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Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. \_\_\_\_\_ S. \_\_\_\_\_ D. \_\_\_\_\_

Re: P1.-ELI LILLY AND COMPANY..-Solicitud de Patente de  
Invención para "COMPUESTOS  
DECAHIDROISOQUINOLINA UTILES COMO  
ANTAGONISTAS SELECTIVOS DEL RECEPTOR iGluR<sub>5</sub>  
PARA EL TRATAMIENTO DE LA MIGRAÑA".-Clase  
A.61.-Expediente número 00-050.073.-

1. Me refiero a la solicitud arriba nombrada de fecha 5 de Julio de 2000 y a los autos dictados por este despacho notificados por Estado de 17 de Agosto y 14 de Septiembre del mismo año.

2. Por medio del presente atentamente manifiesto a usted que, debidamente autorizado por mi poderdante, modifiko el título de la solicitud con el objeto de dar cumplimiento a las exigencias del señor Examinador, para que quede como sigue:

**"COMPUESTOS DECAHIDROISOQUINOLINA UTILES COMO  
ANTAGONISTAS SELECTIVOS DEL RECEPTOR iGluR<sub>5</sub> PARA EL  
TRATAMIENTO DE LA MIGRAÑA"**

3. Anexos me permito presentar a usted:

- (1) Nuevo resumen objeto y finalidad de la invención, en el cual se ha incluido el nuevo título de la solicitud;

(2) Nuevas páginas 1 a 60 del texto de la descripción y las reivindicaciones **que reemplazan las originalmente presentadas** en las cuales:

(a) Se ha modificado la página 1 con el fin de incluir el nuevo título de la solicitud;

(b) Se ha modificado la reivindicación 12 con el fin de reemplazar la expresión "un antagonista selectivo del receptor iGluR<sub>5</sub>" por la expresión "**un compuesto como el reivindicado en la reivindicación 7**". El sustento para dicha modificación se encuentra en la página 30 de la descripción.

Con la modificación realizada a la reivindicación 12 se define aún más el objeto de dicha reivindicación como así lo ha requerido el señor Examinador.

(c) Se presenta un nuevo capítulo descriptivo y reivindicatorio de la presente solicitud, en los cuales se ha mejorado la nitidez del texto de las estructuras químicas allí presentes.

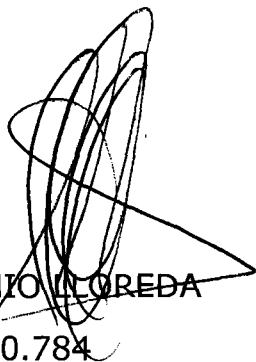
(3) Nuevo extracto, en sus dos formas, **que reemplaza el originalmente presentado**, en el cual se ha incluido el nuevo título de la solicitud;

(4) En original y dos copias, una de ellas de 6cm x 6cm, Arte Final de la figura del invento, para la publicación en la Gaceta de la Propiedad Industrial; y

- (5) Documento que acredita el traspaso que los autores del invento de la referencia hacen a favor de mi poderdante, de sus derechos sobre el mismo, debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 093505 de 11 de Julio de 2000, junto con la traducción oficial número 192 correspondiente a las legalizaciones de dicho documento también debidamente legalizado hasta por el Ministerio de Relaciones Exteriores de Colombia bajo el número 400239 de 19 de Julio de 2000.
4. En relación con el requerimiento de ese Despacho según el cual el solicitante **"Deberá presentar copia certificada su conformidad por la Administración que recibió la solicitud de la cual reivindica prioridad, en cualquier momento dentro del plazo de tres (3) meses, contados a partir de la fecha de depósito de la solicitud posterior. La omisión de esta formalidad implicará la pérdida del derecho de prioridad"**, atentamente me permito manifestar a usted que las copias certificadas de las prioridades que se reivindican en el presente caso, a saber las solicitudes estadinenses números 60/142,485 y 60/151,165 serán presentadas dentro del plazo que el artículo 4(D)3 del Convenio de París establece --esto es dentro de los tres meses siguientes a la fecha de presentación de la solicitud-- que en este caso vence el 5 de Octubre de 2000.

5. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLOREDA

T.P. 10.784

Código 231

Se retiran los folios:  
81-82 Archivo temático y de autor  
83 Extracto de publicación  
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**"COMPUESTOS DE DECAHIDROISOQUINOLINA UTILES COMO ANTAGONISTAS  
SELECTIVOS DEL RECEPTOR iGluR<sub>5</sub> PARA EL TRATAMIENTO DE LA MIGRAÑA"**

La presente invención proporciona un procedimiento para tratar o prevenir la migraña que comprende administrar a un paciente en necesidad del mismo una cantidad eficaz de un antagonista selectivo del receptor iGluR<sub>5</sub>. La presente invención proporciona además nuevos compuestos funcionales como antagonistas selectivos del receptor iGluR<sub>5</sub>, así como composiciones y formulaciones que comprenden dichos antagonistas selectivos del receptor iGluR<sub>5</sub>.

**"COMPUESTOS DE DECAHIDROISOQUINOLINA UTILES COMO ANTAGONISTAS SELECTIVOS  
DEL RECEPTOR  $iGluR_5$  PARA EL TRATAMIENTO DE LA MIGRAÑA"**

**ANTECEDENTES DE LA INVENCIÓN**

5 En el sistema nervioso central (SNC) de los mamíferos, la transmisión de los impulsos nerviosos se controla por la interacción entre un neurotransmisor, que se libera por una neurona emisora, y un receptor superficial presente en una neurona receptora, que provoca la excitación de esta neurona  
10 receptora. El L-glutamato, que es el neurotransmisor más abundante en el SNC, media las rutas excitadoras principales en los mamíferos y se hace referencia a él como un aminoácido excitador (EAA). Los receptores que responden al glutamato se denominan receptores de aminoácidos excitadores  
15 (receptores de EAA). Véase Watkins y Evans, *Ann. Rev. Pharmacol. Toxicol.*, 21, 165 (1981); Monaghan, Bridges y Cotman, *Ann. Rev. Pharmacol. Toxicol.*, 29, 365 (1989); Watkins, Krogsgaard-Larsen y Honore, *Trans. Pharm. Sci.*, 11, 25 (1990). Los aminoácidos excitadores son de gran  
20 importancia fisiológica, jugando un papel en una diversidad de procesos fisiológicos tales como la potenciación a largo plazo (aprendizaje y memoria), el desarrollo de plasticidad sináptica, el control motor, la respiración, la regulación cardiovascular y la percepción sensorial.

25 Los receptores de aminoácidos excitadores se clasifican

en dos tipos generales. Los receptores que están acoplados directamente a la apertura de canales de cationes en la membrana celular de las neuronas se denominan "ionotrópicos". Este tipo de receptores se ha subdividido en al menos tres subtipos, que se definen por las acciones despolarizantes de los agonistas selectivos *N*-metil-D-aspartato (NMDA), ácido  $\alpha$ -amino-3-hidroxi-5-metilisoxazol-4-propiónico (AMPA) y ácido caínico (KA). Ciertos estudios de biología molecular han establecido que los receptores de AMPA están compuestos por subunidades ( $\text{GluR}_1$  -  $\text{GluR}_4$ ), que pueden ensamblarse para formar canales de iones funcionales. Se han identificado cinco receptores de cainato que se clasifican como receptores de Alta Afinidad ( $\text{KA1}$  y  $\text{KA2}$ ) o de Baja Afinidad ( $\text{GluR}_5$ ,  $\text{GluR}_6$  y  $\text{GluR}_7$ ). Bleakman y col., *Molecular Pharmacology*, 49, No. 4, 581 (1996).

El segundo tipo general de receptores es el receptor "metabotrópico" de aminoácidos excitadores asociado a segundos mensajeros o a la proteína G. Este segundo tipo se acopla a múltiples sistemas de segundos mensajeros que conducen al aumento de la hidrólisis del fosfoinosítido, la activación de la fosfolipasa D, aumentos o reducciones de la formación de AMPc y cambios en la función de los canales iónicos. Schoepp y Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Parece ser que los dos tipos de receptores no sólo median la transmisión sináptica normal a lo largo de las vías

excitadoras, sino que también participan en la modificación de las conexiones sinápticas durante el desarrollo y a lo largo de toda la vida. Schoepp, Bockaert y Sladeczek, *Trends in Pharmacol. Sci.*, 11, 508 (1990); McDonald y Johnson, *Brain Research Reviews*, 15, 41 (1990).

Una estimulación excesiva o inapropiada de los receptores de aminoácidos excitadores ocasiona lesiones o pérdida de células neuronales por medio de un mecanismo conocido como excitotoxicidad. Se ha sugerido que este proceso media la degeneración neuronal en una diversidad de trastornos y afecciones neurológicas. Las consecuencias médicas de tal degeneración neuronal hacen al alivio de estos procesos neurológicos degenerativos un importante objetivo terapéutico.

La excitotoxicidad de los aminoácidos excitadores se ha implicado en la patofisiología de numerosos trastornos neurológicos. Por ejemplo, la excitotoxicidad se ha asociado con la etiología de déficits cerebrales posteriores a una cirugía de desviación cardíaca e injertos, apoplejía, isquemia cerebral, lesiones de la médula espinal producidas por traumatismos o inflamación, hipoxia perinatal, paro cardíaco y lesiones neuronales debidas a hipoglucemias. Además, la excitotoxicidad se ha implicado en afecciones neurodegenerativas crónicas que incluyen la Enfermedad de Alzheimer, Corea de Huntington, ataxias hereditarias,

demencia inducida por el SIDA, esclerosis lateral  
amiotrófica, Enfermedad de Parkinson idiopática e inducida  
por fármacos, así como lesiones oculares y retinopatía. Otros  
trastornos neurológicos implicados con la excitotoxicidad y/o  
5 la disfunción del glutamato incluyen espasticidad muscular  
incluyendo temblores, tolerancia y deshabitación a drogas,  
edema cerebral, trastornos convulsivos que incluyen  
epilepsia, depresión, ansiedad y trastornos relacionados con  
la ansiedad tales como síndrome de estrés post-traumático,  
10 discinesia tardía y psicosis relacionada con la depresión,  
esquizofrenia, trastorno bipolar, manía, intoxicación con  
drogas o adicción. Además, también se ha informado que la  
excitotoxicidad de los aminoácidos excitadores participa en  
la etiología de estados de dolor agudo y crónico, incluyendo  
15 el dolor fuerte, dolor intratable, dolor neuropático y dolor  
post-traumático.

Se cree que el uso de un agente neuroprotector, tal como  
un antagonista del receptor de aminoácidos excitadores, es  
útil para tratar o prevenir estos trastornos y/o reducir la  
20 cantidad de lesiones neurológicas asociadas con estos  
trastornos. Los antagonistas de los receptores de aminoácidos  
excitadores también pueden ser útiles como agentes  
analgésicos.

Las primeras teorías con respecto a la patofisiología  
25 de la migraña se han dominado desde 1938 por el trabajo de

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Grahan y Wolff (*Arch. Neurol. Psychiatry*, 39, 737-63 (1938)). Propusieron que la causa de las cefalalgias que reciben el nombre de migrañas es la vasodilatación de los vasos extracraneales. Esta opinión se confirma por el conocimiento  
5 de que los alcaloides del cornezuelo del centeno y el sumatriptan contraen el músculo liso vascular cefálico y son eficaces en el tratamiento de la migraña. El sumatriptan es un agonista hidrófilo de los receptores de serotonina de tipo 5-HT-1 y no atraviesa la barrera hematoencefálica (Humphrey  
10 y col., *Ann. NY Acad. Sci.*, 600, 587-600 (1990)). Por consiguiente, se han creado varias series de compuestos que se dice que son útiles para el tratamiento de la migraña para optimizar la actividad vasoconstrictora del sumatriptan mediada por receptores de tipo 5-HT<sub>1</sub>. Sin embargo, las  
15 contraindicaciones del sumatriptan, incluyendo el vasoespasma coronario, la hipertensión y la angina, también son productos de su actividad vasoconstrictora (MacIntyre, P.D., y col., *British Journal of Clinical Pharmacology*, 34, 541-546 (1992); Chester, A.H., y col., *Cardiovascular Research*, 24, 932-937  
20 (1990); Conner, H.E., y col., *European Journal of Pharmacology*, 161, 91-94 (1990)).

Aunque el mecanismo vascular de la migraña ha conseguido una amplia aceptación, no hay un acuerdo global en cuanto a su validez. Moskowitz, por ejemplo, ha demostrado la  
25 existencia de cefalalgias de migraña independientemente de

cambios del diámetro de los vasos (Cephalalgia, 12, 5-7, (1992)). Se sabe que los ganglios del trigémino y sus vías nerviosas asociadas, están relacionados con sensaciones dolorosas de la cara tales como cefalalgias, en particular la migraña. Moskowitz propuso que activadores desconocidos estimulan los ganglios del trigémino que inervan la vasculatura interna del tejido cefálico, ocasionando la liberación de neuropéptidos vasoactivos por los axones que inervan la vasculatura. Estos neuropéptidos inician una serie de acontecimientos que conducen a la inflamación neurogénica de las meninges, cuya consecuencia es el dolor. Esta inflamación neurogénica se bloquea por el sumatriptan a dosis similares a las requeridas para tratar la migraña aguda en los seres humanos. Sin embargo, tales dosis de sumatriptan, como se ha indicado, están asociadas con contraindicaciones como resultado de las propiedades vasoconstrictoras asociadas del sumatriptan (véase *supra*).

Los receptores 5-HT<sub>1D</sub> se han implicado como mediadores del bloqueo de la extravasación de proteínas neurogénicas. (Neurology, 43 (supl. 3), S16-S20 (1993)). Además, se ha informado que los receptores  $\alpha_2$ , H<sub>3</sub>, m-opioides y de somatostatina también pueden localizarse en fibras trigéminovasculares y pueden bloquear la extravasación neurogénica de plasma (Matsubara y col., Eur. J. Pharmacol., 224, 145-150 (1992)). Weinshank y col. han informado que el

sumatriptan y varios alcaloides del cornezuelo del centeno tienen una alta afinidad por el receptor 5-HT<sub>1F</sub> de la serotonina, lo cual sugiere un papel para el receptor 5-HT<sub>1F</sub> en la migraña (documento WO93/14201).

5 La Publicación de la Solicitud de Patente Europea No. 59078A1 y las Patentes de Estados Unidos No. 5.446.051 y 5.670.516 describen que ciertos compuestos derivados de decahidroisoquinolina son antagonistas del receptor de AMPA y, como tales, son útiles en el tratamiento de muchas  
10 afecciones diferentes, incluyendo el dolor y las cefalalgias denominadas migrañas.

Recientemente se ha informado que los cinco miembros de los receptores de glutamato ionotrópicos del subtipo de cainato se expresan en neuronas de ganglios del trigémino de  
15 rata. En particular, se han observado altos niveles de GluR<sub>5</sub> y KA2. (Sahara y col., *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons y col. informaron que el subtipo de receptores GluR<sub>5</sub> de cainato media la respuesta de nocicepción a formalina en un modelo de dolor persistente en rata.  
20 (*Neuropharmacology*, 37, 25 (1998)). Además, el documento WO98/45270 había descrito previamente que los antagonistas selectivos para el receptor iGluR<sub>5</sub> son útiles para el tratamiento del dolor, incluyendo el dolor fuerte, crónico, intratable y neuropático. Es digna de mención la observación  
25 de que los receptores de cainato no se han implicado

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previamente en la etiología de las migrañas. En particular, los antagonistas selectivos del receptor iGluR<sub>5</sub> no se han presentado previamente como agentes útiles para el tratamiento de la migraña.

5        Sorprendentemente y de acuerdo con esta invención, los Solicitantes han descubierto que los antagonistas selectivos del subtipo de receptores iGluR<sub>5</sub> son eficaces en un modelo animal de inflamación neurogénica y, por lo tanto, pueden ser útiles para el tratamiento de la migraña. Tales antagonistas  
10   podrían ser la respuesta a una necesidad sentida desde hace mucho tiempo de un tratamiento seguro y eficaz para la migraña, sin efectos secundarios asociados. Por lo tanto, por el presente documento se profundiza en el tratamiento de trastornos neurológicos.

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#### RESUMEN DE LA INVENCION

La presente invención proporciona un procedimiento para tratar o prevenir la migraña que comprende administrar a un paciente en necesidad del mismo una cantidad eficaz de un antagonista selectivo del receptor iGluR<sub>5</sub> o una sal  
20   farmacéuticamente aceptable del mismo.

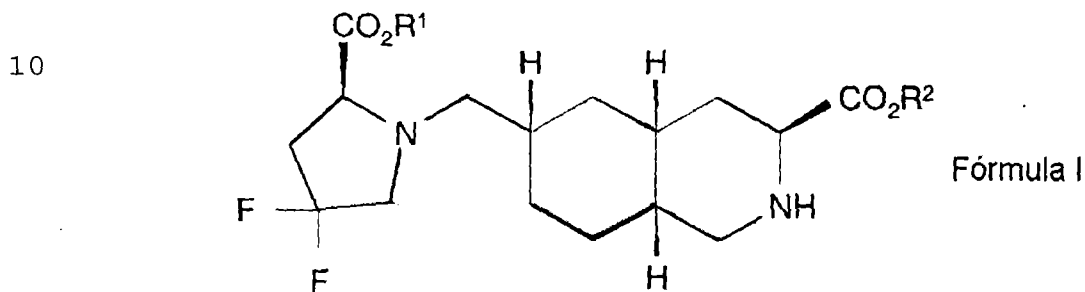
Más específicamente, la presente invención proporciona un procedimiento de tratamiento o prevención de la extravasación de proteínas dures que comprende administrar a un paciente en necesidad del mismo una cantidad eficaz de  
25   un antagonista selectivo del receptor iGluR<sub>5</sub>.

Además, la presente invención proporciona un procedimiento de tratamiento o prevención de la migraña que comprende administrar a un paciente en necesidad del mismo una cantidad eficaz de un compuesto o de una combinación de  
5 compuestos que posee la actividad de un antagonista selectivo del receptor  $iGluR_5$ .

En otra realización, la presente invención proporciona un procedimiento de tratamiento o prevención de un trastorno neurológico o un trastorno neurodegenerativo, que comprende  
10 administrar a un paciente en necesidad del mismo una cantidad eficaz de un antagonista selectivo del receptor  $iGluR_5$  o una sal farmacéuticamente aceptable del mismo. Los ejemplos de tales trastornos neurológicos o trastornos neurodegenerativos incluyen: déficits cerebrales posteriores a una cirugía de  
15 desviación cardíaca e injertos; apoplejía; isquemia cerebral; lesiones de la médula espinal producidas por traumatismos o inflamación; hipoxia perinatal; paro cardíaco; lesiones neuronales debidas a hipoglucemias; Enfermedad de Alzheimer; Corea de Huntington; ataxias hereditarias; demencia inducida  
20 por el SIDA; esclerosis lateral amiotrófica; Enfermedad de Parkinson idiopática e inducida por fármacos; lesión ocular y retinopatía; espasticidad muscular incluyendo temblores; tolerancia y deshabitación a drogas; edema cerebral; trastornos convulsivos que incluyen epilepsia; depresión;  
25 ansiedad y trastornos de ansiedad relacionados tales como

síndrome de estrés post-traumático; discinesia tardía; psicosis relacionada con la depresión, esquizofrenia, trastorno bipolar, manía e intoxicación por drogas o adicción; y estados de dolor agudos o crónicos incluyendo el dolor fuerte, dolor intratable, dolor neuropático y dolor post-traumático.

En un aspecto adicional, la presente invención proporciona un compuesto de Fórmula I



15 en la que cada uno de R<sup>1</sup> y R<sup>2</sup> es independientemente H, alquilo C<sub>1</sub>-C<sub>20</sub>, alquenilo C<sub>2</sub>-C<sub>6</sub>, alquil C<sub>1</sub>-C<sub>6</sub>-arilo, alquil C<sub>1</sub>-C<sub>6</sub>-cicloalquilo(C<sub>3</sub>-C<sub>10</sub>), alquil C<sub>1</sub>-C<sub>6</sub>-N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina, alquil C<sub>1</sub>-C<sub>6</sub>-pirrolidina, alquil C<sub>1</sub>-C<sub>6</sub>-piperidina o alquil C<sub>1</sub>-C<sub>6</sub>-morfolina; o una sal farmacéuticamente aceptable del mismo.

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En otro aspecto, la presente invención proporciona un procedimiento de tratamiento o prevención de la migraña que comprende administrar a un paciente en necesidad del mismo una cantidad eficaz de un compuesto de Fórmula I.

25 Además, la presente invención proporciona composiciones

farmacéuticas útiles para tratar o prevenir la migraña que comprenden antagonistas selectivos del receptor iGluR<sub>5</sub> en combinación con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables.

- 5        La presente invención también proporciona el uso de un antagonista selectivo del receptor iGluR<sub>5</sub> para la fabricación de un medicamento para el tratamiento o prevención de la migraña.

#### DESCRIPCIÓN DETALLADA DE LA INVENCION

- 10        La presente invención proporciona un procedimiento para el tratamiento de la migraña que puede demostrarse por un mecanismo particular de acción, inhibición de la extravasación de proteínas neurogénicas durales. Mediante el tratamiento de una migraña con un compuesto o composición que
- 15        es un antagonista selectivo del receptor iGluR<sub>5</sub> en relación con otros receptores de aminoácidos excitadores, se inhibe la extravasación neurogénica que media la migraña sin los efectos secundarios asociados de agentes diseñados para optimizar la actividad vasoconstrictora del sumatriptan
- 20        mediada por receptores de tipo 5-HT<sub>1</sub>. Además, la presente invención proporciona compuestos funcionales como antagonistas selectivos del receptor iGluR<sub>5</sub>, así como sales farmacéuticamente aceptables, profármacos y composiciones de los mismos.

- 25        El término "sal farmacéuticamente aceptable", como se

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usa en este documento, se refiere a sales de los compuestos proporcionadas o empleadas en la presente invención que son sustancialmente no tóxicas para los organismos vivos. Las sales farmacéuticamente aceptables típicas incluyen las sales preparadas mediante la reacción de los compuestos de la presente invención con un ácido mineral u orgánico o una base orgánica o inorgánica farmacéuticamente aceptables. Tales sales son conocidas como sales de adición de ácidos y sales de adición de bases.

10 Los lectores especialistas entenderán que la mayoría o todos los compuestos usados en la presente invención son capaces de formar sales y que comúnmente se usan las formas de sales de los compuestos farmacéuticos, a menudo porque cristalizan y se purifican más fácilmente que las bases libres. En cualquier caso, en la descripción de este documento se contempla el uso de los fármacos descritos como sales, y a menudo se prefieren, y las sales farmacéuticamente aceptables de todos los compuestos se incluyen en sus nombres.

20 Los ácidos empleados comúnmente para formar sales de adición de ácidos son ácidos inorgánicos tales como el ácido clorhídrico, el ácido bromhídrico, el ácido yodhídrico, el ácido sulfúrico, el ácido fosfórico y similares, y ácidos orgánicos tales como el ácido p-toluenosulfónico, el ácido maleico, el ácido metanosulfónico, el ácido oxálico, el ácido

p-bromofenilsulfónico, el ácido carbónico, el ácido succínico, el ácido cítrico, el ácido benzoico, el ácido acético, el ácido 1,5 naftaleno disulfónico y similares. Son ejemplos de tales sales farmacéuticamente aceptables el

5 sulfato, piro sulfato, bisulfato, sulfito, bisulfito, fosfato, fosfato monoácido, fosfato diácido, metafosfato, pirofosfato, bromuro, yoduro, acetato, propionato, decanoato, caprilato, acrilato, formiato, clorhidrato, diclorhidrato, isobutirato, caproato, heptanoato, propiolato, oxalato, malonato,

10 succinato, suberato, sebacato, fumarato, maleato, butino-1,4-dioato, hexino-1,6-dioato, benzoato, clorobenzoato, metilbenzoato, hidroxibenzoato, metoxibenzoato, ftalato, xilenosulfonato, fenilacetato, fenilpropionato, fenilbutirato, citrato, lactato,  $\alpha$ -hidroxibutirato,

15 glicolato, tartrato, metanosulfonato, propanosulfonato, naftaleno-1-sulfonato, naftaleno-2-sulfonato, napadisilato, mandelato y similares. Las sales de adición de ácidos farmacéuticamente aceptables preferidas son las formadas con ácidos minerales tales como el ácido clorhídrico y el ácido

20 bromhídrico, y las formadas con ácidos orgánicos tales como el ácido maleico y el ácido metanosulfónico.

Las sales de adición de bases incluyen las derivadas de bases inorgánicas tales como hidróxidos, carbonatos, bicarbonatos y similares de amonio o de metales alcalinos o

25 alcalinotérreos. Por lo tanto, tales bases útiles en la

preparación de las sales de esta invención incluyen hidróxido  
sódico, hidróxido potásico, hidróxido amónico, carbonato  
potásico, carbonato sódico, bicarbonato sódico, bicarbonato  
potásico, hidróxido cálcico, carbonato cálcico y similares.

5 Se prefieren particularmente las formas de sal de potasio y  
sodio.

Se reconocerá que los contraiones particulares que  
forman una parte de cualquier sal de esta invención  
habitualmente no son de naturaleza crítica, siempre que la  
10 sal en su conjunto sea farmacológicamente aceptable y siempre  
que el contraión no aporte cualidades indeseables a la sal  
en su conjunto.

Como se usa en este documento, el término  
"estereoisómero" se refiere a compuestos hechos de los mismos  
15 átomos unidos por los mismos enlaces pero que tienen  
diferentes estructuras tridimensionales que no son  
intercambiables. Las estructuras tridimensionales se  
denominan configuraciones. Como se usa en este documento, el  
término "enantiómero" se refiere a dos estereoisómeros cuyas  
20 moléculas son imágenes especulares no superponibles entre sí.  
El término "centro quiral" se refiere a un átomo de carbono  
al que están unidos cuatro grupos diferentes. Como se usa en  
este documento, el término "diastereómeros" se refiere a  
estereoisómeros que no son enantiómeros. Además, dos  
25 diastereómeros que tienen una configuración diferente sólo

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en un centro quiral se denominan en este documento "epímeros". Los términos "racemato", "mezcla racémica" o "modificación racémica" se refieren a una mezcla de partes iguales de enantiómeros.

5 El término "enriquecimiento enantiomérico", como se usa en este documento, se refiere al aumento de la cantidad de un enantiómero en comparación con el otro. Un procedimiento conveniente para expresar el enriquecimiento enantiomérico conseguido es el concepto de exceso enantiomérico, o "ee",  
10 que se encuentra usando la siguiente ecuación:

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

en la que  $E^1$  es la cantidad del primer enantiómero y  $E^2$  es la  
15 cantidad del segundo enantiómero. Así pues, si la relación inicial de los dos enantiómeros es 50:50, tal como se presenta en una mezcla racémica, y se consigue un enriquecimiento enantiomérico suficiente como para producir una relación final de 50:30, el ee con respecto al primer  
20 enantiómero es del 25%. Sin embargo, si la relación final es de 90:10, el ee con respecto al primer enantiómero es del 80%. Se prefiere un ee mayor del 90%, es más preferido un ee mayor del 95% y aún es más preferido especialmente un ee mayor del 99%. El enriquecimiento enantiomérico se determina  
25 fácilmente por un especialista habitual en la técnica usando

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técnicas y procedimientos convencionales tales como cromatografía de gases o cromatografía líquida de alto rendimiento con una columna quirál. La elección de la columna quirál apropiada, el eluyente y las condiciones necesarias  
5 para realizar la separación del par de enantiómeros está bien dentro del conocimiento de un especialista habitual en la técnica. Además, los enantiómeros de los compuestos de fórmula I pueden resolverse por un especialista habitual en la técnica usando técnicas convencionales bien conocidas en  
10 la técnica, tales como las descritas por J. Jacques, y col., "Enantiomers, Racemates and Resolutions", John Wiley and Sons, Inc., 1981.

Los compuestos de la presente invención tienen uno o más centros quirales y pueden existir en una diversidad de  
15 configuraciones estereoisoméricas. Como consecuencia de estos centros quirales, los compuestos de la presente invención existen como racematos, mezclas de enantiómeros y como enantiómeros individuales, así como diastereómeros y mezclas de diastereómeros. Se entiende que tales racematos,  
20 enantiómeros y diastereómeros están dentro del alcance de la presente invención.

Los términos "R" y "S" se usan en este documento como se usan comúnmente en la química orgánica para hacer referencia a la configuración específica de un centro  
25 quirál. El término "R" (recto) se refiere a la configuración

de un centro quiral con una relación en el sentido de las agujas del reloj de prioridades de grupos (de mayor a segundo menor) cuando se ve a lo largo del enlace hacia el grupo de menor prioridad. El término "S" (sinistral) se refiere a la configuración de un centro quiral con una relación en el sentido contrario al de las agujas del reloj de prioridades de grupos (de mayor a segundo menor) cuando se ve a lo largo del enlace hacia el grupo de menor prioridad. La prioridad de los grupos se basa en su número atómico (en el orden de número atómico decreciente). En "Nomenclature of Organic Compounds: Principles and Practice", (J. H. Fletcher y col., eds., 1974), en las páginas 103-120, se incluye una lista parcial de prioridades y una discusión de la estereoquímica.

Los estereoisómeros y enantiómeros específicos de los compuestos de Fórmula (I) pueden prepararse por un especialista habitual en la técnica utilizando técnicas y procedimientos bien conocidos tales como los descritos por Eliel y Wilen, "Stereochemistry of Organic Compounds", John Wiley y Sons, Inc., 1994, Capítulo 7, Separation of Stereoisomers. Resolution. Racemization, y por Collet y Willen, "Enantiomers, Racemates y Resolutions", John Wiley y Sons, Inc., 1981. Por ejemplo, los estereoisómeros y enantiómeros específicos pueden prepararse por síntesis estereoespecíficas usando materiales de partida enantiomérica y geoméricamente puros o enantiomérica o geoméricamente

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enriquecidos. Además, los estereoisómeros y enantiómeros  
específicos pueden resolverse y recuperarse por técnicas  
tales como resolución cromatográfica sobre fases  
estacionarias quirales, resolución enzimática o  
5 recristalización fraccionada de sales de adición formadas por  
reactivos usados para este fin.

También debe entenderse por los especialistas en la  
técnica que todos los compuestos útiles para los  
procedimientos de la presente invención están disponibles  
10 para la formulación de profármacos. "Profármaco", como se usa  
en este documento, se refiere a un derivado éster o diéster  
metabólicamente lábil de los compuestos (fármacos) ácidos  
funcionales proporcionados o empleados en los procedimientos  
de la presente invención. Cuando se administra a un paciente,  
15 el profármaco experimenta escisión enzimática y/o química  
hidrolítica de una manera tal que se libera el ácido  
carboxílico parental (fármaco) o, como puede ser el caso, el  
ácido dicarboxílico parental. En todos los casos se  
contempla, y a menudo se prefiere, el uso de los compuestos  
20 descritos en este documento como profármacos y, por lo tanto,  
en los nombres de los compuestos de este documento se  
incluyen los profármacos de todos los compuestos empleados.

Como se usa en este documento, el término "alquilo C<sub>1</sub>-C<sub>4</sub>"  
se refiere a una cadena alifática saturada monovalente lineal  
25 o ramificada de 1 a 4 átomos de carbono, e incluye, pero sin

limitación, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo y similares.

Como se usa en este documento, el término "alquilo C<sub>1</sub>-C<sub>6</sub>" se refiere a una cadena alifática saturada monovalente lineal o ramificada de 1 a 6 átomos de carbono, e incluye, pero sin limitación, metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, t-butilo, n-pentilo, n-hexilo y similares.

Como se usa en este documento, el término "alquilo C<sub>1</sub>-C<sub>10</sub>" se refiere a una cadena alifática saturada monovalente lineal o ramificada de 1 a 10 átomos de carbono e incluye, pero sin limitación, metilo, etilo, propilo, isopropilo, n-butilo, isobutilo, butilo terciario, pentilo, isopentilo, hexilo, 2,3-dimetil-2-butilo, heptilo, 2,2-dimetil-3-pentilo, 2-metil-2-hexilo, octilo, 4-metil-3-heptilo y similares.

