

Señor

SUPERINTENDENTE DELEGADO PARA LA PROPIEDAD INDUSTRIAL
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: P1.-ELI LILLY AND COMPANY.-Expediente No.
00-050.073.-

1. Me refiero al asunto de la referencia.
2. Por medio del presente, atentamente me permito manifestar que hubo un **cambio** de apoderado para todos los asuntos de la Propiedad Industrial en Bogotá de la sociedad **ELI LILLY AND COMPANY**.
3. En consecuencia, atentamente solicito a ese Despacho reconocirme personería en este asunto, de conformidad con la sustitución de poder adjunta, otorgada a favor de la SUSCRITA.
4. Por lo tanto, ruego a usted notificarme de las providencias expedidas dentro de este expediente y notificadas al anterior apoderado, que actualmente se encuentran pendientes de cumplimiento o de respuesta.
5. Solicito a ese Despacho proceder de conformidad.

Atentamente,


ALICIA LLOREDA RICAURTE

T.P. 53215

Código 231

267
259

Señor
SUPERINTENDENTE DE INDUSTRIA Y COMERCIO
DIVISION DE NUEVAS CREACIONES

E. _____ S. _____ D. _____

Ref: P1.- ELI LILLY AND COMPANY - Expediente
No.00.050.073-

Yo, **JOSE ANTONIO LLOREDA**, mayor de edad y vecino de esta ciudad, abogado titulado e inscrito, identificado como aparece al pie de mi firma, actuando en mi carácter de Representante Legal en Bogotá para asuntos relacionados con la propiedad industrial de **ELI LILLY AND COMPANY**, sociedad organizada y existente de conformidad con las leyes del Estado de Indiana, Estados Unidos de América, domiciliada en Indianapolis, Estado de Indiana, Estados Unidos de América, tal y como consta en este expediente, atentamente manifiesto a usted que **SUSTITUYO** el poder a mi conferido a la doctora **ALICIA LLOREDA RICAURTE**, abogada titulada e inscrita, identificada con la cédula de ciudadanía No. 39.690.713 de Usaquén y Tarjeta Profesional N° 53.215 para que continúe representando a la mencionada sociedad en el expediente de la referencia.

De conformidad con el artículo 66 del C.P.C., manifiesto bajo la gravedad de juramento que los demás apoderados citados en el documento otorgado a mi favor no desean ejercer el poder a ellos conferido.

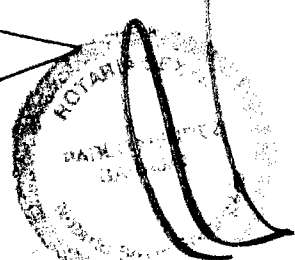
El mencionado apoderado tendrá las mismas facultades a mi conferidas, en especial, renunciar, recibir, sustituir, desistir, presentar recursos, conciliar, transigir, y en fin, para todo lo que se encamine a la correcta defensa de los intereses de la sociedad en cuyo nombre hablo.

tamente,

Jose Lloreda

JOSE ANTONIO LLOREDA
C.P. 10784
Código 231

159681
10784



205
260
375
2005-10-13

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES

2020

Bogotá, DC, 28 de septiembre de 2005

Apoderado: Alicia Lloreda Ricaurte

Oficio:

9442

ASUNTO

Radicación: 00-50073

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:

- ◆ capítulo descriptivo, folios 6 a 62;
- ◆ capítulo reivindicatorio, folios 63 a 65;
- ◆ 1º examen de forma, folios 72 y 73;
- ◆ respuesta al 1º examen de forma, folios 76 a 79;
- ◆ 2º examen de forma, folio 258;
- ◆ solicitud de la cual se reivindica prioridad y la traducción exigida, folios 84 a 256;
- ◆ solicitud del examen de patentabilidad, folios 260 a 262.

Objeto de la invención:

El título de la invención "COMPUESTOS DECAHIDROISOQUINOLINA UTILES COMO ANTAGONISTAS SELECTIVOS DEL RECEPTOR iGluR5 PARA EL TRATAMIENTO DE LA MIGRAÑA"

Tienen como objeto los compuestos derivados decahidro isoqionolina-3-carboxilicos .

El campo de la invención, según la Clasificación Internacional de Patentes: A61K 31/40/ 31/47

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”.

La reivindicación 12, no es clara, puesto que el encabezado no es consistente con el resto del texto de la reivindicación. Una composición no se puede caracterizar técnicamente, como lo exige la norma, por su uso o por el efecto terapéutico, sino por la mezcla de sus elementos constitutivos, con sus cantidades dentro de la formulación.

Reivindicaciones de uso

De acuerdo con la legislación colombiana el uso no se considera 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

361
262

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.

Determinación del estado de la técnica:

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 solictud, de la cual se reivindica prioridad, 06 de agosto-1999. Consultada la fuente de información con que cuenta este despacho se encontró los siguientes documentos:

No.	Documento No.	Título	*Fecha de Publicación
D1	US5.670.516	Excitatory amino acid receptor	06-jul-1982

3

W is $(\text{CH}_2)_n$, S, SO, SO_2 ;Y is CHR^7 , NR^4 , O, S, SO, or SO_2 ;Z is NR^6 , CHR^7 , or CH; orW and Y together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$, or Y and Z together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$; R^4 is hydrogen, C_1 - C_4 alkyl, phenyl, or acyl; R^5 is hydrogen, C_1 - C_4 alkyl, CF_3 , phenyl, hydroxy, amino, bromo, iodo, or chloro; R^6 is acyl; R^7 is independently hydrogen, C_1 - C_4 alkyl, phenyl, or substituted phenyl; R^8 is C_1 - C_4 alkyl or tetrazole-5-yl; and

n is 0, 1, or 2;

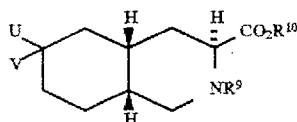
provided that when Y is NR^4 , O, S, SO, or SO_2 , W is $(\text{CH}_2)_n$ and Z is CHR^7 or CH;further provided that when W is S, SO, or SO_2 , Y is CHR^7 , Z is CHR^7 or CH, or Y and Z together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$;further provided that when W and Z are CH_2 , Y is not S;further provided that when W and Y together are $\text{HC}=\text{CH}$ or $\text{C}\equiv\text{C}$, Z is CHR^7 ;

or a pharmaceutically acceptable salt thereof.

The invention also provides pharmaceutical formulations comprising a compound of formula I and a pharmaceutically-acceptable carrier, diluent, or excipient.

Further embodiments of the invention include a method of blocking the AMPA excitatory amino acid receptor, as well as methods of treating a neurological disorder which has been linked to the excitatory amino acid receptors, which comprises administering a compound of formula I. Examples of such neurological disorders which are treated with a formula I compound include cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord trauma, head trauma, Alzheimer's Disease, Huntington's Chorea, amyotrophic lateral sclerosis, AIDS-induced dementia, muscular spasms, migraine headaches, urinary incontinence, psychosis, convulsions, perinatal hypoxia, cardiac arrest, hypoglycemic neuronal damage, opiate tolerance and withdrawal, ocular damage and retinopathy, idiopathic and drug-induced Parkinson's Disease, anxiety, emesis, brain edema, chronic pain, or tardive dyskinesia. The formula I compounds are also useful as analgesic agents.

