

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

DIVISION DE NUEVAS CREACIONES

E. S

150
SUPERINDUSTRIA Y COMERCIO
Radicacion : 80050073 80000002 Folios: 186
Fecha (AMD): 2000-10-03 12:14:11
Tramite : 002 PATENTES D 1 REGISTRO/ 444 REPUESTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Re: P1.- ELI LILLY AND COMPANY.-Solicitud de Patente de Invención para
"COMPUESTOS DECAHIDROISOQUINOLINA UTILES COMO
ANTAGONISTAS SELECTIVOS DEL RECEPTOR IGLuR₂ PARA EL
TRATAMIENTO DE LA MIGRAÑA".-Clase A61.-Expediente número 00-
050.073 .-

1. Me refiero a mi memorial de fecha 26 de Septiembre 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. Anexos me permito presentar a usted:

(1) Copias autenticas (2) de las primeras solicitudes de patente presentadas para el invento arriba nombrado **respecto de la cual reclamo prioridad**, a saber:

(a) Copia autentica debidamente certificada de la solicitud estadinense número 60/142.485 de 6 de Julio de 1999, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho documento;

(b) Copia autentica debidamente certificada de la solicitud estadinense número 60/151.165 de 27 de Agosto de 1999, junto con la traducción oficial, correspondiente a las legalizaciones y reivindicaciones de dicho 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

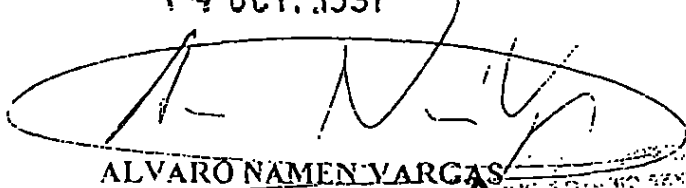
CERTIFICA:

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


ALVARO NAMEN VARGAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 AGO 1999
PASLO MENDEZ BARRAJAS

ICM/mmc

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 25 ABR 2000
PASLO MENDEZ BARRAJAS

Hago constar que esta copia coincide con dos originales que he tenido a la vista.
SANTAFE DE BOGOTA 24 NOV 1997
PASLO MENDEZ BARRAJAS

COMO NOTARIO SEXTO ENCARGADO DE SANTAFE DE BOGOTA
HAGO CONSTAR
QUE LA FOTOCOPIA COINCIDE CON LA FOTOCOPIA AUTENTICA QUE HE TENIDO A LA VISTA.
SANTAFE DE BOGOTA 26 NOV 1997
PASLO MENDEZ BARRAJAS

24 MAR 2000

150
152

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

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 SARAJAS

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 Garcia
BLANCA ACOSTA DE GARCIA
Jefe Area de Legalizaciones (e)

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 SARAJAS

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, 22 MAR. 2000
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
PABLO MENDEZ SARAJAS

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.

Eduardo Calvo
Eduardo Calvo Noriega
"TRU" FOR OFFICIAL
EQU-IPC
Rev 541 febrero 1996

HOJA DE SOLICITUD PROVISIONAL

154

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

Eduardo Calado
Eduardo Calado Saguera
"TRADUCTOR OFICIAL"
INGLES-ESPAÑOL-INGLES
Res 541 Febrero de 1966

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
TRATAMIENTODE MIGRAÑA

DIRECCION PARA LA CORRESPONDENCIA

Eli Lilly and company

Patent Division/D.C. 1104

Lilly Corporate Center

Indianapolis, Indiana 46285

Estado,IndianaCodigo Postal-46285 Pais, Estados Unidos

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

Eduardo Calado
Eduardo Calado Noguera
"TRADUCTOR OFICIAL"
INGLES - ESPAÑOL - INGLES
Res. 511 Febrero de 1996

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 Envío 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.