Como se usa en este documento, el término "alquilo C<sub>1</sub>-C<sub>20</sub>" se refiere a una cadena alifática saturada monovalente lineal o ramificada de 1 a 20 átomos de carbono e incluye, pero sin limitación, metilo, etilo, propilo, isopropilo, butilo, isobutilo, t-butilo, pentilo, isopentilo, hexilo, 3-metilpentilo, 2-etilbutilo, n-heptilo, n-octilo, n-nonilo, n-decilo, n-undecilo, n-dodecilo, n-tridecilo, n-tetradecilo, n-pentadecilo, n-hexadecilo, n-heptadecilo, n-nonadecilo, n-eicosilo y similares.

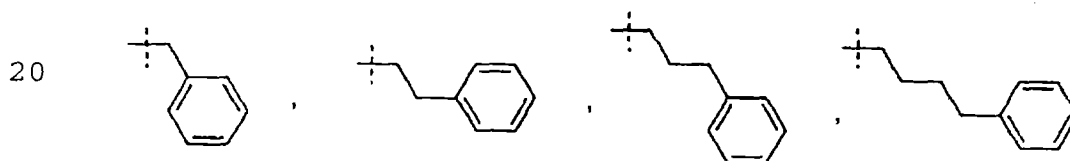
Como se usa en este documento, los términos "Me", "Et", "Pr", "iPr", "Bu" y "t-Bu" se refieren a metilo, etilo,

propilo, isopropilo, butilo y terc-butilo, respectivamente.

Como se usa en este documento, el término "alquenilo C<sub>2</sub>-C<sub>6</sub>" se refiere a una cadena alifática insaturada monovalente lineal o ramificada que tiene de dos a seis átomos de carbono. Los grupos alquenilo C<sub>2</sub>-C<sub>6</sub> típicos incluyen etenilo (también conocido como vinilo), 1-metiletenilo, 1-metil-1-propenilo, 1-butenilo, 1-hexenilo, 2-metil-2-propenilo, 1-propenilo, 2-propenilo, 2-butenilo, 2-pentenilo y similares.

Como se usa en este documento, el término "arilo" se refiere a un grupo carbocíclico monovalente que contiene uno o más anillos de fenilo condensados o no condensados e incluye, por ejemplo, fenilo, 1- ó 2-naftilo, 1,2-dihidronaftilo, 1,2,3,4-tetrahidronaftilo y similares.

Como se usa en este documento, el término "alquil C<sub>1</sub>-C<sub>6</sub>-arilo" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos de carbono, que tiene un grupo arilo unido a la cadena alifática. Dentro del término "alquil C<sub>1</sub>-C<sub>6</sub>-arilo" se incluyen los siguientes:



y similares.

Como se usa en este documento, el término "cicloalquilo (C<sub>3</sub>-C<sub>10</sub>)" se refiere a una estructura de anillo

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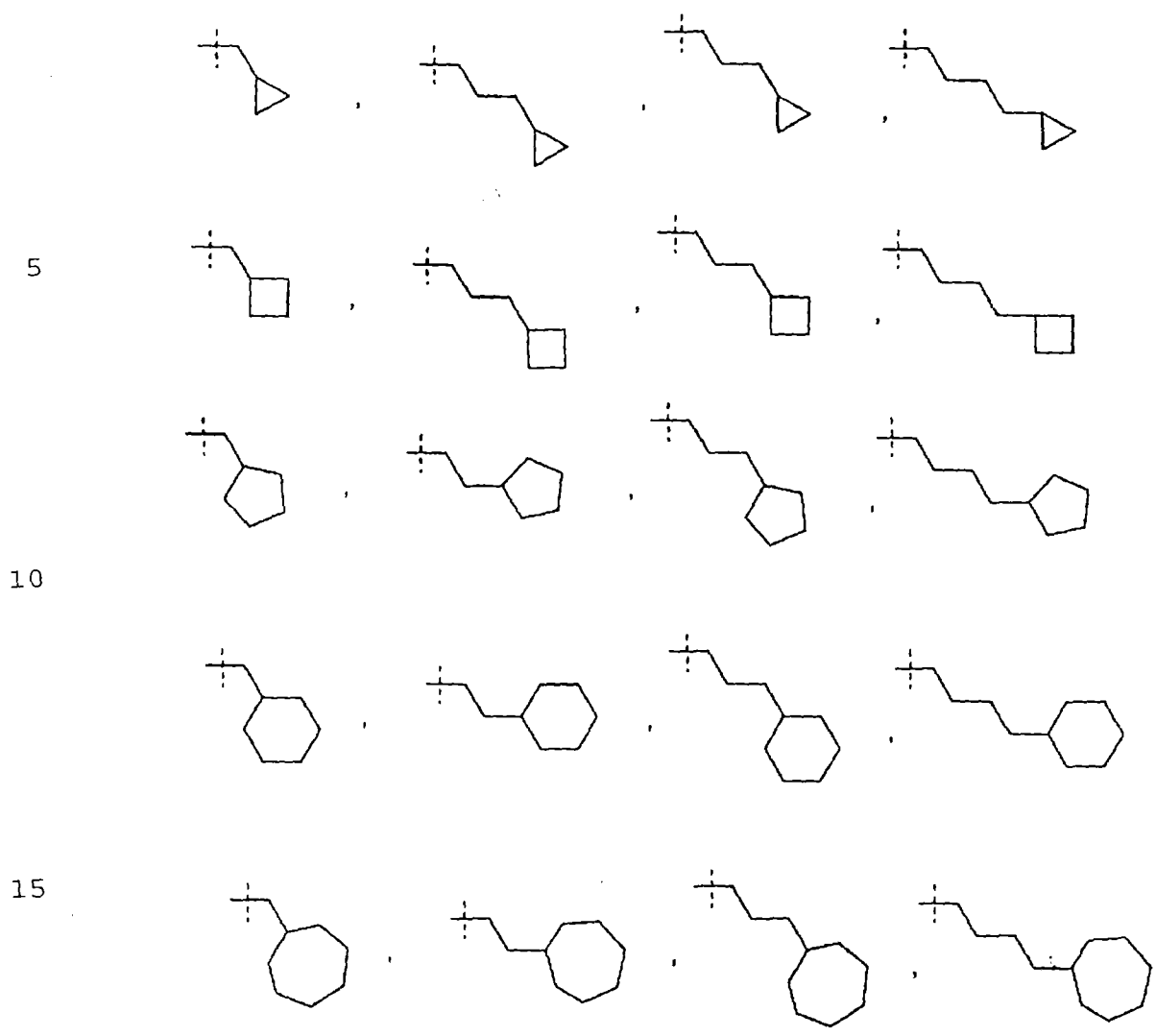
de hidrocarburo saturado que contiene de tres a diez átomos de carbono. Los grupos cicloalquilo  $C_3-C_{10}$  típicos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo y similares. Se entenderá que  
5 dentro del término "cicloalquilo( $C_3-C_{10}$ )" se incluyen el "cicloalquilo( $C_3-C_8$ )" y el "cicloalquilo( $C_4-C_6$ )".

Como se usa en este documento, el término "alquil  $C_1-C_6$ -cicloalquilo( $C_3-C_{10}$ )" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos  
10 de carbono, que tiene un cicloalquilo( $C_3-C_{10}$ ) unido a la cadena alifática. Dentro del término "alquil  $C_1-C_6$ -cicloalquilo( $C_3-C_{10}$ )" se encuentran los siguientes:

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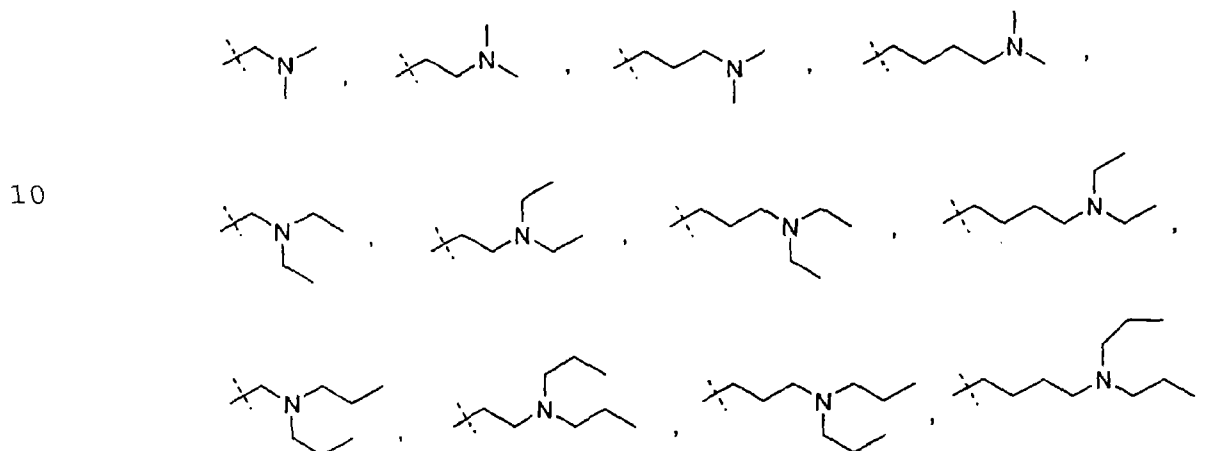


y similares.

20 Como se usa en este documento, el término "N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina" se refiere a un átomo de nitrógeno sustituido con dos cadenas alifáticas saturadas monovalentes, lineales o ramificadas, de 1 a 6 átomos de carbono. Dentro del término "N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina" se incluyen -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -

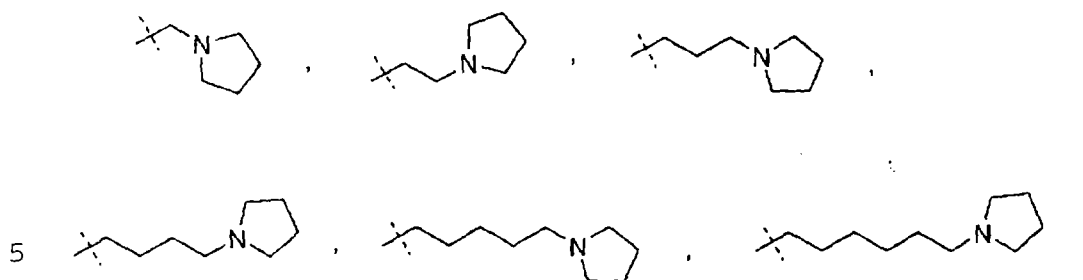
25 N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub> y similares.

Como se usa en este documento, el término "alquil C<sub>1</sub>-C<sub>6</sub>-N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos de carbono, que tiene una N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina unida a la  
5 cadena alifática. Dentro del término "alquil C<sub>1</sub>-C<sub>6</sub>-N,N-dialquil C<sub>1</sub>-C<sub>6</sub>-amina" se incluyen los siguientes:



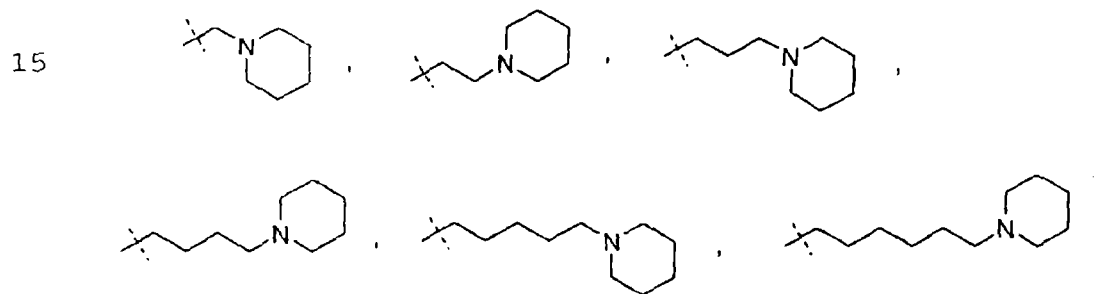
y similares.

Como se usa en este documento, el término "alquil C<sub>1</sub>-C<sub>6</sub>-pirrolidina" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos de carbono,  
20 que tiene una pirrolidina unida a la cadena alifática. Dentro del alcance del término "alquil C<sub>1</sub>-C<sub>6</sub>-pirrolidina" se incluyen los siguientes:



y similares.

Como se usa en este documento, el término "alquil C<sub>1</sub>-C<sub>6</sub>-piperidina" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos de carbono, que tiene una piperidina unida a la cadena alifática. Dentro del alcance del término "alquil C<sub>1</sub>-C<sub>6</sub>-piperidina" se incluyen los siguientes:

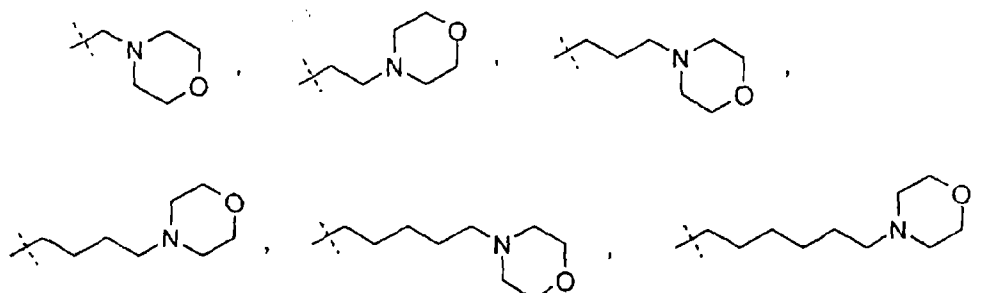


20 y similares.

Como se usa en este documento, el término "alquil C<sub>1</sub>-C<sub>6</sub>-morfolina" se refiere a una cadena alifática saturada monovalente, lineal o ramificada, de 1 a 6 átomos de carbono, que tiene una morfolina unida a la cadena alifática. Dentro del alcance del término "alquil C<sub>1</sub>-C<sub>6</sub>-morfolina" se incluyen

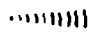
los siguientes:

5



y similares.

La designación "  " se refiere a un enlace que sobresale por delante del plano de la página.

La designación "  " se refiere a un enlace que sobresale por detrás del plano de la página.

Como se usa en este documento, el término "iGluR<sub>5</sub>" se refiere al receptor de glutamato ionotrópico cainato, subtipo 5, de la clase más amplia de receptores de aminoácidos excitadores.

Como se usa en este documento, el término "migraña" se refiere a un trastorno del sistema nervioso caracterizado por ataques recurrentes de dolor de cabeza (que no están causados por una anomalía estructural del cerebro, tales como los resultantes de un tumor o de una apoplejía), trastornos gastrointestinales y posiblemente síntomas neurológicos tales como una distorsión visual. Los dolores de cabeza característicos de la migraña normalmente duran un día y comúnmente van acompañados por náuseas, emesis y fotofobia.

La migraña es una afección "crónica". El término "crónico", como se usa en este documento, significa una afección de progreso lento y continuación prolongada. Como tal, una afección crónica se trata cuando se diagnostica y  
 5. el tratamiento se continúa a lo largo de todo el curso de la enfermedad. Inversamente, el término "agudo" significa un suceso o ataque exacerbado, de curso corto, seguido por un período de remisión. Así pues, el tratamiento de la migraña contempla tanto sucesos agudos como condiciones crónicas. En  
 10 un suceso agudo, el compuesto se administra al inicio de los síntomas y se interrumpe cuando desaparecen los síntomas. Como se ha descrito anteriormente, una afección crónica se trata a lo largo de todo el curso de la enfermedad.

Como se usa en este documento, el término "paciente" se  
 15 refiere a un mamífero tal como un ratón, gerbo, cobaya, rata, perro o ser humano. Sin embargo, se entiende que el paciente preferido es un ser humano.

Se entiende que el término "antagonista selectivo del receptor  $iGluR_5$ ", como se usa en este documento, incluye los  
 20 antagonistas de los receptores de aminoácidos excitadores que se unen selectivamente al subtipo de receptores de cainato  $iGluR_5$ , en lugar de al subtipo de receptores de AMPA  $iGluR_2$ . Preferiblemente, el antagonista selectivo de  $iGluR_5$  para uso de acuerdo con el procedimiento de la presente invención  
 25 tiene una afinidad de unión al menos 10 veces mayor por

iGluR<sub>3</sub> que por iGluR<sub>2</sub>, más preferiblemente al menos 100 veces mayor. Además, se entiende que dentro del alcance de los procedimientos de la presente invención se incluye cualquier antagonista selectivo de iGluR<sub>3</sub>, como se apreciará por un  
5 especialista habitual en la técnica. Tales antagonistas selectivos del receptor iGluR<sub>3</sub> están fácilmente disponibles o se preparan fácilmente por un especialista habitual en la técnica siguiendo procedimientos reconocidos. Los ejemplos de los antagonistas selectivos del receptor iGluR<sub>3</sub> incluyen,  
10 pero sin limitación, los compuestos proporcionados en el documento WO98/45270, cuyo contenido se incorpora en el presente documento por referencia.

Se entiende además que los antagonistas selectivos del receptor iGluR<sub>3</sub> pueden existir como sales farmacéuticamente  
15 aceptables y, por lo tanto, dentro del alcance de la presente invención se incluyen tales sales.

Como se usa en este documento, tanto el término "tratamiento" como el término "tratar" significan aliviar los síntomas, eliminar la causa de los síntomas resultantes en  
20 una base temporal o permanente, y prevenir, ralentizar la aparición o invertir la progresión o la gravedad de los síntomas resultantes del trastorno indicado. Como tales, los procedimientos de esta invención incluyen tanto la administración terapéutica como la administración  
25 profiláctica.

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Como se usa en este documento, el término "cantidad eficaz" se refiere a la cantidad o dosis del compuesto, tras la administración individual o múltiple al paciente, que proporciona el efecto deseado en el paciente bajo diagnóstico o tratamiento.

Una cantidad eficaz puede determinarse fácilmente por el médico que realizó el diagnóstico, como especialista en la técnica, mediante el uso de técnicas conocidas y observando los resultados obtenidos en circunstancias análogas. Para determinar la cantidad eficaz o dosis del compuesto administrado, el médico considerará varios factores incluyendo, pero sin limitación: la especie de mamífero; sus dimensiones, edad y salud general; el grado de implicación o la gravedad de la migraña implicada; la respuesta del paciente individual; el compuesto particular administrado; el modo de administración; las características de biodisponibilidad de la preparación administrada; el régimen de dosificación seleccionado; el uso de medicación concomitante; y otras circunstancias relevantes.

Una dosis diaria típica contendrá de aproximadamente 0,01 mg/kg a aproximadamente 100 mg/kg de cada compuesto usado en el presente procedimiento de tratamiento. Preferiblemente, las dosis diarias serán de aproximadamente 0,05 mg/kg a aproximadamente 50 mg/kg, más preferiblemente de aproximadamente 0,1 mg/kg a aproximadamente 25 mg/kg.

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Los antagonistas selectivos de iGluR<sub>5</sub> para uso de acuerdo con los procedimientos de la presente invención pueden ser un solo compuesto o una combinación de compuestos capaces de funcionar como antagonistas selectivos del receptor iGluR<sub>5</sub>. Por ejemplo, puede ser una combinación de un compuesto capaz de funcionar como antagonista en el receptor iGluR<sub>5</sub> y uno o más receptores de glutamato distintos, en combinación con uno o más compuestos capaces de bloquear sus acciones en el receptor iGluR<sub>5</sub>. Sin embargo, se entiende que el antagonista selectivo de iGluR<sub>5</sub> para uso en los procedimientos de la presente invención es preferiblemente un solo compuesto.

La administración oral es una vía de administración preferida de los compuestos empleados en la presente invención se administren solos o como una combinación de compuestos capaces de actuar como un antagonista selectivo del receptor iGluR<sub>5</sub>. Sin embargo, la administración oral no es la única vía, ni siquiera es la única vía preferida. Otras vías de administración preferidas incluyen la vía transdérmica, percutánea, intravenosa, intramuscular, intranasal, bucal o intrarrectal. Cuando el antagonista selectivo del receptor iGluR<sub>5</sub> se administra como una combinación de compuestos, uno de los compuestos puede administrarse por una vía, tal como la vía oral, y el otro puede administrarse mediante la vía transdérmica, percutánea,

114  
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intravenosa, intramuscular, intranasal, bucal o intrarrectal, según requieran las circunstancias particulares. La vía de administración puede variarse de cualquier forma, estando limitada por las propiedades físicas de los compuestos y la  
5 conveniencia del paciente y el cuidador.

Los compuestos empleados en la presente invención pueden administrarse como composiciones farmacéuticas y, por lo tanto, las composiciones farmacéuticas que incorporan dichos compuestos son realizaciones importantes de la presente  
10 invención. Tales composiciones pueden tomar cualquier forma física que sea farmacéuticamente aceptable, pero se prefieren particularmente las composiciones farmacéuticas administradas por vía oral. Tales composiciones farmacéuticas contienen una cantidad eficaz de un antagonista selectivo del receptor  
15 iGluR<sub>5</sub>, cantidad eficaz que está relacionada con la dosis diaria del compuesto a administrar. Cada unidad de dosificación puede contener la dosis diaria de un compuesto dado o puede contener una fracción de la dosis diaria, tal como una mitad o un tercio de la dosis. La cantidad de cada  
20 compuesto contenida en cada unidad de dosificación depende de la identidad del compuesto particular elegido para la terapia y de otros factores tales como la indicación para la que se administra. Las composiciones farmacéuticas de la presente invención pueden formularse para proporcionar la  
25 liberación rápida, sostenida o retrasada del ingrediente

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activo después de la administración al paciente, empleando procedimientos bien conocidos.

Las composiciones se formulan preferiblemente en una forma de dosificación unitaria, conteniendo cada dosis de aproximadamente 1 a aproximadamente 500 mg de cada compuesto individualmente o en una sola forma de dosificación unitaria, más preferiblemente de aproximadamente 5 a aproximadamente 300 mg (por ejemplo, 25 mg). El término "forma de dosificación unitaria" se refiere a una unidad físicamente discreta adecuada como dosis unitaria para un paciente, conteniendo cada unidad una cantidad predeterminada de material activo calculada para producir el efecto terapéutico deseado, junto con un vehículo, diluyente o excipiente farmacéutico adecuado.

Los ingredientes inertes y la forma de formulación de las composiciones farmacéuticas son convencionales. En la presente invención pueden usarse los procedimientos habituales de formulación usados en la ciencia farmacéutica. Pueden usarse todos los tipos habituales de composiciones, incluyendo comprimidos, comprimidos masticables, cápsulas, soluciones, soluciones parenterales, pulverizaciones o polvos intranasales, trociscos, supositorios, parches transdérmicos y suspensiones. En general, las composiciones contienen de aproximadamente un 0,5% a aproximadamente un 50% de los compuestos en total, dependiendo de las dosis deseadas y del

116  
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tipo de composición a usar. Sin embargo, la cantidad del compuesto se define mejor como "cantidad eficaz", es decir, la cantidad de cada compuesto que proporciona la dosis deseada al paciente en necesidad de tal tratamiento. La actividad de los compuestos empleados en la presente invención no depende de la naturaleza de la composición, por lo tanto, las composiciones se eligen y formulan solamente considerando la conveniencia y la economía.

Las cápsulas se preparan mezclando el compuesto con un diluyente apropiado e introduciendo la cantidad apropiada de la mezcla en cápsulas. Los diluyentes habituales incluyen sustancias en polvo inertes tales como almidones, celulosa en polvo, especialmente celulosa cristalina y microcristalina, azúcares tales como fructosa, manitol y sacarosa, harinas de cereales y polvos comestibles similares.

Los comprimidos se preparan por compresión directa, por granulación en húmedo o por granulación en seco. Sus formulaciones normalmente incorporan diluyentes, aglutinantes, lubricantes y disgregantes, así como el compuesto. Los diluyentes típicos incluyen, por ejemplo, diversos tipos de almidón, lactosa, manitol, caolín, fosfato o sulfato cálcico, sales inorgánicas tales como cloruro sódico y azúcar en polvo. También son útiles los derivados de celulosa en polvo. Los aglutinantes de comprimidos típicos son sustancias tales como almidón, gelatina y azúcares tales

como lactosa, fructosa, glucosa y similares. También son convenientes las gomas naturales y sintéticas, incluyendo la goma arábica, alginatos, hipromelosa, polivinilpirrolidona y similares. También sirven como aglutinantes el  
5 polietilenglicol, la etilcelulosa y las ceras.

Los comprimidos a menudo se recubren con azúcar como aromatizante y sellante. Los compuestos también pueden formularse como comprimidos masticables, usando grandes cantidades de sustancias de sabor agradables, tales como  
10 manitol, en la formulación, como está bien establecido en la práctica actualmente. También se usan ahora con frecuencia formulaciones parecidas a comprimidos que se disuelven instantáneamente, para asegurar que el paciente consume la forma de dosificación y para evitar la dificultar de tragar  
15 objetos sólidos que padecen algunos pacientes.

En una formulación de comprimidos a menudo es necesario un lubricante para prevenir que el comprimido y los punzones se peguen en la matriz. El lubricante se elige entre sólidos resbaladizos tales como el talco, el estearato de magnesio  
20 y de calcio, el ácido esteárico y aceites vegetales hidrogenados.

Los disgregantes de comprimidos son sustancias que se hinchan cuando se mojan para romper el comprimido y liberar el compuesto. Incluyen almidones, arcillas, celulosas,  
25 alginas y gomas. Más particularmente, pueden usarse almidones

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de maíz y patata, hipromelosa, agar, bentonita, celulosa de  
madera, esponja natural en polvo, resinas de intercambio  
catiónico, ácido algínico, goma guar, pulpa de cítricos y  
carboxihipromelosa, por ejemplo, así como lauril sulfato  
5 sódico.

A menudo se usan formulaciones entéricas para proteger  
un ingrediente activo del contenido fuertemente ácido del  
estómago. Tales formulaciones se crean recubriendo una forma  
de dosificación sólida con una película de un polímero que  
10 es insoluble en medios ácidos y soluble en medios básicos.  
Son películas ejemplares el acetato ftalato de celulosa, el  
acetato ftalato de polivinilo, el ftalato de hidroxipropil  
hipromelosa y el acetato succinato de hidroxipropil  
hipromelosa.

15 Cuando se desea administrar el compuesto como un  
supositorio, pueden usarse las bases habituales. La manteca  
de cacao es la base de supositorios convencional, que puede  
modificarse mediante la adición de ceras para elevar  
ligeramente su punto de fusión. También se usan ampliamente  
20 bases de supositorios miscibles con agua que comprenden,  
particularmente, polietilenglicoles de diversos pesos  
moleculares.

Los parches transdérmicos se han hecho populares  
recientemente. Típicamente, comprenden una composición  
25 resinosa en la que los fármacos se disolverán o se disolverán

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parcialmente, que se mantiene en contacto con la piel por una película que protege a la composición. Recientemente han aparecido muchas patentes en el campo. También están en uso otras composiciones de parche más complicadas, particularmente las que tienen una membrana perforada con innumerables poros a través de los cuales se bombean los fármacos por acción osmótica.

La siguiente tabla proporciona una lista ilustrativa de formulaciones adecuadas para uso con los compuestos empleados en la presente invención. Lo siguiente se proporciona sólo para ilustrar la invención y no debe interpretarse como limitante de la presente invención de forma alguna.

Formulación 1

Se preparan cápsulas de gelatina dura usando los siguientes ingredientes:

|                       | Cantidad<br>(mg/cápsula) |
|-----------------------|--------------------------|
| Ingrediente activo    | 250                      |
| Almidón, seco         | 200                      |
| Estearato de magnesio | <u>10</u>                |
| Total                 | 460 mg                   |

Los ingredientes anteriores se mezclan y se introducen

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en cápsulas de gelatina dura en cantidades de 460 mg.

Formulación 2

Se prepara un comprimido usando los siguientes  
5 ingredientes:

|                          |                                   | Cantidad        |
|--------------------------|-----------------------------------|-----------------|
|                          |                                   | (mg/comprimido) |
| Ingrediente activo       |                                   | 250             |
| Celulosa microcristalina |                                   | 400             |
| 10                       | Dióxido de silicio, sin volátiles | 10              |
| Ácido esteárico          |                                   | <u>5</u>        |
| Total                    |                                   | 665 mg          |

15 Los componentes se mezclan y se comprimen para formar comprimidos con un peso individual de 665 mg.

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Formulación 3

Se prepara una solución de aerosol que contiene los siguientes componentes:

|                         | % en peso |
|-------------------------|-----------|
| 5    Ingrediente activo | 0,25      |
| Etanol                  | 29,75     |
| Propulsor 22            | 70,00     |
| (Clorodifluorometano)   |           |
| 10   Total              | 100,00    |

El compuesto activo se mezcla con etanol y la mezcla se añade a una porción del Propulsor 22, se enfría a -30°C y se transfiere a un dispositivo de rellenado. Después se introduce la cantidad requerida en un recipiente de acero inoxidable y se diluye con el resto del propulsor. Posteriormente se ajustan unidades de válvula al recipiente.

Formulación 4

20        Se preparan comprimidos, cada uno con un contenido de ingrediente activo de 60 mg, como se muestra a continuación:

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|   |                             |             |
|---|-----------------------------|-------------|
|   | Ingrediente activo          | 60 mg       |
|   | Almidón                     | 45 mg       |
|   | Celulosa microcristalina    | 35 mg       |
|   | Polivinilpirrolidona        | 4 mg        |
| 5 | Carboximetil almidón sódico | 4,5 mg      |
|   | Estearato de magnesio       | 0,5 mg      |
|   | Talco                       | <u>1 mg</u> |
|   | Total                       | 150 mg      |

10

El ingrediente activo, el almidón y la celulosa se pasan a través de un tamiz de malla U.S. No. 45 y se mezclan minuciosamente. La solución de polivinilpirrolidona se mezcla con los polvos resultantes, que después se pasan a través de un tamiz de malla U.S. No. 14. Los gránulos así producidos se secan a 50°C y se pasan a través de un tamiz de malla U.S. No. 18. Después se añaden el carboximetil almidón sódico, el estearato de magnesio y el talco, previamente pasados a través de un tamiz de malla U.S. No. 60, a los gránulos, que, después de la mezcla, se comprimen en una máquina de comprimidos produciendo comprimidos con un peso individual de 150 mg.

Formulación 5

25 Se fabrican cápsulas, cada una con un contenido de

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medicamento de 80 mg, como se indica a continuación:

|   |                          |             |
|---|--------------------------|-------------|
|   | Ingrediente activo       | 80 mg       |
|   | Almidón                  | 59 mg       |
|   | Celulosa microcristalina | 59 mg       |
| 5 | Estearato de magnesio    | <u>2 mg</u> |
|   | Total                    | 200 mg      |

El ingrediente activo, la celulosa, el almidón y el  
10 estearato de magnesio se mezclan, se pasan a través de un  
tamiz de malla No. 45 y se introducen en cápsulas de gelatina  
dura en cantidades de 200 mg.

Formulación 6

15 Pueden fabricarse supositorios, cada uno con un  
contenido de 225 mg de ingrediente activo, como se indica a  
continuación:

|    |                                       |                 |
|----|---------------------------------------|-----------------|
|    | Ingrediente activo                    | 225 mg          |
|    | Glicéridos de ácidos grasos saturados | <u>2.000 mg</u> |
| 20 | Total                                 | 2.225 mg        |

El ingrediente activo se pasa a través de un tamiz de  
malla U.S. No. 60 y se suspende en glicéridos de ácidos

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grasos saturados previamente fundidos usando el calor mínimo necesario. La mezcla después se vierte en un molde de supositorios de capacidad nominal de 2 g y se deja enfriar.

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**Formulación 7**

Se fabrican suspensiones, conteniendo cada una 50 mg de medicamento, como se indica a continuación:

|    |                                   |         |
|----|-----------------------------------|---------|
|    | Ingrediente activo                | 50 mg   |
|    | Carboxihipromelosa sódica         | 50 mg   |
| 10 | Jarabe                            | 1,25 ml |
|    | Solución de ácido benzoico        | 0,10 ml |
|    | Aromatizante                      | C.S.    |
|    | Colorante                         | C.S.    |
|    | Agua purificada hasta un total de | 5 ml    |

15

El medicamento se pasa a través de un tamiz de malla U.S. No. 45 y se mezcla con la carboxihipromelosa sódica y el jarabe formando una pasta sin grumos. La solución de ácido benzoico, el aroma y el colorante se diluyen con algo de agua y se añaden, con agitación. Después se añade suficiente agua como para producir el volumen requerido.