This invention also provides compounds which are useful in the preparation of the AMPA receptor antagonists. A second aspect of the present invention relates to a compound of the formula:



wherein:

 R^9 is acyl or alkoxycarbonyl; R^{10} is hydrogen, C_1 - C_6 alkyl, or aryl;

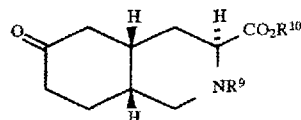
U is hydroxyl, hydroxymethyl, formyl, bromomethyl, methoxymethyl, or hydroxyethyl;

V is hydrogen; or

U and V together are methylene or methoxymethylene.

The present invention also provides processes for the preparation of compounds of formula VIIIb

4

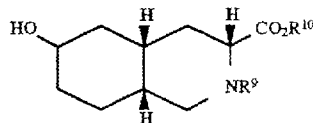


VIIIb

wherein:

 R^9 is acyl or alkoxycarbonyl; R^{10} is a chiral ammonium group, hydrogen, C_1 - C_6 alkyl, or aryl.

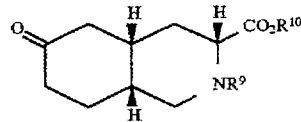
A fourth aspect of the present invention is a process for preparing a compound of the formula



wherein:

 R^9 is acyl or alkoxycarbonyl; R^{10} is hydrogen, C_1 - C_6 alkyl, or acyl.

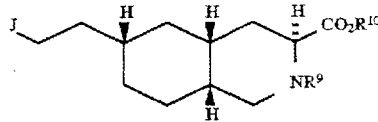
Another aspect of the present invention is a process for preparing a compound of the formula



wherein:

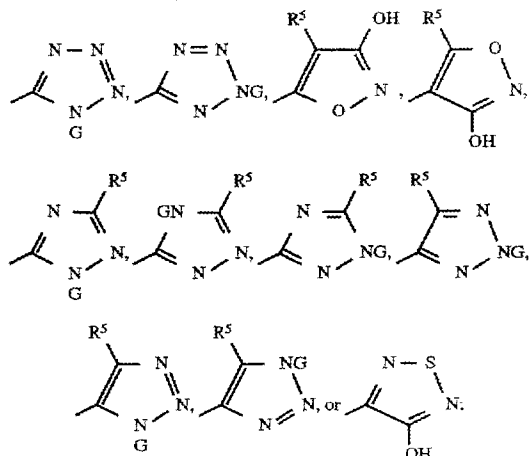
 R^9 is acyl or alkoxycarbonyl; R^{10} is hydrogen, C_1 - C_6 alkyl, or acyl.

Another aspect of the present invention is a process for preparing a compound of formula:



wherein:

J is a group of the formula

G is a nitrogen protecting group or hydrogen;
 R^5 is as defined previously;

5

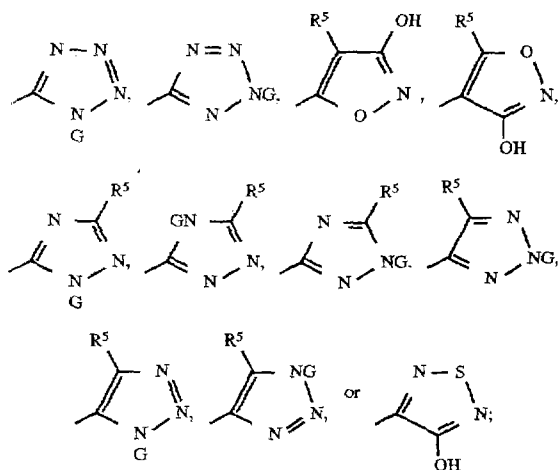
R^9 is acyl or alkoxycarbonyl; and
 R^{10} is C_1 - C_6 alkyl or aryl.

This invention also provides compounds which are useful in the preparation of a number of the AMPA receptor antagonists. Another aspect of the present invention relates to a compound of the formula:



wherein:

J is a group of the formula



Q is $CHR^7P(Ph)_3X^-$, $CHR^7PO(Ph)_2$, $CR^7MSiR'^3$, $CH(SiR'^3)PO(OR')_2$, or $CH_2SnR'^3$;

R^1 is C_1 - C_6 alkyl or phenyl;

R^5 and R^7 are as defined previously; and

G is a nitrogen protecting group or hydrogen;

M is Li^+ or $Mg^{+2}X^-$; and

X^- is bromide, chloride, iodide, tetrafluoroborate, or hexafluorophosphate.

DETAILED DESCRIPTION OF THE INVENTION

In the above formula, the term " C_1 - C_{10} alkyl" represents a straight or branched alkyl chain having from one to ten carbon atoms. Typical C_1 - C_{10} alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, n-hexyl, 2-methylpentyl, n-octyl, decyl, and the like. The term " C_1 - C_{10} alkyl" includes within it the terms " C_1 - C_6 alkyl" and " C_1 - C_4 alkyl". Typical C_1 - C_6 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, isopentyl, and n-hexyl. Typical C_1 - C_4 alkyl groups include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, and t-butyl.

The term "acyl" represents a hydrogen or C_1 - C_6 alkyl group attached to a carbonyl group. Typical acyl groups include formyl, acetyl, propionyl, butyryl, valeryl, and caproyl.

The term "substituted alkyl," as used herein, represents a C_1 - C_6 alkyl group that is substituted by one or more of the following: hydroxy, fluoro, chloro, bromo, and iodo. Examples of a substituted alkyl group include hydroxymethyl, chloromethyl, bromomethyl, iodomethyl, trichloromethyl, trifluoromethyl, chloroethyl, bromoethyl, perfluoroethyl, and the like.

6

The term " C_1 - C_4 alkoxy" represents groups such as methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, t-butoxy, and like groups. The term "halogen" refers to the fluoro, chloro, bromo, or iodo groups.

The term "substituted phenyl," as used herein, represents a phenyl group substituted with one or two moieties chosen from the group consisting of halogen, hydroxy, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_4 alkoxy, alkoxycarbonyl, protected carboxy, carboxymethyl, hydroxymethyl, amino, aminomethyl, or trifluoromethyl. Examples of a substituted phenyl group include 4-chlorophenyl, 2,6-dichlorophenyl, 2,5-dichlorophenyl, 3,4-dichlorophenyl, 3-chlorophenyl, 3-bromophenyl, 4-bromophenyl, 3,4-dibromophenyl, 3-chloro-4-fluorophenyl, 2-fluorophenyl, 4-hydroxyphenyl, 3-hydroxyphenyl, 2,4-dihydroxyphenyl, 3-nitrophenyl, 4-nitrophenyl, 4-cyanophenyl, 4-methylphenyl, 4-diphenylmethyl, 4-ethylphenyl, 4-methoxyphenyl, 4-carboxyphenyl, 4-(hydroxymethyl)phenyl, 4-aminophenyl, and the like.

