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SUPERINDUSTRIA Y COMERCIO
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Tramite : 011 PCT-PATENT 379 FASE NACI 352 DESISTIMI
Dependencia: 2000 DIVISION DE NUEVAS CREACIONES

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIC
DIVISION DE NUEVAS CREACIONES
E. S. D.

Re: P1.-**ELI LILLY AND COMPANY**.-Solicitud de Patente de Invención en Fase Nacional PCT para **"DERIVADOS SULFONAMIDA"**.-Clase **A61K 31/18**.-Expediente número **02-103.448**.-

1. Me refiero a mi memorial de fecha 7 de Enero de 2004.

2. Por medio del presente atentamente me permito manifestar a usted que, debidamente autorizado por mis representados, desisto de la solicitud de patente de invención arriba nombrada.

Señor Superintendente,

JOSE ANTONIO LLOREDA
T. P. 10.784
Código 231

NOTARIA SEXTA DE BOGOTA
RECONOCIMIENTO Y PRESENTACION PERSONAL
Bogotá D.C. 31 MAYO 2004
Ante mi JUEZ MANUEL BOTERO MEDINA
NOTARIO SEXTO DEL CIRCULO DE BOGOTA

Compareció(ron): JOSE ANTONIO Lloreda
quien(es) se identificó(aron) con C.C.
No. 17.159.681 de
y T.P. 10.784
y dijo(eron) que el contenido de este escrito es cierto y que la(s) firma(s) que aparece(n) en el presente documento es(son) suya(s) y que el contenido del mismo es cierto. En constancia se firma esta diligencia.

JOSE ANTONIO LLOREDA
C.C. No. 17.159.681 de Bogotá

Industria y Comercio
SUPERINTENDENCIA

126124

DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. **02-103448**

EL EXTRACTO DE LA PRESENTE SOLICITUD DE **PATENTE DE INVENCION - PCT** FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No **532**, DE FECHA **30** DE **SEPTIEMBRE** DE **2003**, EL TERMINO HABIL SEÑALADO POR LA LEY EXPIRA EL **30** DE **DICIEMBRE** DE **2003**.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI ____ _____ NO ___ X____

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

125

2020
Bogotá, DC, 15 de diciembre de 2006

Apoderado: Alicial Lloreda Ricaurte Oficio: 0419

ASUNTO Radicación: 02-103448
Trámite 002
Evento 001
Actuación 430
Folios

Como resultado del examen de fondo, realizado con fundamento en el artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica:

Documentos estudiados:

◆Capitulo descriptivo, folios 26 a 67;
◆Capitulo reivindicatorio modificado, folios 107 a 119;
◆Solicitud PCT/US01/11747 en face nacional;
◆ Solicitud del examen de patentabilidad, folios 202, 203 y 204.

bjeto de la invención:

El título de la invención "DERIVADOS DE SULFONAMIDA".
Tienencomo objeto el compuesto {(2R)-2-[4-(-4-{2-[(metilsulfonil)amino]etil}fenil]propil}[(metiletil)sulfonil]amino

El campo de la invención, según la Clasificación Internacional de Patentes: C07C311/05A61K 31/41 // 31/4196

Claridad de la solicitud:

En el artículo 30 de la Decisión 486 de la Comisión de la Comunidad Andina se establece: *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

Lo que se afirma en el memorial del día 2003-06-11, que se modifica el capitulo reivindicatorio "quedando con 22 reivindicaciones", no es cierto, tenía 22 y se aumento a 29.

-Las reivindicaciones 8 a 12, que se refieren a un producto que no esta definid como tal, no es claro es una mezcla de las formas universales de comercialización de medicamentos con método terapéutico, de acuerdo con el efecto farmacológico divulgado en WO 0006537.

Las composiciones 13 a 15, 23, 24, que reivindican una composición y se le caracteriza por la cantidad de microgramos que debe comprender de un principio activo, eso no es una invención porque la cantidad de principio activo en cualquier composición no es de la invención o hace parte de la imaginación de la mente humana, es solo regida por la naturaleza de la molécula quien da la ventana terapéutica, la concentración mínima efectiva, la toxicidad, y todas la propiedades fisicoquímicas y farmacológicas, no es producto de la mente humana conferirle tales propiedades por libre albedrío.
-Las reivindicaciones 28 y 29 reclaman un compuesto y lo caracterizan por el uso o el efecto terapéutico a conseguir; cuando lo correcto es caracterizarlo por su estructura química, máxime cuando ya es conocido en WO 0006537.