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**Formulación 8**

Puede prepararse una formulación intravenosa como se indica a continuación:

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|                                   |        |
|-----------------------------------|--------|
| Ingrediente activo                | 100 mg |
| Manitol                           | 100 mg |
| Hidróxido sódico 5 N              | 200 ml |
| Agua purificada hasta un total de | 5 ml   |

5

Un especialista habitual en la técnica entenderá que los procedimientos anteriores también pueden aplicarse a un procedimiento para tratar la migraña que comprende administrar a un paciente una cantidad eficaz de un compuesto que posee la actividad de un antagonista selectivo del receptor iGluR<sub>5</sub>.

La inhibición de la extravasación dural de proteínas neuronales es un mecanismo ejemplar de acción para el procedimiento de la presente invención. El procedimiento además requiere que los compuestos que presentan tal inhibición también demuestren una unión selectiva e inhibición del receptor iGluR<sub>5</sub>. A continuación se describen la serie de compuestos usada para ilustrar el principio de la presente invención y los ensayos farmacológicos empleados para demostrar la eficacia del mecanismo de la invención. Se cree que los Compuestos III, IV(a) y IV(b) de este documento representan nuevos compuestos y, como tales, no se han descrito previamente como antagonistas selectivos de iGluR<sub>5</sub> ni se han presentado como agentes eficaces contra la migraña. Por lo tanto, los Compuestos III, IV(a) y IV(b) se

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proporcionan como realizaciones adicionales de la presente invención.

Los siguientes ejemplos ilustran los procedimientos de la presente invención. Los reactivos y los materiales de  
5 partida están disponibles fácilmente para un especialista habitual en la técnica. Se entiende que estos ejemplos son sólo ilustrativos y no deben considerarse limitantes del alcance de la invención en forma alguna. Como se usa en este documento, los siguientes términos tienen los significados  
10 indicados: "i.v." se refiere a por vía intravenosa; "p.o." se refiere a por vía oral; "i.p." se refiere a por vía intraperitoneal; "eq" o "equiv" se refiere a equivalentes; "g" se refiere a gramos; "mg" se refiere a miligramos; "l" se refiere a litros; "ml" se refiere a mililitros; " $\mu$ l" se  
15 refiere a microlitros; "mol" se refiere a moles; "mmol" se refiere a milimoles; "psi" se refiere a libras por pulgada al cuadrado; "mm Hg" se refiere a milímetros de mercurio; "min" se refiere a minutos; "h" o "hr" se refiere a horas; "°C" se refiere a grados centígrados; "TLC" se refiere a  
20 cromatografía de capa fina; "HPLC" se refiere a cromatografía líquida de alto rendimiento; "R<sub>f</sub>" se refiere a factor de retención; "R<sub>t</sub>" se refiere a tiempo de retención; " $\delta$ " se refiere a partes por millón campo abajo de tetrametilsilano; "THF" se refiere a tetrahidrofurano; "DMF" se refiere a N,N-  
25 dimetilformamida; "DMSO" se refiere a dimetil sulfóxido; "ac"

se refiere a acuoso; "EtOAc" se refiere a acetato de etilo; "iPrOAc" se refiere a acetato de isopropilo; "MeOH" se refiere a metanol; "MTBE" se refiere a terc-butil metil éter; "TA" se refiere a temperatura ambiente; "K<sub>i</sub>" se refiere a la constante de disociación de un complejo enzima-antagonista y sirve como índice de la unión de un ligando; y "DI<sub>50</sub>" y "DI<sub>100</sub>" se refieren a dosis de un agente terapéutico administrado que produce, respectivamente, una reducción del 50% y del 100% en una respuesta fisiológica.

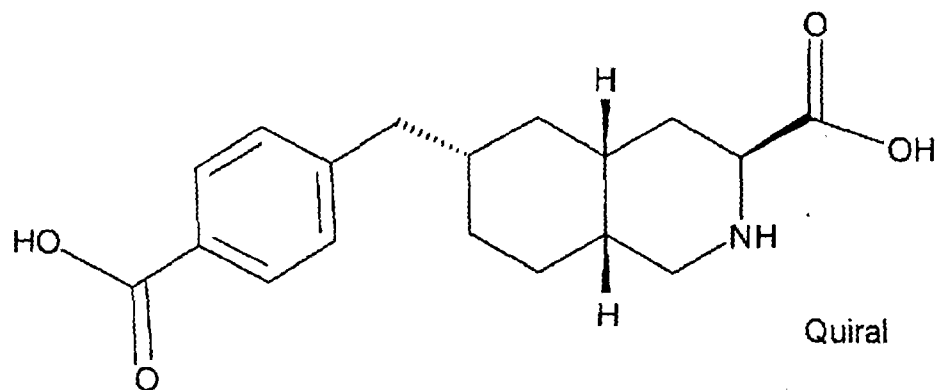
10

### EJEMPLO 1

#### Compuesto I

Ácido 3S,4aR,6S,8aR-6-(((4-carboxi)fenil)metil)-  
1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílico

15



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Los especialistas en la técnica reconocerán al Compuesto I como un antagonista del receptor de aminoácidos excitadores, selectivo para el subtipo de receptores iGluR<sub>5</sub>.

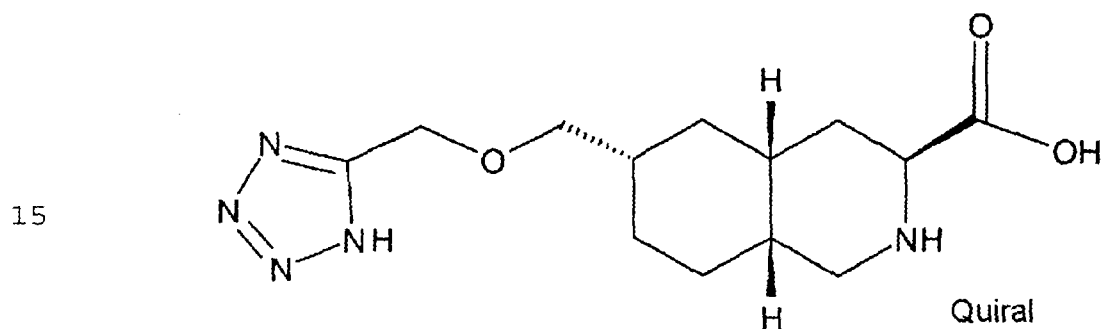
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El Compuesto I puede prepararse fácilmente por un especialista habitual en la técnica siguiendo los procedimientos generales reconocidos descritos en la Patente de Estados Unidos No. 5.446.051 y, más específicamente, como se ha publicado recientemente en la solicitud internacional WO 98/45279, publicada el 15 de Octubre de 1998.

Compuesto II

10      Ácido 3S,4aR,6S,8aR-6-((((1H-tetrazol-5-il)metil)oxi)metil)-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílico



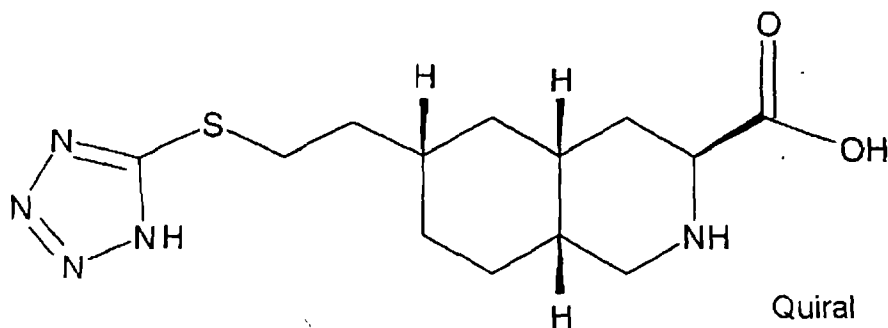
Los especialistas en la técnica reconocerán al Compuesto II como un antagonista del receptor de aminoácidos excitadores, selectivo para el subtipo de receptores iGluR<sub>5</sub>. El Compuesto II puede prepararse fácilmente por un especialista habitual en la técnica siguiendo los procedimientos generales reconocidos descritos en la Patente de Estados Unidos No. 5.670.516 (véase el Ejemplo No. 11, 20 Compuesto No. 7) y, más específicamente, como se ha publicado 25

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recientemente en la solicitud internacional WO 98/45279,  
publicada el 15 de Octubre de 1998.

Compuesto III

5



10

El Compuesto III representa un nuevo compuesto funcional  
como antagonista selectivo del receptor iGluR<sub>5</sub>. El Compuesto  
III puede prepararse fácilmente; el enantiómero deseado puede  
resolverse ópticamente; y las composiciones farmacéuticas que  
15 comprenden el Compuesto III pueden formularse fácilmente  
siguiendo los procedimientos generales esencialmente como se  
describe para el Ejemplo No. 8, Compuesto No. 8 de la  
Patente de Estados Unidos No. 5.670.516, cuyo contenido se  
incorpora en este documento por referencia.

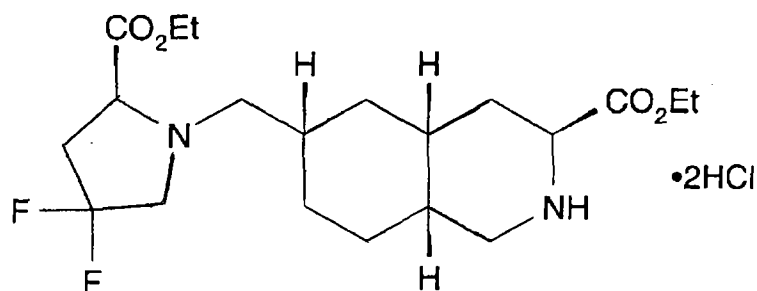
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Compuesto IV(b)

3S,4aR,6S,8aR-6-(((2S)-2-(Etoxicarbonil)-4,4-  
difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-  
decahidroisoquinolina-3-carboxilato de etilo

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A. Preparación de 3S,4aR,6S,8aR-6-((4-metilfenil)-sulfoniloxi)metil)-2-metoxycarbonil-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxilato de etilo

A una solución de 15,0 g (50,1 mmol) de intermedio de hidroximetilo (Véase Col. 11-12, Esquema II de la Patente de Estados Unidos No. 5.356.902, cuyo contenido se incorpora en este documento por referencia) enfriada a 0°C en CH<sub>2</sub>Cl<sub>2</sub> (100 ml), se añadió trietilamina (20,9 ml, 150,3 mmol) seguida de cloruro de toluenosulfonilo (19,1 g, 100,2 mmol) disuelto en CH<sub>2</sub>Cl<sub>2</sub> (100 ml). La reacción se calentó a temperatura ambiente y se agitó durante 16 h, después se repartió entre CH<sub>2</sub>Cl<sub>2</sub> y NaHSO<sub>4</sub> acuoso al 10%. La capa acuosa se extrajo con CH<sub>2</sub>Cl<sub>2</sub> y los extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y se concentraron al vacío. La cromatografía en columna (EtOAc al 10-50%/hexano) produjo 20,1 g (89%) del compuesto del título intermedio deseado en forma de un aceite incoloro:

EM (m/e): 451,5 (M<sup>+</sup>)

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Calculado para  $C_{22}H_{31}NO_7S$  0,1  $CH_2Cl_2$ : Teórico: C, 57,45; H, 6,81; N, 3,03. Encontrado: C, 57,76; H, 6,93; N, 3,35.

$^{13}C$  RMN ( $DMSO-d_6$ ):  $\delta$  171,4, 144,8, 132,4, 130,1, 127,6, 74,6, 60,4, 53,1, 52,4, 44,1, 34,6, 31,8, 31,0, 29,8, 28,8, 24,9, 23,3, 21,0, 14,0.

B. Preparación de 3S,4aR,6S,8aR-6-(((3S,5S)-5-(etoxicarbonil)-3-hidroxipirrolidinil)metil)-2-metoxicarbonil-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxilato de etilo

10 Una mezcla de éster etílico de 4-hidroxiprolina (6,5 g, 33,1 mmol), el compuesto de la Etapa A anterior (10,0 g, 22,0 mmol) y carbonato potásico (4,6 g, 33,1 mmol) se calentó a reflujo en acetonitrilo (22 ml) durante 60 h. La mezcla de reacción se enfrió a temperatura ambiente y se repartió entre  
15  $CH_2Cl_2$  y agua. La capa acuosa se extrajo dos veces con  $CH_2Cl_2$  y los extractos orgánicos reunidos se secaron sobre  $MgSO_4$ , se filtraron y se concentraron al vacío. La cromatografía en columna (EtOAc al 50%/hexano, seguido de MeOH al 5%/  $CH_2Cl_2$ ) dio 9,2 g (95%) del compuesto del título intermedio deseado  
20 en forma de un aceite incoloro:

EM (m/e): 441,3 ( $M^+$ )

Calculado para  $C_{22}H_{36}N_2O_7S$ : Teórico: C, 59,98; H, 8,24; N, 6,36. Encontrado: C, 60,17; H, 8,23; N, 6,42.

C. Preparación de 3S,4aR,6S,8aR-6-(((5S)-5-(etoxicarbonil)-3-oxopirrolidinil)-2-metoxicarbonil-1,2,3,4,4a,5,6,7,8,8a-

25

decahidroisoquinolina-3-carboxilato de etilo

A una solución de DMSO (2,3 ml, 32,5 mmol) enfriada a -78°C en CH<sub>2</sub>Cl<sub>2</sub> (25 ml) se añadió, gota a gota, cloruro de oxalilo (1,4 ml, 16,3 mmol). La mezcla de reacción se agitó 5 durante 5 minutos y después se añadió el compuesto de la Etapa B anterior (6,0 g, 13,6 mmol) disuelto en 20 ml de CH<sub>2</sub>Cl<sub>2</sub>. Después de agitar durante 45 minutos a -78°C, se añadió trietilamina (9,5 ml, 32,5 mmol). La reacción se calentó a temperatura ambiente durante aproximadamente 2 10 horas y se inactivó mediante la adición de NaHSO<sub>4</sub> acuoso al 10%. La capa acuosa se extrajo con CH<sub>2</sub>Cl<sub>2</sub> y los extractos orgánicos reunidos se secaron sobre MgSO<sub>4</sub>, se filtraron y se concentraron al vacío. La cromatografía en columna (EtOAc al 25-50%/hexano) proporcionó 4,6 g (78%) del compuesto del 15 título intermedio deseado en forma de un aceite incoloro.

EM (m/e): 439,1 (M<sup>+</sup>)

D. Preparación de 3S,4aR,6S,8aR-6-(((2S)-2-(etoxicarbonil)-4,4-difluoropirrolidinil)metil)-2-metoxicarbonil-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxilatode 20 etilo

A una mezcla del compuesto de la Etapa C anterior (4,62 g, 10,5 mmol) enfriada a -78°C en CH<sub>2</sub>Cl<sub>2</sub> (50 ml), se añadió gota a gota trifluoruro de dietilaminoazufre (3,5 ml, 26,3 mmol). La reacción se dejó calentar a temperatura ambiente, 25 se agitó durante 48 horas más y después se interrumpió

mediante la adición de MeOH. Después de concentrar al vacío, el residuo se repartió entre  $\text{CH}_2\text{Cl}_2$  y  $\text{NaHCO}_3$  acuoso saturado. La capa acuosa se extrajo con  $\text{CH}_2\text{Cl}_2$  y los extractos orgánicos reunidos se secaron sobre  $\text{MgSO}_4$ , se filtraron y se concentraron al vacío. La cromatografía en columna (EtOAc al 25-50%/hexano) proporcionó 3,3 g (68%) del compuesto del título intermedio deseado en forma de un aceite incoloro:

EM (m/e): 461,2 ( $\text{M}^+$ )

Calculado para  $\text{C}_{22}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_6$ : Teórico: C, 57,38; H, 7,44; N, 6,08. Encontrado: C, 58,25; H, 7,59; N, 6,50.

E. Preparación de 3S,4aR,6S,8aR-6-(((2S)-2-(etoxicarbonil)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxilato de etilo (Compuesto IV (b))

Una solución del compuesto de la Etapa D anterior (3,3 g, 7,10 mmol) disuelto en  $\text{CH}_2\text{Cl}_2$  (40 ml) se enfrió a  $0^\circ\text{C}$  y se cargó con yoduro de trimetilsililo (3,0 ml, 21,3 mmol). La reacción se dejó calentar a temperatura ambiente, se agitó durante 4 horas más y después se interrumpió mediante la adición de  $\text{NaHCO}_3$  acuoso saturado (50 ml). La capa acuosa se extrajo con  $\text{CH}_2\text{Cl}_2$  y los extractos orgánicos reunidos se lavaron con una solución 1 N de tiosulfato sódico, se secaron sobre  $\text{MgSO}_4$ , se filtraron y se concentraron al vacío. El material se cromatografió ( $\text{MeOH}$  al 2%/  $\text{CH}_2\text{Cl}_2$ ), se disolvió en 20 ml de  $\text{Et}_2\text{O}$  y a esto se añadieron 50 ml de una solución de

HCl/Et<sub>2</sub>O. El disolvente se retiró al vacío proporcionando 2,6 g (76%) del compuesto del título final en forma de un sólido blanco:

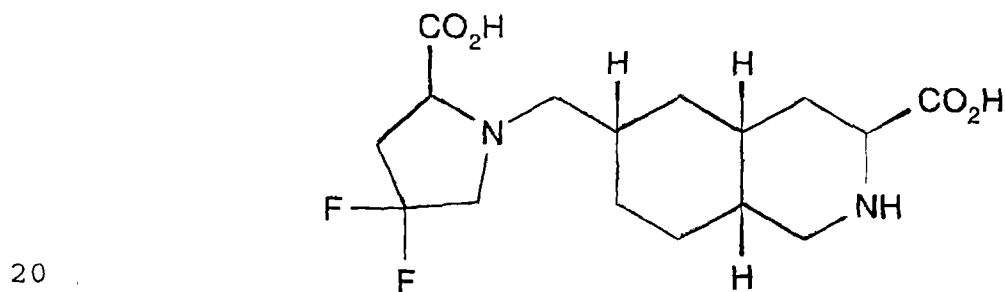
EM (m/e): 403,4 (M<sup>+</sup>)

5      Calculado para C<sub>20</sub>H<sub>32</sub>Cl<sub>2</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub>: Teórico: C, 50,53; H, 7,21; N, 5,89. Encontrado: C, 50,90; H, 7,41; N, 5,84.

<sup>13</sup>C RMN (D<sub>2</sub>O): δ 170,3, 167,7, 125,1 (t, J<sub>CF</sub> = 249,1 Hz), 65,9, 65,0, 64,1, 63,4, 60,1 (t, J<sub>CF</sub> = 33,9 Hz), 57,6, 52,8, 42,9, 37,2 (t, J<sub>CF</sub> = 26,4 Hz), 34,5, 31,7, 31,3, 10      30,5, 28,4, 26,9, 24,3, 13,6.

Compuesto IV(a)

Ácido 3S,4aR,6S,8aR-6-(((2S)-2-(ácido carboxílico)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-  
15      decahidroisoquinolina-3-carboxílico



Una solución de 3S,4aR,6S,8aR-6-(((2S)-2-(etoxycarbonil)-4,4-difluoropirrolidinil)metil)-2-metoxycarbonil-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-  
25      carboxilato de etilo (3,3 g, 7,10 mmol), el compuesto de la

130 135

Etapa D anterior, disuelto en HCl acuoso 5 N (15 ml) se calentó a 90°C durante 18 horas. La mezcla de reacción se enfrió a temperatura ambiente y se concentró al vacío. La espuma bruta resultante se disolvió en agua (75 ml) y se agitó en presencia de resina de intercambio iónico Dowex 50X8 (100-200) (10 g) durante 2 horas. La resina se filtró, se lavó secuencialmente con una mezcla 1:1 de THF/H<sub>2</sub>O y agua y después se agitó en presencia de piridina al 10%/H<sub>2</sub>O durante 2 h. Después de la filtración, la resina se lavó con agua y el filtrado se concentró al vacío proporcionando el compuesto del título (0,6 g, 97%) en forma de una espuma blanca:

EM (m/e): 347,2 (M<sup>+</sup>)

Calculado para C<sub>16</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> 0,1 H<sub>2</sub>O: Teórico: C, 55,19; H, 7,01; N, 8,05. Encontrado: C, 54,81; H, 6,82; N, 8,13.

<sup>13</sup>C RMN (D<sub>2</sub>O): δ 175,1, 171,1, 125,6 (t, J<sub>CF</sub> = 249,4 Hz), 67,9, 63,0, 59,3 (t, J<sub>CF</sub> = 34,0 Hz), 54,5, 42,5, 37,5 (t, J<sub>CF</sub> = 24,9 Hz), 34,3, 32,7, 32,4, 30,6, 28,2, 27,0, 24,3.

20

## EJEMPLO 2

Para establecer que el subtipo de receptores iGluR<sub>5</sub> está mediando la extravasación de proteínas neurogénicas, una característica funcional de la migraña, se mide en primer lugar la afinidad de unión de la serie de compuestos por el receptor iGluR<sub>5</sub> usando procedimientos convencionales. Por

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ejemplo, la actividad de los compuestos que actúan como antagonistas del receptor iGluR<sub>5</sub> puede determinarse mediante estudios de unión de ligandos marcados con radioisótopos en el receptor iGluR<sub>5</sub> humano clonado y expresado (Korczak y col., 1994, Recept. Channels 3; 41-49) y por registros electrofisiológicos de fijación de voltaje en células enteras de corrientes en neuronas de ganglio raquídeo aislado de rata agudamente (Bleakman y col., 1996, Mol. Pharmacol. 49; 581-585). Después puede determinarse la selectividad de los compuestos que actúan en el subtipo de receptores iGluR<sub>5</sub> comparando la actividad antagonista en el receptor iGluR<sub>5</sub> con la actividad antagonista en otros receptores de AMPA y cainato. Los procedimientos útiles para tales estudios de comparación incluyen: estudios de unión receptor-ligando y registros electrofisiológicos de fijación de voltaje en células enteras de la actividad funcional en los receptores GluR<sub>1</sub>, GluR<sub>2</sub>, GluR<sub>3</sub> y GluR<sub>4</sub> humanos (Fletcher y col., 1995, Recept. Channels 3; 21-31); estudios de unión de receptor-ligando y registros electrofisiológicos de fijación de voltaje en células enteras de la actividad funcional en los receptores GluR<sub>6</sub> humanos (Hoo y col., Recept. Channels 2; 327-338); y registros electrofisiológicos de fijación de voltaje en células enteras de la actividad funcional en los receptores de AMPA en neuronas de Purkinje del cerebelo aisladas agudamente (Bleakman y col., 1996, Mol. Pharmacol.

132  
137

49; 581-585) y otros tejidos que expresan receptores de AMPA (Fletcher y Lodge, 1996, Pharmacol. Ther. 70; 65-89).

Perfiles de afinidad de unión de antagonistas de iGluR<sub>5</sub>

Se emplearon líneas celulares (células HEK293) transfectadas de forma estable con receptores iGluR humanos. Se midió el desplazamiento de <sup>3</sup>[H] AMPA por concentraciones crecientes de antagonistas sobre células que expresaban iGluR<sub>1</sub>, iGluR<sub>2</sub>, iGluR<sub>3</sub> e iGluR<sub>4</sub>, mientras que el desplazamiento de <sup>3</sup>[H] cainato (KA) se midió en células que expresaban iGluR<sub>5</sub>, iGluR<sub>6</sub>, iGluR<sub>7</sub> y KA2. Se determinó la actividad de unión de antagonistas estimada (K<sub>i</sub>) en  $\mu$ M para los Compuestos I-IV. Como indicio de selectividad, también se determinó la relación de la afinidad de unión al subtipo de receptor de AMPA iGluR<sub>2</sub>, frente a la afinidad de unión al subtipo de receptor de cainato iGluR<sub>5</sub>. Los compuestos proporcionados por la presente invención presentaron una afinidad de unión de al menos 10 veces mayor para el iGluR<sub>5</sub> con respecto a la de iGluR<sub>2</sub>, más preferible de al menos 100 veces.

EJEMPLO 3

Se empleó el siguiente modelo animal para determinar la actividad de cada uno de la serie de compuestos de inhibir la extravasación de proteínas, un ensayo funcional ejemplar del mecanismo neuronal de la migraña. Los resultados obtenidos para la serie de compuestos en este modelo se

resumen en la Tabla I (infra).

Modelo Animal de Extravasación de Proteínas Durales

Se anestesiaron ratas Harlan Sprague-Dawley (225-325 g) o cobayas de Charles River Laboratories (225-325 g) con pentobarbital sódico por vía intraperitoneal (65 mg/kg o 45 mg/kg, respectivamente) y se pusieron en un bastidor estereotáxico (David Kopf Instruments) con la barra de incisión fijada a -3,5 mm para las ratas o -4,0 mm para los cobayas. Después de una incisión sagital en la línea media del cuero cabelludo, se perforaron dos pares de agujeros bilaterales a través del cráneo (6 mm posteriormente, 2,0 y 4,0 mm lateralmente en las ratas; 4 mm posteriormente y 3,2 y 5,2 mm lateralmente en cobayas, indicándose todas las coordenadas tomando como referencia el bregma). Se insertaron pares de electrodos de estimulación de acero inoxidable, aislados excepto en las puntas (Rhodes Medical Systems, Inc.) a través de los agujeros en los dos hemisferios hasta una profundidad de 9 mm (ratas) o de 10,5 mm (cobayas) de la duramadre.

Se expuso la vena femoral y se inyectó una dosis de compuesto de ensayo por vía intravenosa (i.v.) a un volumen de dosificación de 1 mg/kg o, como alternativa, el compuesto de ensayo se administró por vía oral (p.o.) mediante una sonda, en un volumen de 2,0 ml/kg. Aproximadamente 7 minutos después de la inyección i.v., también se inyectó por vía

intravenosa una dosis de 50 mg/kg de Evans Blue, un colorante fluorescente. El Evans Blue formó complejos con proteínas de la sangre y funcionó como un marcador de la extravasación de proteínas. Exactamente 10 minutos después de la inyección del  
5 compuesto de ensayo, se estimuló el ganglio del trigémino izquierdo durante 3 minutos a una intensidad de corriente de 1,0 mA (5 Hz, duración 4 mseg) con un potenciostato/galvanostato Modelo 273 (EG&G Princeton Applied Research).

10 Quince minutos después de la estimulación, los animales se sacrificaron y se desangraron con 20 ml de solución salina. Se retiró la parte superior del cráneo para facilitar la recolección de las membranas durales. Se extrajeron muestras de membrana de los dos hemisferios, se aclararon con  
15 agua y se extendieron sobre portaobjetos de microscopio. Una vez secos, los tejidos se cubrieron con una solución de glicerol al 70% en agua.

Se usó un microscopio de fluorescencia (Zeiss) equipado con un monocromador reticulado y un espectrofotómetro para  
20 cuantificar la cantidad de colorante Evans Blue en cada muestra. Se utilizó una longitud de onda de excitación de aproximadamente 535 nm y se determinó la intensidad de emisión a 600 nm. El microscopio disponía de un elemento motorizado y también de una interfaz con un ordenador  
25 personal. Esto facilitó el movimiento controlado por

ordenador del elemento con medidas de fluorescencia a 25 puntos (etapas de 500 mm) en cada muestra de la duramadre. La media y la desviación típica de las medidas se determinaron por el ordenador.

5        La extravasación inducida por la estimulación eléctrica del ganglio del trigémino era un efecto ipsilateral (es decir, se produce sólo en el lado de la duramadre en el que se estimuló el ganglio del trigémino). Esto permite usar la otra mitad (no estimulada) de la duramadre como control. Se  
10        calculó la relación de la cantidad de extravasación en la duramadre desde el lado estimulado con respecto a la cantidad de extravasación en el lado no estimulado. Los animales de control que recibieron sólo una dosis de solución salina, produjeron una relación de aproximadamente 2,0 en ratas y de  
15        aproximadamente 1,8 en ratones. Por el contrario, un compuesto que previniera eficazmente la extravasación en la duramadre desde el lado estimulado produciría una relación de aproximadamente 1,0.

20        Se generaron curvas de dosis-respuesta para cada uno de la serie de compuestos y se calculó una aproximación de la dosis que inhibía la extravasación en un 50% ( $DI_{50}$ ) o en un 100% ( $DI_{100}$ ). En la Tabla I mostrada a continuación se resumen los valores respectivos de  $DI_{50}$  y/o  $DI_{100}$ , para cada uno de la serie de compuestos empleada en la presente invención.

136 ~~141~~

Tabla I

Inhibición de Extravasación de Proteína Dural (ng/kg)

| Compuesto | Vía de administración | DI <sub>50</sub> (ng/kg) | DI <sub>100</sub> |      |
|-----------|-----------------------|--------------------------|-------------------|------|
|           |                       |                          | (ng/kg)           |      |
| 5         | I                     | i.v.                     | 6,5 (rata)        | --   |
|           |                       |                          | 4,0 (cobaya)      | --   |
|           | II                    | i.v.                     | 15 (rata)         | --   |
|           | III                   | i.v.                     | 0,0053 (rata)     | 0,10 |
|           | IV(b)                 | p.o.                     | --                | 0,01 |

Habiendo descrito la invención como antecede, se declara como propiedad lo contenido en las siguientes

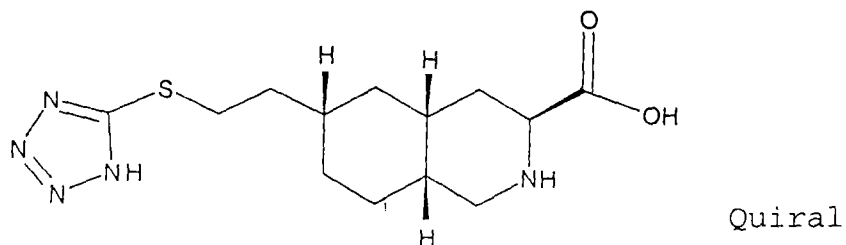
# REIVINDICACIONES

1. El uso de un antagonista selectivo del receptor iGluR<sub>5</sub> para la fabricación de un medicamento para el tratamiento de la migraña.

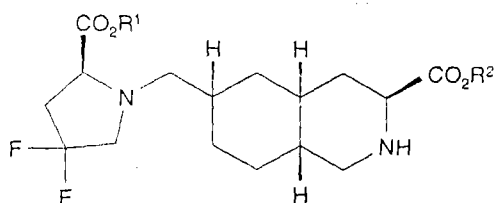
2. El uso de acuerdo con la Reivindicación 1, en el que el antagonista selectivo del receptor iGluR<sub>5</sub> es el ácido 3S, 4aR, 6S, 8aR-6-(((4-carboxi)fenil)metil)-1,2,3,4,4a,5,6,7,8,8a,-decahidroisoquinolina-3-carboxílico.

3. El uso de acuerdo con la Reivindicación 1, en el que el antagonista selectivo del receptor iGluR<sub>5</sub> es el ácido 3S, 4aR, 6S, 8aR-6-(((1H-tetrazol-5-il)metil)oxi)metil)-1,2,3,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílico.

4. El uso de acuerdo con la Reivindicación 1, en el que el antagonista selectivo del receptor iGluR<sub>5</sub> viene dado por la fórmula



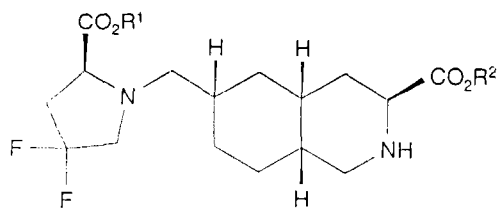
5. El uso de acuerdo con la Reivindicación 1, en el que el antagonista selectivo del receptor iGluR<sub>5</sub> es un compuesto de Fórmula I



en la que cada uno de  $R^1$  y  $R^2$  es independientemente H, alquilo  $C_1C_{20}$ , alquenilo  $C_2-C_6$ , alquil  $C_1-C_6$ -arilo, alquilo  $C_1-C_6$ -cicloalquilo ( $C_3-C_{10}$ ), alquil  $C_1-C_6$ -N,N-dialquil  $C_1-C_6$ -amina, alquil  $C_1C_6$ -pirrolidina, alquil  $C_1-C_6$ piperidina o alquil  $C_1-C_6$ -morfolina, o una sal farmacéuticamente aceptable del mismo.

6. El uso de acuerdo con la Reivindicación 5, en el que el antagonista selectivo del receptor  $iGluR_5$  se selecciona entre 3S, 4aR, 6S, 8aR-6-(((2S)-2-(etoxicarbonil)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a decahidroisoquinolina-3-carboxilato de etilo o ácido 3S, 4aR, 6S, 8aR-6-(((2S)-2-(ácido carboxílico)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílico.