The term "aryl" represents groups such as phenyl and substituted phenyl as described above. The term "aryllalkyl" represents a C_1 - C_4 alkyl group bearing an aryl group. Representatives of this latter group include benzyl, 1-phenylethyl, 2-phenylethyl, 3-phenylpropyl, 4-phenylbutyl, 2-methyl-2-phenylpropyl, (4-chlorophenyl)methyl, (2,6-dichlorophenyl)methyl, (4-hydroxyphenyl)methyl, (2,4-dinitrophenyl)methyl, and the like.

The term "cycloalkyl" represents a C_3 - C_7 cyclic alkyl group such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and the like.

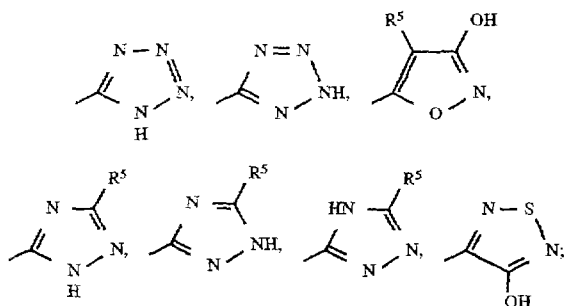
The term "alkoxycarbonyl" means a carboxyl group having a C_1 - C_6 alkyl group attached to the carbonyl carbon through an oxygen atom. Representatives of this group include t-butoxycarbonyl and methoxycarbonyl.

The term "aryloxycarbonyl" represents a carboxyl group bearing an aryl group attached to the carbonyl carbon through an oxygen atom. Representatives of this group include phenoxycarbonyl, (4-chlorophenoxy)carbonyl, and (3-nitrophenoxy)carbonyl.

The term "chiral ammonium group" represents an amine having a chiral group, said amine forming the addition salt with the carboxylic acid group on the carbon atom adjacent to the nitrogen of the decahydroisoquinoline ring (C-3). Examples of amines having a chiral group that may react with the C-3 carboxylic acid group to form a chiral ammonium addition salt include R-(+)- α -methylbenzylamine, S-(-)- α -methylbenzylamine, (-)- α -(2-naphthyl)ethylamine, yohimbine, (+)-amphetamine, (-)-ephedrine, strychnine, brucine, quinine, quinidine, cinchonine, cinchonidine, and the like.

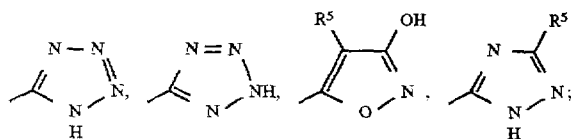
The term "nitrogen protecting group" includes trityl, benzyl, t-butyl, t-butyldimethylsilyl, and triphenylsilyl.

While all the formula I compounds of the present invention are believed to be antagonists of the AMPA excitatory amino acid receptor, certain compounds of the invention are preferred for such use. Preferably, R^1 is hydrogen or alkoxy-carbonyl; R^2 is hydrogen or C_1 - C_6 alkyl; R^3 is a group selected from the group consisting of CO_2H , SO_3H , $CONHSO_2R^8$.



W is S or (CH₂)_n, where n=0, 1, or 2; Y is CHR⁷, S, SO₂, or O; Z is CHR⁷ or NR⁶; R⁵ is hydrogen, C₁-C₄ alkyl, CF₃, or phenyl; R⁶ is formyl; R⁷ is hydrogen, C₁-C₄ alkyl, or phenyl; and R⁸ is C₁-C₄ alkyl or tetrazole-5-yl. Representative compounds from this preferred group of compounds include: 6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[N-(1(2)H-tetrazole-5-yl)methylformamido]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-2-thiaethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)prop-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)methoxymethyl]decahydroisoquinoline-3-carboxylic acid, 6-[3-(1(2)H-tetrazole-5-yl)-3-thiapro-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)but-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-(2-carboxyethyl)decahydroisoquinoline-3-carboxylic acid, 6-(2-sulfoethyl)decahydroisoquinoline-3-carboxylic acid, 6-[2-(3-hydroxyisoxazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-1,2,4-triazole-5-yl)-2-thiaethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-1,2,4-triazole-5-yl)sulfonylmethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-((N-methanesulfonyl)carboxamido)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(N-(1(2)H-tetrazole-5-yl)carboxamido)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-methylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-phenylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(3-hydroxy-1,2,5-thiadiazole-4-yl)ethenyl]decahydroisoquinoline-3-carboxylic acid, and the like.

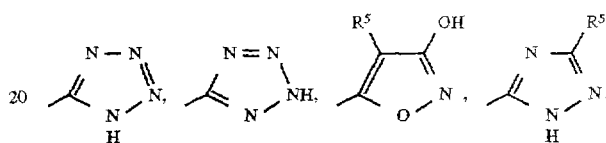
Certain compounds of the present invention are more preferred for use as antagonists of the AMPA excitatory amino acid receptor. More preferably, R¹ is hydrogen or alkoxycarbonyl; R² is hydrogen or C₁-C₆; R³ is a group selected from SO₃H and a group of the formula:



W is S, SO₂, or (CH₂)_n; n is 0, 1, or 2; Y is CHR⁷, S, or SO₂; Z is CHR⁷; R⁵ is hydrogen, C₁-C₄ alkyl, or CF₃; and R⁷ is hydrogen, C₁-C₄ alkyl, or phenyl. Representative compounds from this more preferred group of compounds include: 6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-2-thiaethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)prop-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)methoxymethyl]decahydroisoquinoline-3-carboxylic acid, 6-[3-(1(2)H-tetrazole-5-yl)-3-thiapro-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)but-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-(2-carboxyethyl)decahydroisoquinoline-3-carboxylic acid, 6-(2-sulfoethyl)decahydroisoquinoline-3-carboxylic acid, 6-[2-(3-hydroxyisoxazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-1,2,4-triazole-5-yl)-2-thiaethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-1,2,4-triazole-5-yl)sulfonylmethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-((N-methanesulfonyl)carboxamido)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(N-(1(2)H-tetrazole-5-yl)carboxamido)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-methylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-phenylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(3-hydroxy-1,2,5-thiadiazole-4-yl)ethenyl]decahydroisoquinoline-3-carboxylic acid, and the like.

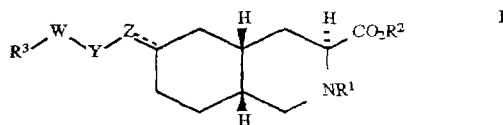
tetrazole-5-yl)methoxymethyl]decahydroisoquinoline-3-carboxylic acid, 6-[3-(1(2)H-tetrazole-5-yl)-3-thiapro-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-tetrazole-5-yl)but-1-yl]decahydroisoquinoline-3-carboxylic acid, 6-(2-sulfoethyl)decahydroisoquinoline-3-carboxylic acid, 6-(2-(3-hydroxyisoxazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-1,2,4-triazole-5-yl)sulfonylmethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-methylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-phenylethyl]decahydroisoquinoline-3-carboxylic acid, and the like.