Reivindicaciones de uso:

De acuerdo con la legislación colombiana el uso que se reclama en las reivindicaciones 25 a 27 no se consideran para protección por patente, como se lee en el artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina"... Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología..."; AQUÍ NO se hace alusión al uso.
Continuando con la última parte del Artículo 14"... (Los Países Miembros otorgarán patentes para las invenciones sean de **productos o procedimientos** en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial." El hecho que se diga que el producto o el procedimiento tengan aplicación industrial no quiere decir que la aplicación industrial sea susceptible de patente.

Así mismo, citando **completamente** el artículo 19 este reza: " Se considerará que una **invención** *(léase producto o procedimiento)* es susceptible de aplicación industrial *(una característica de la invención)* cuando su objeto puede ser producido o utilizado en cualquier clase de industria, entendiéndose por industria la referida a cualquier actividad productiva, incluidos los servicios." Esta diciendo que una invención, producto o procedimiento, debe servir para algo. En ningún momento se dice que un uso pueda ser protegido como patente.

El artículo 16 dice: " Los productos o procedimientos *(o sea, los inventos, nótese que nunca se refieren a nada diferente)* ya patentados comprendidos en el estado de la técnica de conformidad con el Artículo 21 de la presente Decisión, no serán objeto de nueva patente por el simple hecho de atribuirse un uso distinto al originalmente comprendido por la patente inicial." Nunca se refieren a una protección para el uso, como erróneamente se podría interpretar. Se trata de no conceder nueva patente a un invento (exclusivamente productos o procedimientos) al que se le ha encontrado nueva función, pero que se trata exactamente del mismo producto o procedimiento. Es decir, si el compuesto, aparato, etc. o método ya esta dentro del estado de la técnica, el hecho que se haya descubierto una nueva aplicación para el mismo compuesto, aparato, etc. o método, implica que no es merecedor de nueva patente, o que el nuevo uso le reestablezca la novedad. En ningún caso se dice que se esta protegiendo el uso. Simplemente se dice que el producto o procedimiento ya esta dentro del estado de la técnica y una utilización diferente no esta contemplada para permitir conceder patente al producto o al procedimiento nuevamente.

Los usos o segundos usos no son patentables, de conformidad con la sentencia del TJAC 89-AI-2000, los usos en general no son patentables.

Excepciones de Patentabilidad:

El artículo 20 de la Decisión 486 de la Comisión de la Comunidad Andina establece en su inciso d) que no serán patentables: "*los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales*".

Las reivindicaciones 4 a 7, reclaman un método para tratamiento del cuerpo humano o animal, el cual incluye la administración de un compuesto de la presente solicitud en una cantidad eficaz, por lo tanto están inmersas bajo el alcance del artículo 20 de la Decisión 486.

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Determinación del estad de la técnica:

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El artículo 16 de la Decisión 486 de la Comisión establece: *"El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*
Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40."

Se realizo la búsqueda del estado de la técnica con fecha anterior a la fecha de presentación de la primera solicitud, de la cual se reivindica prioridad, 12 de enero1999. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

No.	Documento No.	Título	*Fecha de Publicación
D1	WO 0006537	N-subtituted sulfonamide Derivatives	10-feb-2000

Evaluación de los requisitos de patentabilidad:

El artículo 14 de la Decisión 486 de la Comisión de la Comunidad Andina establece: *"Los Países Miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial."*

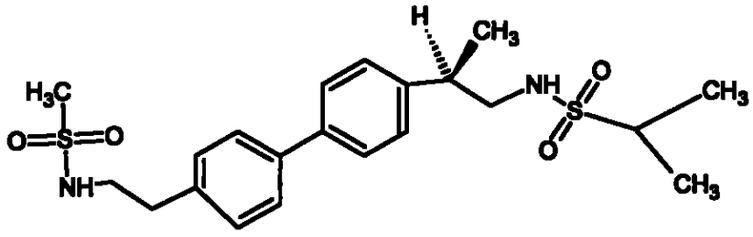
En cumplimiento con este artículo, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

Evaluación de la Novedad:

El art.16 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Una invención se considerará nueva cuando no está comprendida en el estado de la técnica.*" "*El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.*

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40." .

