaceutical composition, which comprises a compound of formula I or IA, or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

The pharmaceutical compositions are prepared by known procedures using well-known and readily available ingredients. In making the compositions of the present invention, the active ingredient will usually be mixed with a carrier, or diluted by a carrier, or enclosed within a carrier, and may be in the form of a capsule, sachet, paper, or other container. When the carrier serves as a diluent, it may be a solid, semi-solid, or liquid material which acts as a vehicle, excipient, or medium for the active ingredient. The compositions can be in the form of tablets, pills, powders, lozenges, sachets, cachets, elixirs, suspensions, emulsions, solutions, syrups, aerosols, ointments containing, for example, up to 10% by weight of active compound, soft and hard gelatin capsules, suppositories, sterile injectable solutions, and sterile packaged powders.

Some examples of suitable carriers, excipients, and diluents include lactose, dextrose, sucrose, sorbitol, mannitol, starches, gum, acacia, calcium phosphate, alginates, tragcanth, gelatin, calcium silicate, micro-crystalline cellulose, polyvinylpyrrolidone, cellulose, water syrup, methyl cellulose, methyl and propyl hydroxybenzoates, talc, magnesium stearate, and mineral oil. The formulations can additionally include lubricating agents, wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents, or flavoring agents. Compositions of the invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing procedures well known in the art.

The compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 mg to about 500 mg, more preferably about 5 mg to about 300 mg (for example 25 mg) of the active ingredient. The term "unit dosage form" refers to a physically discrete unit suitable as unitary dosages for human subjects and other mammals, each unit containing a predetermined quantity of active material calculated to produce the desired therapeutic effect, in association with a suitable pharmaceutical carrier, diluent, or excipient. The following formulation examples are illustrative only and are not intended to limit the scope of the invention in any way.

Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

	Quantify (mg/capsule)
Active Ingredient	250
Starch, dried	200
Magnesium Stearate	10
Total	**460**

The above ingredients are mixed and filled into hard gelatin capsules in 460 mg quantities.

Formulation 2

Tablets each containing 60 mg of active ingredient are made as follows:

	Quantity (mg/tablet)
Active Ingredient	60
Starch	45
Microcrystalline Cellulose	35
Polyvinylpyrrolidone	4
Sodium Carboxymethyl Starch	4.5
Magnesium Stearate	0.5
Talc	1
Total	**150**

The active ingredient, starch, and cellulose are passed through a No. 45 mesh U.S. sieve and mixed thoroughly. The solution of polyvinylpyrrolidone is mixed with the resultant powders which are then passed through a No. 14 mesh U.S. sieve. The granules so produced are dried at 50°C and passed through a No. 18 mesh U.S. sieve. The sodium carboxymethyl starch, magnesium stearate, and talc, previously passed through a No. 60 mesh U.S. sieve, are then added to the granules which, after mixing, are compressed on a tablet machine to yield tablets each weighing 150 mg.

As used herein the term "patient" refers to a mammal, such as a mouse, guinea pig, rat, dog or human. It is understood that the preferred patient is a human.

As used herein, the terms "treating" or "to treat" each mean to alleviate symptoms, eliminate the causation either on a temporary or permanent basis, or to prevent or slow the appearance of symptoms of the named disorder. As such, the methods of this invention encompass both therapeutic and prophylactic administration.

As used herein, the term "effective amount" refers to the amount of a compound of formulas I or IA which is effective, upon single or multiple dose administration to a patient, in treating the patient suffering from the named disorder.

An effective amount can be readily determined by the attending diagnostician, as one skilled in the art, by the use of known techniques and by observing results obtained under analogous circumstances. In determining the effective amount or dose, a number of factors are considered by the attending diagnostician, including, but not limited to: the species of mammal; its size, age, and general health; the specific disease or disorder involved; the degree of or involvement or the severity of the disease or disorder; the response of the individual patient; the particular compound administered; the mode of administration; the bioavailability characteristics of the preparation administered; the dose regimen selected; the use of concomitant medication; and other relevant circumstances.

The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, bucal or intranasal routes. Alternatively, the compound may be administered by continuous infusion. A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of the active compound of this invention. Preferably, daily doses will be about 0.05 mg/kg to about 50 mg/kg, more preferably from about 0.1 mg/kg to about 25 mg/kg.