Certain compounds of the invention are most preferred for use as antagonists of the AMPA excitatory amino acid receptor. Most preferably, R¹ and R² are hydrogen; R³ is a group selected from a group of the formula



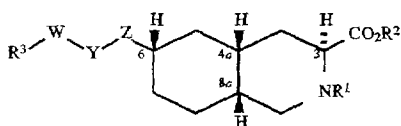
W is (CH₂)_n, where n is 0; Y is CHR⁷, S, or SO₂; Z is CHR⁷; R⁵ is hydrogen or C₁-C₄ alkyl; and R⁷ is hydrogen, C₁-C₄ alkyl, or phenyl. Representative compounds from this most preferred group of compounds include: 6-[2-(1(2)H-tetrazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-2-thiaethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(3-hydroxyisoxazole-5-yl)ethyl]decahydroisoquinoline-3-carboxylic acid, 6-[(1(2)H-1,2,4-triazole-5-yl)sulfonylmethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-methylethyl]decahydroisoquinoline-3-carboxylic acid, 6-[2-(1(2)H-tetrazole-5-yl)-1-phenylethyl]decahydroisoquinoline-3-carboxylic acid, and the like.

The formula I compounds of the present invention are the compounds having the relative stereochemistry as shown below:

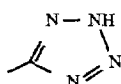


The compounds of the present invention, wherein Z is other than CH, possess at least four asymmetric carbon atoms. The asymmetric centers are the substituted carbon atom adjacent to the ring NR¹ group (3), the carbon atom where Z is attached to the ring (6), and the two bridgehead carbon atoms (4a and 8a). As such, the compounds can exist as diastereomers, each of which can exist as the racemic mixture of enantiomers. The compounds of the present invention include not only the racemates, but also the respective enantiomers. When Z is NR⁶, the preferred configuration for the diastereomer is 3SR,4aSR,6SR,8aRS, and the preferred configuration for the enantiomer is 3S,4aS,6S,8aR. When Z is CHR⁷, the preferred configuration for the diastereomer is 3SR,4aRS,6SR,8aRS, except for the following: when R⁷ is hydrogen, Y is CH₂, W is (CH₂)_n, and n=0, the preferred configuration for the diastereomer is 3SR,4aRS,6RS,8aRS; when R⁷ is hydrogen and Y and Z together are HC=CH, the preferred configuration for the diastereomer is 3SR,4aRS,6RS,8aRS; and when Y is S, SO, or SO₂, W is (CH₂)_n, and n=0, the preferred configuration for this diastereomer is 3SR,4aRS,6SR,8aRS. When Z is CHR⁷, the

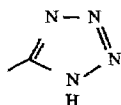
preferred configuration for the enantiomer is 3S,4aR,6S,8aR, except for the following: when R⁷ is hydrogen, Y is CH₂, W is (CH₂)_n, and n=0, the preferred configuration for the enantiomer is 3S,4aR,6R,8aR; when R⁷ is hydrogen and Y and Z together are HC=CH, the preferred configuration for the enantiomer is 3S,4aR,6R,8aR; and when Y is S, SO, or SO₂, W is (CH₂)_n, and n=0, the preferred configuration for this enantiomer is 3S,4aR,6S,8aR. When Z is CH, the preferred configuration for the diastereomer is 3SR,4aRS,8aRS, except when W is (CH₂)_n and n=0, the preferred configuration of the diastereomer 3SR,4aRS,8aRS. When Z is CH, the preferred configuration for the enantiomer is 3S,4aR,8aR, except when W is (CH₂)_n and n=0, the preferred configuration of the enantiomer 3S,4aR,8aR. When Z and Y together are HC=CH or C≡C, the preferred configuration for the diastereomer is 3SR,4aRS,6SR,8aRS; except when W is (CH₂)_n and n=0, the preferred configuration for the diastereomer is 3SR,4aRS,6SR,8aRS. When Z and Y together are HC=CH or C≡C, the preferred configuration for the enantiomer is 3S,4aR,6S,8aR; except when W is (CH₂)_n and n=0, the preferred configuration for the enantiomer is 3S,4aR,6S,8aR. The more preferred relative and absolute stereochemistry is shown in the following formula.



The compounds of the present invention may contain a tetrazole ring, which is known to exist as tautomeric structures. The tetrazole, having the double bond on the nitrogen atom at the 1-position and the hydrogen on the nitrogen atom at the 2-position is named as a 2H-tetrazole and is represented by the following structure.



The corresponding tautomeric form wherein the hydrogen is at the nitrogen atom at the 1-position and the double bond on the nitrogen atom at the 4-position is named as a 1H-tetrazole. The 1H-tetrazole is represented by the following formula.



Mixtures of the two tautomers are referred to herein as 1(2)H-tetrazoles. The present invention contemplates both tautomeric forms as well as the combination of the two tautomers.

Similarly, the compounds of the present invention may contain a triazole ring. The triazoles exist in two positional isomeric forms, the 1,2,4-triazole and the 1,2,3-triazole. Each of these forms may exist as tautomeric structures. The triazole having the double bond on the nitrogen atom at the 1-position and the hydrogen on the nitrogen atom at the 2-position is named the 2H-triazole. The tautomeric form, wherein the hydrogen is on the nitrogen atom at the 1-position and the double bond on the nitrogen atom at the

2-position is named the 1H-triazole. The tautomeric form wherein the hydrogen is on the nitrogen atom at the 3-position or 4-position is named the positional 3H-triazole or 4H-triazole, respectively. Mixtures of the these tautomers are referred to herein as 1(2-4)H-triazoles. The present invention contemplates both positional isomers and individual tautomeric forms, as well as the combination thereof.

The present invention includes the pharmaceutically acceptable salts of the compounds defined by formula I. These salts can exist in conjunction with the acidic or basic portion of the molecule and can exist as acid addition, primary, secondary, tertiary, or quaternary ammonium, alkali metal, or alkaline earth metal salts. Generally, the acid addition salts are prepared by the reaction of an acid with a compound of formula I, wherein R¹ is hydrogen, C₁-C₁₀ alkyl, or arylalkyl. The alkali metal and alkaline earth metal salts are generally prepared by the reaction of the hydroxide form of the desired metal salt with a compound of formula I, wherein R² is hydrogen.