La solicitud en estudio reclama el compuesto de formula:



Y además sus sales de ácido fisiológicamente compatibles.
N-2-(4-(4-(2-metansulfonamido etil)fenil)fenil)propil-2-propansulfonamida, sus sales farmaceuticament aceptables, igualmente esta escrito que los esteroisomeros, los enatiomeros y también el desarrollo de formulas químicas para obtener determinado enantiomero enriquecido, también los método más efectivos para obtener los isomeros puros, usando dichas técnicas estándar, como cromatografía líquida quiral o cualquier técnica de síntesis quiral, para la resolución de racematos, además en esta anterioridad se estudian los efectos farmacológicos de esta clase de derivados sulfonamida, por lo tanto no es la primera ves que se sabe que este compuesto posee centros quirales, y que posee enantiomeros, y que tienen el efecto potenciador sobre el receptor de función glutamato, por lo tanto carece de novedad.

Evaluación del Nivel Inventivo:

El art. 18 de la Decisión 486 de la Comisión de la Comunidad Andina establece: "*Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica.*"

Observando los documento D1 vemos que el compuesto no es nuevo, que se le pretende restaurar la novedad al compuesto argumentando que es un enantiomero, pero la molécula ya es conocida en el estado de la técnica, D1 ejemplo 51, además, vemos que el efecto farmacológico es el conocido en el estado de la técnica, solamente ahora por la resolución de la mezcla racemica por los métodos estándar, y luego mediante estudios conocidos identificar cual es el enantiomero de mayor actividad, ese descubrimiento no le restablece la novedad a la molécula, y además no se modifica el efecto farmacológico, y para una persona normalmente versada en la materia sabe que cualquier compuesto que tenga un carbono quiral tiene enantiomeros. Por otro lado se conocen múltiples métodos de resolución de enantiomeros, además se sabe por la naturaleza misma por ejemplo en el caso de los aminoácidos que siempre hay un enantiomero de mayor actividad, de otro lado el hombre no inventa que determinado enantiomero tenga mayor actividad, porque si fuese así el hombre simplemente los separaría y les conferiría el mismo efecto por separado, no tendría que descubrirlo, entonces esta oficina considera que se deriva evidentemente del estadote la técnica, porque para una persona del nivel medio del arte, puede separar una mezcla racémica y esperar que una de los enantiomeros tenga una mayor actividad pero conservando su efecto farmacológico como la anterioridad D1 y dicho descubrimiento seria una solución original, porque no se aparta del camino previsto por lo conocido para los enantiomeros puro o enriquecidos, por lo tanto se considera que, la presente solicitud no posee nivel inventivo.

En conclusión los requisitos de Patentabilidad de la presente solicitud **están** afectados así:

No.	Documento	Reivindicaiones	Requisito que afecta
D1.		1 a 29	Nivel inventivo

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2,literal e), del capítulo quinto del título primero de la circular única No. 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de División de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista, de fecha 12 ENE 2007.

CONCEPTO TÉCNICO No. 1983	EXAMINADOR TÉCNICO Código No. 202012

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PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6:
C07C 303/00, 307/00, 309/00, 311/00, A61K 31/00, 31/34, 31/38, 31/395, 31/41, 31/42, 31/425, 31/44, 31/445, 31/455, 31/495, 31/505, 31/535, 31/54, C07D 207/00, 211/06, 213/24, 239/02, 257/04, 261/02, 271/06, 277/02, 277/62, 279/02, 295/00, 307/02, 333/04, 333/52, 401/12, 409/12

A1

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(30) Priority Data:
60/094,921 31 July 1998 (31.07.98) US

(71) Applicant *(for all designated States except US)*: ELI LILLY AND COMPANY [US/US]; Lilly Corporate Center, Indianapolis, IN 46285 (US).