7. Un compuesto de la fórmula



en la que cada uno de  $R^1$  y  $R^2$  es independientemente H, alquilo  $C_1-C_{20}$ , alquenilo  $C_2-C_6$ , alquil  $C_1-C_6$ -arilo, alquil  $C_1-C_6$ -cicloalquilo ( $C_3-C_{10}$ ), alquil  $C_1-C_6$ -N,N-dialquil  $C_1-C_6$ -amina, alquil  $C_1-C_6$ -pirrolidina, alquil  $C_1-C_6$ -piperidina o alquil  $C_1-C_6$ -morfolina; o una sal farmacéuticamente aceptable del mismo.

1-44  
139

8. Un compuesto de acuerdo con la reivindicación 7, en el que cada uno de  $R^1$  y  $R^2$  es independientemente H ó alquilo  $C_1-C_{20}$ .

9. Un compuesto que es el 3S, 4aR, 6S, 8aR-6-(((2S)-2-(etoxicarbonil)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílate de etilo o una sal farmacéuticamente aceptable del mismo.

10. Un compuesto que es el ácido 3S, 4aR, 6S, 8aR-6-(((2S)-2-(ácido carboxílico)-4,4-difluoropirrolidinil)metil)-1,2,3,4,4a,5,6,7,8,8a-decahidroisoquinolina-3-carboxílico o una sal farmacéuticamente aceptable del mismo.

11. Una composición farmacéutica que comprende un compuesto de acuerdo con la reivindicación 7, en combinación con uno o más vehículos, diluyentes o excipientes farmacéuticamente aceptables.

12. Una composición farmacéutica para el tratamiento de la migraña que comprende un compuesto como el reivindicado en la reivindicación 7 en combinación con un vehículo, diluyente o excipiente farmacéuticamente aceptable.

El: Lilly  
X-12149  
140

**TRADUCCION OFICIAL No. 192**

**TRADUCCION DE UN DOCUMENTO PRESENTADO SIMULTANEAMENTE EN INGLÉS Y ESPAÑOL. LEGALIZACION TRASPASO DE LA INVENCION DENOMINADA ANTAGONISTAS SELECTIVOS DEL RECEPTOR  $iGluR_5$  PARA EL TRATAMIENTO DE LA MIGRAÑA A FAVOR DE ELI LILLY AND COMPANY.**

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**TRASPASO**

**COLOMBIA**

**CASO: X-12149**

**INVENCION:      ANTAGONISTAS SELECTIVOS DEL RECEPTOR  $iGluR_5$   
PARA EL TRATAMIENTO DE LA MIGRAÑA**

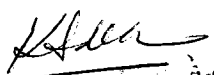
Firmado:    **David Bleakman**

Firmado:    **Amy Suzon Chappell**

Firmado:    **Sandra Ann Filla**

Firmado:    **Kirk Willis Johnson**

Firmado:    **Paul Leslie Omstein**

  
SANTA GUERINDELLA DE ABOU  
TRADUCTORA OFICIAL  
RES. MINISTERIO DE JUSTICIA

446  
191

## CERTIFICADO NOTARIAL

**ESTADO: Indiana**  
**CONDADO: Marion**

El 23 de mayo, 2000, comparecieron personalmente ante mí **David Bleakman**, **Sandra Ann Filla**, **Kirk Willis Johnson**, y **Paul Leslie Ornstein**, quienes reconocieron que firmaron el documento anterior como un acto voluntario suyo para los propósitos en él establecidos.

Firmado: **Sandra L. Bradshaw**  
NOTARIO PUBLICO

Sandra L. Bradshaw  
Mi comisión expira abril 30, 2008  
Residencia: Condado de Marion

Sello del Notario Público de Indiana  
Sello del Consulado General de Colombia en Chicago

## CERTIFICADO NOTARIAL

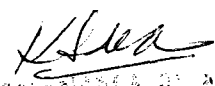
**ESTADO: Indiana**  
**CONDADO: Marion**

El 23 de mayo, 2000, comparecieron personalmente ante mí **Amy Suzon**, quien reconoció que firmó el documento anterior como un acto voluntario suyo para los propósitos en él establecidos.

Firmado: **Sandra L. Bradshaw**  
NOTARIO PUBLICO

Sandra L. Bradshaw  
Mi comisión expira abril 30, 2008  
Residencia: Condado de Marion

Sello del Notario Público de Indiana

  
MARIA SALAS  
TRADUCTORA GENERAL  
DES MINISTROS

147  
142

**ESTADOS UNIDOS DE AMERICA**  
**CERTIFICADO DE OFICIO**  
**ESTADO DE INDIANA**

Certificación del Secretario de Estado de Indiana **Sue Anne Gilroy** sobre el cargo y las funciones de **Sandra L. Bradshaw**, como Notario Público del Condado de Marion, en la fecha de expedición del documento adjunto, expedido el 9 de junio del 2000.

Firmado: **Sue Anne Gilroy**  
Secretario de Estado

Firmado: **Mary Reeve**  
Delegado

Sello en papel dorado del Estado de Indiana  
Sello del Consulado General de Colombia en Washington

**ESTADOS UNIDOS DE AMERICA**  
**CERTIFICADO DE OFICIO**  
**ESTADO DE INDIANA**

Certificación del Secretario de Estado de Indiana **Sue Anne Gilroy** sobre el cargo y las funciones de **Sandra L. Bradshaw**, como Notario Público del Condado de

  
SUE ANNE GILROY  
SECRETARY OF STATE  
OFFICE OF THE SECRETARY  
OF STATE  
INDIANA

148  
143

Marion, en la fecha de expedición del documento adjunto, expedido el 9 de junio del 2000.

Firmado: **Sue Anne Gilroy**  
Secretario de Estado

Firmado: **Mary Reeve**  
Delegado

Sello en papel dorado del Estado de Indiana

Sello del Consulado General de Colombia en Washington

**CONSULADO DE COLOMBIA**

**Chicago, Illinois 60611**

**No. 2044**

CERTIFICA la firma y funciones de la señora **Mary Reeve** como Secretaria delegada de Estado

Fecha: Junio 27, 2000.

Firmado: **JOSE FERNANDO GOMEZ MORA**  
Cónsul General de Colombia

Hay sello del Consulado de Colombia en Chicago

  
MARIA SALAZAR DE MORA  
INADVERTIDA OFICIAL  
RES. MINISTERIO DE ASUNTOS EXTERIORES

144  
144

MINISTERIO DE RELACIONES EXTERIORES

SANTA FE DE BOGOTA

N°093565

CERTIFICA la firma y el cargo del funcionario consular **José Fernando Gómez**, el  
día 11 de julio, 2000.

(Firma) Ilegible

JEFE DE LEGALIZACIONES  
Santafé de Bogotá, D.C.

  
MATERIA CONSULAR D. ACHU  
INTERPRETE OFICIAL  
RES. MINISTERIO 1311

MINISTERIO DE RELACIONES  
EXTERIORES  
11 00 239  
KATIA SALAMAKA  
CORREO A LA AGENCIA EN EL  
PROCESO DE CANCELACION  
DE LOS ALTA ENVIADOS

NO SE ASUME  
RESPONSABILIDAD DEL TEXTO  
2000 JUL 19 11:09  
JEFE DE LEGALIZACIONES  
CONSULADO DE BOGOTA D.C.

ASSIGNMENT

The undersigned

David Bleakman, Amy Suzon Chappell, Sandra Ann Filla, Kirk Willis Johnson, and Paul Leslie Ornstein  
domiciled in  
720 Eagle Creek Court, Zionsville, Indiana 46077 US,  
9040 Woodacre Boulevard, South Drive, Indianapolis,  
Indiana 46234 US, 1680 Williamsburg Lane, Franklin,  
Indiana 46131 US, 1177 Helford Lane, Carmel, Indiana  
46032 US, Paul Leslie Ornstein, 10441 Bosahan Court,  
Carmel, Indiana 46032 US, respectively

hereby state under oath to be the  
sole and true inventor(s) of

**SELECTIVE iGluR<sub>5</sub> RECEPTOR ANTAGONISTS  
FOR THE TREATMENT OF MIGRAINE**

states as well that he/they  
assign, without reservations or  
limitation, in favor of

**ELI LILLY AND COMPANY**

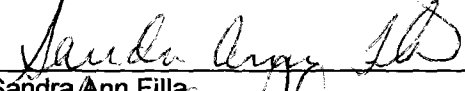
a corporation organized and  
existing under the laws of the  
State of Indiana, United States  
of America

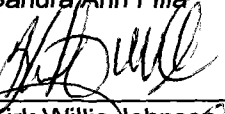
domiciled in Lilly Corporate Center  
Indianapolis, Indiana 46285  
United States of America

All rights inherent to said  
invention, and that the above  
mentioned corporation hereby to  
apply, in its name, for the cor-  
responding patent in the Republic  
of Colombia.

  
David Bleakman

  
Amy Suzon Chappell

  
Sandra Ann Filla

  
Kirk Willis Johnson

  
Paul Leslie Ornstein

COLOMBIA  
CASE:

X-12149

TRASPASO

abajo firmado

David Bleakman, Amy Chappell, Sandra Ann Filla  
Kirk Willis Johnson, y Paul Leslie Ornstein

domiciliado en

720 Eagle Creek Court, Zionsville, Indiana  
46077 US, 9040 Woodacre Boulevard, South Drive  
Indianapolis, Indiana 46234 US, 1680 Williamsbur  
Lane, Franklin, Indiana 46131 US, 1177 Helfor  
Lane, Carmel Indiana 46032 US, Paul Leslie Ornst  
10441 Bosahan Court, Carmel, Indiana 46032 US  
respectivamente

decia bajo juramnto ser único  
y verdadero inventor de

**ANTAGONISTAS SELECTIVOS DEL RECEPTOR iGluR<sub>5</sub>**

PARA EL TRATAMIENTO DE LA MIGRAÑA

Declaramos asimismo que cedemos  
y transf sin reserva ni limitacion,  
a favor de la sociedad

**ELI LILLY AND COMPANY**

organizada y existente de  
conformidad con las leyes del  
Estado de Indiana, Estados Unidos de  
América.

domiciliada en Lilly Corporate  
Center Indianapolis, Indiana  
46285 Estados Unidos de  
América

todos los derechos inherentes a  
dicha invención y que la citada  
sociedad queda facultada para  
solicitar en su nombre la patente  
correspondiente en la República de  
Colombia.

UNITED STATES OF AMERICA  
CERTIFICATE OF OFFICE  
STATE OF INDIANA

I, Sue Anne Gilroy, Secretary of State of Indiana, DO HEREBY CERTIFY: That  
according to records on file in my office, Sandra L. Bradshaw was duly elected  
or appointed to the office of Notary Public in and for Marion County  
and that the term of said office included the date of May 23, 2000: that to all his/her official acts as said offi-

cial, full faith and credit ought to be given in all Courts of  
Justice and elsewhere. In testimony whereof, I have here unto  
set my hand and affixed the Great Seal of the State of Indiana,  
at Indianapolis, this Ninth day of  
June, 2000



Sue Anne Gilroy  
Secretary of State

by: Mary Weaver  
Deputy

DECEMBER (VEINTI)

JOSE FERNANDO GOMEZ MORA  
Cónsul General de Colombia  
NSUL

3149

NOTARIAL CERTIFICATE

STATE: INDIANA)  
COUNTY: MARION)

On this 23 day of May 2000, 2000, personally  
appeared before me the named, David Bleakman, Sandra Ann Filla,  
Kirk Willis Johnson, and Paul Leslie Ornstein, who acknowledged that  
they signed the document as their voluntary act for the purposes therein  
set forth.

Sandra L. Bradshaw  
NOTARY PUBLIC SANDRA L. BRADSHAW  
MY COMMISSION EXPIRES  
APRIL 30, 2008  
RESIDENCE: MARION COUNTY



NOTARIAL CERTIFICATE

STATE: INDIANA)  
COUNTY: MARION)

On this 24 day of May, 2000, personally  
appeared before me the named, Amy Suzon Chappell who acknowledged she  
signed the document as her voluntary act for the purposes therein set forth.

Sandra L. Bradshaw  
NOTARY PUBLIC SANDRA L. BRADSHAW  
MY COMMISSION EXPIRES  
APRIL 30, 2008  
RESIDENCE: MARION COUNTY



Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E.

S

D.

Re: P1.- ELI LILLY AND COMPANY.-Solicitud de Patente de Invención para

~~FRAMMENTOS DE COTIZACION~~

~~UTILES~~

~~COMO~~

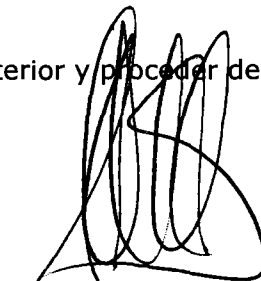
20001003121411

documento;

- (2) Copia debidamente autenticada por el Notario Sexto del Circulo de Bogotá, de los documentos que acreditan la calidad de Traductor Oficial del señor Eduardo Calado Noguera quien elaboró la traducción de las solicitudes estadinenses número 60/142.485 y 60/151.165, respecto de las cuales se reivindica prioridad en el presente caso.

3. Ruego a usted tomar atenta nota de lo anterior y proceder de conformidad.

Señor Superintendente,



JOSE ANTONIO LLOREDA

T.P. 10.784

Código 231

157/151

República de Colombia



Ministerio de Justicia y del Derecho

EL SECRETARIO GENERAL (E) DEL MINISTERIO DE  
JUSTICIA Y DEL DERECHO

CERTIFICA:

Que por Resolución 541 del 27 de febrero de 1976, le fue expedida licencia para ejercer funciones de Traductor e Intérprete Oficial en los idiomas INGLÉS y ESPAÑOL al señor EDUARDO CALADO NOGUERA, identificado con la cédula de ciudadanía No. 17.177.588 expedida en Bogotá.

Que dicha Resolución se encuentra vigente en la fecha.

Se expide la presente certificación a solicitud del interesado.

Dada en Santa Fe de Bogotá, D.C., a

14 OCT. 1997

*[Firma manuscrita]*

ALVARO NAMEN YARGAS

COMO NOTARIO SEXTO ENCARGADO  
DE SANTA FE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA.  
SANTA FE DE BOGOTA 25 AGO. 1999  
PABLO MENDEZ BARRUAS

ICM/mmc

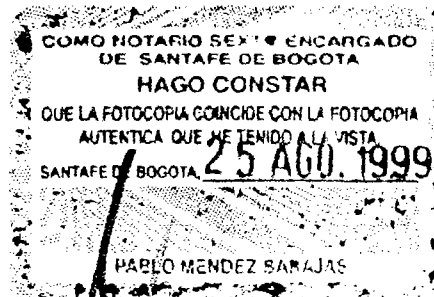
COMO NOTARIO SEXTO ENCARGADO  
DE SANTA FE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA.  
SANTA FE DE BOGOTA 25 ABR. 2000  
PABLO MENDEZ BARRUAS

COMO NOTARIO SEXTO ENCARGADO  
DE SANTA FE DE BOGOTA  
HAGO CONSTAR  
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA  
AUTENTICA QUE HE TENIDO A LA VISTA.  
SANTA FE DE BOGOTA 26 NOV. 1997  
22 MAR. 2000  
04 NOV. 1997  
SANTA FE DE BOGOTA

150  
152

REPUBLICA DE COLOMBIA  
MINISTERIO DE RELACIONES EXTERIORES

EL SUSCRITO JEFE DEL AREA DE  
LEGALIZACIONES DEL MINISTERIO DE  
RELACIONES EXTERIORES



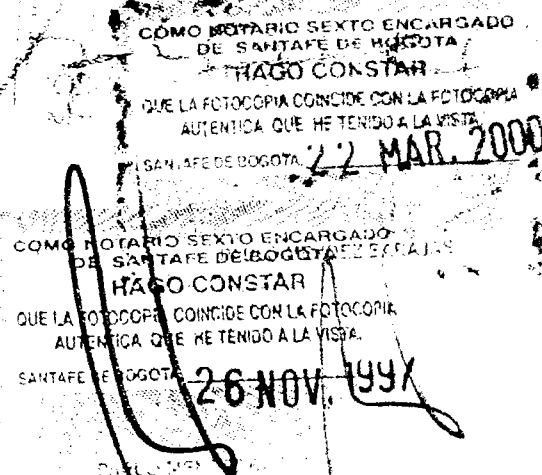
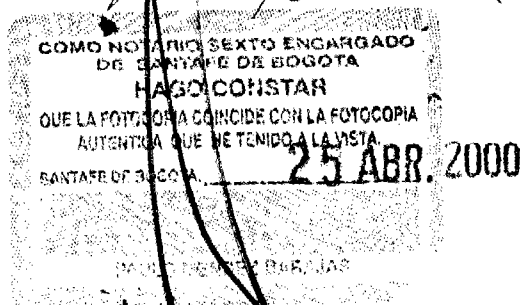
CERTIFICA

Que revisados los registros que se llevan en la oficina de Legalizaciones aparece la firma del señor **EDUARDO CALADO NOGUERA**, como traductor e intérprete oficial para los idiomas INGLES- ESPAÑOL, ESPAÑOL- INGLES, según resolución 541 del 27 de febrero de 1976.

La anterior certificación se expide a solicitud del interesado quien se identificó con cédula de ciudadanía 17.177.588 expedida en Bogotá.

Dada en Santa Fe de Bogotá, D.C., a los seis (6) de noviembre de 1997.

*Blanca Acosta de García*  
**BLANCA ACOSTA DE GARCIA**  
Jefe Area de Legalizaciones (e)



Julio 12, 2000  
Traducción Oficial No. 0289  
REF:ELI LILLY AND COMPANY  
Patente No.60/142,485

Eli Lilly and Co.  
Caso -X-12149

152  
153

DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS  
OFICINA DE MARCAS Y PATENTES

Junio 08, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/142,485

Fecha de Registro:Julio 06,1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: N WOODSON

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes de color dorado.

*Edmundo Calvado*

158  
154

## HOJA DE SOLICITUD PROVISIONAL

Esta es una petición para registrar una SOLICITUD PROVISIONAL bajo el código 37

CFR 1.53(c)

Número de Caso:P-12149A

### INVENTORES / SOLICITANTES

Apellidos:BLEAKMAN

Nombre:DAVID

Segundo Nombre:

Domicilio (ciudad y Estado o país extranjero):ZIONSVILLE, INDIANA

Apellidos:CHAPPELL

Nombre : AMY

Segundo Nombre: SUZON

Domicilio (ciudad y Estado o país extranjero):INDIANAPOLIS, INDIANA

Apellidos:FILLA

Nombre : SANDRA

Segundo Nombre: ANN

Domicilio (ciudad y Estado o país extranjero):FRANKLIN, INDIANA

Apellidos:JOHNSON

Nombre : KIRK

Segundo Nombre: WILLIS

Domicilio (ciudad y Estado o país extranjero):CARMEL, INDIANA

*Edmundo Calandina*

Apellidos: ORNSTEIN

Nombre :PAUL

Segundo Nombre: LESLIE

Domicilio (ciudad y Estado o país extranjero):CARMEL , INDIANA

TITULO DE LA INVENCION (Máximo 200 caracteres)  
RECEPTORES ANTAGONISTAS SELECTIVOS iGluR5 PARA EL  
TRATAMIENTO DE MIGRAÑA

DIRECCION PARA LA CORRESPONDENCIA

Eli Lilly and company

Patent Division/D.C. 1104

Lilly Corporate Center

Indianapolis, Indiana 46285

Estado,IndianaCodigo Postal-46285 País, Estados Unidos

1. PARTES DE LA SOLICITUD INCLUIDAS (Verificar de que todas apliquen)

☒ ESPECIFICACIONES

☒ Número de Páginas

☐ GRAFICA (S)

☐ Número de Páginas

☐ DECLARACION DE PEQUEÑA EMPRESA

☐ Número de Páginas

☐ Otros (especificar)

☐ Número de Páginas

*Eduardo Calado*

FORMA DE PAGO DE HONORARIOS DE SOLICITUD PROVISIONAL

[ ] Se encuentra un cheque adjunto para el pago Provisional de honorarios de registro.

[x] Por medio de la presente el Asistente Comisionado autoriza el cobro de los honorarios de registro al Número de Cuenta Corriente: 05-0840

SUMA DE HONORARIOS PROVISIONALES DE REGISTRO: \$150.00

[x] No La invencion fué realizada por una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

[ ] Si, el nombre de la agencia del Gobierno de los Estados Unidos y el número de contrato son:

Atentamente,

FIRMA: PAUL J. GAYLO

Fecha: 8/27/99

No de Registro: 36,808

[ ] se adjuntan hojas con los nombres de inventores adicionales

SOLICITUD PROVISIONAL SOLO PARA REGISTRO PATENTE

No. de Envio Correo Postal :EL 342548079 US

Fecha de depósito: Agosto 27,1999

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado bajo el Código 37 de Regulaciones Federales § 1.10

como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

*Edmundo Palado*

93  
164-157

Firma: Diedre Arciniega-Holtz

Nombre Impreso: Diedre Arciniega-Holtz

Edwards Calado N

8/11  
162  
158

## HOJA DE SOLICITUD PROVISIONAL

Esta es una petición para registrar una SOLICITUD PROVISIONAL bajo el código 37 CFR 1.53(c)

Número de Caso:P-12149

### INVENTORES / SOLICITANTES

Apellidos:BLEAKMAN

Nombre:DAVID

Segundo Nombre:

Domicilio (ciudad y Estado o país extranjero):ZIONSVILLE, INDIANA

Apellidos:CHAPPELL

Nombre : AMY

Segundo Nombre: SUZON

Domicilio (ciudad y Estado o país extranjero):INDIANAPOLIS, INDIANA

Apellidos:FILLA

Nombre : SANDRA

Segundo Nombre: ANN

Domicilio (ciudad y Estado o país extranjero):FRANKLIN, INDIANA

Apellidos:JOHNSON

*Eduardo Calzadilla*

163  
159

Nombre : KIRK

Segundo Nombre: WILLIS

Domicilio (ciudad y Estado o país extranjero): CARMEL, INDIANA

Apellidos: ORNSTEIN

Nombre : PAIL

Segundo Nombre: LESLIE

Domicilio (ciudad y Estado o país extranjero): CARMEL, INDIANA

TITULO DE LA INVENCION (Máximo 200 caracteres)  
RECEPTORES ANTAGONISTAS SELECTIVOS  $\alpha_1$  PARA EL  
TRATAMIENTO DE MIGRAÑA

DIRECCION PARA LA CORRESPONDENCIA

Eli Lilly and company

Patent Division/D.C. 1104

Lilly Corporate Center

Indianapolis, Indiana 46285

Estado, Indiana

Código Postal-46285

País, Estados Unidos

*Eduardo Calvo*

164  
160

1. PARTES DE LA SOLICITUD INCLUIDAS (Verificar de que todas apliquen)

☒ ESPECIFICACIONES

[34] Número de Páginas

☐ GRAFICA (S)

☐ Número de Páginas

☐ DECLARACION DE PEQUEÑA EMPRESA ☐ Número de Páginas

☐ Otros (especificar)

☐ Número de Páginas

#### FORMA DE PAGO DE HONORARIOS DE SOLICITUD PROVISIONAL

☐ Se encuentra un cheque adjunto para el pago Provisional de honorarios de registro.

☒ Por medio de la presente el Asistente Comisionado autoriza el cobro de los honorarios de registro al Número de Cuenta Corriente: 05-0840

SUMA DE HONORARIOS PROVISIONALES DE REGISTRO: \$150.00

La invencion fué realizada por una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

☒ No

*Eduardo Calzado*

165/61

[ ] Si, el nombre de la agencia del Gobierno de los Estados Unidos y el número de contrato son:

Atentamente,

FIRMA:ROBERT A. CONRAD

Fecha: 7/6/99

No de Registro:32,089

[ ] se adjuntan hojas con los nombres de inventores adicionales

#### SOLICITUD PROVISIONAL SOLO PARA REGISTRO PATENTE

No. de Envio Correo Postal :EL 342547895 US

Fecha de depósito: Julio 6, 1999

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado bajo el Código 37 de Regulaciones Federales § 1.10 como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

*Eduardo Calzado*

Firma:Olga M. Franz

Nombre Impreso: Olga M. Franz

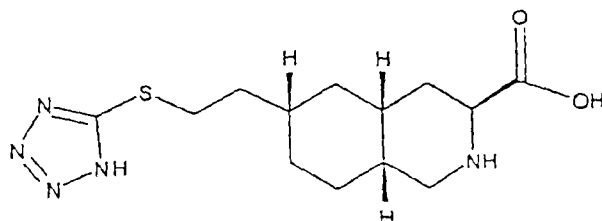
166  
162

## REIVINDICACIONES:

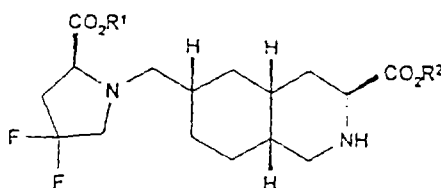
1. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva con el antagonista selectivo del receptor iGluR5 o una sal farmacéuticamente aceptable del mismo.
2. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite tratamiento, una composición farmacéutica que comprende un antagonista selectivo del receptor iGluR5 en combinación con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables.
3. El método de acuerdo a la Reivindicación 1 en el cual el ácido - 3S, 4aR, 6S, 8aR-6-(((4-carboxi) fenil) metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina-carboxílico.
4. El método de acuerdo a la Reivindicación 1 en el cual el antagonista selectivo del receptor iGluR5 es el ácido -3S, 4aR, 6S, 8aR-6-((((1H-Tetrazol-5-il) metil) oxi) metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina-3- carboxílico.

*Eduardo*

5. El método de acuerdo a la reivindicación 1 en el cual el antagonista selectivo del receptor iGluR5 se presenta en la formula:



6. El método de acuerdo a la reivindicación 1 en el cual el antagonista selectivo del receptor iGluR5 es un compuesto de acuerdo a la formula



en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1$ - $C_{20}$  , alquilo -alquenilo  $C_2$ - $C_6$ , alquilarilo  $C_1$ - $C_6$ , alquilo  $C_1$ - $C_6$  cicloalquilo( $C^3$  - $C^{10}$ ), alquilo  $C_1$ - $C^{10}$  -N,N- dialquiloamino  $C_1$ - $C_6$ , alquilo  $C_1$ - $C_6$ -pirrolidina, alquilo  $C_1$ - $C_6$ -piperidina, alquilo  $C_1$ - $C_6$ -morfolino o una sal farmacéuticamente aceptable del mismo.

*Eduardo Calvo*

168/64

7. El método de acuerdo a la Reivindicación 6 en el cual el antagonista selectivo del receptor iGluR5 es seleccionado de 3S, 4aR, 6S, 8aR Etilo-6-(((2S)-2-(Etoxicarbonilo)- 4, 4-difluoropirrolidinil) metil-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o ácido 3S, 4aR, 6S, 8aR 6-(((2S)-2-(ácido Carboxílico)-4,4- difluoropirrolidinil)metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina -3- carboxílico.

8. Un método para tratar la extravasación de proteína dural la cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un antagonista selectivo del receptor iGluR5.

9. Un método para tratar la migraña el cual consiste en suministrar a un paciente que necesite dicho tratamiento, una cantidad efectiva del compuesto, o una combinación del mismo, el cual posee la actividad de un antagonista selectivo del receptor iGluR5.

10. El uso de un antagonista selectivo del receptor iGluR5, para la preparación de un medicamento para tratar la migraña.

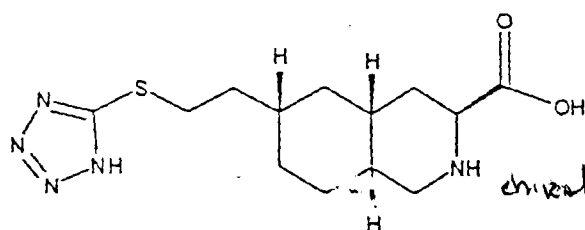
*Eduardo Calado*

169  
165

11. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 6S,8aR-6-(((4-carboxi) fenil) metil) 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina- carboxílico.

12. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 8aR-6-((((1H-Tetrazol-5-il) metil) oxi) metil- 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina- 3-carboxílico.

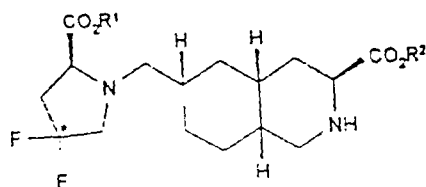
13. El uso de acuerdo a la reivindicación 10, en el cual el antagonista selectivo del receptor iGluR5, se presenta en la formula



14. El uso de acuerdo a la reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es un compuesto de acuerdo a la formula I

*EdUARdo Calvado*

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en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1-C_{20}$ , alquilo -alquenilo  $C^1-C_6$ , alquilarilo  $C_1-C_6$ , alquilo  $C_1-C_6$  cicloalquilo( $C^3-C^{10}$ ), alquilo  $C_1-C^{10}$  -N,N- dialquiloamino  $C_1-C_6$ , alquilo  $C_1-C_6$ -pirrolidina, alquilo  $C_1-C_6$ -piperidina, alquilo  $C_1-C_6$ -morfolino o una sal farmacéuticamente aceptable del mismo.

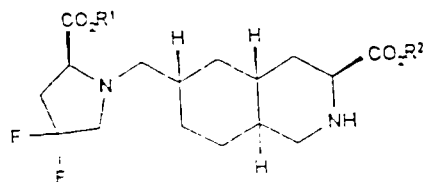
15. El uso para un tratamiento de acuerdo a la Reivindicación 14, en el cual el antagonista selectivo del receptor iGluR5, es seleccionado de 3S, 4aR, 6S, 8aR Etil-6-(((2S)-2-(Etoxicarbonil)- 4, 4-difluoropirrolidino)metil-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o ácido 3S, 4aR, 6S, 8aR 6-(((2S)-2-(ácido Carboxílico) -4,4-difluoropirrolidinilo)metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3- Carboxílico.

16. Un compuesto de la formula

1  
2  
3  
10

*Edmundo Calado*

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167



en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1-C_{20}$  ,  
alquilo -alquenilo  $C^2-C_6$ , alquilarilo  $C_1-C_6$ , alquilo  $C_1-C_6$   
cicloalquilo( $C^3-C^{10}$ ), alquilo  $C_1-C^{10}$  -N,N- dialquilamino  $C_1-C_6$ ,  
alquilo  $C_1-C_6$ -pirrolidina, alquilo  $C_1-C_6$ -piperidina, alquilo  $C_1-C_6$ -  
morfolino o una sal farmacéuticamente aceptable del mismo

17. Un compuesto de acuerdo a la Reivindicación 16 en el cual  $R^1$   
y  $R^2$  son cada uno independientemente H o alquilo  $C_1-C_{20}$ .

18. Un compuesto el cual es 3S, 4aR, 6S, 8aR Etil 6-(((2S)-2-  
(Etoxicarbonil)-4, 4-difluoropirrolidinilo)metil), 1, 2, 3, 4, 4a, 5,  
6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o una sal  
farmacéuticamente aceptable del mismo.

1  
2  
3  
10  
1  
2

*Eduardo Ceballos*

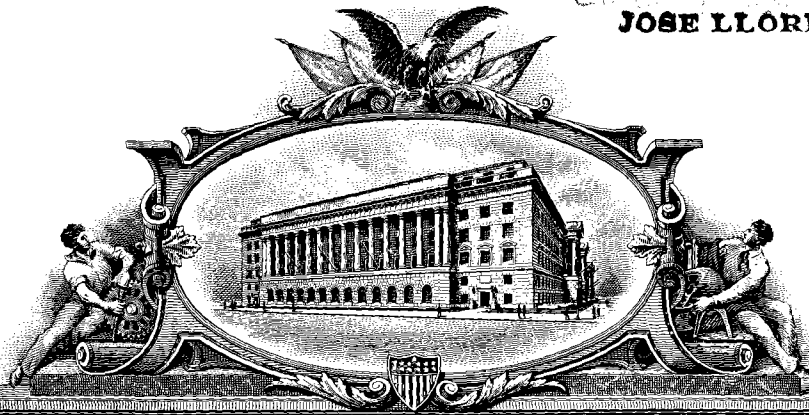
19. Un compuesto el cual es el ácido 3S, 4aR, 6S, 8aR Etil 6-(((2S)-2-(ácido Carboxílico)- 4, 4-difluoropirrolidinil) metil)- 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3- carboxílico o una sal farmacéuticamente aceptable del mismo.