EdUARDO OLADO
EdUARDO OLADO
"TRADUCTOR OFICIAL"
INGLES-ESPAÑOL-INGLES
"TRADUCTOR OFICIAL"

Firma: Diedre Arciniega-Holtz
Nombre Impreso: Diedre Arciniega-Holtz

Charles Calash
"TRANSLATOR OFFICIAL"
INGLES "ESPAÑOL-ING"
Re: " " "

83
Ket-157

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

KLIN, INDIANA

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 α_1 CLUS 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 Celado
Eduardo Celado Noguera
"TR" POR OF. AL
P. 52-BA
Rev. 541 febrero de 19.6

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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 Calvo
Eduardo Calvo Vaguera
"TRA" "CANCL. P. S."
Rev. del 1 febrero de 1966

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[] 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.

Firma:Olga M. Franz

Nombre Impreso: Olga M. Franz

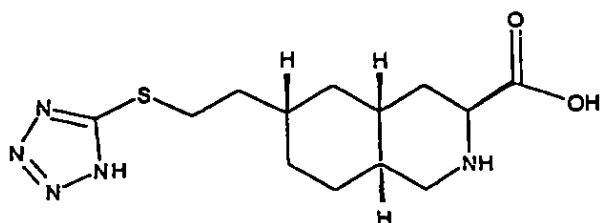
Eduardo Calado
Eduardo Calado Segura
"TRAF" 108 011 111
REC- 2002-03-23
Rev 541 febrero de 1998

REIVINDICACIONES:

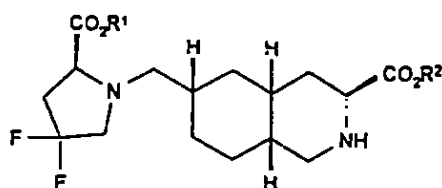
1. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva con el antagonista selectivo del receptor iGluRs o una sal farmacéuticamente aceptable del mismo.
2. Un método para tratar la migraña el cual consiste en administrar 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 Calado Sotomayor
"TR" POR DE FALTA
"TR" POR DE FALTA
RESOLUCIÓN de 15 de febrero de 1964

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.

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Eduardo Calvo
Firma: _____
-TR (M) - FOR (M) - FLE (M)
INGL: CANCL-INCLES
Rev 541 febrero de 1996

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7. El método de acuerdo a la Reivindicación 6 en el cual el antagonista selectivo del receptor iGluRs 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 iGluRs.

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 iGluRs.

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

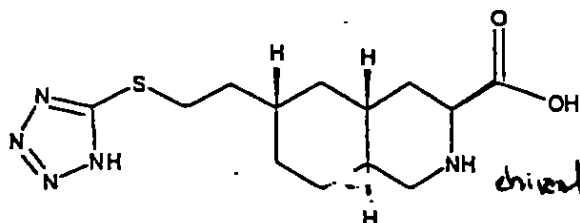
Eduardo Calado
Eduardo Calado Soguero
"TRABAJADOR SOCIAL"
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11. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 6S,8aR-6-(((4-carboxi) fenil) metil) 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-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

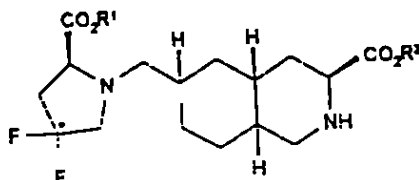
13. El uso de acuerdo a la reivindicación 10, en el cual el antagonista selectivo del receptor iGluR5, se presenta en la formula



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

Eduardo Calvo
 TRADUCCION
 INGLES
 Res 541
 Febrero de 2011

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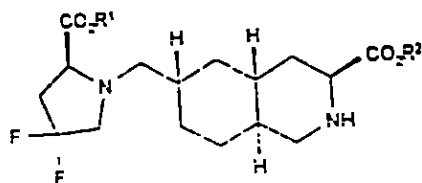
en el cual R^1 y R^2 son cada cual independientemente H, C_1-C_{20} , alquilo -alquenilo C^1-C_6 , alquilarilo C_1-C_6 , alquilo C_1-C_6 cicloalquilo(C^3-C^{10}), alquilo C_1-C^{10} -N,N- dialquiloamino C_1-C_6 , alquilo C_1-C_6 -pirrolidina, alquilo C_1-C_6 -piperidina, alquilo C_1-C_6 -morfolino o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