(72) Inventors; and

(75) Inventors/Applicants *(for US only)*: ARNOLD, Macklin, Brian [US/US]; 6667 North Lawson Road, Morgantown, IN 46160 (US). JONES, Winton, Dennis [US/US]; 1227 East 126th Street, Carmel, IN 46033 (US). ORNSTEIN, Paul, Leslie [US/US]; 10441 Bosshan Court, Carmel, IN 46032 (US). ZARRINMAYEH, Hamidah [IR/US]; 924 Sable Run, Carmel, IN 46032 (US). ZIMMERMAN, Dennis, Michael [US/US]; 10343 Oak Ridge Drive, Zionsville, IN 46077 (US).

(74) Agents: LENTZ, Nelsen, L. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published
With international search report.

(54) Title: N-SUBSTITUTED SULFONAMIDE DERIVATIVES

(57) Abstract

The present invention provides certain N-substituted sulfonamide derivatives 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.

N-SUBSTITUTED SULFONAMIDE DERIVATIVES

The present invention relates to the potentiation of glutamate receptor function using certain N-substituted sulfonamide derivatives. It also relates to novel N-substituted sulfonamide derivatives, to processes for their preparation and to pharmaceutical compositions containing them.

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. The physiological implications of rapid desensitization, and deactivation if any, are unknown.

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. Compounds which potentiate AMPA receptors, like cyclothiazide, are often referred to as ampakines.

International Patent Application Publication Number WO 9625926 discloses a group of phenylthioalkylsulfonamides, S-oxides and homologs which are said to potentiate membrane currents induced by kainic acid and AMPA.

United States Patent Specification Number 3,143,549 discloses certain phenylalkylsulfamides, including 1-methyl-2-phenylethyl dimethylsulfamide. The compounds are said to have central nervous system activity, in particular anti-anxiety and tranquilizing properties.

United States Patent Specification Number 3,267,139 discloses certain N'-trimethylacetyl-N-phenylalkylsulfamides and -phenylcyclopropylsulfamides having central nervous system activity and anticonvulsant activity. The compounds are also said to produce Parkinson-like symptoms in experimental animals.

United States Patent Specification Number 3,860,723 discloses a method of increasing feed intake of healthy animals using certain phenylalkylsulfamides.

Foye *et al.*, *J. Pharm. Sci.* (1971), 60(7), 1095-6 discloses certain phenylalkyl methylsulfonamides including N-1-methyl-2-phenylethyl methanesulfonamide, having hypotensive activity.

British Patent Specification Number 1,059,360 discloses certain phenylalkylsulfamides having activity as sedatives, narcotics and anti-convulsants, including 1-(1-methyl-2-phenylethylaminosulphonyl)piperidine.

United States Patent Specification Number 4,210,749 discloses N-1-methyl-2-phenyl-3-methoxy ethyl butane-sulfonamide.

Gualtieri *et al., J. Pharm. Sci.*, (1973), 62(5), 849-851 discloses N-1-methyl-2-phenylethyl butanesulfonamide and its evaluation as a mosquito repellent.

Foye *et al., J. Pharm. Sci.* (1979), 68(5), 591-5 discloses N-1-methyl-2-(4-chlorophenyl)ethyl methane-sulfonamide.

Foye and Sane, *J. Pharm. Sci.* (1977), 66(7), 923-6 discloses N-methanesulfonyl and N-trifluoromethanesulfonyl derivatives of amphetamines and certain 4-substituted analogs thereof, and their evaluation for central nervous system and anorexic effects.

R^5, R^6, R^7 and R^8 are each independently selected from the group consisting of hydrogen, (1-6C)alkyl; aryl(1-6C)alkyl; (2-6C)alkenyl; aryl(2-6C)alkenyl and aryl; or

two of R^5, R^6, R^7 and R^8 together with the carbon atom or carbon atoms to which they are attached form a (3-8C) carbocyclic ring; and the remainder of R^5, R^6, R^7 and R^8 represent hydrogen; or a pharmaceutically acceptable salt thereof.