Acids commonly employed to form such salts include inorganic acids such as hydrochloric, hydrobromic, hydriodic, sulfuric, and phosphoric acid, as well as organic acids such as para-toluenesulfonic, methanesulfonic, oxalic, para-bromophenylsulfonic, carbonic, succinic, citric, benzoic, and acetic acid, and related inorganic and organic acids. Such pharmaceutically acceptable salts thus include sulfate, pyrosulfate, bisulfate, sulfite, bisulfite, phosphate, ammonium, monohydrogenphosphate, dihydrogenphosphate, meta-phosphate, pyrophosphate, chloride, bromide, iodide, acetate, propionate, decanoate, caprylate, acrylate, formate, isobutyrate, caprate, heptanoate, propionate, oxalate, malonate, succinate, suberate, sebacate, fumarate, hippurate, maleate, butyne-1,4-dioate, hexyne-1,6-dioate, benzoate, chlorobenzoate, methylbenzoate, dinitrobenzoate, hydroxybenzoate, methoxybenzoate, phthalate, sulfonate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate, α-hydroxybutyrate, glycolate, maleate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-2-sulfonate, mandelate, ammonium, magnesium, tetramethylammonium, potassium, trimethylammonium, sodium, methylammonium, calcium, and the like salts.

While all the formula II compounds of the present invention are believed to be useful in the preparation of the AMPA receptor antagonists, certain compounds of the invention are preferred for such use. Preferably, R⁹ is alkoxycarbonyl; R¹⁰ is C₁-C₆ alkyl; U is hydroxyl, hydroxymethyl, hydroxyethyl, or formyl; V is hydrogen; or U and V together are methylene or methoxymethylene. More preferably, U is hydroxymethyl or formyl, or U and V together are methylene or methoxymethylene. Most preferably, R⁹ is methoxycarbonyl and R¹⁰ is ethyl. Representative compounds of this most preferred group include ethyl 6-methylidene-2-methoxycarbonyldecahydroisoquinoline-3-carboxylate, ethyl 2-methoxycarbonyl-6-(methoxymethylene) decahydroisoquinoline-3-carboxylate, ethyl 6-hydroxymethyl-2-methoxycarbonyldecahydroisoquinoline-3-carboxylate, and ethyl 6-formyl-2-methoxycarbonyldecahydroisoquinoline-3-carboxylate.

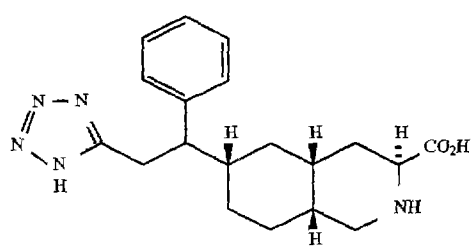
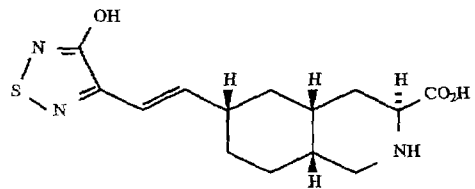
The compounds of the general formula



wherein J and Q are as defined previously are useful for the synthesis of the formula I compounds wherein Z is CH or

277
272

TABLE I-continued

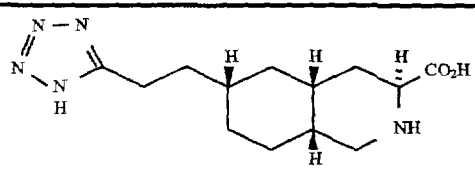
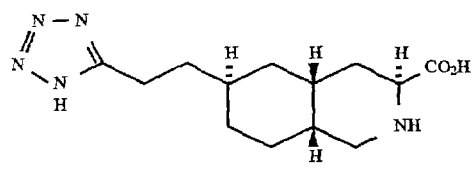
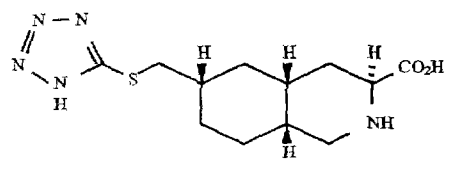
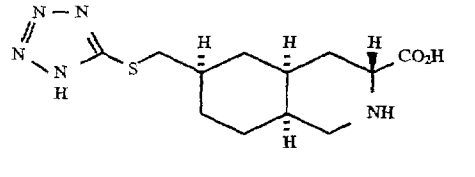
Receptor Binding of Racemic Formula I Compounds				
Compound ^a		IC ₅₀ (μM) ^b		
No.	Structure	NMDA	AMPA	KA
19		13.8 ^c	6.58 ^c	>100
20		>100	83.4 ^c	>100

^aThe compounds were tested as racemic mixtures with the relative stereochemistry as shown.

^bMean ± standard error (n = 3), unless otherwise indicated.

^cThe data is the result of a single experiment.

TABLE II

Receptor Binding of Enantiopure Formula I Compounds				
Compound ^a		IC ₅₀ (μM) ^b		
No.	Structure	NMDA	AMPA	KA
21		12.1 ± 2.0	1.35 ± 0.13	28.1 ± 1.7
22		99.2 ^c	15.3 ^c	85.3 ^c
23		16.3 ^c	0.58 ± 0.03	12.5 ^c
24		>10	21.9 ^c	>100

278
223



PCT

WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁶ : C07D 217/06, A61K 31/47		A1	(11) International Publication Number: WO 98/45270 (43) International Publication Date: 15 October 1998 (15.10.98)
(21) International Application Number: PCT/US98/06905 (22) International Filing Date: 6 April 1998 (06.04.98) (30) Priority Data: 60/042,795 7 April 1997 (07.04.97) 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): BLEAKMAN, David [GB/US]; 720 Eagle Creek Court, Zionsville, IN 46077 (US). HELTON, David, R. [US/US]; -LODGE, David [GB/US]; 7440 Bush's Run, Indianapolis, IN 46278 (US). IYENGAR, Smriti [IN/US]; 1507 Redwood Drive, Carmel, IN 46032 (US). ORNSTEIN, Paul, L. [US/US]; 10441 Bosahan Court, Carmel, IN 46032 (US). (74) Agents: HAY, Martin, A. et al.; Eli Lilly and Company, Lilly Corporate Center, Indianapolis, IN 46285 (US).			(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, GM, GW, HU, ID, IL, 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, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, 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, ML, MR, NE, SN, TD, TG). Published <i>With international search report.</i>
(54) Title: PHARMACOLOGICAL AGENTS (57) Abstract Antagonists selective for the GluR5 receptor are useful for the treatment of pain. Also disclosed are novel decahydroisoquinoline derivatives which are selective GluR5 receptor antagonists. DZ.			

-1-

Pharmacological Agents

The present invention relates to a new class of glutamate receptor antagonists useful for the treatment of pain.

L-Glutamate mediates excitatory neurotransmission in the mammalian central nervous system through its action at glutamate receptors. There are two broad classes of glutamate receptors, known as the ionotropic glutamate receptor and the metabotropic glutamate receptor. Within the class of ionotropic glutamate receptor are three classes, known as the N-methyl-D-aspartate (NMDA), (R,S)-2-amino-3-(3-hydroxy-5-methyl-isoxazol-4-yl)propanoate (AMPA) and kainate (KA) receptors. Molecular biological studies have established that AMPA receptors are composed of subunits (GluR1-4) that can assemble to form functional channels. Five kainate receptors, classified as either high affinity (KA1 and KA2) or low affinity (GluR5, GluR6 and GluR7) kainate receptors have been identified. (Bleakman et al, *Molecular Pharmacology*, 1996, Vol. 49, No. 4, pgs. 581-585).