The compounds of formulas I or IA as a class are particularly useful in the treatment methods of the present invention, but certain groups, substituents, and configurations are preferred for compounds of formulas I or IA. The following paragraphs describe such preferred groups, substituents, and configurations. It will be understood that these preferences are applicable both to the treatment methods and to the new compounds of the present invention.

a) R^1 is preferably (1-6C)alkyl, most preferably methyl, ethyl, propyl or isopropyl, and it is most especially preferred that R^1 is isopropyl;

b) R^2 is preferably hydrogen or methyl with hydrogen be most preferred;

c) R^3 is preferably hydrogen or methyl with hydrogen being most preferred;

d) R^4 is preferably hydrogen or methyl with hydrogen being preferred;

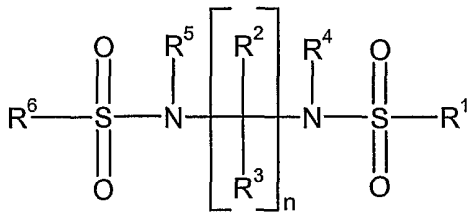
e) R^5 is preferably hydrogen or methyl with hydrogen being preferred;

f) R^6 is preferably (1-6C)alkyl. most preferably methyl, ethyl, propyl or isopropyl, and it is most especially preferred that R^6 is isopropyl;

g) n is preferably 6, 7, 8, 9, or 10, with 10 being preferred.

WE CLAIM:

1. A method of potentiating glutamate receptor function in a patient, which comprises administering to said patient an effective amount of a compound of formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

R^6 represents (1-6C)alkyl;

n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof.

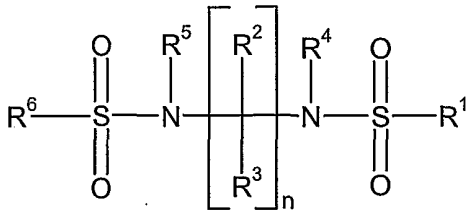
2. A method according to claim 1 wherein R^1 represents (1-6C) alkyl.

3. A method according to claim 1 or 2 wherein R^6 represents isopropyl.

4. A method according to any one of claims 1 to 3 wherein n is an integer 6, 7, 8, 9, or 10.

5. A method according to any one of claims 1 to 4 wherein R^1 represents isopropyl.

6. A method of treating depression, Alzheimer's disease, cognitive disorders, cognitive deficits associated with schizophrenia, or schizophrenia in a patient, which comprises administering to a patient in need thereof an effective amount of a compound of formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

R^6 represents (1-6C)alkyl;

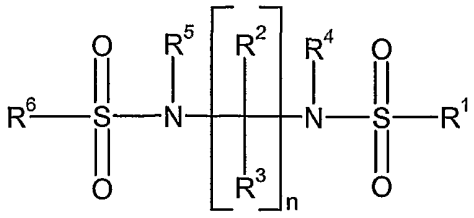
n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof.

7. A pharmaceutical composition, which comprises a compound as claimed in claim 1 and a pharmaceutically acceptable diluent or carrier.

8. An article of manufacture comprising packaging material and a compound of formula



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

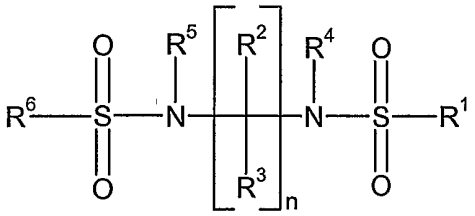
R^6 represents (1-6C)alkyl;

n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof, contained within said packaging material, wherein said packaging material comprises a label which indicates that said compound can be used for treating at least one of the following; Alzheimer's disease, schizophrenia, cognitive deficits associated with schizophrenia, depression, and cognitive disorders.

9. A compound of the formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each independently represent hydrogen, (1-4C)alkyl, F, aryl, or (1-6C)alkylaryl;

R^4 and R^5 each independently represent hydrogen;

R^6 represents (1-6C)alkyl;

n is an integer 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof.

10. A compound according to claim 9 wherein R^2 and R^3 are each hydrogen.

11. A compound according to any one of claims 9 to 10 wherein R^1 represents (1-6C)alkyl.

12. A compound according to any one of claims 9 to 10 wherein R^1 and R^6 each represent methyl, ethyl, propyl, or isopropyl.