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 desensitisation or deactivation of AMPA receptors to glutamate.

A wide variety of conditions may be treated or prevented by the compounds of formula I 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; neuro-degenerative disorders such as Alzheimer's disease; age-related dementias; age-induced memory impairment; movement disorders such as tardive dyskinesia, Hungtington'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 compounds of formula I 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 formula I for the treatment of each of these conditions.

The term "treating" (or "treat") as used herein includes its generally accepted meaning which encompasses prohibiting, preventing, restraining, and slowing, stopping, or reversing progression, severity, or a resultant symptom.

The present invention includes the pharmaceutically acceptable salts of the compounds defined by formula I. A compound of this invention can possess a sufficiently acidic, a sufficiently basic, 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.

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, 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, caprylate, acrylate, formate, hydrochloride, dihydrochloride, isobutyrate, caproate, heptanoate, propiolate, oxalate, malonate, succinate, suberate, sebacate, fumarate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, g-hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, napthalene-2-sulfonate, mandelate 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 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 "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:

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

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 50:30 is achieved, the ee with respect to the first enantiomer is 25%. 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 enantiomers of compounds of formula I can be resolved by one of ordinary skill in the art using standard techniques well known in the art, such as those described by J. Jacques, et al., "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981. 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.

EXAMPLE 48

N-2-(4-(2-(hydroxymethyl)phenyl)phenyl)propyl 2-propanesulfonamide

Prepared as in Example 46, using 2.0 g (5.8 mmol) of the material from Example 47 and 0.22 g (5.8 mmol) of sodium borohydride in 5 mL of ethanol. Afforded 1.7 g (84%) of the title compound.

Analysis calculated for $C_{19}H_{25}NO_3S$: %C, 65.68; %H, 7.25; %N, 4.03. Found: %C, 65.14; %H, 6.73; %N, 3.76.

Field Desorption Mass Spectrum: M = 347

EXAMPLE 49

N-2-(4-(4-(2-t-butoxycarbonylamino)ethyl)phenyl)phenylpropyl 2-propanesulfonamide

To a solution of 2.0 g (3.8 mmol) of material from Preparation 40 and 1.4g (4.5 mmol) of material from Preparation 41 in 15 mL of toluene was added 0.2 g (0.2 mmol) of tetrakis(triphenylphosphine) palladium (0). The mixture was heated to 100°C for 6.5 hours, cooled to room temperature and diluted with 15 mL of ethyl ether. The mixture was washed once with 15 mL of saturated aqueous potassium fluoride, the organic layer was separated and the aqueous layer was extracted three times with 10 mL each of ethyl ether. The combined organics were dried ($MgSO_4$), filtered and concentrated *in vacuo*. Chromatography (100 g silica gel, 30% ethyl acetate/hexane) of the residue affords 0.6 g (35%) of the title compound.

Analysis calculated for $C_{25}H_{36}N_2O_4S$: %C, 65.19; %H, 7.88; %N, 6.08. Found: %C, 65.29; %H, 7.84; %N, 5.84.

Mass Spectrum: M = 460.

EXAMPLE 50

N-2-(4-(4-(2-aminoethyl)phenyl)phenyl)propyl 2-propanesulfonamide

A solution of 0.6 g (1.3 mmol) of material from Example 49 in 5 mL of 20% trifluoroacetic acid/dichloromethane was stirred at room temperature for 1.5 hours. The mixture was concentrated *in vacuo* and the residue was partitioned

between 10 mL of dichloromethane and 5 mL of 5 N aqueous sodium hydroxide. The organic layer was separated and the aqueous layer was extracted three times with 5 mL each of dichloromethane. The combined organics were dried (Na_2SO_4), filtered and concentrated *in vacuo*. The resulting solid was suspended in hexane, filtered, rinsed once with hexane and dried *in vacuo* at ambient temperature to afford 0.4 g (88%) of the title compound.

Analysis calculated for $C_{20}H_{28}N_2O_2S$: %C, 66.63; %H, 7.83; %N, 7.77. Found: %C, 66.93; %H, 7.79; %N, 7.94.

Mass Spectrum: M = 360.