European Patent Application Publication No. 590789A1 and United States Patent No. 5,446,051 disclose that certain decahydroisoquinoline derivatives are AMPA receptor antagonists, and as such are useful in the treatment of many different conditions, including pain. There is no disclosure of any compound actually being tested for use in the treatment of pain.

280
275

-2-

Surprisingly, it has now been found that a compound within the scope of European Patent Application Publication No. 590789A1, namely (3S,4aR,6S,8aR)-6-[(1(2)H-tetrazol-5-yl)methoxymethyl]decahydroisoquinoline-3-carboxylic acid, is
5 a selective GluR5 antagonist and is effective in animal models of pain. It is therefore believed that a new pharmacological class of agents, represented by (3S,4aR,-6S,8aR)-6-[(1(2)H-tetrazol-5-yl)methoxymethyl]decahydro-isoquinoline-3-carboxylic acid, has been found for the
10 treatment of pain.

According to one aspect, therefore, the present invention provides a method for the treatment of pain, which comprises administering to a mammal in need of treatment an effective amount of a selective GluR5 receptor antagonist.

15 According to another aspect, the present invention provides the use of a selective GluR5 receptor antagonist for the manufacture of a medicament for the treatment of pain.

GluR5 receptor antagonists may be identified by
20 radiolabelled ligand binding studies at the cloned and expressed human GluR5 receptor (Korczak *et al.*, 1994, Recept. Channels 3; 41-49), by whole cell voltage clamp electro-physiological recordings of functional activity at the human GluR5 receptor (Korczak *et al.*, 1994, Recept.
25 Channels 3; 41-49) and by whole cell voltage clamp electrophysiological recordings of currents in acutely isolated rat dorsal root ganglion neurons (Bleakman *et al.*, 1996, *Mol. Pharmacol.* 49; 581-585).

-3-

281
273

The selectivity of compounds acting at GluR5 receptors may be determined by measurement of activity at other AMPA and kainate receptors including receptor-ligand binding studies and whole-cell voltage clamp electro-physiological recordings of functional activity at human GluR1, GluR2, GluR3 and GluR4 receptors (Fletcher et al., 1995, Recept. Channels 3; 21-31), receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR6 receptors (Hoo et al., Recept. Channels 2; 327-338) and whole-cell voltage clamp electrophysiological recordings of functional activity at AMPA receptors in acutely isolated cerebellar Purkinje neurons (Bleakman et al., 1996, *Mol. Pharmacol.* 49; 581-585) and other tissues expressing AMPA receptors (Fletcher and Lodge, 1996, *Pharmacol. Ther.* 70; 65-89).

Preferably, the selective GluR5 receptor antagonist has a binding affinity of at least 10 fold greater for GluR5 than that for other glutamate receptors, more preferably at least 100 fold greater.

The selective GluR5 antagonist for use according to the invention may be a single compound or combination of compounds capable of functioning as an antagonist that is selective for the GluR5 receptor over other ionotropic glutamate receptors. For example, it may be a combination of a compound capable of functioning as an antagonist at the GluR5 receptor and one or more other glutamate receptors in combination with one or more compounds capable of blocking its actions at the one or more other ionotropic glutamate

282
277

receptors. Preferably, the selective GluR5 antagonist is a single compound.

The following compounds have been found to be selective GluR5 receptor antagonists and are therefore preferred for use according to the invention: 3SR,4aRS,6SR,8aRS-6-((((1H-tetrazole-5-yl)methyl)oxy)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid, 3S,4aR,6S,8aR-6-((((1H-tetrazole-5-yl)methyl)oxy)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid, 3SR,4aRS,6SR,8aRS-6-(((4-carboxy)phenyl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid and 3S,4aR,6S,8aR-6-(((4-carboxy)phenyl)methyl)-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid.

The results of evaluating the activity of the aforementioned decahydroisoquinoline derivatives at the GluR5 receptor and other ionotropic glutamate receptors in the tests described above are given in Tables 1 and 2 below.

TABLE 1
Selectivity Profile for Compounds
of the Invention in Binding Studies

Cell lines (HEK293 cells) stably transfected with human GluR receptors were employed. Displacement of 3H AMPA by increasing concentrations of test compound was used on GluR1-4-expressing cells and 3H kainate (KA) on GluR5 and expressing cells. Estimated activity (Ki) in nM was as follows.

Test Compound	GluR1	GluR2	GluR3	GluR4	GluR5	GluR6
A*	150686± 49789 (3)	35337± 6163 (3)	47793± 8770 (3)	31606± 5914 (3)	3061± 1038 (3)	6±5% displ @ 100µM (3)
B*	--	--	--	--	5823 (2)	--
C*	21% at 1mM	55% at 1mM	--	23% at 1mM	6810	--

- 5 A - 3SR,4aRS,6SR,8aRS-6-[(1(2)H-tetrazol-5-yl)methoxy-
methyl]decahydroisoquinoline-3-carboxylic acid
(average of 3 results)
- B - Compound of Example 1 (average of 2 results)
- 10 C - 3SR,4aRS,6SR,8aRS-6-(((4-carboxy)phenyl)methyl)-1,2,3-
4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic acid
(one result only)
- D - Compound of Example 2
- 15 -- Not tested

TABLE 2

Selectivity Profile for Compounds
of the Invention in Electrophysiological Studies

Functional studies were carried out on HEK293 cells
20 stably transfected with human GluR receptors and on acutely
isolated dorsal root ganglion neurons (DRG) using patch-
clamp technology (Bleakman et al., 1996, *Mol. Pharmacol.*,
49, 581-585). IC50 values (μM) for test Compound A were
estimated for GluR1-4 vs 100 μM AMPA and GluR5 and GluR6 vs
25 100 μM KA with the following results:

Test Compound	GluR1	GluR2	GluR3	GluR4	GluR5	GluR6	DRG*
A	>100	>100	>100	>100	3.9±0.5	>100	0.60±0.06
D	--	--	--	>100	--	>100	0.98±0.07

*Based on % inhibition of 30 μ M kainate induced current.

-6-

The forms of pain which may be treated according to the invention include severe, chronic, intractable and neuropathic pain.

The compounds 3*S*,4*aR*,6*S*,8*aR*-6-((((1*H*-Tetrazole-5-yl)methyl)oxy)methyl)1,2,3,4,4*a*,5,6,7,8,8*a*-decahydro-isoquinoline-3-carboxylic acid; and 3*S*,4*aR*,6*S*,8*aR*-6-(((4-carboxy)phenyl)methyl)1,2,3,4,4*a*,5,6,7,8,8*a*-decahydro-isoquinoline-3-carboxylic acid and their pharmaceutically acceptable salts are believed to be novel and are provided as a further aspect of the invention. The invention also provides a pharmaceutical composition comprising one of these compounds and a pharmaceutically acceptable diluent or carrier. They may be prepared, and formulated into pharmaceutical compositions, by the general methods described in European Patent Application No. 590789A1 and United States Patent No. 5,446,051.