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EdUARDO Calado
EdUARDO Calado Vaguera
"TRADUCTOR OFICIAL"
R. S. 341 1 de 179



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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Eduardo Calado
Eduardo Calado Viqueira
"TRABAJADOR SOCIAL"
"OL-60-73"
"6"

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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.

o excipiente

Eduardo Calado
Eduardo Calado Noguera
FOR OFFICIAL
SPANISH-ARABIC
BY ... Herrera de 196

Eli Lilly and Company
JOSE LLOREDA CAMACHO & SON
C-X-12149
169

PA 250223

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)
Bleakman	David	Suzon	Zionsville, Indiana
Chappell	Amy	Ann	Indianapolis, Indiana
Filla	Sandra	Willis	Franklin, Indiana
Johnson	Kirk	Leslie	Carmel, Indiana
Ornstein	Paul		Carmel, Indiana

TITLE OF THE INVENTION (280 characters max)

SELECTIVE iGluR₅ RECEPTOR ANTAGONISTS FOR THE
TREATMENT OF MIGRAINE

CORRESPONDENCE ADDRESS

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

STATE	IN	ZIP CODE	46285	COUNTRY	USA
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ENCLOSED APPLICATION PARTS (check all that apply)

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☐ Drawing(s)	Number of Sheets		☐ Other (Specify)

METHOD OF PAYMENT (check one)

☐ A check or money order is enclosed to cover the Provisional filing fees	PROVISIONAL FILING FEE AMOUNT (\$)	\$150.00
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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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SELECTIVE iGluR₅ 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), α -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 (GluR₁ - GluR₄), 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 (GluR₅, GluR₆, and GluR₇). 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-HT₁-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-HT₁-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

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

5 5-HT_{1D} 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 α_2 , H₃, 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_{1F} receptor, suggesting a role for the 5-HT_{1F} 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 GluR₅ and KA2 have been observed. (Sahara *et al.*, *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons *et al.* reported that the kainate GluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ receptor antagonist or a pharmaceutically acceptable salt thereof.

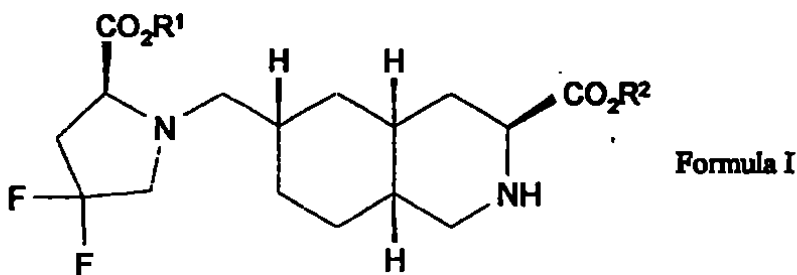
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More specifically, the present invention provides a method of treating or preventing dural protein extravasation comprising administering to a patient in need thereof an effective amount of a selective iGluR₅ receptor antagonist.

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 iGluR₅ receptor antagonist.

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



wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₄ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ 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 iGluR₅ receptor antagonists in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The present invention also provides the use of a selective iGluR₅ 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

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a selective antagonist of the iGluR₅ 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-HT₁-like mediated vasoconstrictive activity of sumatriptan. In addition, the present invention provides compounds functional as selective iGluR₅ 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, α -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.

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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

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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
10 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
15 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
20 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",
25 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
30 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"
35 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

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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 "C₁-C₄ 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 "C₁-C₆ 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 "C₁-C₁₀ 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 "C₁-C₂₀ 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 "C₂-C₆ alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C₂-C₆ 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.