20. Una composición farmacéutica la cual consta de un compuesto tal como lo reivindica la Reivindicación 16 en combinación con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables.

21. Una composición farmacéutica para el tratamiento de migraña, la cual consiste de un antagonista selectivo del receptor iGluR5 en combinación con un portador, diluyente o excipiente farmacéuticamente aceptable.

*Edwardo Celada*

PA 258223



# THE UNITED STATES OF AMERICA

TO ALL TO WHOM THESE PRESENTS SHALL COME:

UNITED STATES DEPARTMENT OF COMMERCE

United States Patent and Trademark Office

June 08, 2000

THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.

APPLICATION NUMBER: 60/142,485

FILING DATE: July 06, 1999

By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS



*N. Woodson*  
N. WOODSON  
Certifying Officer

# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

|               |         |                                          |   |
|---------------|---------|------------------------------------------|---|
| Docket Number | P-12149 | Type a plus sign (+) inside this box --> | + |
|---------------|---------|------------------------------------------|---|

## INVENTOR(S)/APPLICANT(S)

| LAST NAME | FIRST NAME | MIDDLE NAME | RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY) |
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## TITLE OF THE INVENTION (280 characters max)

SELECTIVE iGluR<sub>5</sub> RECEPTOR ANTAGONISTS FOR THE  
TREATMENT OF MIGRAINE

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## ENCLOSED APPLICATION PARTS (check all that apply)

|                                                   |                  |    |                                                 |
|---------------------------------------------------|------------------|----|-------------------------------------------------|
| <input checked="" type="checkbox"/> Specification | Number of pages  | 34 | <input type="checkbox"/> Small Entity Statement |
| <input type="checkbox"/> Drawing(s)               | Number of Sheets |    | <input type="checkbox"/> Other (Specify)        |

## METHOD OF PAYMENT (check one)

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The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are.

Respectfully submitted,  
SIGNATURE Robert A. Conrad

Date 7 / 6 / 99

TYPED or PRINTED NAME ROBERT A. CONRAD

REGISTRATION NO.  
(if appropriate)

32,089

☐ Additional inventors are being named on separately numbered sheets attached hereto

## PROVISIONAL APPLICATION FOR PATENT FILING ONLY

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Olga M. Frank Printed Name Olga M. Frank Signature

**SELECTIVE iGluR<sub>5</sub> RECEPTOR ANTAGONISTS FOR THE  
TREATMENT OF MIGRAINE**

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**BACKGROUND OF THE INVENTION**

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 pathways 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). Molecular biological studies have established that AMPA receptors are composed of subunits (GluR<sub>1</sub> – GluR<sub>4</sub>), which can assemble to form functional ion channels. Five kainate receptors have been identified which are classified as either High Affinity (KA1 and KA2) or Low Affinity (GluR<sub>5</sub>, GluR<sub>6</sub>, and GluR<sub>7</sub>). Bleakman et al., *Molecular Pharmacology*, 49, No.4, 581, (1996).

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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 cAMP 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 to 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).

Early theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff (*Arch. Neurol. Psychiatry*, 39, 737-63 (1938)). They proposed that the cause of migraine headache is vasodilatation of extracranial vessels. This view is supported by knowledge that ergot alkaloids and sumatriptan contract cephalic vascular smooth muscle and are effective in the treatment of migraine. Sumatriptan is a hydrophilic agonist at the serotonin 5-HT<sub>1</sub>-like receptors and does not cross the blood-brain barrier (Humphrey, *et al.*, *Ann. NY Acad. Sci.*, 600, 587-600 (1990)). Consequently, several series of compounds said to be useful for the treatment of migraine, have been developed to optimize the 5-HT<sub>1</sub>-like mediated vasoconstrictive activity of sumatriptan. However, sumatriptan's contraindications, including coronary vasospasm, hypertension, and angina are also products of its vasoconstrictive activity (MacIntyre, P.D., *et al.*, *British Journal of Clinical Pharmacology*, 34, 541-546 (1992); Chester, A.H., *et al.*, *Cardiovascular Research*, 24, 932-937 (1990); Conner, H.E., *et al.*, *European Journal of Pharmacology*, 161, 91-94 (1990)).

While the vascular mechanism for migraine has gained wide acceptance, there is not total agreement as to its validity. Moskowitz, for example, has shown the occurrence of migraine headaches, independent of changes in vessel diameter (*Cephalalgia*, 12, 5-7, (1992)). It is known that the trigeminal ganglion, and its associated nerve pathways, are associated with painful sensations from the face such as headache, in particular migraine. Moskowitz proposed that unknown triggers stimulate the trigeminal ganglia which innervate vasculature within cephalic tissue, giving rise to the release of vasoactive neuropeptides from axons innervating the vasculature. These neuropeptides initiate a series of events leading to neurogenic inflammation of the meninges, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan at doses similar to those required to treat acute migraine in humans. However, such doses of sumatriptan, as

stated, are associated with contraindications as a result of sumatriptan's attendant vasoconstrictive properties. (see *supra*.)

5 5-HT<sub>1D</sub> receptors have been implicated as mediating the blockade of neurogenic protein extravasation. (*Neurology*, 43(suppl. 3), S16-S20 (1993)). In addition, it has been reported that  $\alpha_2$ , H<sub>3</sub>, m-opioid and somatostatin receptors may also be located on trigeminovascular fibers and may block neurogenic plasma extravasation (Matsubara *et al.*, *Eur. J. Pharmacol.*, 224, 145-150 (1992)). Weinshank *et al.* have reported that sumatriptan and several ergot alkaloids have a high affinity for the serotonin 5-HT<sub>1F</sub> receptor, suggesting a role for the 5-HT<sub>1F</sub> receptor in migraine (WO93/14201).

10 European Patent Application Publication No. 590789A1 and United States Patents No. 5,446,051 and 5,670,516 disclose that certain decahydroisoquinoline derivative compounds are AMPA receptor antagonists and, as such, are useful in the treatment of many different conditions, including pain and migraine headache.

15 Recently, it has been reported that all five members of the kainate subtype, of ionotropic glutamate receptors, are expressed on rat trigeminal ganglion neurons. In particular, high levels of GluR<sub>5</sub> and KA2 have been observed. (Sahara *et al.*, *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons *et al.* reported that the kainate GluR<sub>5</sub> receptor subtype mediates the nociceptive response to formalin in a rat model of persistent pain. (*Neuropharmacology*, 37, 25 (1998)). Further, WO98/45270 previously disclosed  
20 that antagonists selective for the iGluR<sub>5</sub> receptor are useful for the treatment of pain, including; severe, chronic, intractable, and neuropathic pain. Noteworthy is the observation that kainate receptors have not previously been implicated in the etiology of migraine headache. In particular, selective iGluR<sub>5</sub> receptor antagonists have not been previously reported as being useful for the treatment of migraine.

25 Surprisingly, and in accordance with this invention, Applicants have discovered that selective antagonists of the iGluR<sub>5</sub> receptor subtype are efficacious in an animal model of neurogenic inflammation and, thus, could be useful for the treatment of migraine. Such antagonists could address a long felt need for a safe and effective treatment for migraine, without attending side effects. The treatment of neurological disorders is hereby  
30 furthered.

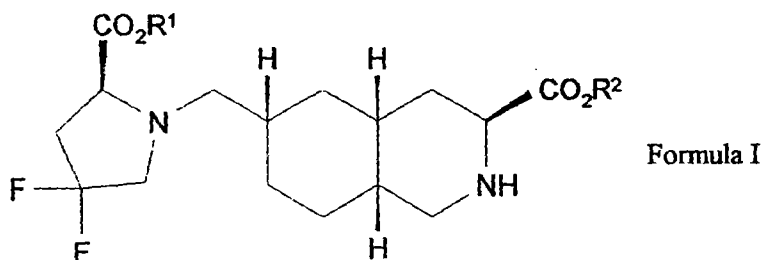
#### SUMMARY OF THE INVENTION

35 The present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist or a pharmaceutically acceptable salt thereof.

More specifically, the present invention provides a method of treating or preventing dural protein extravasation comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist.

In addition, the present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a compound, or combination of compounds, which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

In a further aspect, the present invention provides a compound of Formula I



wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, or C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine; or a pharmaceutically acceptable salt thereof.

In yet another aspect, the present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

In addition, the present invention provides pharmaceutical compositions useful for treating or preventing migraine comprising selective iGluR<sub>5</sub> receptor antagonists in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The present invention also provides the use of a selective iGluR<sub>5</sub> receptor antagonist for the manufacture of a medicament for treating or preventing migraine.

#### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for the treatment of migraine which can be demonstrated by a particular mechanism of action, inhibition of neurogenic dural protein extravasation. By treating a migraineur with a compound or composition which is

178  
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a selective antagonist of the iGluR<sub>5</sub> receptor relative to other excitatory amino acid receptors, the neurogenic extravasation which mediates migraine is inhibited without the attending side effects of agents designed to optimize the 5-HT<sub>1</sub>-like mediated vasoconstrictive activity of sumatriptan. In addition, the present invention provides

5 compounds functional as selective iGluR<sub>5</sub> receptor antagonists as well as pharmaceutically acceptable salts, prodrugs, and compositions thereof.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds provided by, or employed in the present invention which are substantially non-toxic to living organisms. Typical pharmaceutically acceptable salts include those salts

10 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.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of

15 pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described herein as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

20 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,

25 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,

30 chlorobenzoate, methylbenzoate, hydroxybenzoate, methoxybenzoate, phthalate, xylenesulfonate, phenylacetate, phenylpropionate, phenylbutyrate, citrate, lactate,  $\alpha$ -hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-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

35 methanesulfonic acid.

178  
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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.

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.,

5 "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, Inc., 1981.

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.

The specific stereoisomers and enantiomers of compounds of Formula (I) can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7, Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

It should also be understood by the skilled artisan that all of the compounds useful for the methods of the present invention are available for prodrug formulation. "Prodrug" as used herein, refers to metabolically labile ester or diester derivative of the functional acid compounds(drugs) provided by, or employed in the methods of, the present invention. When administered to a patient, the prodrug undergoes enzymatic and/or chemical

hydrolytic cleavage in such a manner that the parent carboxylic acid (drug), or as the case may be the parent dicarboxylic acid, is released. In all cases, the use of the compounds described herein as prodrugs is contemplated, and often is preferred, and thus, the prodrugs of all of the compounds employed are encompassed in the names of the compounds herein.

As used herein the term "C<sub>1</sub>-C<sub>4</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like.

As used herein the term "C<sub>1</sub>-C<sub>10</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl, isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like.

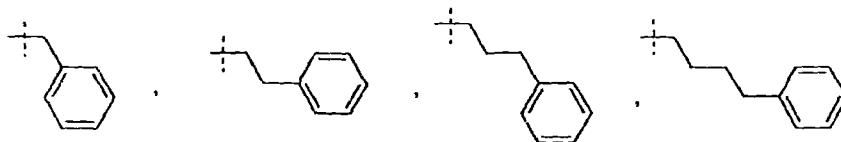
As used herein the term "C<sub>1</sub>-C<sub>20</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-nonadecyl, n-eicosyl and the like.

As used herein, the terms "Me", "Et", "Pr", "iPr", "Bu" and "t-Bu" refer to methyl, ethyl, propyl, isopropyl, butyl and tert-butyl respectively.

As used herein the term "C<sub>2</sub>-C<sub>6</sub> alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C<sub>2</sub>-C<sub>6</sub> alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

As used herein, the term "aryl" refers to monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkylaryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkylaryl" are the following:



and the like.

As used herein the term "(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" refers to a saturated hydrocarbon ring structure containing from three to ten carbon atoms. Typical C<sub>3</sub>-C<sub>10</sub> cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. It is understood that "(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl" and "(C<sub>4</sub>-C<sub>6</sub>)cycloalkyl" is included within the term "(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl".

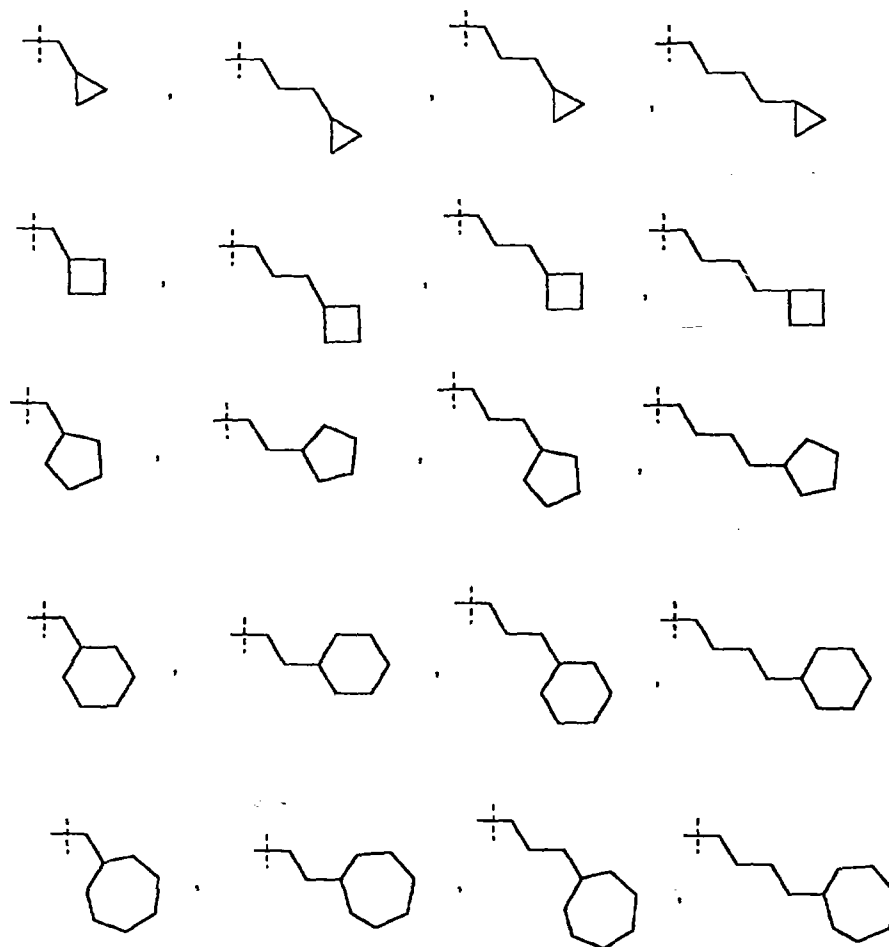
As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" are the following:

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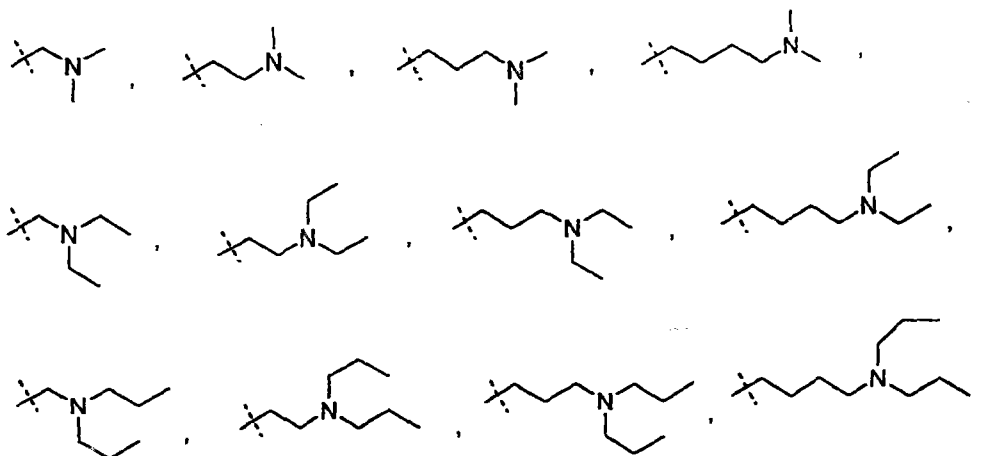


and the like.

As used herein the term "N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" refers to a nitrogen atom substituted with two straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms. Included within the term "N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" are -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, and the like.

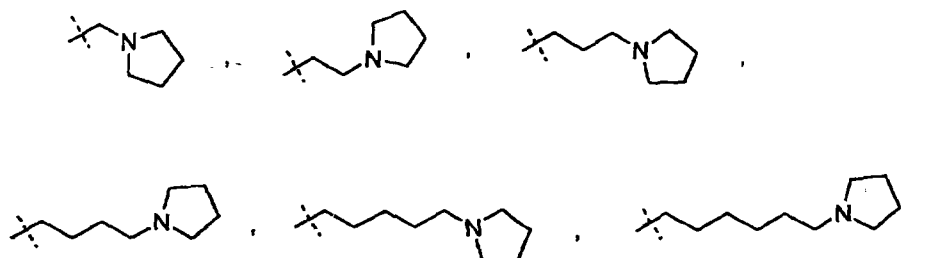
As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" are the following:

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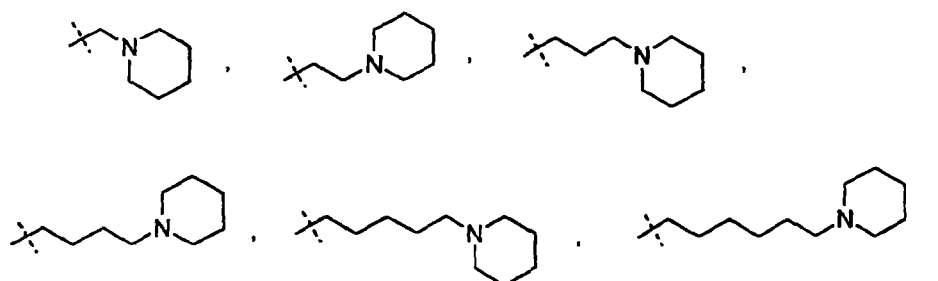
and the like.

- 5 As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a pyrrolidine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine" are the following:



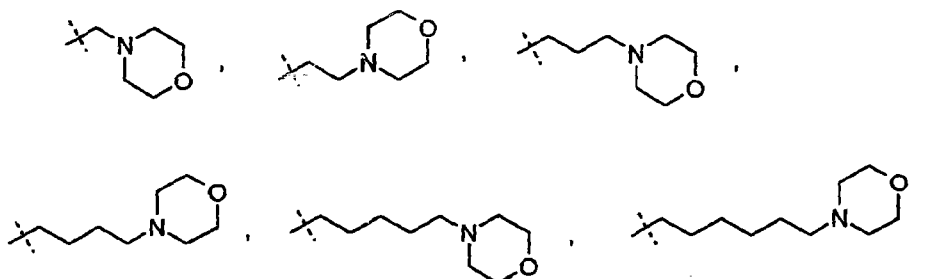
and the like.

- 10 As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a piperidine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine" are the following:



and the like.

As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a morpholine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine" are the following:



and the like.

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The designation "  " refers to a bond that protrudes backward out of the plane of the page.

As used herein the term "iGluR<sub>5</sub>" refers to the kainate ionotropic glutamate receptor, subtype 5, of the larger class of excitatory amino acid receptors.

As used herein the term "migraine" refers a disorder of the nervous system characterized by recurrent attacks of head pain (which are not caused by a structural brain abnormality such as those resulting from tumor or stroke), gastrointestinal disturbances, and possibly neurological symptoms such as visual distortion. Characteristic headaches of migraine usually last one day and are commonly accompanied by nausea, emesis, and photophobia.

Migraine is a "chronic" condition. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of migraine contemplates both acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear. As described above, a chronic condition is treated throughout the course of the disease.

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

186  
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It is understood that the term "selective iGluR<sub>5</sub> receptor antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to the iGluR<sub>5</sub> kainate receptor subtype, relative to the iGluR<sub>2</sub> AMPA receptor subtype. Preferably the selective iGluR<sub>5</sub> antagonist for use according to the method of the present invention has a binding affinity at least 10 fold greater for iGluR<sub>5</sub> than for iGluR<sub>2</sub>, more preferably at least 100 fold greater. It is further understood that any selective iGluR<sub>5</sub> antagonist, as appreciated by one of ordinary skill in the art, is included within the scope of the methods of the present invention. Such selective iGluR<sub>5</sub> receptor antagonists are readily available to, or are readily prepared by, one of ordinary skill in the art following recognized procedures. Examples of selective iGluR<sub>5</sub> receptor antagonists include, but are not limited to, the compounds provided in WO 98/45270, the entire contents of which is herein incorporated by reference.

It is further understood that the selective iGluR<sub>5</sub> receptor antagonists may exist as pharmaceutically acceptable salts and, as such, salts are therefore included within the scope of the present invention.

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

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

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

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of each compound used in the present method of treatment. 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.

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184  
184

The selective iGluR<sub>5</sub> antagonists for use according to the methods of the present invention may be a single compound or a combination of compounds capable of functioning as a selective iGluR<sub>5</sub> receptor antagonist. For example, it may be a combination of a compound capable of functioning as an antagonist at the iGluR<sub>5</sub> receptor and one or more other glutamate receptors, in combination with one or more compounds capable of blocking its actions at the iGluR<sub>2</sub> receptor. It is understood, however, that the selective iGluR<sub>5</sub> antagonist for use in the methods of the present invention, is preferably a single compound.

Oral administration is a preferred route of administering the compounds employed in the present invention whether administered alone, or as a combination of compounds capable of acting as a selective iGluR<sub>5</sub> receptor antagonist. Oral administration, however, is not the only route, nor even the only preferred route. Other preferred routes of administration include transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal routes. Where the selective iGluR<sub>5</sub> receptor antagonist is administered as a combination of compounds, one of the compounds may be administered by one route, such as oral, and the other may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal route, as particular circumstances require. The route of administration may be varied in any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds employed in the present invention may be administered as pharmaceutical compositions and, therefore, pharmaceutical compositions incorporating said compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally administered pharmaceutical compositions are particularly preferred. Such pharmaceutical compositions contain an effective amount of a selective iGluR<sub>5</sub> receptor antagonist, which effective amount is related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a given compound, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. The amount of each compound to be contained in each dosage unit depends on the identity of the particular compound chosen for the therapy, and other factors such as the indication for which it is given. The pharmaceutical compositions of the present invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing well known procedures.

Compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg of each compound individually or in a single unit dosage form, more preferably about 5 to about 300 mg (for example 25 mg). The term

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188  
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"unit dosage form" refers to a physically discrete unit suitable as unitary dosages for a patient, 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.

5       The inert ingredients and manner of formulation of the pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or  
10       powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compound, however, is best defined as the "effective amount", that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the compounds employed in the present invention do not depend on the  
15       nature of the composition, hence, the compositions are chosen and formulated solely for convenience and economy.

      Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starches, powdered cellulose especially crystalline and microcrystalline  
20       cellulose, sugars such as fructose, mannitol and sucrose, grain flours, and similar edible powders.

      Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various  
25       types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol,  
30       ethylcellulose and waxes can also serve as binders.

      Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the  
35       patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

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Tablet disintegrators are substances which swell when wetted to break up the tablet  
5 and release the compound. They include starches, clays, celluloses, algin and gums.

10 Enteric formulations are often used to protect an active ingredient from the  
strongly acid contents of the stomach. Such formulations are created by coating a solid  
dosage form with a film of a polymer which is insoluble in acid environments, and soluble  
in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate  
phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose  
15 acetate succinate.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following table provides an illustrative list of formulations suitable for use with the compounds employed in the present invention. The following is provided only to illustrate the invention and should not be interpreted as limiting the present invention in any way.

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187

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### Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

|    |                    |                          |
|----|--------------------|--------------------------|
| 5  |                    | Quantity<br>(mg/capsule) |
| 10 | Active Ingredient  | 250                      |
|    | Starch, dried      | 200                      |
|    | Magnesium stearate | <u>10</u>                |
| 15 | Total              | 460 mg                   |

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

### Formulation 2

A tablet is prepared using the ingredients below:

|    |                             |                         |
|----|-----------------------------|-------------------------|
| 25 |                             | Quantity<br>(mg/tablet) |
| 30 | Active Ingredient           | 250                     |
|    | Cellulose, microcrystalline | 400                     |
|    | Silicon dioxide, fumed      | 10                      |
|    | Stearic acid                | <u>5</u>                |
| 35 | Total                       | 665 mg                  |

The components are blended and compressed to form tablets each weighing 665 mg.

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197  
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**Formulation 3**

An aerosol solution is prepared containing the following components:

|    |                         |              |
|----|-------------------------|--------------|
| 5  |                         |              |
|    |                         | Weight %     |
|    | Active Ingredient       | 0.25         |
| 10 | Ethanol                 | 29.75        |
|    | Propellant 22           | <u>70.00</u> |
|    | (Chlorodifluoromethane) |              |
|    | Total                   | 100.00       |
| 15 |                         |              |

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

**Formulation 4**

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

|    |                             |             |
|----|-----------------------------|-------------|
| 25 |                             |             |
|    | Active Ingredient           | 60 mg       |
|    | Starch                      | 45 mg       |
|    | Microcrystalline cellulose  | 35 mg       |
| 30 | Polyvinylpyrrolidone        | 4 mg        |
|    | Sodium carboxymethyl starch | 4.5 mg      |
|    | Magnesium stearate          | 0.5 mg      |
|    | Talc                        | <u>1 mg</u> |
| 35 | Total                       | 150 mg      |

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

147  
139

**Formulation 5**

Capsules each containing 80 mg medicament are made as follows:

|    |                            |             |
|----|----------------------------|-------------|
| 5  |                            |             |
|    | Active Ingredient          | 80 mg       |
|    | Starch                     | 59 mg       |
|    | Microcrystalline cellulose | 59 mg       |
|    | Magnesium stearate         | <u>2 mg</u> |
| 10 | Total                      | 200 mg      |

15 The active ingredient, cellulose, starch, and magnesium stearate are blended, passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

**Formulation 6**

Suppositories each containing 225 mg of active ingredient may be made as follows:

|    |                                 |                 |
|----|---------------------------------|-----------------|
| 20 |                                 |                 |
|    | Active Ingredient               | 225 mg          |
|    | Saturated fatty acid glycerides | <u>2,000 mg</u> |
| 25 | Total                           | 2,225 mg        |

30 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in the saturated fatty acid glycerides previously melted using the minimum heat necessary. The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to cool.

**Formulation 7**

35 Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

|    |                                |         |
|----|--------------------------------|---------|
|    |                                |         |
|    | Active Ingredient              | 50 mg   |
|    | Sodium carboxymethyl cellulose | 50 mg   |
| 40 | Syrup                          | 1.25 ml |
|    | Benzoic acid solution          | 0.10 ml |
|    | Flavor                         | q.v.    |
|    | Color                          | q.v.    |
| 45 | Purified water to total        | 5 ml    |

103  
190

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring.

5 Sufficient water is then added to produce the required volume.

### Formulation 8

An intravenous formulation may be prepared as follows:

10

|                            |        |
|----------------------------|--------|
| Active Ingredient          | 100 mg |
| Mannitol                   | 100 mg |
| 5 N Sodium hydroxide       | 200 ml |
| 15 Purified water to total | 5 ml   |

20

It is understood by one of ordinary skill in the art that the above procedures can also be applied to a method of treating migraine comprising administering to a patient an effective amount of a compound which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

25

Inhibition of neuronal protein dural extravasation is an exemplary mechanism of action for the method of the present invention. The method further requires that compounds which exhibit such inhibition, also demonstrate selective binding and inhibition of the iGluR<sub>5</sub> receptor. The panel of compounds used to illustrate the principle of the present invention, and the pharmacological assays employed to demonstrate the mechanistic effectiveness of the invention, are described below. It is believed that Compounds III, IV(a), and IV(b) herein, represent novel compounds and, as such, have not previously been described as selective iGluR<sub>5</sub> receptor antagonists, nor reported as efficacious in treating migraine. Compounds III, IV(a), and IV(b) therefore, are provided as additional embodiments of the present invention.

30

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The following examples illustrate the methods of the present invention. The reagents and starting materials are readily available to one of ordinary skill in the art. These examples are intended to be illustrative only and are not to be construed so as to limit the scope of the invention in any way. As used herein, the following terms have the meanings indicated: "i.v." refers to intravenously; "p.o." refers to orally, "i.p." refers to intraperitoneally; "eq" or "equiv." 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; "mm

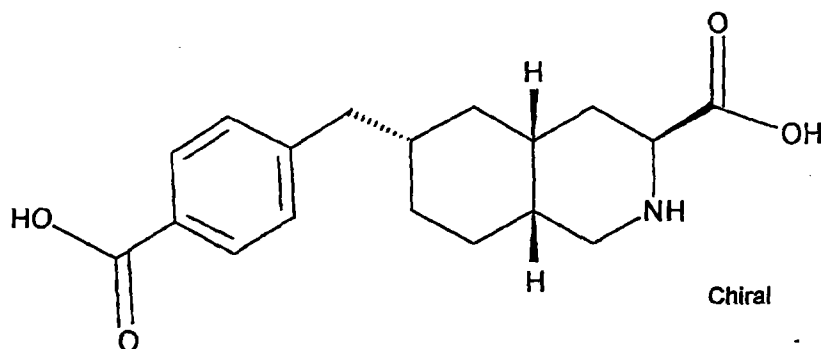
198  
191

Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R<sub>f</sub>" refers to retention factor; "R<sub>t</sub>" 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 dimethyl sulfoxide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "RT" refers to room temperature; "K<sub>i</sub>" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID<sub>50</sub>" and "ID<sub>100</sub>" refer to doses of an administered therapeutic agent which produce, respectively, a 50 % and 100% reduction in a physiological response.

### EXAMPLE 1

#### Compound I

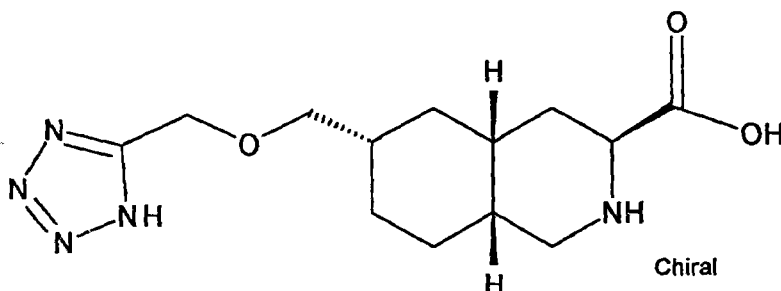
3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid



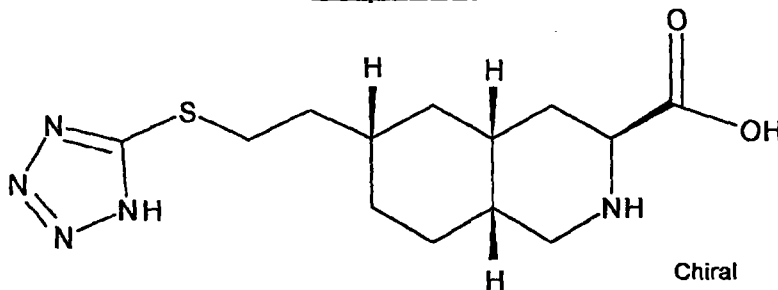
Those skilled in the art will recognize Compound I as an excitatory amino acid receptor antagonist, selective for the iGluR<sub>5</sub> receptor subtype. Compound I may be readily prepared by one of ordinary skill in the art following recognized general procedures as described in United States Patent No. 5,446,051, and more specifically as recently published in international application WO 98/45270, published October 15, 1998.

147  
192Compound II

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



Those skilled in the art will recognize Compound II as an excitatory amino acid receptor antagonist, selective for the iGluR<sub>5</sub> receptor subtype. Compound II may be readily prepared and resolved by one of ordinary skill in the art following recognized general procedures as described in United States Patent No. 5,670,516 (see Example No. 11, Compound No. 7), and more specifically as recently published in international application WO 98/45270, published October 15, 1998.