The ability of selective GluR5 receptor antagonists to treat pain in mammals may be demonstrated using the well known formalin, tail flick and acetic acid-induced writhing tests.

1) formalin test

Male Sprague-Dawley rats (200-250g; Charles River, Portage, MI) were housed in group cages and maintained in a constant temperature and a 12h light/12h dark cycle 4-7 days before the studies were performed. Animals had free access to food and water at all times prior to the day of the experiment.

285
200

-7-

Drugs or vehicles were administered intraperitoneally (i.p.) or orally (p.o.) by gavage in a volume of 1 ml/kg.

The test was performed in custom made Plexiglas® boxes 25x25x20x cm in size (according to Shibata *et al.*, Pain 38; 347-352, 1989, Wheeler-Aceto *et al.*, Pain, 40; 229-238, 1990). A mirror placed at the back of the cage allowed the unhindered observation of the formalin injected paw. Rats were acclimated individually in the cubicles at least 1 hour prior to the experiment. All testing was conducted between 08:00 and 14:00 h and the testing room temperature was maintained at 21-23°C. Test compounds were administered 30 minutes prior to the formalin injection. Formalin (50 µl of a 5% solution in saline) was injected subcutaneously into the dorsal lateral surface of the right hind paw with a 27 gauge needle. Observation started immediately after the formalin injection. Formalin-induced pain was quantified by recording in 5 minute intervals the number of formalin injected paw licking events and the number of seconds each licking event lasted. These recordings were made for 50 minutes after the formalin injection.

Different scoring parameters have been reported for the formalin test. The total time spent licking and biting the injected paw was demonstrated to be most relevant (Coderre *et al.*, *Eur. J. Neurosci.* 6; 1328-1334, 1993; Abbott *et al.*, Pain, 60; 91-102, 1995) and was chosen for the testing score. The early phase score is the sum of time spent licking in seconds from time 0 to 5 minutes. The late phase was scored in 5 minute blocks from 15 minutes to 40 minutes

286
11

-8-

and is expressed accordingly or also by adding the total number of seconds spent licking from minute 15 to minute 40 of the observation period. Data are presented as means with standard errors of means ($\pm$ SEM). Data were evaluated by one-way analysis of variance (ANOVA) and the appropriate contrasts analyzed by Dunnett "t" test for two sided comparisons. Differences were considered to be significant if the P-value was less than 0.05 and indicated by asterisk. Statistics were determined at the 5 minute time point and at 5 minute intervals between 15 and 40 minutes. Where data are expressed as total amount of time spent licking in the late phase, statistics were performed on the total time spent licking as well and are indicated accordingly.

In this test, the compound of Example 1 was found to be active at doses in the range 10 to 100 mg/kg in reducing second phase paw licking time.

2) Tail flick test

This well known test measures the effect of a test compound on the time taken for an animal to flick its tail out of a focused beam of light. In the test, a beam of light from a lamp is focused on a surface, and the lamp is then switched off. Treated and untreated (control) animals are restrained, with their tails positioned at the focal point of the beam of light from the lamp. The lamp is then switched on, and the time taken for the animal's tail to respond by moving is recorded.

Subcutaneous administration of the compound of Example 1 in mice at doses of 3, 10, and 30 mg/kg produced a dose

287
162

-9-

dependent increase in response time. Oral administration of the same compound at doses of 0.03, 0.1, 0.3 and 3 mg/kg to cynomolgous primates also produced a dose dependent increase in response time. These data show that the compound of

5 Example 1, which is a selective GluR5 antagonist, is effective at treating pain, and has unexpected oral activity in cynomolgous primates.

3) Acetic acid induced mouse writhing test.

This test measures the ability of a test compound to
10 reduce the amount of writhing induced by intraperitoneal injection of acetic acid in mice.

Doses of test compound or control are administered to male CD-1 mice. Each animal is then administered 0.5% acetic acid in a volume of 0.01 mg/g intraperitoneally. The
15 animals are then placed in individual plexiglas observation chambers and the total number of writhes (flattening of the abdominal wall and asymmetric stretching and extending of the body and hindlimbs) recorded between 5 and 10 minutes after acetic acid administration.

20 The compound of Example 1 was administered at a dose of 1, 3, 10 and 30 mg/kg, and produced a dose dependent reduction in writhing.

The particular dose of antagonist administered according to this invention will of course be determined by
25 the particular circumstances surrounding the case, including the activity of the particular antagonist administered, the route of administration, the particular condition being treated, and similar considerations. The antagonist can be

288
783

-10-

administered by a variety of routes including oral, rectal, transdermal, subcutaneous, intravenous, intramuscular, or intranasal routes. Alternatively, the antagonist may be administered by continuous infusion. A typical daily dose will contain from about 0.001 mg/kg to about 100 mg/kg of the antagonist. 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 20 mg/kg.

The following examples illustrate the preparation of novel compounds that are selective GluR5 antagonists.

Tetrahydrofuran was dried by distillation from sodium. All other solvents and reagents were used as obtained. The reactions were generally monitored for completion using thin layer chromatography (TLC). Thin layer chromatography was performed using E. Merck Kieselgel 60 F254 plates, 5 cm X 10 cm, 0.25 mm thickness. Spots were detected using a combination of UV and chemical detection (plates dipped in a ceric ammonium molybdate solution [75 g of ammonium molybdate and 4 g of cerium (IV) sulfate in 500 mL of 10% aqueous sulfuric acid] and then heated on a hot plate). Elemental analyses for carbon, hydrogen and nitrogen were determined on a Control Equipment Corporation 440 Elemental Analyzer. "Chromatography" refers to flash chromatography (Still, WC; Kahn, M; Mitra, A. *J. Org. Chem.* **1978**, 43, 2923) on 230-400 mesh Silica Gel 60, using the amount of silica gel and solvent of elution referred to parenthetically in the text. "Cation exchange chromatography" refers to ion exchange with Dowex 50X-8

289
284

-11-

(100-200) resin (H^+ form). The resin was prepared by washing (in a coarse porosity sintered glass funnel) with water, then methanol, then water, then 3N ammonium hydroxide (pH $\approx$ 12), then water, then 1N HCl (pH $\approx$ 1), then water
5 until the pH is neutral. The resin was packed into a glass column in water, and the compound (which is dissolved in water at a pH between 2 and 7) was slowly eluted onto the resin, then the column washed with water until the pH is neutral, then 50% aqueous THF, then water. The compound is
10 eluted off of the resin with 10% aqueous pyridine, and product containing fractions (which are detected with ninhydrin stain on a TLC plate) are combined and concentrated *in vacuo*. Water is added and the mixture concentrated *in vacuo*. This procedure is repeated two more
15 times, and ensures complete removal of pyridine.