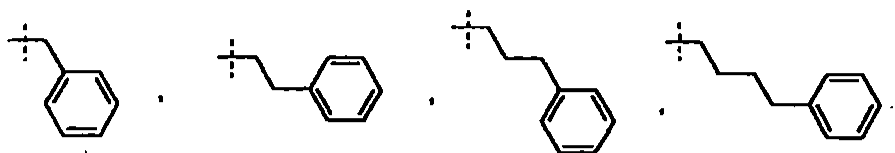
As used herein, the term "C₁-C₆ alkylaryl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an aryl group attached to the aliphatic chain. Included within the term "C₁-C₆ alkylaryl" are the following:

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and the like.

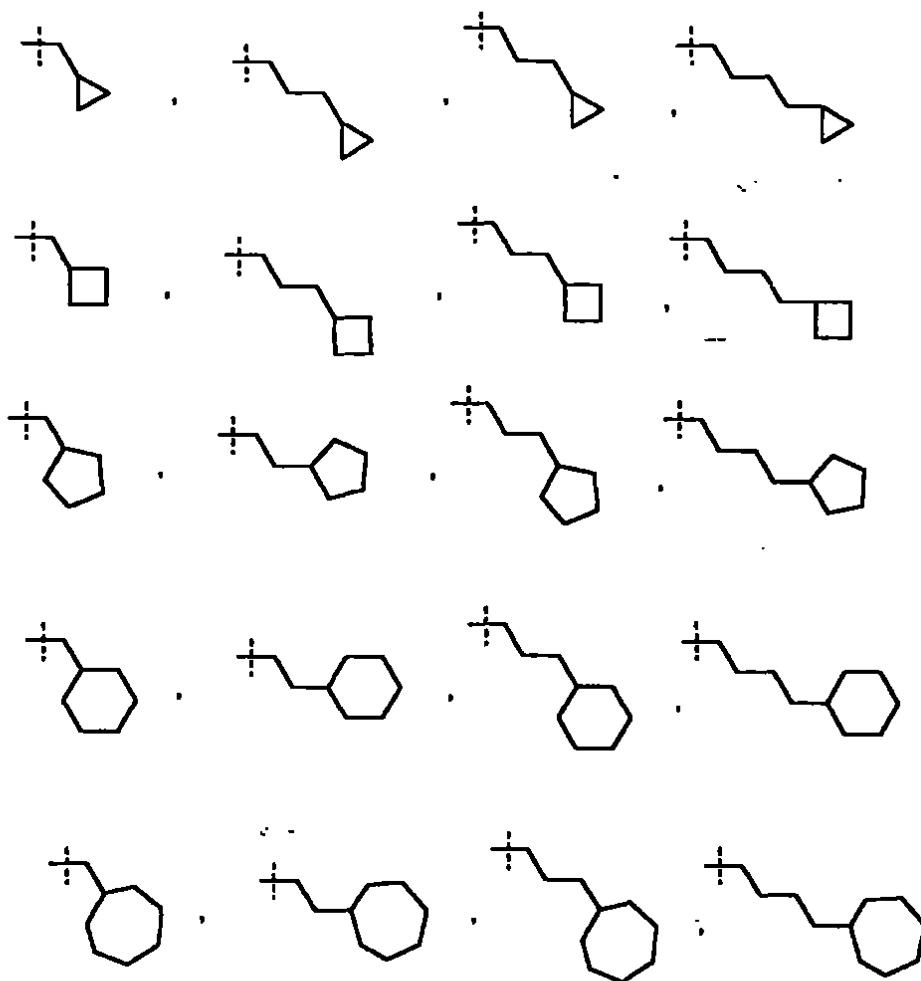
As used herein the term "(C₃-C₁₀)cycloalkyl" refers to a saturated hydrocarbon ring structure containing from three to ten carbon atoms. Typical C₃-C₁₀ cycloalkyl groups
5 include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. It is understood that "(C₃-C₆)cycloalkyl" and "(C₄-C₆)cycloalkyl" is included within the term "(C₃-C₁₀)cycloalkyl".