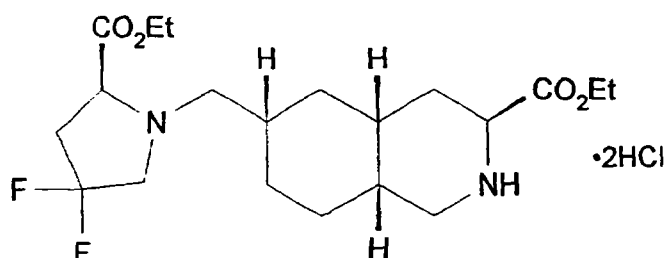
Compound III

Compound III represents a novel compound, functional as a selective iGluR<sub>5</sub> receptor antagonist. Compound III may be readily prepared; the desired enantiomer may be optically resolved; and pharmaceutical compositions comprising Compound III may be readily formulated by following general methods essentially as described for Example No. 8, Compound No. 8 of United States Patent No. 5,670,516, the entire contents of which is herein incorporated by reference.

Compound IV(b)

3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

5



- 10 A. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-((4-Methylphenyl)sulfonyloxy)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a solution of 15.0 g (50.1 mmol) of hydroxymethyl intermediate (See Col.11-12, Scheme II of United States Patent No. 5,356,902, the entire contents of which are herein incorporated by reference) cooled to 0 °C in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), was added triethylamine (20.9 mL, 150.3 mmol) followed by toluenesulfonyl chloride (19.1 g, 100.2 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The reaction was warmed to room temperature and stirred 16 h, then partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aqueous NaHSO<sub>4</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. Column chromatography (10-50% EtOAc/hexane) provided 20.1 g (89%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 451.5 (M<sup>+</sup>)  
 Calculated for C<sub>22</sub>H<sub>31</sub>NO<sub>7</sub>S 0.1 CH<sub>2</sub>Cl<sub>2</sub>: Theory: C, 57.45; H, 6.81; N, 3.03. Found: C, 57.76; H, 6.93; N, 3.35.  
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 171.4, 144.8, 132.4, 130.1, 127.6, 74.6, 60.4, 53.1, 52.4, 44.1, 34.6, 31.8, 31.0, 29.8, 28.8, 24.9, 23.3, 21.0, 14.0.

- 25  
 30 B. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((3S, 5S)-5-(Ethoxycarbonyl)-3-hydroxypyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

149  
194

A mixture of 4-hydroxyproline ethyl ester (6.5 g, 33.1 mmol), the compound of Step A above (10.0 g, 22.0 mmol), and potassium carbonate (4.6 g, 33.1 mmol) were heated at reflux in acetonitrile (22 mL) for 60 h. The reaction mixture was cooled to room temperature, and partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The aqueous layer was extracted two times with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (50% EtOAc/hexane followed by 5% MeOH/  $\text{CH}_2\text{Cl}_2$ ) gave 9.2 g (95%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 441.3 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_7\text{S}$ : Theory: C, 59.98; H, 8.24; N, 6.36. Found: C, 60.17; H, 8.23; N, 6.42.

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C. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((5S)-5-(Ethoxycarbonyl)-3-oxopyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a solution of DMSO (2.3 mL, 32.5 mmol) cooled to  $-78^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added, dropwise, oxalyl chloride (1.4 mL, 16.3 mmol). The reaction mixture was stirred for 5 min, then the compound of Step B above (6.0 g, 13.6 mmol) dissolved in 20 mL of  $\text{CH}_2\text{Cl}_2$  was added. Upon stirring for 45 min at  $-78^\circ\text{C}$ , triethylamine (9.5 mL, 32.5 mmol) was added. The reaction was warmed to room temperature over approximately 2 hours, and quenched by the addition of 10% aqueous  $\text{NaHSO}_4$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (25–50% EtOAc/hexane) provided 4.6 g (78%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 439.1 ( $\text{M}^+$ )

D. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a mixture of the compound of Step C above (4.62 g, 10.5 mmol) cooled to  $-78^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added, dropwise, diethylaminosulfur trifluoride (3.5 mL, 26.3 mmol). The reaction was allowed to warm to room temperature, stirred an additional 48 h, then quenched by the addition of MeOH. After concentrating in vacuo, the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was

extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (25-50% EtOAc/hexane) provided 3.3 g (68%) of the desired intermediate title compound as a colorless oil:

- 5 MS(m/e): 461.2 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{22}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_6$ : Theory: C, 57.38; H, 7.74; N, 6.08. Found: C, 58.25; H, 7.59; N, 6.50.

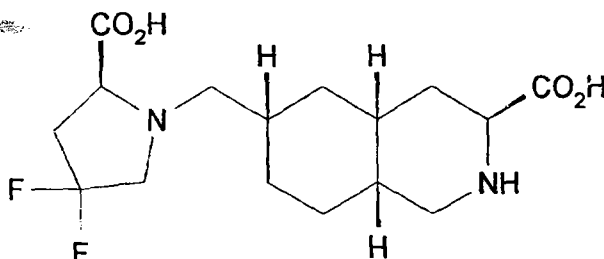
- 10 E. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (Compound IV(b))

- 15 A solution of the compound of Step D above (3.3 g, 7.10 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (40 mL) was cooled to 0 °C and charged with trimethylsilyl iodide (3.0 mL, 21.3 mmol). The reaction was allowed to warm to room temperature, stirred an additional 4 h, then quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (50 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics washed with a 1 N solution of sodium thiosulfate, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The material was chromatographed, (2% MeOH/ $\text{CH}_2\text{Cl}_2$ ), dissolved in 20 mL of  $\text{Et}_2\text{O}$ , and to it was  
20 added 50 mL of a HCl/ $\text{Et}_2\text{O}$  solution. The solvent was removed in vacuo, providing 2.6 g (76%) of the final title compound as a white solid:

- 25 MS(m/e): 403.4 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{20}\text{H}_{32}\text{Cl}_2\text{F}_2\text{N}_2\text{O}_4$ : Theory: C, 50.53; H, 7.21; N, 5.89.  
Found: C, 50.90; H, 7.41; N, 5.84.  
 $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ):  $\delta$  170.3, 167.7, 125.1 (t,  $J_{\text{C-F}} = 249.1$  Hz), 65.9, 65.0, 64.1, 63.4, 60.1 (t,  $J_{\text{C-F}} = 33.9$  Hz), 57.6, 52.8, 42.9, 37.2 (t,  $J_{\text{C-F}} = 26.4$  Hz), 34.5, 31.7, 31.3, 30.5, 28.4, 26.9, 24.3, 13.6.

Compound IV(a)

3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid



5 A solution of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (3.3 g, 7.10 mmol), the compound of Step D above, dissolved in 5 N aqueous HCl (15 mL) was heated at 90 °C for 18 h. The reaction mixture  
10 was cooled to room temperature and concentrated in vacuo. The resulting crude foam was dissolved in water (75 mL) and stirred in the presence of Dowex 50X8 (100–200) ion-exchange resin (10 g) for 2 h. The resin was filtered, washed sequentially with 1:1 THF/H<sub>2</sub>O and water, then stirred in the presence of 10% pyridine/H<sub>2</sub>O for 2 h. After  
15 filtration, the resin was washed with water, and the filtrate was concentrated in vacuo to provide the title compound (0.6 g, 97%) as a white foam:

MS(m/e): 347.2 (M<sup>+</sup>)

Calculated for C<sub>16</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> 0.1 H<sub>2</sub>O: Theory: C, 55.19; H, 7.01; N, 8.05. Found: C, 54.81; H, 6.82; N, 8.13.

20 <sup>13</sup>C NMR (D<sub>2</sub>O): δ 175.1, 171.1, 125.6 (t, J<sub>C-F</sub> = 249.4 Hz), 67.9, 63.0, 59.3 (t, J<sub>C-F</sub> = 34.0 Hz), 54.5, 42.5, 37.5 (t, J<sub>C-F</sub> = 24.9 Hz), 34.3, 32.7, 32.4, 30.6, 28.2, 27.0, 24.3.

EXAMPLE 2

25 To establish that the iGluR<sub>5</sub> receptor subtype is mediating neurogenic protein extravasation, a functional characteristic of migraine, the binding affinity of the panel compounds to the iGluR<sub>5</sub> receptor is first measured using standard methods. For  
30 example, the activity of compounds acting at the iGluR<sub>5</sub> receptor antagonists can be determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR<sub>5</sub> receptor (Korczak et al., 1994, Recept. 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). The selectivity of compounds acting at the iGluR<sub>5</sub> receptor subtype can then be determined by comparing antagonist activity at the iGluR<sub>5</sub> receptor with antagonist activity at other AMPA and kainate receptors. Methods useful for such comparison studies include: receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR<sub>1</sub>, GluR<sub>2</sub>, GluR<sub>3</sub> and GluR<sub>4</sub> 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 GluR<sub>6</sub> 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).

#### iGluR<sub>5</sub> antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors were employed. Displacement of <sup>3</sup>[H] AMPA by increasing concentrations of antagonist was measured on iGluR<sub>1</sub>, iGluR<sub>2</sub>, iGluR<sub>3</sub>, and iGluR<sub>4</sub> expressing cells, while displacement of <sup>3</sup>[H] kainate (KA) was measured on iGluR<sub>5</sub>, iGluR<sub>6</sub>, iGluR<sub>7</sub>, and KA2-expressing cells. Estimated antagonist binding activity (K<sub>d</sub>) in μM was determined for Compounds I – IV. As an indicia of selectivity, the ratio of binding affinity to the iGluR<sub>2</sub> AMPA receptor subtype, versus the binding affinity to iGluR<sub>5</sub> kainate receptor subtype, was also determined. Compounds provided by the present invention displayed a binding affinity of at least 10 fold greater for iGluR<sub>5</sub> than that for iGluR<sub>2</sub>, more preferably at least 100 fold.

#### EXAMPLE 3

The following animal model was employed to determine the ability of each of the panel of compounds to inhibit protein extravasation, an exemplary functional assay of the neuronal mechanism of migraine. The results obtained for the panel of compounds in this model are summarized in Table I (infra).

#### Animal Model of Dural Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River Laboratories (225-325 g) were anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs.

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Following a midline sagittal scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.), were lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein was exposed and a dose of the test compound was injected intravenously (i.v.) at a dosing volume of 1ml/Kg or, in the alternative, test compound was administered orally (p.o) via gavage at a volume of 2.0ml/Kg. Approximately 7 minutes post i.v. injection, a 50 mg/Kg dose of Evans Blue, a fluorescent dye, was also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals were killed and exsanguinated with 20 mL of saline. The top of the skull was removed to facilitate the collection of the dural membranes. The membrane samples were removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues were coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm was utilized and the emission intensity at 600 nm was determined. The microscope was equipped with a motorized stage and also interfaced with a personal computer. This facilitated the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 nm steps) on each dural sample. The mean and standard deviation of the measurements were determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, was calculated. Control animals dosed with only with saline, yielded a ratio of approximately 2.0 in rats and approximately 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0.

202  
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Dose-response curves were generated for each of the panel of compounds and the dose that inhibited the extravasation by 50% (ID<sub>50</sub>) or 100% (ID<sub>100</sub>) was approximated. The respective ID<sub>50</sub> and/or ID<sub>100</sub> values, for each of the panel of compounds employed in the present invention, are summarized in Table I below.

5

Table I

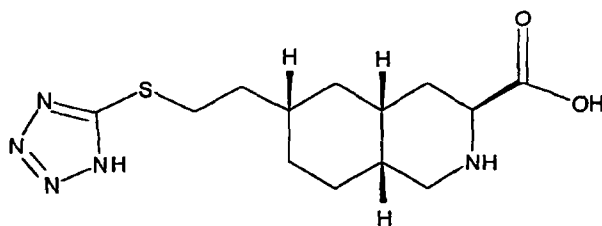
Inhibition of Dural Protein Extravasation (ng/Kg)

| Compound | Route of administration | ID <sub>50</sub> (ng/Kg) | ID <sub>100</sub> (ng/Kg) |
|----------|-------------------------|--------------------------|---------------------------|
| I        | i.v.                    | 6.5 (rat),               | --                        |
|          |                         | 4.0 (Gpig)               | --                        |
| II       | i.v                     | 15 (rat)                 | --                        |
| III      | i.v                     | .0053 (rat)              | 0.10                      |
| IV(b)    | p.o                     | --                       | 0.01                      |

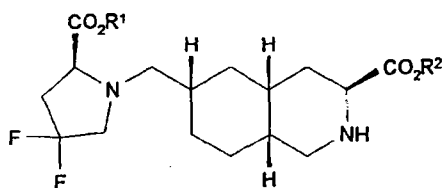
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What is claimed is:

1. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist or a pharmaceutically acceptable salt thereof.
2. A method of treating migraine comprising administering to a patient in need thereof a pharmaceutical composition comprising a selective iGluR<sub>5</sub> receptor antagonist in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.
3. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.
4. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is 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. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is given by the formula



6. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is a compound of the formula



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wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine or a pharmaceutically acceptable salt thereof.

5

7. The method according to Claim 6 wherein the selective iGluR<sub>5</sub> receptor antagonist is selected from 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

10

8. A method of treating dural protein extravasation comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist.

15

9. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a compound, or combination thereof, which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

20

10. The use of a selective iGluR<sub>5</sub> receptor antagonist for the manufacture of a medicament for treating migraine.

25

11. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.

30

12. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is 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.

13. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is given by the formula

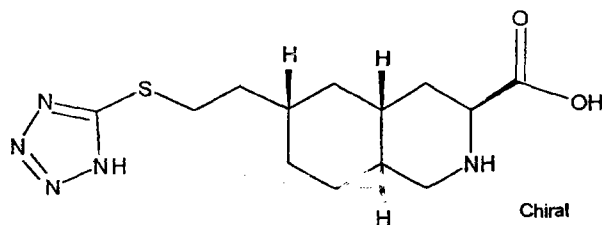
**FORMATO DE DIGITALIZACION**  
**RELACION DE ANEXOS**



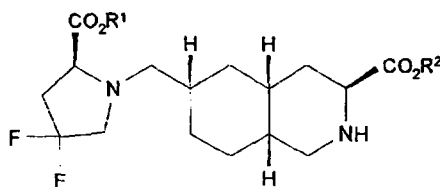
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| Expediente No |                            | 00-050.073     | No de Folio |
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| 2             | DVD                        |                |             |
| 3             | REVISTA                    |                |             |
| 4             | LIBRO                      |                |             |
| 5             | PERIODICO                  |                |             |
| 6             | DISQUETES                  |                |             |
| 7             | SOBRE DE MANILA X          |                |             |
| 8             | SOBRE BLANCO TAMAÑO CARTA  |                |             |
| 9             | SOBRE BLANCO TAMAÑO OFICIO |                |             |
| 10            | OTROS:                     |                |             |

Observaciones: Arte Final

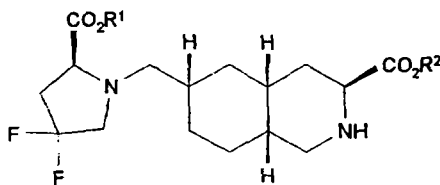


14. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is  
5 a compound of Formula I



- 10 wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, or C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine; or a pharmaceutically acceptable salt thereof.
- 15 15. The use according to Claim 14 wherein the selective iGluR<sub>5</sub> receptor antagonist is selected from 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-
- 20 carboxylic Acid

16. A compound of the formula



206  
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P-12149

-33-

wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine or a pharmaceutically acceptable salt thereof.

5

17. \* A compound according to Claim 16 wherein R<sup>1</sup> and R<sup>2</sup> are each independently H or C<sub>1</sub>-C<sub>20</sub> alkyl.

10

18. A compound which is 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or a pharmaceutically acceptable salt thereof.

15

19. A compound which is 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

20

20. A pharmaceutical composition which comprises a compound as claimed in Claim 16 in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

21. A pharmaceutical composition for the treatment of migraine which comprises a selective iGluR<sub>5</sub> receptor antagonist in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

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P-12149

-34-

# ABSTRACT

The present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist. The present invention further provides novel compounds functional as selective iGluR<sub>5</sub> receptor antagonists as well as compositions and formulations comprising said selective iGluR<sub>5</sub> receptor antagonists.

009020-55427109

Julio 12, 2000  
Traducción Oficial No. 0290  
REF:ELI LILLY AND COMPANY  
Patente No.60/151,165

Eli Lilly and Co.  
Caso -X-12149

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DEPARTAMENTO DE COMERCIO DE LOS ESTADOS UNIDOS  
OFICINA DE MARCAS Y PATENTES

Junio 08, 2000

Por medio del presente documento se certifica que adjunta se encuentra una fiel copia de los registros de la Oficina de Marcas y Patentes de los Estados Unidos, correspondientes a los documentos para la solicitud tal como se presentaron, con el fin de asignarle una fecha de registro bajo la norma del código 35 USC 111.

Número de Solicitud: 60/151,165

Fecha de Registro: Agosto 27,1999

Autorizado por:

COMISIONADO DE MARCAS Y PATENTES

Firma: N. WOODSON

Funcionario Encargado de Certificaciones

Hay sello de la Oficina de Marcas y Patentes de color dorado

*Eduardo Calado N*

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## HOJA DE SOLICITUD PROVISIONAL

Esta es una petición para registrar una SOLICITUD PROVISIONAL bajo el código 37  
CFR 1.53(c)

Número de Caso:P-12149A

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Nombre :PAIL

Segundo Nombre: LESLIE

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TITULO DE LA INVENCION (Máximo 200 caracteres)  
RECEPTORES ANTAGONISTAS SELECTIVOS iCluR5 PARA EL  
TRATAMIENTO DE MIGRAÑA

DIRECCION PARA LA CORRESPONDENCIA

Eli Lilly and company  
Patent Division/D.C. 1104  
Lilly Corporate Center  
Indianapolis, Indiana 46285

Estado, Indiana Código Postal-46285 País, Estados Unidos

1. PARTES DE LA SOLICITUD INCLUIDAS (Verificar de que todas apliquen)

- |                                                         |                                                            |
|---------------------------------------------------------|------------------------------------------------------------|
| <input checked="" type="checkbox"/> ESPECIFICACIONES    | <input checked="" type="checkbox"/> [35] Número de Páginas |
| <input type="checkbox"/> GRAFICA (S)                    | <input type="checkbox"/> Número de Páginas                 |
| <input type="checkbox"/> DECLARACION DE PEQUEÑA EMPRESA | <input type="checkbox"/> Número de Páginas                 |
| <input type="checkbox"/> Otros (especificar)            | <input type="checkbox"/> Número de Páginas                 |

FORMA DE PAGO DE HONORARIOS DE SOLICITUD PROVISIONAL

- ☐ Se encuentra un cheque adjunto para el pago Provisional de honorarios de registro.
- ☒ Por medio de la presente el Asistente Comisionado autoriza el cobro de los honorarios de registro al Número de Cuenta Corriente: 05-0840

SUMA DE HONORARIOS PROVISIONALES DE REGISTRO: \$150.00

- ☒ No, el invento fué realizado por una agencia del Gobierno de los Estados Unidos o bajo contrato con una agencia del Gobierno de los Estados Unidos.

*Eduardo C. Calvo*

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[ ] Si, el nombre de la agencia del Gobierno de los Estados Unidos y el número de contrato son:

Atentamente,

FIRMA:PAUL J. GAYLO

Fecha: 8/ 27 /99

No de Registro:36,808

[ ] se adjuntan hojas con los nombres de inventores adicionales

### SOLICITUD PROVISIONAL SOLO PARA REGISTRO PATENTE

No. de Envio Correo Postal :EL 342548079 US

Fecha de depósito:Agosto 27, 1999

Yo, por medio del presente documento certifico que ha sido enviado por Correo Certificado bajo el Código 37 de Regulaciones Federales § 1.10

como Correo Postal al Destinatario y al Comisionado Asistente para Patentes, Box Patent Application, Washington, DC., 20231.

Firma: Diedre Arciniela-Holtz

Nombre Impreso: Diedre Arciniela-Holtz

*Eduardo Calcedo*

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2009

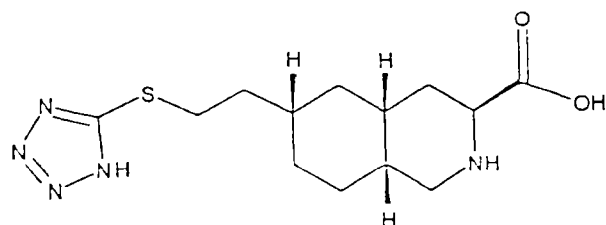
## REIVINDICACIONES:

1. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva con el antagonista selectivo del receptor iGluRs o una sal farmacéuticamente aceptable del mismo.
2. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite tratamiento, una composición farmacéutica que comprende un antagonista selectivo del receptor iGluRs en combinación con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables.
3. El método de acuerdo a la Reivindicación 1 en el cual el ácido -3S, 4aR, 6S, 8aR-6-(((4-carboxi) fenil) metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina-carboxílico.
4. El método de acuerdo a la Reivindicación 1 en el cual el antagonista selectivo del receptor iGluRs es el ácido -3S, 4aR, 6S 8aR-6-(((1H-Tetrazol-5-il) metil) oxi) metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina-3- carboxílico.

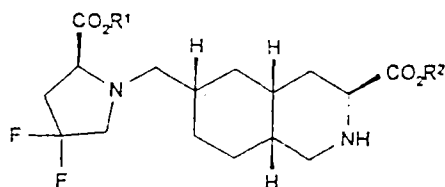
*Eduardo Calzadilla*

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5. El método de acuerdo a la reivindicación 1 en el cual el antagonista selectivo del receptor iGluR5 se presenta en la formula:



6. El método de acuerdo a la reivindicación 1 en el cual el antagonista selectivo del receptor iGluR5 es un compuesto de acuerdo a la formula



en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1-C_{20}$  , alquilo -alquenilo  $C_2-C_6$ , alquilarilo  $C_1-C_6$ , alquilo  $C_1-C_6$  cicloalquilo( $C^3-C^{10}$ ), alquilo  $C_1-C^{10}$  -N,N- dialquiloamino  $C_1-C_6$ , alquilo  $C_1-C_6$ -pirrolidina, alquilo  $C_1-C_6$ -piperidina, alquilo  $C_1-C_6$ -morfolino o una sal farmacéuticamente aceptable del mismo.

*Eduardo Calas*

211/215

7. El método de acuerdo a la Reivindicación 6 en el cual el antagonista selectivo del receptor iGluR5 es seleccionado de 3S, 4aR, 6S, 8aR Etilo-6-(((2S)-2-(Etoxicarbonilo)- 4, 4-difluoropirrolidinil) metil-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o ácido 3S, 4aR, 6S, 8aR 6-(((2S)-2-(ácido Carboxílico)-4,4- difluoropirrolidinil)metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina -3- carboxílico.

8. Un método para tratar la extravasación de proteína dural la cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva de un antagonista selectivo del receptor iGluR5.

9. Un método para tratar la migraña el cual consiste en suministrar a un paciente que necesite dicho tratamiento, una cantidad efectiva del compuesto, o una combinación del mismo, el cual posee la actividad de un antagonista selectivo del receptor iGluR5.

10. El uso de un antagonista selectivo del receptor iGluR5, para la preparación de un medicamento para tratar la migraña.

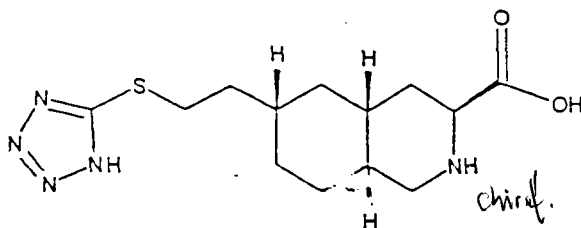
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11. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 6S,8aR-6-(((4-carboxi) fenil) metil) 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina- carboxílico.

12. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 8aR-6-(((1H-Tetrazol-5-il) metil) oxi) metil- 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a- decahidroisoquinolina- 3-carboxílico.

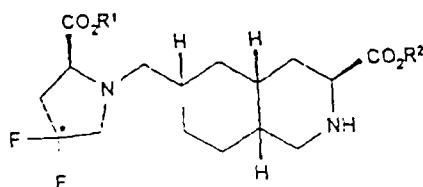
13. El uso de acuerdo a la reivindicación 10, en el cual el antagonista selectivo del receptor iGluR5, se presenta en la formula



14. El uso de acuerdo a la reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es un compuesto de acuerdo a la formula I

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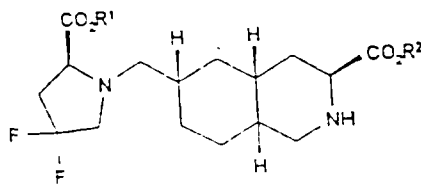
en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1-C_{20}$ , alquilo -alquenilo  $C^1-C_6$ , alquilarilo  $C_1-C_6$ , alquilo  $C_1-C_6$  cicloalquilo( $C^3-C^{10}$ ), alquilo  $C_1-C^{10}$  -N,N- dialquiloamino  $C_1-C_6$ , alquilo  $C_1-C_6$ -pirrolidina, alquilo  $C_1-C_6$ -piperidina, alquilo  $C_1-C_6$ -morfolino o una sal farmacéuticamente aceptable del mismo.

15. El uso para un tratamiento de acuerdo a la Reivindicación 14, en el cual el antagonista selectivo del receptor iGluRs, es seleccionado de 3S, 4aR, 6S, 8aR Etil-6-(((2S)-2-(Etoxicarbonil)- 4, 4-difluoropirrolidino)metil-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o ácido 3S, 4aR, 6S, 8aR 6-(((2S)-2-(ácido Carboxílico) -4,4-difluoropirrolidinilo)metil)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3- Carboxílico.

16. Un compuesto de la formula

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en el cual  $R^1$  y  $R^2$  son cada cual independientemente H,  $C_1-C_{20}$  ,  
alquilo -alquenilo  $C^2-C_6$ , alquilarilo  $C_1-C_6$ , alquilo  $C_1-C_6$   
cicloalquilo( $C^3-C^{10}$ ), alquilo  $C_1-C^{10}$  -N,N- dialquilamino  $C_1-C_6$ ,  
alquilo  $C_1-C_6$ -pirrolidina, alquilo  $C_1-C_6$ -piperidina, alquilo  $C_1-C_6$ -  
morfolino o una sal farmacéuticamente aceptable del mismo

17. Un compuesto de acuerdo a la Reivindicación 16 en el cual  $R^1$   
y  $R^2$  son cada uno independientemente H o alquilo  $C_1-C_{20}$ .

18. Un compuesto el cual es 3S, 4aR, 6S, 8aR Etil 6-(((2S)-2-  
(Etoxicarbonil)-4, 4-difluoropirrolidinilo)metil), 1, 2, 3, 4, 4a, 5,  
6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o una sal  
farmacéuticamente aceptable del mismo.

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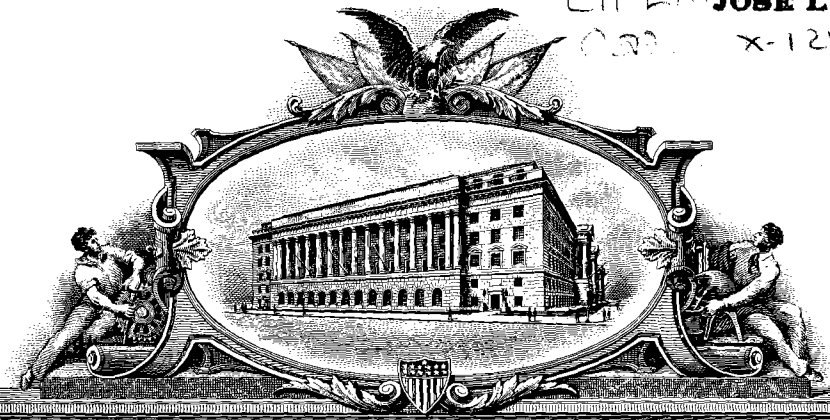
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19. Un compuesto el cual es el ácido 3S, 4aR, 6S, 8aR Etil 6-(((2S)-2-(ácido Carboxílico)- 4, 4-difluoropirrolidinil) metil)- 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3- carboxílico o una sal farmacéuticamente aceptable del mismo.
20. Una composición farmacéutica la cual consta de un compuesto tal como lo reivindica la Reivindicación 16 en combinación con uno o más portadores, diluyentes o excipientes farmacéuticamente aceptables.
21. Una composición farmacéutica para el tratamiento de migraña, la cual consiste de un antagonista selectivo del receptor iGluR5 en combinación con un portador, diluyente o excipiente farmacéuticamente aceptable.

Edwards Calado

PA 258223



# THE UNITED STATES OF AMERICA

**TO ALL TO WHOM THESE PRESENTS SHALL COME:**

**UNITED STATES DEPARTMENT OF COMMERCE**

**United States Patent and Trademark Office**

**June 08, 2000**

**THIS IS TO CERTIFY THAT ANNEXED HERETO IS A TRUE COPY FROM THE RECORDS OF THE UNITED STATES PATENT AND TRADEMARK OFFICE OF THOSE PAPERS OF THE BELOW IDENTIFIED PATENT APPLICATION THAT MET THE REQUIREMENTS TO BE GRANTED A FILING DATE UNDER 35 USC 111.**

**APPLICATION NUMBER: 60/151,165**

**FILING DATE: August 27, 1999**

**By Authority of the  
COMMISSIONER OF PATENTS AND TRADEMARKS**



*N. Woodson*  
**N. WOODSON**  
**Certifying Officer**

08/27/99  
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Modified PTO/SB/16 (6-95)  
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# PROVISIONAL APPLICATION FOR PATENT COVER SHEET

This is a request for filing a PROVISIONAL APPLICATION FOR PATENT under 37 CFR 1.53 (c)

|               |          |                                          |   |
|---------------|----------|------------------------------------------|---|
| Docket Number | P-12149A | Type a plus sign (+) inside this box --> | + |
|---------------|----------|------------------------------------------|---|

| INVENTOR(s)/APPLICANT(s)                                                                                                                     |                  |             |                                                      |
|----------------------------------------------------------------------------------------------------------------------------------------------|------------------|-------------|------------------------------------------------------|
| LAST NAME                                                                                                                                    | FIRST NAME       | MIDDLE NAME | RESIDENCE (CITY AND EITHER STATE OR FOREIGN COUNTRY) |
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| Johnson                                                                                                                                      | Kirk             | Willis      | Carmel, Indiana                                      |
| Ornstein                                                                                                                                     | Paul             | Leslie      | Carmel, Indiana                                      |
| TITLE OF THE INVENTION (280 characters max)                                                                                                  |                  |             |                                                      |
| SELECTIVE iGluR <sub>5</sub> RECEPTOR ANTAGONISTS FOR THE TREATMENT OF MIGRAINE                                                              |                  |             |                                                      |
| CORRESPONDENCE ADDRESS                                                                                                                       |                  |             |                                                      |
| Eli Lilly and Company<br>Patent Division/D.C. 1104<br>Lilly Corporate Center<br>Indianapolis, Indiana 46285                                  |                  |             |                                                      |
| STATE                                                                                                                                        | IN               | ZIP CODE    | 46285                                                |
| COUNTRY                                                                                                                                      | USA              |             |                                                      |
| ENCLOSED APPLICATION PARTS (check all that apply)                                                                                            |                  |             |                                                      |
| <input checked="" type="checkbox"/> Specification                                                                                            | Number of pages  | 35          | <input type="checkbox"/> Small Entity Statement      |
| <input type="checkbox"/> Drawing(s)                                                                                                          | Number of Sheets |             | <input type="checkbox"/> Other (Specify)             |
| METHOD OF PAYMENT (check one)                                                                                                                |                  |             |                                                      |
| <input type="checkbox"/> A check or money order is enclosed to cover the Provisional filing fees                                             |                  |             | PROVISIONAL FILING FEE AMOUNT (\$)                   |
| <input checked="" type="checkbox"/> The Assistant Commissioner is hereby authorized to charge filing fees and credit Deposit Account Number: | 05-0840          | \$150.00    |                                                      |

The invention was made by an agency of the United States Government or under a contract with an agency of the United States Government.

☒ No.

☐ Yes, the name of the U.S. Government agency and the Government contract number are:

Respectfully submitted,  
SIGNATURE

Date 8 / 27 / 99

TYPED or PRINTED NAME PAUL J. GAYLO

REGISTRATION NO.  
(if appropriate)

36,808

☐ Additional inventors are being named on separately numbered sheets attached hereto

## PROVISIONAL APPLICATION FOR PATENT FILING ONLY

"Express Mail" mailing label number EL342548079US Date of Deposit August 27, 1999  
I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office To Addressee" service under 37 C.F.R. 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Washington, D.C., 20231.