13. A compound according to any one of claims 9 to 10 wherein R^1 and R^6 each represent isopropyl.

14. A compound according to any one of claims 9 to 13 wherein n is 6.

15. A compound according to any one of claims 9 to 13 wherein n is 7.

16. A compound according to any one of claims 9 to 13 wherien n is 8.

17. A compound according to any one of claims 9 to 13 wherien n is 9.

18. A compound according to any one of claims 9 to 13 wherien n is 10.

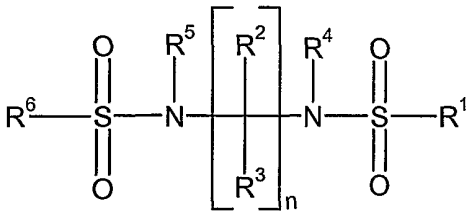
19. A compound selected from the group consisting of:

[(methylethyl)sulfonyl](6-{[(methylethyl)sulfonyl]amino}hexyl)amine;

[(methylethyl)sulfonyl](7-{[(methylethyl)sulfonyl]amino}heptyl)amine;

[(methylethyl)sulfonyl](8-{[(methylethyl)sulfonyl]amino}octyl)amine; and [(methylethyl)sulfonyl](10-{[(methylethyl)sulfonyl]amino}decyl)amine; or a pharmaceutically acceptable salt thereof.

20. The use of a compound of formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

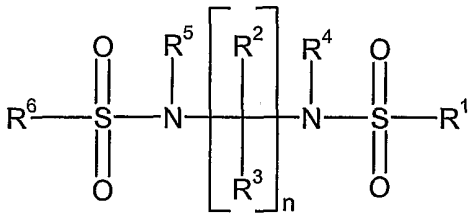
R^6 represents (1-6C)alkyl;

n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for potentiating glutamate receptor function.

21. The use of a compound of formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

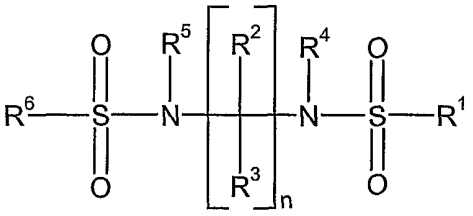
R^6 represents (1-6C)alkyl;

n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof, for the manufacture of a medicament for treating depression in a patient.

22. A compound of formula:



wherein

R^1 represents (1-6C)alkyl, (2-6C)alkenyl, or NR^7R^8;

R^2 and R^3 each represent hydrogen;

R^4 and R^5 each independently represent hydrogen;

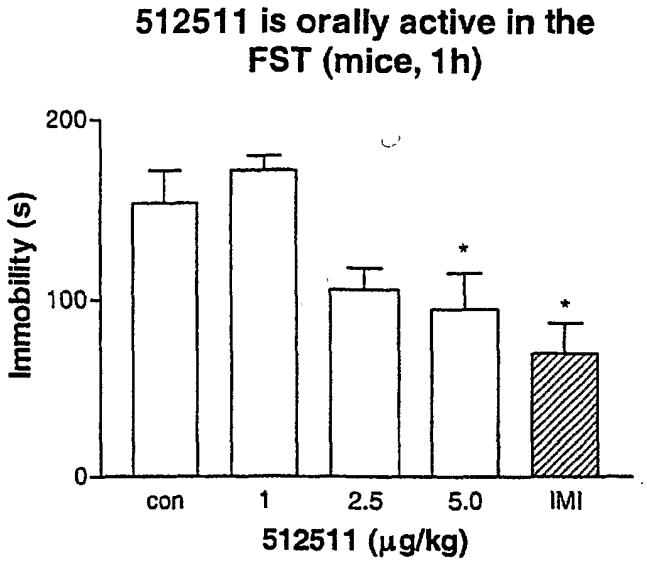
R^6 represents (1-6C)alkyl;

n is an integer 6, 7, 8, 9, 10, 11, 12, 13, or 14; and

R^7 and R^8 each independently represent hydrogen or (1-4C)alkyl;

or a pharmaceutically acceptable salt thereof, for use as a pharmaceutical.

Figure 1


512511 is orally active in the FST (mice, 1h)
Immobility (s)
200
100
0
con
1
2.5
5.0
IMI
*
*
512511 (µg/kg)