EXAMPLE 51

N-2-(4-(4-(2-methanesulfonamido ethyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a room temperature solution of 0.1 g (0.3 mmol) of material from Example 50 and 0.06 mL (0.4 mmol) of triethylamine in 2 mL of dichloromethane was added 0.03 mL (0.4 mmol) of methanesulfonyl chloride. The mixture was stirred at ambient temperature for 16 hours. Chromatography (10 g silica gel, 50% ethyl acetate/hexane) of the reaction mixture afforded 0.1 g (94%) of the title compound.

Analysis calculated for $C_{21}H_{30}N_2O_4S_2$: %C, 57.51; %H, 6.89; %N, 6.39. Found: %C, 57.90; %H, 6.72; %N, 6.33.

Mass Spectrum: M = 438.

EXAMPLE 52

N-2-(4-(4-hydroxymethyl)phenyl)phenyl)propyl 2-propanesulfonamide

To a solution of 0.5 g (1.5 mmol) of material from Example 45 in 5 mL ethanol was added 0.06 g (1.5 mmol) of sodium borohydride. The mixture was stirred at ambient temperature for 16 hours, concentrated *in vacuo* and partitioned between 10 mL of ethyl acetate and 5 mL of water. The organic layer was separated and the aqueous portion was extracted three times with 5 mL each of ethyl acetate. The combined organics were dried (MgSO4), filtered and

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, they produce a greater than 30% 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.

According to another aspect, the present invention provides a pharmaceutical composition, which comprises a compound of formula I or a pharmaceutically acceptable salt thereof as defined hereinabove 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**

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.

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Hard gelatin capsules are prepared using the following ingredients:

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

case, including the compound administered, the route of administration, the particular condition being treated, and similar considerations. The compounds can be administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, 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 following examples represent typical syntheses of starting materials for the compounds of formula I, and of compounds of formula I as described generally above. These examples are illustrative only and are not intended to limit the invention in any way. 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; "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; "°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; "EtOAc" refers to ethyl acetate; and "LDA" refers to lithium diisopropylamide.

Preparation 1

2-(4-Bromophenyl)propionitrile

A solution of 50.0 g (225.0 mmol) of 4-bromophenyl-acetonitrile and 1.8 g (12.8 mmol) of potassium carbonate in 387 mL of dimethyl carbonate was heated to 180°C in a sealed vessel for 16 hours. The solution was then cooled, diluted with 200 ml of ethyl acetate and washed once with 100 ml water, once with 100 ml of 10% aqueous sodium bisulfate and once with 100 ml brine. The organic portion was dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

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RADICACIÓN: 2-103448 EDICTO No. 2899

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió Resolución No. 2062 de 31-ENE-2007. Que el contenido de la parte resolutiva es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Revocar el oficio 0419 del 12 de enero del 2007 proferido por la División de Nuevas Creaciones de esta Superintendencia, de acuerdo con las razones expuestas en la parte considerativa de la presente resolución.

ARTICULO SEGUNDO: Aceptar el desistimiento de la solicitud de que se da cuenta en la parte considerativa.

ARTICULO TERCERO: Hacer las anotaciones correspondientes y archivar el expediente.

ARTICULO CUARTO: Notificar personalmente el contenido de la presente resolución al doctor José Antonio Llorente, o a quien haga sus veces, en su calidad de apoderado de Eli Lilly And Company., entregándole copia de la misma, advirtiéndole que contra ella procede el recurso de reposición interpuesto ante el Superintendente de Industria y Comercio, al momento de la notificación o dentro de los 5 días hábiles siguientes a ella.

NOTIFÍQUESE Y CUMPLASE
Dada en Bogotá, D.C., a los 31 ENE. 2007

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,

JAIME PIZANO PIÇOBAR

Para notificar a los interesados, se fija el presente EDICTO en lugar visible al público en la SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO, por el término de (10) diez días hábiles contados a partir de las 8:00 a.m. de hoy.

Secretaria General Ad-Hoc 15-FEB-2007 Este edicto se desfija hoy 28-FEB-2007 a las 4:30 p.m.
Secretaria General Ad-Hoc
EDICTO No. 2899