DIEDRE ARCINIEGA-HOLTZ

Printed Name

Signature

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- 1 -

SELECTIVE iGluR<sub>5</sub> RECEPTOR ANTAGONISTS FOR THE  
TREATMENT OF MIGRAINE

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## BACKGROUND OF THE INVENTION

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 pathways 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). Molecular biological studies have established that AMPA receptors are composed of subunits (GluR<sub>1</sub> - GluR<sub>4</sub>), which can assemble to form

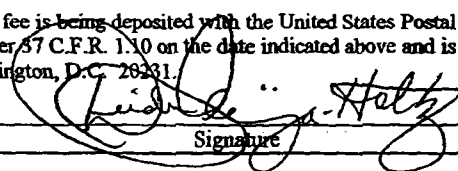
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functional ion channels. Five kainate receptors have been identified which are classified as either High Affinity (KA1 and KA2) or Low Affinity (GluR<sub>5</sub>, GluR<sub>6</sub>, and GluR<sub>7</sub>). Bleakman et al., *Molecular Pharmacology*, 49, No.4, 581,(1996).

- 5           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 cAMP formation, and changes in ion channel function. Schoepp and Conn, *Trends in Pharmacol. Sci.*, 14, 13 (1993). Both types of
- 10 receptors appear not only to mediate normal synaptic transmission along excitatory pathways, but also to 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).
- 15           The excessive or inappropriate stimulation of excitatory amino acid receptors leads to neuronal cell damage or loss by way of a mechanism known as excitotoxicity. This process has been suggested to mediate neuronal degeneration in a variety of neurological disorders and conditions. The medical consequences of such neuronal degeneration makes the abatement of these degenerative neurological processes an important therapeutic goal.
- 20           Excitatory amino acid excitotoxicity has been implicated in the pathophysiology of numerous neurological disorders. For example, excitotoxicity has been linked with the etiology of cerebral deficits subsequent to cardiac bypass surgery and grafting, stroke, cerebral ischemia, spinal cord lesions resulting from trauma or inflammation, perinatal hypoxia, cardiac arrest, and hypoglycemic neuronal damage. In addition, excitotoxicity
- 25 has been implicated in chronic neurodegenerative conditions including Alzheimer's Disease, Huntington's Chorea, inherited ataxias, AIDS-induced dementia, amyotrophic lateral sclerosis, idiopathic and drug-induced Parkinson's Disease, as well as ocular damage and retinopathy. Other neurological disorders implicated with excitotoxicity and/or glutamate dysfunction include muscular spasticity including tremors, drug tolerance
- 30 and withdrawal, brain edema, convulsive disorders including epilepsy, depression, anxiety and anxiety related disorders such as post-traumatic stress syndrome, tardive dyskinesia, and psychosis related to depression, schizophrenia, bipolar disorder, mania, and drug intoxication or addiction. In addition, it has also been reported that excitatory amino acid excitotoxicity participates in the etiology of acute and chronic pain states including severe
- 35 pain, intractable pain, neuropathic pain, and post-traumatic pain.

The use of a neuroprotective agent, such as an excitatory amino acid receptor antagonist, is believed to be useful in treating or preventing these disorders and/or

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reducing the amount of neurological damage associated with these disorders. Excitatory amino acid receptor antagonists may also be useful as analgesic agents.

Early theories regarding the pathophysiology of migraine have been dominated since 1938 by the work of Graham and Wolff (*Arch. Neurol. Psychiatry*, 39, 737-63 (1938)). They proposed that the cause of migraine headache is vasodilatation of extracranial vessels. This view is supported by knowledge that ergot alkaloids and sumatriptan contract cephalic vascular smooth muscle and are effective in the treatment of migraine. Sumatriptan is a hydrophilic agonist at the serotonin 5-HT<sub>1</sub>-like receptors and does not cross the blood-brain barrier (Humphrey, *et al.*, *Ann. NY Acad. Sci.*, 600, 587-600 (1990)). Consequently, several series of compounds said to be useful for the treatment of migraine, have been developed to optimize the 5-HT<sub>1</sub>-like mediated vasoconstrictive activity of sumatriptan. However, sumatriptan's contraindications, including coronary vasospasm, hypertension, and angina are also products of its vasoconstrictive activity (MacIntyre, P.D., *et al.*, *British Journal of Clinical Pharmacology*, 34, 541-546 (1992); Chester, A.H., *et al.*, *Cardiovascular Research*, 24, 932-937 (1990); Conner, H.E., *et al.*, *European Journal of Pharmacology*, 161, 91-94 (1990)).

While the vascular mechanism for migraine has gained wide acceptance, there is not total agreement as to its validity. Moskowitz, for example, has shown the occurrence of migraine headaches, independent of changes in vessel diameter (*Cephalalgia*, 12, 5-7, (1992)). It is known that the trigeminal ganglion, and its associated nerve pathways, are associated with painful sensations from the face such as headache, in particular migraine. Moskowitz proposed that unknown triggers stimulate the trigeminal ganglia which innervate vasculature within cephalic tissue, giving rise to the release of vasoactive neuropeptides from axons innervating the vasculature. These neuropeptides initiate a series of events leading to neurogenic inflammation of the meninges, a consequence of which is pain. This neurogenic inflammation is blocked by sumatriptan at doses similar to those required to treat acute migraine in humans. However, such doses of sumatriptan, as stated, are associated with contraindications as a result of sumatriptan's attendant vasoconstrictive properties.(see *supra*.)

5-HT<sub>1D</sub> receptors have been implicated as mediating the blockade of neurogenic protein extravasation. (*Neurology*, 43(suppl. 3), S16-S20 (1993)). In addition, it has been reported that  $\alpha_2$ , H<sub>3</sub>, m-opioid and somatostatin receptors may also be located on trigeminovascular fibers and may block neurogenic plasma extravasation (Matsubara *et al.*, *Eur. J. Pharmacol.*, 224, 145-150 (1992)). Weinshank *et al.* have reported that sumatriptan and several ergot alkaloids have a high affinity for the serotonin 5-HT<sub>1F</sub> receptor, suggesting a role for the 5-HT<sub>1F</sub> receptor in migraine (WO93/14201).

European Patent Application Publication No. 590789A1 and United States Patents No. 5,446,051 and 5,670,516 disclose that certain decahydroisoquinoline derivative compounds are AMPA receptor antagonists and, as such, are useful in the treatment of many different conditions, including pain and migraine headache.

5 Recently, it has been reported that all five members of the kainate subtype, of ionotropic glutamate receptors, are expressed on rat trigeminal ganglion neurons. In particular, high levels of GluR<sub>5</sub> and KA2 have been observed. (Sahara *et al.*, *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons *et al.* reported that the kainate GluR<sub>5</sub> receptor subtype mediates the nociceptive response to formalin in a rat model of persistent  
10 pain. (*Neuropharmacology*, 37, 25 (1998)). Further, WO98/45270 previously disclosed that antagonists selective for the iGluR<sub>5</sub> receptor are useful for the treatment of pain, including; severe, chronic, intractable, and neuropathic pain. Noteworthy is the observation that kainate receptors have not previously been implicated in the etiology of migraine headache. In particular, selective iGluR<sub>5</sub> receptor antagonists have not been  
15 previously reported as being useful for the treatment of migraine.

Surprisingly, and in accordance with this invention, Applicants have discovered that selective antagonists of the iGluR<sub>5</sub> receptor subtype are efficacious in an animal model of neurogenic inflammation and, thus, could be useful for the treatment of migraine. Such antagonists could address a long felt need for a safe and effective treatment for  
20 migraine, without attending side effects. The treatment of neurological disorders is hereby furthered.

### SUMMARY OF THE INVENTION

25 The present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist or a pharmaceutically acceptable salt thereof.

More specifically, the present invention provides a method of treating or preventing dural protein extravasation comprising administering to a patient in need  
30 thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist.

In addition, the present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a compound, or combination of compounds, which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

35 In another embodiment, the present invention provides a method of treating or preventing a neurological disorder, or neurodegenerative condition, comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub>

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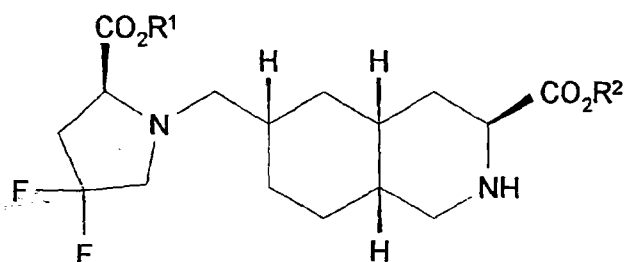
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receptor antagonist or a pharmaceutically acceptable salt thereof. Examples of such neurological disorders, or neurodegenerative conditions, include: cerebral deficits subsequent to cardiac bypass surgery and grafting; stroke; cerebral ischemia; spinal cord lesions resulting from trauma or inflammation; perinatal hypoxia; cardiac arrest;

5 hypoglycemic neuronal damage; Alzheimer's Disease; Huntington's Chorea; inherited ataxias; AIDS-induced dementia; amyotrophic lateral sclerosis; idiopathic and drug-induced Parkinson's Disease; ocular damage and retinopathy; muscular spasticity including tremors; drug tolerance and withdrawal; brain edema; convulsive disorders including epilepsy; depression; anxiety and anxiety related disorders such as post-traumatic stress

10 syndrome; tardive dyskinesia; psychosis related to depression, schizophrenia, bipolar disorder, mania, and drug intoxication or addiction; and acute and chronic pain states including severe pain, intractable pain, neuropathic pain, and post-traumatic pain.

In a further aspect, the present invention provides a compound of Formula I



Formula I

15 wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, or C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine; or

20 a pharmaceutically acceptable salt thereof.

In yet another aspect, the present invention provides a method of treating or preventing migraine comprising administering to a patient in need thereof an effective amount of a compound of Formula I.

25 In addition, the present invention provides pharmaceutical compositions useful for treating or preventing migraine comprising selective iGluR<sub>5</sub> receptor antagonists in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The present invention also provides the use of a selective iGluR<sub>5</sub> receptor antagonist for the manufacture of a medicament for treating or preventing migraine.

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-6-

### DETAILED DESCRIPTION OF THE INVENTION

The present invention provides a method for the treatment of migraine which can be demonstrated by a particular mechanism of action, inhibition of neurogenic dural protein extravasation. By treating a migraineur with a compound or composition which is a selective antagonist of the iGluR<sub>5</sub> receptor relative to other excitatory amino acid receptors, the neurogenic extravasation which mediates migraine is inhibited without the attending side effects of agents designed to optimize the 5-HT<sub>1</sub>-like mediated vasoconstrictive activity of sumatriptan. In addition, the present invention provides compounds functional as selective iGluR<sub>5</sub> receptor antagonists as well as pharmaceutically acceptable salts, prodrugs, and compositions thereof.

The term "pharmaceutically acceptable salt" as used herein, refers to salts of the compounds provided by, or employed in the present invention 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.

It will be understood by the skilled reader that most or all of the compounds used in the present invention are capable of forming salts, and that the salt forms of pharmaceuticals are commonly used, often because they are more readily crystallized and purified than are the free bases. In all cases, the use of the pharmaceuticals described herein as salts is contemplated in the description herein, and often is preferred, and the pharmaceutically acceptable salts of all of the compounds are included in the names of them.

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,  $\alpha$ -

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-7-

hydroxybutyrate, glycolate, tartrate, methanesulfonate, propanesulfonate, naphthalene-1-sulfonate, naphthalene-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.

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:

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

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

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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.

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.

The specific stereoisomers and enantiomers of compounds of Formula (I) can be prepared by one of ordinary skill in the art utilizing well known techniques and processes, such as those disclosed by Eliel and Wilen, "Stereochemistry of Organic Compounds", John Wiley & Sons, Inc., 1994, Chapter 7, Separation of Stereoisomers. Resolution. Racemization, and by Collet and Wilen, "Enantiomers, Racemates, and Resolutions", John Wiley & Sons, Inc., 1981. For example, the specific stereoisomers and enantiomers can be prepared by stereospecific syntheses using enantiomerically and geometrically pure, or enantiomerically or geometrically enriched starting materials. In addition, the specific stereoisomers and enantiomers can be resolved and recovered by techniques such as chromatography on chiral stationary phases, enzymatic resolution or fractional recrystallization of addition salts formed by reagents used for that purpose.

It should also be understood by the skilled artisan that all of the compounds useful for the methods of the present invention are available for prodrug formulation. "Prodrug" as used herein, refers to metabolically labile ester or diester derivative of the functional acid compounds(drugs) provided by, or employed in the methods of, the present invention.

- 5 When administered to a patient, the prodrug undergoes enzymatic and/or chemical hydrolytic cleavage in such a manner that the parent carboxylic acid (drug), or as the case may be the parent dicarboxylic acid, is released. In all cases, the use of the compounds described herein as prodrugs is contemplated, and often is preferred, and thus, the prodrugs of all of the compounds employed are encompassed in the names of the  
10 compounds herein.

As used herein the term "C<sub>1</sub>-C<sub>4</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 4 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl and the like.

- As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl" refers to a straight or branched, monovalent,  
15 saturated aliphatic chain of 1 to 6 carbon atoms and includes, but is not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, t-butyl, n-pentyl, n-hexyl, and the like.

- As used herein the term "C<sub>1</sub>-C<sub>10</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 10 carbon atoms and includes, but is not limited to methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, tertiary butyl, pentyl,  
20 isopentyl, hexyl, 2,3-dimethyl-2-butyl, heptyl, 2,2-dimethyl-3-pentyl, 2-methyl-2-hexyl, octyl, 4-methyl-3-heptyl and the like.

- As used herein the term "C<sub>1</sub>-C<sub>20</sub> alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl,  
25 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, n-nonyl, n-decyl, n-undecyl, n-dodecyl, n-tridecyl, n-tetradecyl, n-pentadecyl, n-hexadecyl, n-heptadecyl, n-nonadecyl, n-eicosyl and the like.

As used herein, the terms "Me", "Et", "Pr", "iPr", "Bu" and "t-Bu" refer to methyl, ethyl, propyl, isopropyl, butyl and tert-butyl respectively.

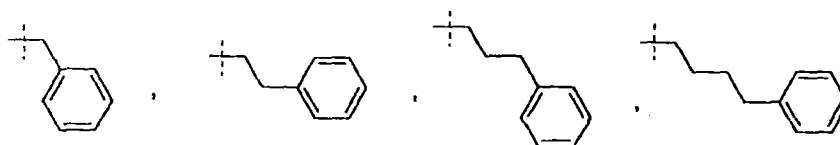
- 30 As used herein the term "C<sub>2</sub>-C<sub>6</sub> alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C<sub>2</sub>-C<sub>6</sub> alkenyl groups include ethenyl (also known as vinyl), 1-methylethenyl, 1-methyl-1-propenyl, 1-butenyl, 1-hexenyl, 2-methyl-2-propenyl, 1-propenyl, 2-propenyl, 2-butenyl, 2-pentenyl, and the like.

237  
227

-10-

As used herein, the term "aryl" refers to monovalent carbocyclic group containing one or more fused or non-fused phenyl rings and includes, for example, phenyl, 1- or 2-naphthyl, 1,2-dihydronaphthyl, 1,2,3,4-tetrahydronaphthyl, and the like.

- As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkylaryl" refers to a straight or branched,
- 5 monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkylaryl" are the following:

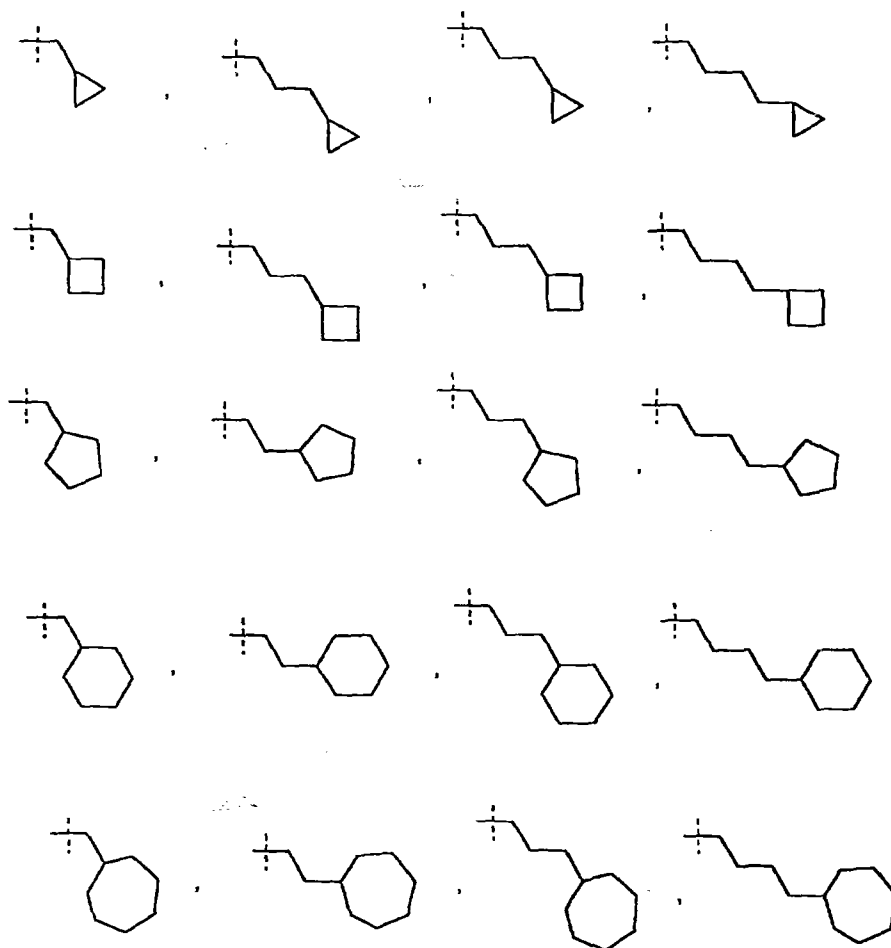


and the like.

- 10 As used herein the term "(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" refers to a saturated hydrocarbon ring structure containing from three to ten carbon atoms. Typical C<sub>3</sub>-C<sub>10</sub> cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. It is understood that "(C<sub>3</sub>-C<sub>8</sub>)cycloalkyl" and "(C<sub>4</sub>-C<sub>6</sub>)cycloalkyl" is included within the term "(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl".
- 15 As used herein, the term "C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C<sub>3</sub>-C<sub>10</sub>)cycloalkyl attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl" are the following:

238  
213

-11-



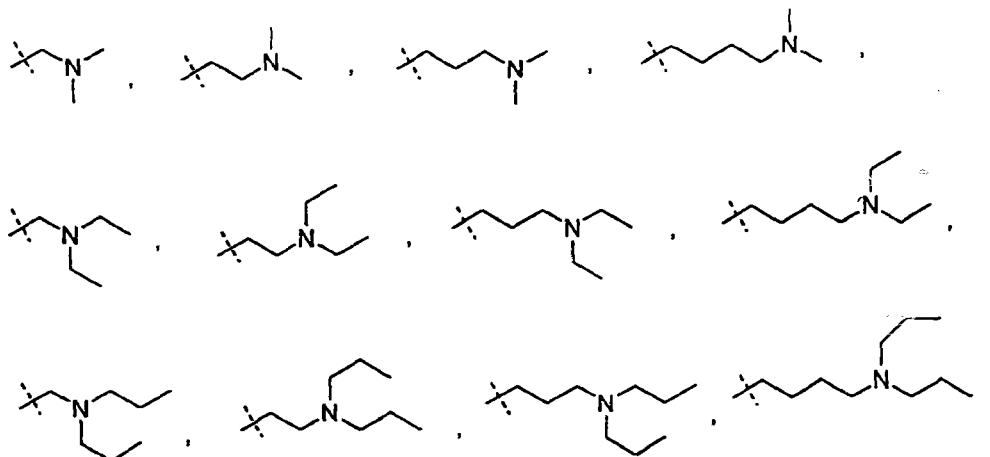
and the like.

As used herein the term "N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" refers to a nitrogen atom substituted with two straight or branched, monovalent, saturated aliphatic chains of 1 to 6 carbon atoms. Included within the term "N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" are -N(CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, -N(CH<sub>2</sub>CH<sub>2</sub>CH<sub>2</sub>CH<sub>3</sub>)<sub>2</sub>, and the like.

As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine attached to the aliphatic chain. Included within the term "C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine" are the following:

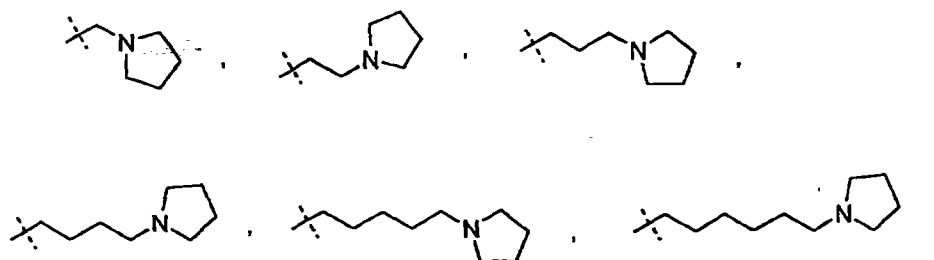
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-12-



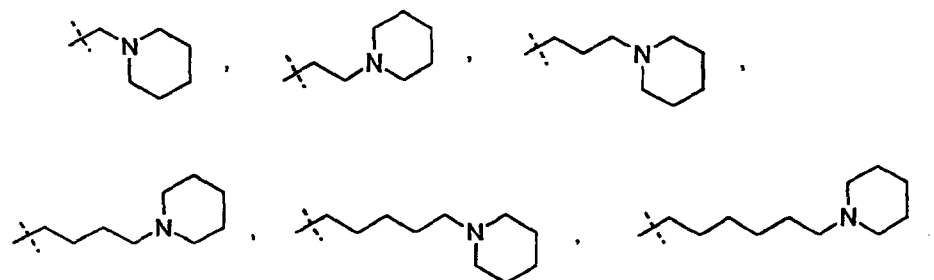
and the like.

- As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a pyrrolidine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine" are the following:
- 5



and the like.

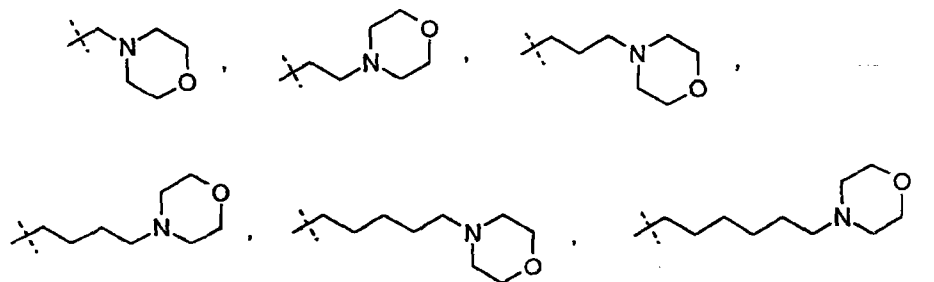
- As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a piperidine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine" are the following:
- 10



-13-

and the like.

As used herein the term "C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a morpholine attached to the aliphatic chain. Included within the scope of the term "C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine" are the following:



and the like.

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10 The designation "  " refers to a bond that protrudes backward out of the plane of the page.

As used herein the term "iGluR<sub>5</sub>" refers to the kainate ionotropic glutamate receptor, subtype 5, of the larger class of excitatory amino acid receptors.

15 As used herein the term "migraine" refers a disorder of the nervous system characterized by recurrent attacks of head pain (which are not caused by a structural brain abnormality such as those resulting from tumor or stroke), gastrointestinal disturbances, and possibly neurological symptoms such as visual distortion. Characteristic headaches of migraine usually last one day and are commonly accompanied by nausea, emesis, and photophobia.

20 Migraine is a "chronic" condition. The term "chronic", as used herein, means a condition of slow progress and long continuance. As such, a chronic condition is treated when it is diagnosed and treatment continued throughout the course of the disease. Conversely, the term "acute" means an exacerbated event or attack, of short course, followed by a period of remission. Thus, the treatment of migraine contemplates both  
25 acute events and chronic conditions. In an acute event, compound is administered at the onset of symptoms and discontinued when the symptoms disappear. As described above, a chronic condition is treated throughout the course of the disease.

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

235  
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-14-

It is understood that the term "selective iGluR<sub>5</sub> receptor antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to the iGluR<sub>5</sub> kainate receptor subtype, relative to the iGluR<sub>2</sub> AMPA receptor subtype. Preferably the selective iGluR<sub>5</sub> antagonist for use according to the method of the present invention has a binding affinity at least 10 fold greater for iGluR<sub>5</sub> than for iGluR<sub>2</sub>, more preferably at least 100 fold greater. It is further understood that any selective iGluR<sub>5</sub> antagonist, as appreciated by one of ordinary skill in the art, is included within the scope of the methods of the present invention. Such selective iGluR<sub>5</sub> receptor antagonists are readily available to, or are readily prepared by, one of ordinary skill in the art following recognized procedures. Examples of selective iGluR<sub>5</sub> receptor antagonists include, but are not limited to, the compounds provided in WO 98/45270, the entire contents of which is herein incorporated by reference.

It is further understood that the selective iGluR<sub>5</sub> receptor antagonists may exist as pharmaceutically acceptable salts and, as such, salts are therefore included within the scope of the present invention.

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

As used herein the term "effective amount" refers to the amount or dose of the compound, upon single or multiple dose administration to the patient, which provides the desired effect in the patient under diagnosis or treatment.

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

A typical daily dose will contain from about 0.01 mg/kg to about 100 mg/kg of each compound used in the present method of treatment. 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.

236  
232

-15-

The selective iGluR<sub>5</sub> antagonists for use according to the methods of the present invention may be a single compound or a combination of compounds capable of functioning as a selective iGluR<sub>5</sub> receptor antagonist. For example, it may be a combination of a compound capable of functioning as an antagonist at the iGluR<sub>5</sub> receptor and one or more other glutamate receptors, in combination with one or more compounds capable of blocking its actions at the iGluR<sub>2</sub> receptor. It is understood, however, that the selective iGluR<sub>5</sub> antagonist for use in the methods of the present invention, is preferably a single compound.

Oral administration is a preferred route of administering the compounds employed in the present invention whether administered alone, or as a combination of compounds capable of acting as a selective iGluR<sub>5</sub> receptor antagonist. Oral administration, however, is not the only route, nor even the only preferred route. Other preferred routes of administration include transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal routes. Where the selective iGluR<sub>5</sub> receptor antagonist is administered as a combination of compounds, one of the compounds may be administered by one route, such as oral, and the other may be administered by the transdermal, percutaneous, intravenous, intramuscular, intranasal, buccal, or intrarectal route, as particular circumstances require. The route of administration may be varied in any way, limited by the physical properties of the compounds and the convenience of the patient and the caregiver.

The compounds employed in the present invention may be administered as pharmaceutical compositions and, therefore, pharmaceutical compositions incorporating said compounds are important embodiments of the present invention. Such compositions may take any physical form which is pharmaceutically acceptable, but orally administered pharmaceutical compositions are particularly preferred. Such pharmaceutical compositions contain an effective amount of a selective iGluR<sub>5</sub> receptor antagonist, which effective amount is related to the daily dose of the compound to be administered. Each dosage unit may contain the daily dose of a given compound, or may contain a fraction of the daily dose, such as one-half or one-third of the dose. The amount of each compound to be contained in each dosage unit depends on the identity of the particular compound chosen for the therapy, and other factors such as the indication for which it is given. The pharmaceutical compositions of the present invention may be formulated so as to provide quick, sustained, or delayed release of the active ingredient after administration to the patient by employing well known procedures.

Compositions are preferably formulated in a unit dosage form, each dosage containing from about 1 to about 500 mg of each compound individually or in a single unit dosage form, more preferably about 5 to about 300 mg (for example 25 mg). The term

-16-

"unit dosage form" refers to a physically discrete unit suitable as unitary dosages for a patient, 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.

5       The inert ingredients and manner of formulation of the pharmaceutical compositions are conventional. The usual methods of formulation used in pharmaceutical science may be used here. All of the usual types of compositions may be used, including tablets, chewable tablets, capsules, solutions, parenteral solutions, intranasal sprays or  
10       powders, troches, suppositories, transdermal patches and suspensions. In general, compositions contain from about 0.5% to about 50% of the compounds in total, depending on the desired doses and the type of composition to be used. The amount of the compound, however, is best defined as the "effective amount", that is, the amount of each compound which provides the desired dose to the patient in need of such treatment. The activity of the compounds employed in the present invention do not depend on the  
15       nature of the composition, hence, the compositions are chosen and formulated solely for convenience and economy.

      Capsules are prepared by mixing the compound with a suitable diluent and filling the proper amount of the mixture in capsules. The usual diluents include inert powdered substances such as starches, powdered cellulose especially crystalline and microcrystalline  
20       cellulose, sugars such as fructose, mannitol and sucrose, grain flours, and similar edible powders.

      Tablets are prepared by direct compression, by wet granulation, or by dry granulation. Their formulations usually incorporate diluents, binders, lubricants and disintegrators as well as the compound. Typical diluents include, for example, various  
25       types of starch, lactose, mannitol, kaolin, calcium phosphate or sulfate, inorganic salts such as sodium chloride and powdered sugar. Powdered cellulose derivatives are also useful. Typical tablet binders are substances such as starch, gelatin and sugars such as lactose, fructose, glucose and the like. Natural and synthetic gums are also convenient, including acacia, alginates, methylcellulose, polyvinylpyrrolidone and the like. Polyethylene glycol,  
30       ethylcellulose and waxes can also serve as binders.

      Tablets are often coated with sugar as a flavor and sealant. The compounds may also be formulated as chewable tablets, by using large amounts of pleasant-tasting substances such as mannitol in the formulation, as is now well-established practice. Instantly dissolving tablet-like formulations are also now frequently used to assure that the  
35       patient consumes the dosage form, and to avoid the difficulty in swallowing solid objects that bothers some patients.

238  
234

-17-

A lubricant is often necessary in a tablet formulation to prevent the tablet and punches from sticking in the die. The lubricant is chosen from such slippery solids as talc, magnesium and calcium stearate, stearic acid and hydrogenated vegetable oils.

Tablet disintegrators are substances which swell when wetted to break up the tablet and release the compound. They include starches, clays, celluloses, algin and gums. More particularly, corn and potato starches, methylcellulose, agar, bentonite, wood cellulose, powdered natural sponge, cation-exchange resins, alginic acid, guar gum, citrus pulp and carboxymethylcellulose, for example, may be used, as well as sodium lauryl sulfate.

Enteric formulations are often used to protect an active ingredient from the strongly acid contents of the stomach. Such formulations are created by coating a solid dosage form with a film of a polymer which is insoluble in acid environments, and soluble in basic environments. Exemplary films are cellulose acetate phthalate, polyvinyl acetate phthalate, hydroxypropyl methylcellulose phthalate and hydroxypropyl methylcellulose acetate succinate.

When it is desired to administer the compound as a suppository, the usual bases may be used. Cocoa butter is a traditional suppository base, which may be modified by addition of waxes to raise its melting point slightly. Water-miscible suppository bases comprising, particularly, polyethylene glycols of various molecular weights are in wide use, also.

Transdermal patches have become popular recently. Typically they comprise a resinous composition in which the drugs will dissolve, or partially dissolve, which is held in contact with the skin by a film which protects the composition. Many patents have appeared in the field recently. Other, more complicated patch compositions are also in use, particularly those having a membrane pierced with innumerable pores through which the drugs are pumped by osmotic action.

The following table provides an illustrative list of formulations suitable for use with the compounds employed in the present invention. The following is provided only to illustrate the invention and should not be interpreted as limiting the present invention in any way.

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239  
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-18-

**Formulation 1**

Hard gelatin capsules are prepared using the following ingredients:

|    |                    |                          |
|----|--------------------|--------------------------|
| 5  |                    |                          |
|    |                    | Quantity<br>(mg/capsule) |
|    |                    |                          |
| 10 | Active Ingredient  | 250                      |
|    | Starch, dried      | 200                      |
|    | Magnesium stearate | <u>10</u>                |
|    | Total              | 460 mg                   |
| 15 |                    |                          |

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

20

25

**Formulation 2**

A tablet is prepared using the ingredients below:

|    |                             |                         |
|----|-----------------------------|-------------------------|
| 30 |                             |                         |
|    |                             | Quantity<br>(mg/tablet) |
|    |                             |                         |
| 35 | Active Ingredient           | 250                     |
|    | Cellulose, microcrystalline | 400                     |
|    | Silicon dioxide, fumed      | 10                      |
|    | Stearic acid                | <u>5</u>                |
|    | Total                       | 665 mg                  |
| 40 |                             |                         |

The components are blended and compressed to form tablets each weighing 665 mg.