-12-

EXAMPLE 1

3S,4aR,6S,8aR-6-(((1H-Tetrazole-5-yl)methyl)oxy)methyl)-
1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylic
Acid

5

A. Ethyl 3S,4aR,6S,8aR 6-(((Cyanomethyl)oxy)methyl)-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate: A solution of 12.8 g (42.6 mmol) of ethyl 3S,4aR,6S,8aR-6-hydroxymethyl-2-methoxycarbonyl-1,2,3,4,4a,5,6,7,8,8a-decahydroisoquinoline-3-carboxylate (Ornstein, et al., *Journal of Organic Chemistry*, **1994**, 59, 7862-7869), 10.6 g (85.3 mmol) of ((methoxy)ethoxy)methyl chloride 16.5 g (127.9 mmol) of *N,N*-diisopropylethylamine and 20 mg of 4-*N,N*-dimethylaminopyridine in 70 mL of methylene chloride was
10 heated to reflux for four hours, then cooled, diluted with 150 mL of ether and washed twice with 100 mL each of 10% aqueous sodium bisulfate. The organic phase was dried (magnesium sulfate), filtered, and concentrated *in vacuo*. The residual oil was dissolved in 70 mL of methylene and
20 treated with 17.0 mL (12.7 g, 127.9 mmol) of trimethyl-silyl cyanide, then the solution was cooled to 0°C and treated with 1.3 mL (1.5 g, 10.7 mmol) of boron trifluoride etherate. The resulting solution was allowed to warm to room temperature. After three hours at room temperature,
25 the reaction mixture was treated with 100 mL of 10% aqueous potassium carbonate, then 150 mL of ether. The phases were separated and the organic phase washed one more time with 100 mL of 10% aqueous potassium carbonate. The organic

-13-

phase was dried (magnesium sulfate), filtered, and concentrated *in vacuo*. Chromatography of the residue (350 g of silica gel, 30% ethyl acetate/hexane) afforded 11.9 g (83%) of the title compound.

- 5 Analysis calculated for $C_{17}H_{26}N_2O_5$: C, 60.34; H, 7.74; N, 8.28. Found: C, 60.06; H, 7.69; N, 8.31.
[α]_D = -33.5° (c = 1, CH₂Cl₂).

- B. A mixture of 11.7 g (34.6 mmol) of the compound from
10 Example 1A and 23.0 g (69.2 mmol) of tributyltin azide was heated to 100°C for five days. The mixture was treated with 100 mL of 6 N hydrochloric acid, and heated continued at 100°C. After about 18 hours, the reaction mixture was allowed to cool to room temperature, then extracted with 50
15 mL of ether, 50 mL of dichloromethane and 50 mL of ether, then the aqueous phase was concentrated *in vacuo*. Cation exchange chromatography of the residue afforded a solid that was suspended in acetone, refluxed for one hour, then filtered and washed with acetone and ether, and dried in
20 *vacuo* at 60°C to afford 8.5 g (83%) of the title compound. Analysis calculated for $C_{13}H_{21}N_5O_3 \cdot 0.33 H_2O \cdot 0.33 C_3H_6O$: C, 52.43; H, 7.44; N, 21.84. Found: C, 52.74; H, 7.22; N, 21.50.
[α]_D = -21.6° (c = 1, 1N HCl).

-14-

EXAMPLE 2

Preparation of 3*S*,4*aR*,6*S*,8*aR*-6-(((4-carboxy)phenyl)methyl)-1,2,3,4,4*a*,5,6,7,8,8*a*-decahydroisoquinoline-3-carboxylic acid

5

- A. Methyl 4-(diethylphosphonomethyl)benzoate: A solution of 25.0 g (110 mmol) of methyl 4-bromomethylbenzoate and 37 mL (36.3 g, 220 mmol) of triethyl phosphite in 150 mL of toluene was heated for 18 hours at reflux, then cooled and concentrated *in vacuo*. Chromatography (400 g of silica gel, ethyl acetate) of the residue afforded 30.6 g (98%) of the title compound.
- B. Ethyl 3*S*,4*aR*,6*S*,8*aR*-6-(((4-methoxycarbonyl)phenyl)-methyl)-1,2,3,4,4*a*,5,6,7,8,8*a*-decahydroisoquinoline-3-carboxylate: 14.1 g (49.4 mmol) of the compound from Example 2A and 48 mL (of a 1.0 M solution) of sodium bis(trimethyl-silyl)amide in 100 mL of THF was stirred 45 min at 0°C, then treated with 10.0 g of ethyl 3*S*,4*aR*,8*aR*-6-oxo-2-methoxy-carbonyl-1,2,3,4,4*a*,5,6,7,8,8*a*-decahydroisoquinoline-3-carboxylate in 40 mL of THF. After 15 minutes at 0°C, the reaction was quenched with 100 mL of water and extracted three times with 150 mL each of ether. The combined organics were dried (magnesium sulfate), filtered and concentrated *in vacuo*. The residue was dissolved in 500 mL of ether, treated with 3.0 g of 5% palladium on carbon, and hydrogenated at room temperature and one atmosphere of hydrogen for 24 hours. The mixture

293
268

-15-

was diluted with 500 mL of ether, filtered through a pad of diatomaceous earth, and the filtrate concentrated *in vacuo*. Chromatography (400 g of silica gel, 25% ethyl acetate/hexane) of the residue afforded 12.0 g (81%) of the
5 title compound, as a mixture of methyl and ethyl esters from transesterification of the methyl ester during hydrogenation.

C. 12.0 g of the compound from Example 2B was heated to
10 reflux for 18 hours with 100 mL of 6N hydrochloric acid, then cooled to room temperature. The resulting solid was filtered, washing with water, acetone and ether, and dried *in vacuo* at 60°C to afford 6.2 g (57%) of the title compound.

15 Analysis calculated for $C_{18}H_{23}NO_4 \cdot HCl \cdot 1.25 H_2O$: C, 57.44; H, 7.10; N, 3.72. Found: C; 57.44; H, 6.69; N, 3.76.
[α]_D = -4.8° (c = 1, 1N HCl).

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RADICACIÓN: 0-50073

EDICTO No. 2905

LA SECRETARÍA GENERAL AD-HOC
HACE SABER:

Que esta Superintendencia profirió **Resolución No. 1972 de 31-ENE-2006**. Que el contenido de la parte resolutive es como sigue: El Superintendente de Industria y Comercio.

RESUELVE

ARTICULO PRIMERO: Negar el privilegio de patente de invención para la solicitud correspondiente a "COMPUESTOS DECAHIDROISOQUINOLINA UTILES COMO ANTAGONISTAS SELECTIVOS DEL RECEPTOR $iGluR_5$ PARA EL TRATAMIENTO DE LA MIGRAÑA".

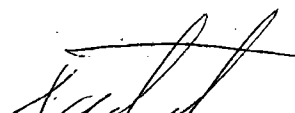
Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10

ARTICULO SEGUNDO: Notificar personalmente el contenido de la presente resolución a la doctora Alicia Lloreda Ricaurte, o a quien haga sus veces, en su calidad de apoderada 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. 2006**

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO,


JAIRO RUBIO ESCOBAR

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 8:30 a.m. de hoy.

Secretaría General Ad-Hoc **21-FEB-2006**
Secretaría General Ad-Hoc
EDICTO No. 2905

Este edicto se desfija hoy **06-MAR-2006** a las cinco (5:00 p.m.)