As used herein, the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C₃-
10 C₁₀)cycloalkyl attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" are the following:

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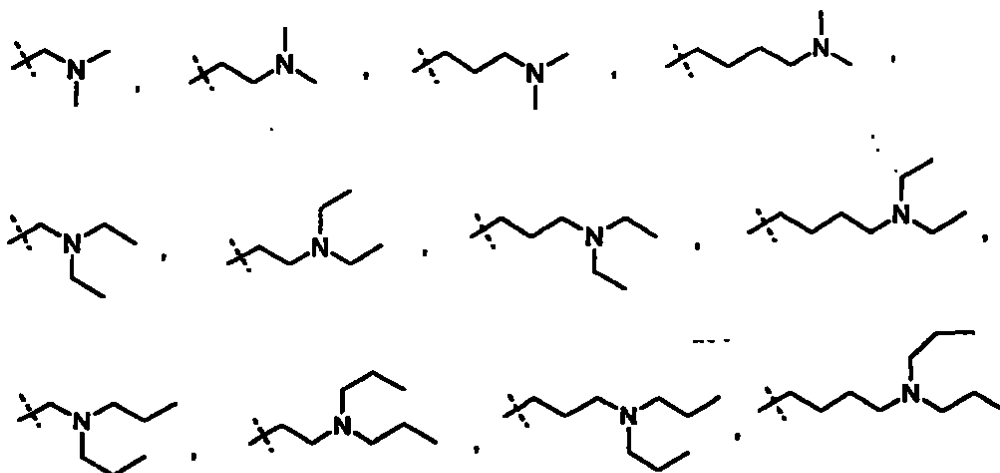


and the like.

As used herein the term "N,N-C₁-C₆ 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-C₁-C₆ dialkylamine" are -N(CH₃)₂, -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -N(CH₂CH₂CH₂CH₃)₂, and the like.

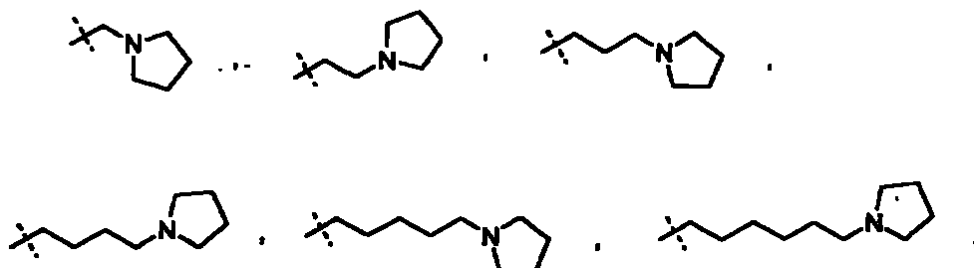
As used herein the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C₁-C₆ dialkylamine attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" are the following:

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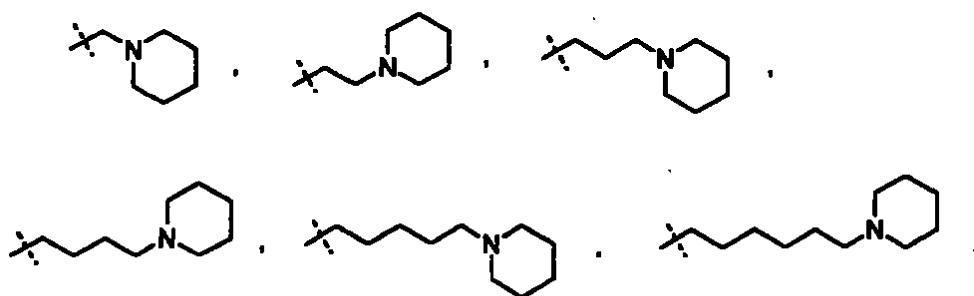
and the like.