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240  
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-19-

**Formulation 3**

An aerosol solution is prepared containing the following components:

|    |                         |              |
|----|-------------------------|--------------|
| 5  |                         |              |
|    |                         | Weight %     |
|    | Active Ingredient       | 0.25         |
| 10 | Ethanol                 | 29.75        |
|    | Propellant 22           | <u>70.00</u> |
|    | (Chlorodifluoromethane) |              |
|    | Total                   | 100.00       |
| 15 |                         |              |

The active compound is mixed with ethanol and the mixture added to a portion of the Propellant 22, cooled to -30°C and transferred to a filling device. The required amount is then fed to a stainless steel container and diluted with the remainder of the propellant. The valve units are then fitted to the container.

**Formulation 4**

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

|    |                             |             |
|----|-----------------------------|-------------|
| 25 |                             |             |
|    | Active Ingredient           | 60 mg       |
|    | Starch                      | 45 mg       |
|    | Microcrystalline cellulose  | 35 mg       |
| 30 | Polyvinylpyrrolidone        | 4 mg        |
|    | Sodium carboxymethyl starch | 4.5 mg      |
|    | Magnesium stearate          | 0.5 mg      |
|    | Talc                        | <u>1 mg</u> |
| 35 | Total                       | 150 mg      |

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

244  
234

-20-

**Formulation 5**

Capsules each containing 80 mg medicament are made as follows:

|    |                            |             |
|----|----------------------------|-------------|
| 5  |                            |             |
|    | Active Ingredient          | 80 mg       |
|    | Starch                     | 59 mg       |
|    | Microcrystalline cellulose | 59 mg       |
|    | Magnesium stearate         | <u>2 mg</u> |
| 10 | Total                      | 200 mg      |

15 The active ingredient, cellulose, starch, and magnesium stearate are blended,  
passed through a No. 45 sieve, and filled into hard gelatin capsules in 200 mg quantities.

**Formulation 6**

Suppositories each containing 225 mg of active ingredient may be made as follows:

|    |                                 |                 |
|----|---------------------------------|-----------------|
| 20 |                                 |                 |
|    | Active Ingredient               | 225 mg          |
|    | Saturated fatty acid glycerides | <u>2,000 mg</u> |
| 25 | Total                           | 2,225 mg        |

30 The active ingredient is passed through a No. 60 mesh U.S. sieve and suspended in  
the saturated fatty acid glycerides previously melted using the minimum heat necessary.  
The mixture is then poured into a suppository mold of nominal 2 g capacity and allowed to  
cool.

**Formulation 7**

35 Suspensions each containing 50 mg of medicament per 5 ml dose are made as follows:

|    |                                |         |
|----|--------------------------------|---------|
|    |                                |         |
|    | Active Ingredient              | 50 mg   |
|    | Sodium carboxymethyl cellulose | 50 mg   |
| 40 | Syrup                          | 1.25 ml |
|    | Benzoic acid solution          | 0.10 ml |
|    | Flavor                         | q.v.    |
|    | Color                          | q.v.    |
|    | Purified water to total        | 5 ml    |
| 45 |                                |         |

247  
233

-21-

The medicament is passed through a No. 45 mesh U.S. sieve and mixed with the sodium carboxymethyl cellulose and syrup to form a smooth paste. The benzoic acid solution, flavor and color are diluted with some of the water and added, with stirring.

5 Sufficient water is then added to produce the required volume.

#### Formulation 8

An intravenous formulation may be prepared as follows:

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|                            |        |
|----------------------------|--------|
| Active Ingredient          | 100 mg |
| Mannitol                   | 100 mg |
| 5 N Sodium hydroxide       | 200 ml |
| 15 Purified water to total | 5 ml   |

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20

It is understood by one of ordinary skill in the art that the above procedures can also be applied to a method of treating migraine comprising administering to a patient an effective amount of a compound which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

25

Inhibition of neuronal protein dural extravasation is an exemplary mechanism of action for the method of the present invention. The method further requires that compounds which exhibit such inhibition, also demonstrate selective binding and inhibition of the iGluR<sub>5</sub> receptor. The panel of compounds used to illustrate the principle of the present invention, and the pharmacological assays employed to demonstrate the mechanistic effectiveness of the invention, are described below. It is believed that Compounds III, IV(a), and IV(b) herein, represent novel compounds and, as such, have not previously been described as selective iGluR<sub>5</sub> receptor antagonists, nor reported as efficacious in treating migraine. Compounds III, IV(a), and IV(b) therefore, are provided as additional embodiments of the present invention.

30

The following examples illustrate the methods of the present invention. The reagents and starting materials are readily available to one of ordinary skill in the art. These examples are intended to be illustrative only and are not to be construed so as to limit the scope of the invention in any way. As used herein, the following terms have the meanings indicated: "i.v." refers to intravenously; "p.o." refers to orally; "i.p." refers to intraperitoneally; "eq" or "equiv." 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; "mm

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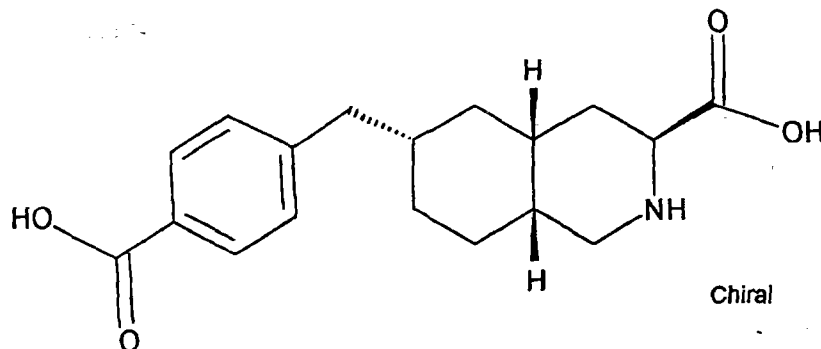
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Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R<sub>f</sub>" refers to retention factor; "R<sub>t</sub>" 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 dimethyl sulfoxide; "aq" refers to aqueous; "EtOAc" refers to ethyl acetate; "iPrOAc" refers to isopropyl acetate; "MeOH" refers to methanol; "MTBE" refers to tert-butyl methyl ether; "RT" refers to room temperature; "K<sub>i</sub>" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID<sub>50</sub>" and "ID<sub>100</sub>" refer to doses of an administered therapeutic agent which produce, respectively, a 50 % and 100% reduction in a physiological response.

### EXAMPLE 1

#### Compound I

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



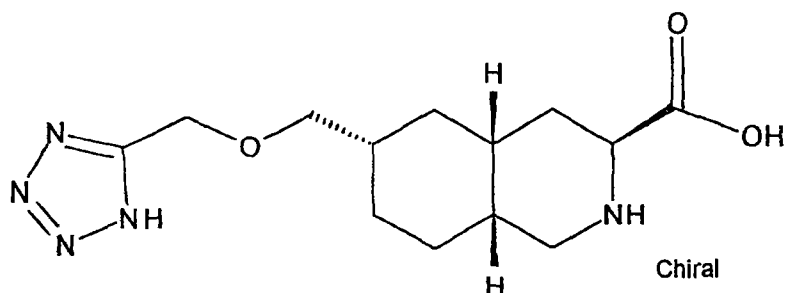
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Those skilled in the art will recognize Compound I as an excitatory amino acid receptor antagonist, selective for the iGluR<sub>5</sub> receptor subtype. Compound I may be readily prepared by one of ordinary skill in the art following recognized general procedures as described in United States Patent No. 5,446,051, and more specifically as recently published in international application WO 98/45270, published October 15, 1998.

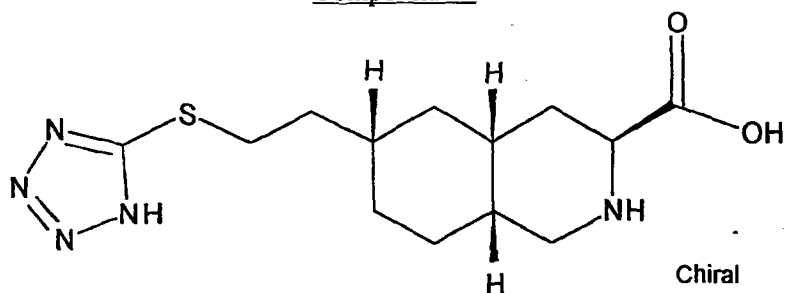
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Compound II

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



Those skilled in the art will recognize Compound II as an excitatory amino acid receptor antagonist, selective for the iGluR<sub>5</sub> receptor subtype. Compound II may be readily prepared and resolved by one of ordinary skill in the art following recognized general procedures as described in United States Patent No. 5,670,516 (see Example No. 11, Compound No. 7), and more specifically as recently published in international application WO 98/45270, published October 15, 1998.

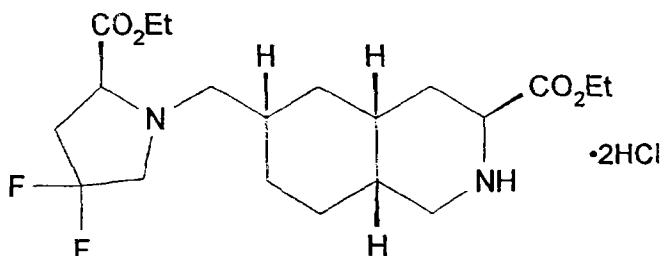
Compound III

Compound III represents a novel compound, functional as a selective iGluR<sub>5</sub> receptor antagonist. Compound III may be readily prepared; the desired enantiomer may be optically resolved; and pharmaceutical compositions comprising Compound III may be readily formulated by following general methods essentially as described for Example No. 8, Compound No. 8 of United States Patent No. 5,670,516, the entire contents of which is herein incorporated by reference.

Compound IV(b)

3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

5



- 10 A. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-((4-Methylphenyl)sulfonyloxy)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a solution of 15.0 g (50.1 mmol) of hydroxymethyl intermediate (See Col. 11-12, Scheme II of United States Patent No. 5,356,902, the entire contents of which are herein incorporated by reference) cooled to 0 °C in CH<sub>2</sub>Cl<sub>2</sub> (100 mL), was added triethylamine (20.9 mL, 150.3 mmol) followed by toluenesulfonyl chloride (19.1 g, 100.2 mmol) dissolved in CH<sub>2</sub>Cl<sub>2</sub> (100 mL). The reaction was warmed to room temperature and stirred 16 h, then partitioned between CH<sub>2</sub>Cl<sub>2</sub> and 10% aqueous NaHSO<sub>4</sub>. The aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> and the combined organics were dried over MgSO<sub>4</sub>, filtered, and concentrated in vacuo. Column chromatography (10-50% EtOAc/hexane) provided 20.1 g (89%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 451.5 (M<sup>+</sup>)  
 Calculated for C<sub>22</sub>H<sub>31</sub>NO<sub>7</sub>S 0.1 CH<sub>2</sub>Cl<sub>2</sub>: Theory: C, 57.45; H, 6.81; N, 3.03. Found: C, 57.76; H, 6.93; N, 3.35.  
<sup>13</sup>C NMR (DMSO-d<sub>6</sub>): δ 171.4, 144.8, 132.4, 130.1, 127.6, 74.6, 60.4, 53.1, 52.4, 44.1, 34.6, 31.8, 31.0, 29.8, 28.8, 24.9, 23.3, 21.0, 14.0.

- 25 B. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((3S, 5S)-5-(Ethoxycarbonyl)-3-hydroxypyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

246  
242

-25-

A mixture of 4-hydroxyproline ethyl ester (6.5 g, 33.1 mmol), the compound of Step A above (10.0 g, 22.0 mmol), and potassium carbonate (4.6 g, 33.1 mmol) were heated at reflux in acetonitrile (22 mL) for 60 h. The reaction mixture was cooled to room temperature, and partitioned between  $\text{CH}_2\text{Cl}_2$  and water. The aqueous layer was extracted two times with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (50% EtOAc/hexane followed by 5% MeOH/  $\text{CH}_2\text{Cl}_2$ ) gave 9.2 g (95%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 441.3 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_7\text{S}$ : Theory: C, 59.98; H, 8.24; N, 6.36. Found: C, 60.17; H, 8.23; N, 6.42.

C. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((5S)-5-(Ethoxycarbonyl)-3-oxopyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a solution of DMSO (2.3 mL, 32.5 mmol) cooled to  $-78^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  (25 mL) was added, dropwise, oxalyl chloride (1.4 mL, 16.3 mmol). The reaction mixture was stirred for 5 min, then the compound of Step B above (6.0 g, 13.6 mmol) dissolved in 20 mL of  $\text{CH}_2\text{Cl}_2$  was added. Upon stirring for 45 min at  $-78^\circ\text{C}$ , triethylamine (9.5 mL, 32.5 mmol) was added. The reaction was warmed to room temperature over approximately 2 hours, and quenched by the addition of 10% aqueous  $\text{NaHSO}_4$ . The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (25–50% EtOAc/hexane) provided 4.6 g (78%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 439.1 ( $\text{M}^+$ )

D. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate

To a mixture of the compound of Step C above (4.62 g, 10.5 mmol) cooled to  $-78^\circ\text{C}$  in  $\text{CH}_2\text{Cl}_2$  (50 mL) was added, dropwise, diethylaminosulfur trifluoride (3.5 mL, 26.3 mmol). The reaction was allowed to warm to room temperature, stirred an additional 48 h, then quenched by the addition of MeOH. After concentrating in vacuo, the residue was partitioned between  $\text{CH}_2\text{Cl}_2$  and saturated aqueous  $\text{NaHCO}_3$ . The aqueous layer was

243

-26-

extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics were dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. Column chromatography (25-50% EtOAc/hexane) provided 3.3 g (68%) of the desired intermediate title compound as a colorless oil:

- 5 MS(m/e): 461.2 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{22}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_6$ : Theory: C, 57.38; H, 7.44; N, 6.08. Found: C, 58.25; H, 7.59; N, 6.50.

- 10 E. Preparation of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (Compound IV(b))

- 15 A solution of the compound of Step D above (3.3 g, 7.10 mmol) dissolved in  $\text{CH}_2\text{Cl}_2$  (40 mL) was cooled to  $0^\circ\text{C}$  and charged with trimethylsilyl iodide (3.0 mL, 21.3 mmol). The reaction was allowed to warm to room temperature, stirred an additional 4 h, then quenched by the addition of saturated aqueous  $\text{NaHCO}_3$  (50 mL). The aqueous layer was extracted with  $\text{CH}_2\text{Cl}_2$  and the combined organics washed with a 1 N solution of sodium thiosulfate, dried over  $\text{MgSO}_4$ , filtered, and concentrated in vacuo. The material was chromatographed, (2% MeOH/ $\text{CH}_2\text{Cl}_2$ ), dissolved in 20 mL of  $\text{Et}_2\text{O}$ , and to it was  
20 added 50 mL of a HCl/ $\text{Et}_2\text{O}$  solution. The solvent was removed in vacuo, providing 2.6 g (76%) of the final title compound as a white solid:

- 25 MS(m/e): 403.4 ( $\text{M}^+$ )  
Calculated for  $\text{C}_{20}\text{H}_{32}\text{Cl}_2\text{F}_2\text{N}_2\text{O}_4$ : Theory: C, 50.53; H, 7.21; N, 5.89.  
Found: C, 50.90; H, 7.41; N, 5.84.  
 $^{13}\text{C}$  NMR ( $\text{D}_2\text{O}$ ):  $\delta$  170.3, 167.7, 125.1 (t,  $J_{\text{C-F}} = 249.1$  Hz), 65.9, 65.0, 64.1, 63.4, 60.1 (t,  $J_{\text{C-F}} = 33.9$  Hz), 57.6, 52.8, 42.9, 37.2 (t,  $J_{\text{C-F}} = 26.4$  Hz), 34.5, 31.7, 31.3, 30.5, 28.4, 26.9, 24.3, 13.6.

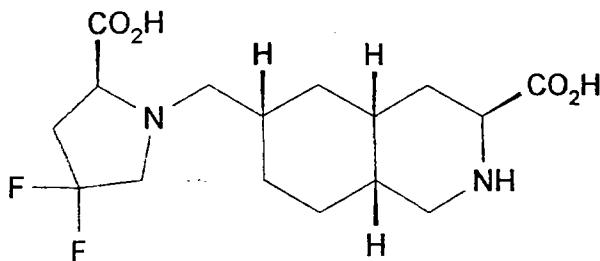
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Compound IV(a)

3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

548  
2/14

-27-



A solution of 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-2-methoxycarbonyl-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate (3.3 g, 7.10 mmol), the compound of Step D above,  
 5 dissolved in 5 N aqueous HCl (15 mL) was heated at 90 °C for 18 h. The reaction mixture was cooled to room temperature and concentrated in vacuo. The resulting crude foam was dissolved in water (75 mL) and stirred in the presence of Dowex 50X8 (100–200) ion-exchange resin (10 g) for 2 h. The resin was filtered, washed sequentially with 1:1 THF/H<sub>2</sub>O and water, then stirred in the presence of 10% pyridine/H<sub>2</sub>O for 2 h. After  
 10 filtration, the resin was washed with water, and the filtrate was concentrated in vacuo to provide the title compound (0.6 g, 97%) as a white foam:

MS(m/e): 347.2 (M<sup>+</sup>)

15 Calculated for C<sub>16</sub>H<sub>24</sub>F<sub>2</sub>N<sub>2</sub>O<sub>4</sub> 0.1 H<sub>2</sub>O: Theory: C, 55.19; H, 7.01; N, 8.05. Found: C, 54.81; H, 6.82; N, 8.13.

<sup>13</sup>C NMR (D<sub>2</sub>O): δ 175.1, 171.1, 125.6 (t, *J*<sub>C-F</sub> = 249.4 Hz), 67.9, 63.0, 59.3 (t, *J*<sub>C-F</sub> = 34.0 Hz), 54.5, 42.5, 37.5 (t, *J*<sub>C-F</sub> = 24.9 Hz), 34.3, 32.7, 32.4, 30.6, 28.2, 27.0, 24.3.

20

## EXAMPLE 2

To establish that the iGluR<sub>5</sub> receptor subtype is mediating neurogenic protein extravasation, a functional characteristic of migraine, the binding affinity of the panel compounds to the iGluR<sub>5</sub> receptor is first measured using standard methods. For  
 25 example, the activity of compounds acting at the iGluR<sub>5</sub> receptor antagonists can be determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR<sub>5</sub> receptor (Korczak et al., 1994, Recept. 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). The selectivity  
 30 of compounds acting at the iGluR<sub>5</sub> receptor subtype can then be determined by comparing antagonist activity at the iGluR<sub>5</sub> receptor with antagonist activity at other AMPA and kainate receptors. Methods useful for such comparison studies include: receptor-ligand

249  
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-28-

binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR<sub>1</sub>, GluR<sub>2</sub>, GluR<sub>3</sub> and GluR<sub>4</sub> 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 GluR<sub>6</sub> 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).

10 iGluR5 antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors were employed. Displacement of <sup>3</sup>[H] AMPA by increasing concentrations of antagonist was measured on iGluR<sub>1</sub>, iGluR<sub>2</sub>, iGluR<sub>3</sub>, and iGluR<sub>4</sub> expressing cells, while displacement of <sup>3</sup>[H] kainate (KA) was measured on iGluR<sub>5</sub>, iGluR<sub>6</sub>, iGluR<sub>7</sub>, and KA2-expressing cells.

15 Estimated antagonist binding activity (K<sub>i</sub>) in μM was determined for Compounds I – IV. As an indicia of selectivity, the ratio of binding affinity to the iGluR<sub>2</sub> AMPA receptor subtype, versus the binding affinity to iGluR<sub>5</sub> kainate receptor subtype, was also determined. Compounds provided by the present invention displayed a binding affinity of at least 10 fold greater for iGluR<sub>5</sub> than that for iGluR<sub>2</sub>, more preferably at least 100 fold.

20

EXAMPLE 3

The following animal model was employed to determine the ability of each of the panel of compounds to inhibit protein extravasation, an exemplary functional assay of the neuronal mechanism of migraine. The results obtained for the panel of compounds in this

25 model are summarized in Table I (infra).

Animal Model of Dural Protein Extravasation

Harlan Sprague-Dawley rats (225-325 g) or guinea pigs from Charles River

30 Laboratories (225-325 g) were anesthetized with sodium pentobarbital intraperitoneally (65 mg/kg or 45 mg/kg respectively) and placed in a stereotaxic frame (David Kopf Instruments) with the incisor bar set at -3.5 mm for rats or -4.0 mm for guinea pigs. Following a midline sagittal scalp incision, two pairs of bilateral holes were drilled through the skull (6 mm posteriorly, 2.0 and 4.0 mm laterally in rats; 4 mm posteriorly and 3.2 and

35 5.2 mm laterally in guinea pigs, all coordinates referenced to bregma). Pairs of stainless steel stimulating electrodes, insulated except at the tips (Rhodes Medical Systems, Inc.),

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-29-

were lowered through the holes in both hemispheres to a depth of 9 mm (rats) or 10.5 mm (guinea pigs) from dura.

The femoral vein was exposed and a dose of the test compound was injected intravenously (i.v.) at a dosing volume of 1ml/Kg or, in the alternative, test compound was administered orally (p.o) via gavage at a volume of 2.0ml/Kg. Approximately 7 minutes post i.v. injection, a 50 mg/Kg dose of Evans Blue, a fluorescent dye, was also injected intravenously. The Evans Blue complexed with proteins in the blood and functioned as a marker for protein extravasation. Exactly 10 minutes post-injection of the test compound, the left trigeminal ganglion was stimulated for 3 minutes at a current intensity of 1.0 mA (5 Hz, 4 msec duration) with a Model 273 potentiostat/ galvanostat (EG&G Princeton Applied Research).

Fifteen minutes following stimulation, the animals were killed and exsanguinated with 20 mL of saline. The top of the skull was removed to facilitate the collection of the dural membranes. The membrane samples were removed from both hemispheres, rinsed with water, and spread flat on microscopic slides. Once dried, the tissues were coverslipped with a 70% glycerol/water solution.

A fluorescence microscope (Zeiss) equipped with a grating monochromator and a spectrophotometer was used to quantify the amount of Evans Blue dye in each sample. An excitation wavelength of approximately 535 nm was utilized and the emission intensity at 600 nm was determined. The microscope was equipped with a motorized stage and also interfaced with a personal computer. This facilitated the computer-controlled movement of the stage with fluorescence measurements at 25 points (500 nm steps) on each dural sample. The mean and standard deviation of the measurements were determined by the computer.

The extravasation induced by the electrical stimulation of the trigeminal ganglion was an ipsilateral effect (i.e. occurs only on the side of the dura in which the trigeminal ganglion was stimulated). This allows the other (unstimulated) half of the dura to be used as a control. The ratio of the amount of extravasation in the dura from the stimulated side, over the amount of extravasation in the unstimulated side, was calculated. Control animals dosed with only with saline, yielded a ratio of approximately 2.0 in rats and approximately 1.8 in guinea pigs. In contrast, a compound which effectively prevented the extravasation in the dura from the stimulated side would yield a ratio of approximately 1.0.

Dose-response curves were generated for each of the panel of compounds and the dose that inhibited the extravasation by 50% (ID<sub>50</sub>) or 100% (ID<sub>100</sub>) was approximated. The respective ID<sub>50</sub> and/or ID<sub>100</sub> values, for each of the panel of compounds employed in the present invention, are summarized in Table I below.

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247

-30-

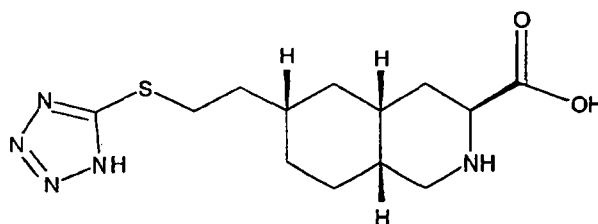
Table I

Inhibition of Dural Protein Extravasation (ng/Kg)

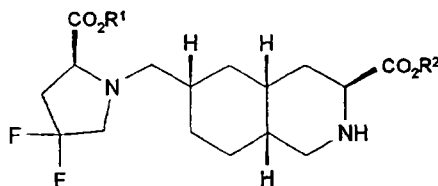
| Compound | Route of administration | ID <sub>50</sub> (ng/Kg) | ID <sub>100</sub> (ng/Kg) |
|----------|-------------------------|--------------------------|---------------------------|
| I        | i.v.                    | 6.5 (rat),               | --                        |
|          |                         | 4.0 (Gpig)               | --                        |
| II       | i.v                     | 15 (rat)                 | --                        |
| III      | i.v                     | .0053 (rat)              | 0.10                      |
| IV(b)    | p.o                     | --                       | 0.01                      |

What is claimed is:

1. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist or a pharmaceutically acceptable salt thereof.
2. A method of treating migraine comprising administering to a patient in need thereof a pharmaceutical composition comprising a selective iGluR<sub>5</sub> receptor antagonist in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.
3. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.
4. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is 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. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is given by the formula



6. The method according to Claim 1 wherein the selective iGluR<sub>5</sub> receptor antagonist is a compound of the formula



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-32-

wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine or a pharmaceutically acceptable salt thereof.

5

7. The method according to Claim 6 wherein the selective iGluR<sub>5</sub> receptor antagonist is selected from 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic Acid

10

8. A method of treating dural protein extravasation comprising administering to a patient in need thereof an effective amount of a selective iGluR<sub>5</sub> receptor antagonist.

15

9. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a compound, or combination thereof, which possesses the activity of a selective iGluR<sub>5</sub> receptor antagonist.

20

10. The use of a selective iGluR<sub>5</sub> receptor antagonist for the manufacture of a medicament for treating migraine.

25

11. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.

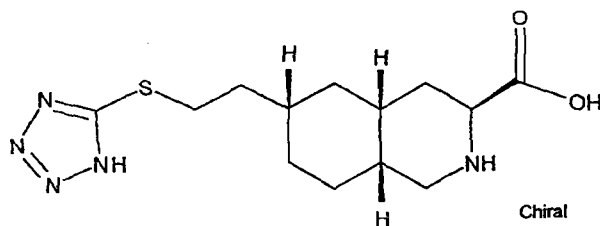
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12. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((1H-Tetrazole-5-yl) methyl) oxy) methyl) - 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid.

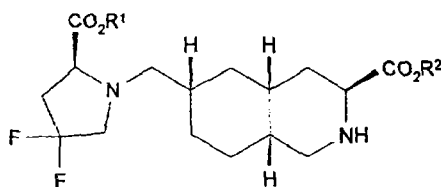
13. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is given by the formula

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-33-

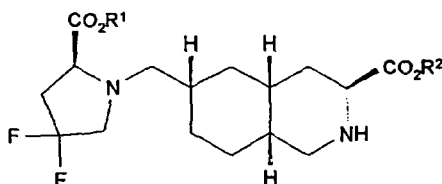


14. The use according to Claim 10 wherein the selective iGluR<sub>5</sub> receptor antagonist is  
5 a compound of Formula I



- 10 wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl,  
C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-  
pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, or C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine; or a pharmaceutically  
acceptable salt thereof.
- 15 15. The use according to Claim 14 wherein the selective iGluR<sub>5</sub> receptor antagonist is  
selected from 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-  
difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-  
carboxylate, or 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-  
difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-  
20 carboxylic Acid

16. A compound of the formula



255  
251

-34-

wherein R<sup>1</sup> and R<sup>2</sup> are each independently H, C<sub>1</sub>-C<sub>20</sub> alkyl, C<sub>2</sub>-C<sub>6</sub> alkenyl, C<sub>1</sub>-C<sub>6</sub> alkylaryl, C<sub>1</sub>-C<sub>6</sub> alkyl(C<sub>3</sub>-C<sub>10</sub>)cycloalkyl, C<sub>1</sub>-C<sub>6</sub> alkyl-N,N-C<sub>1</sub>-C<sub>6</sub> dialkylamine, C<sub>1</sub>-C<sub>6</sub> alkyl-pyrrolidine, C<sub>1</sub>-C<sub>6</sub> alkyl-piperidine, C<sub>1</sub>-C<sub>6</sub> alkyl-morpholine or a pharmaceutically acceptable salt thereof.

5

17. A compound according to Claim 16 wherein R<sup>1</sup> and R<sup>2</sup> are each independently H or C<sub>1</sub>-C<sub>20</sub> alkyl.

10 18. A compound which is 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or a pharmaceutically acceptable salt thereof.

15 19. A compound which is 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid, or a pharmaceutically acceptable salt thereof.

20 20. A pharmaceutical composition which comprises a compound as claimed in Claim 16 in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

21. A pharmaceutical composition for the treatment of migraine which comprises a selective iGluR<sub>5</sub> receptor antagonist in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

[illegible]

2do. EXAMEN DE FORMA PATENTE DE INVENCION

Folio 258

Radicación no 00-50073

Concepto Técnico no 1402

Clasificación Internacional de Patentes A61K 31/40//31/47

Practicado el examen de acuerdo a lo establecido en el Art. 38 de la Decisión 486 se determinó que esta solicitud de **Patente de Invención**:

- SI [☒] NO [☐] Contiene un resumen de la invención (Art.26-e).
- SI [☒] NO [☐] Contiene el título o nombre de la invención (Art.27-d).
- SI [☒] NO [☐] Contiene la descripción de la invención (Art.26-b).
- SI [☒] NO [☐] NO ES APLICABLE [☐] Contiene los dibujos necesarios para comprender la invención (Art.26-d)
- SI [☒] NO [☐] Contiene una o más reivindicaciones. (Art.26-c).
- SI [☐] NO [☐] NO ES APLICABLE [☒] Han sido desarrollados los productos y/o procedimientos a partir de recursos genéticos o de sus productos derivados de los que cualquiera de los Países Miembros es país de origen. (Art. 26- h).
- SI [☐] NO [☐] NO ES APLICABLE [☒] Los productos y/o procedimientos han sido obtenidos o desarrollados a partir de los conocimientos tradicionales de las comunidades indígenas, afroamericanas, o locales de los países miembros, de acuerdo a lo establecido en la Decisión 391 y sus modificaciones y reglamentaciones vigentes.(Art.26-i).
- SI [☐] NO [☒] La invención se refiere a un producto relativo a un material biológico. (Art.26-J).
- SI [☒] NO [☐] La prioridad coincide con la materia reivindicada.
- SI [☒] NO [☐] **CUMPLE LOS REQUISITOS TÉCNICOS**

OBSERVACIONES Y OTROS: SI [☒] NO [☐] ver hoja(s) anexa(s)

1. Anexa copia autentica de la solicitud estadinense número 60/142.485 de Julio de 1999 y copia autentica de la solicitud estadinense número 60/151.165 de 27 de Agosto de 1999, a partir del folio No. 156.
2. Anexa nuevo extracto para publicación, arte final en original y dos copias.
3. Anexa documento que acredita el traspaso que los autores del invento hacen en favor del solicitante.

EXAMINADOR TÉCNICO  
202047

Bogotá D. C., Octubre 17 de 2002

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416  
2003-03-31

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Folio 259

2020  
Bogotá DC

Doctor  
JOSE ANTONIO LLOREDA  
Apoderado

|                    |                |          |
|--------------------|----------------|----------|
| <b>REFERENCIA:</b> | Radicación No. | 00-50073 |
|                    | Trámite        | 002      |
|                    | Evento         | 001      |
|                    | Actuación      | 416      |
|                    | Oficio No.     | 1897     |
|                    | Folios         | 001      |

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en los artículos 26 y 27 de la Decisión 486 de la Comisión de la Comunidad Andina, y en las demás disposiciones vigentes sobre la materia, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial, conforme lo establece el artículo 40 de la misma Decisión.

**Cúmplase**  
Dado en Bogotá DC, a los

**ALIX CARMENZA CÉSPEDES DE VERGEL**  
Jefe de la División de Nuevas Creaciones

Bogotá, DC, 01-07-07 El extracto de esta solicitud fue publicado en el número 526 de la Gaceta de Propiedad Industrial, de fecha 31-03-2003. El término hábil señalado por la ley expiró el 01-07-2003 y SI ☐ NO ☒ se presentaron oposiciones por parte de terceros.

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