- 5 As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-pyrrolidine" are the following:



and the like.

- 10 As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-piperidine" are the following:



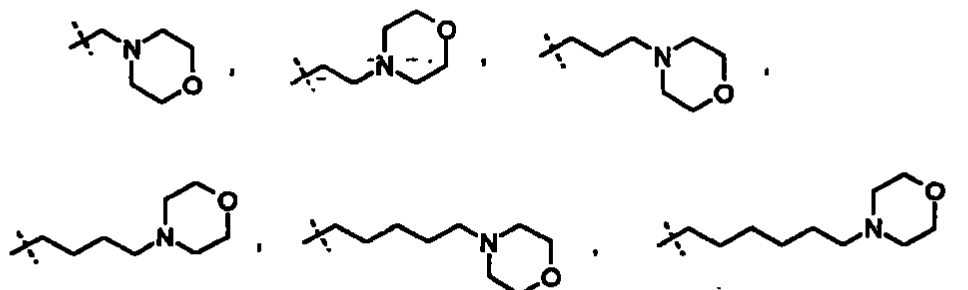
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and the like.

As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-

5 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 "iGluR₅" 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.

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It is understood that the term "selective iGluR₅ receptor antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to the iGluR₅ kainate receptor subtype, relative to the iGluR₂ AMPA receptor subtype. Preferably the selective iGluR₅ antagonist for use according to the method of the present invention has a binding affinity at least 10 fold greater for iGluR₅ than for iGluR₂, more preferably at least 100 fold greater. It is further understood that any selective iGluR₅ 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 iGluR₅ receptor antagonists are readily available to, or are readily prepared by, one of ordinary skill in the art following recognized procedures. Examples of selective iGluR₅ 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 iGluR₅ 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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The selective iGluR₅ 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 iGluR₅ receptor antagonist. For example, it may be a combination of a compound capable of functioning as an antagonist at the iGluR₅ receptor and one or more other glutamate receptors, in combination with one or more compounds capable of blocking its actions at the iGluR₂ receptor. It is understood, however, that the selective iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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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"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 powders, troches, suppositories, transdermal patches and suspensions. In general,
10 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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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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Formulation 1

Hard gelatin capsules are prepared using the following ingredients:

5		
		Quantity (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 (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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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.

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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

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

Formulation 8

An intravenous formulation may be prepared as follows:

10

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Active Ingredient	100 mg
Mannitol	100 mg
5 N Sodium hydroxide	200 ml
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 iGluR5 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 iGluR5 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 iGluR5 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

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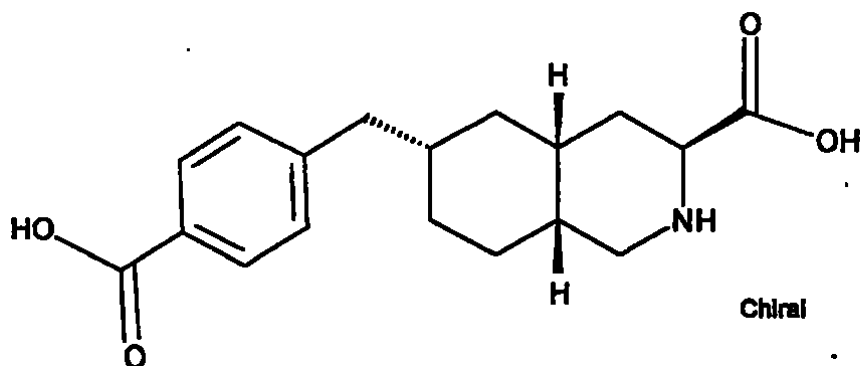
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Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to 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_i" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID₅₀" and "ID₁₀₀" 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

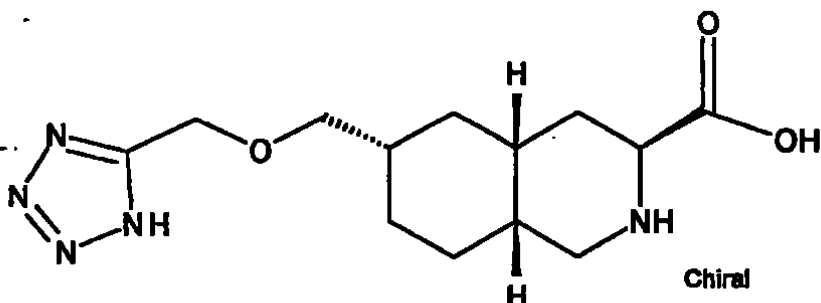


Those skilled in the art will recognize Compound I as an excitatory amino acid receptor antagonist, selective for the iGluR₅ receptor subtype. Compound I may be readily prepared by one of ordinary skill in the art following recognized general procedures as described in United States Patent No. 5,446,051, 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

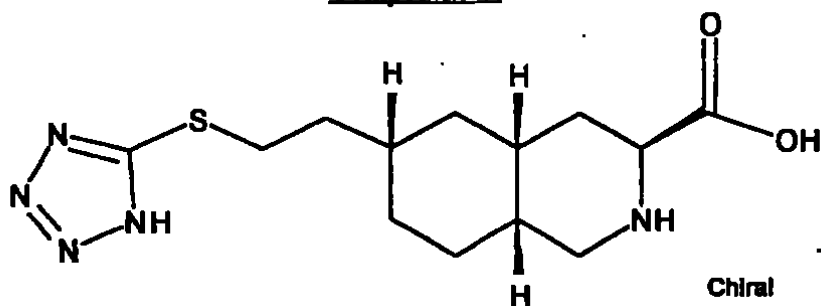


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Those skilled in the art will recognize Compound II as an excitatory amino acid receptor antagonist, selective for the iGluR₅ receptor subtype. Compound II may be readily prepared and resolved by one of ordinary skill in the art following recognized 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.

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Compound III



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Compound III represents a novel compound, functional as a selective iGluR₅ 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.

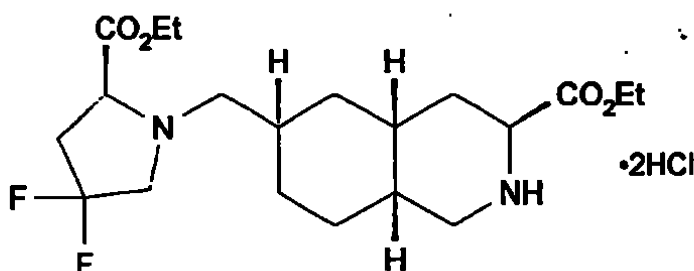
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193Compound IV(b)

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

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- 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 CH₂Cl₂ (100 mL), was added triethylamine (20.9 mL, 150.3 mmol) followed by toluenesulfonyl chloride (19.1 g, 100.2 mmol) dissolved in CH₂Cl₂ (100 mL). The reaction was warmed to room temperature and stirred 16 h, then partitioned between CH₂Cl₂ and 10% aqueous NaHSO₄. The aqueous layer was extracted with CH₂Cl₂ and the combined organics were dried over MgSO₄, 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⁺)
 Calculated for C₂₂H₃₁NO₇S 0.1 CH₂Cl₂: Theory: C, 57.45; H, 6.81; N, 3.03. Found: C, 57.76; H, 6.93; N, 3.35.
¹³C NMR (DMSO-d₆): 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.

- 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

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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 CH_2Cl_2 and water. The aqueous layer was extracted two times with CH_2Cl_2 and the combined organics were dried over MgSO_4 , filtered, and concentrated in vacuo. Column chromatography (50% EtOAc/hexane followed by 5% MeOH/ CH_2Cl_2) gave 9.2 g (95%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 441.3 (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°C in CH_2Cl_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 CH_2Cl_2 was added. Upon stirring for 45 min at -78°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 NaHSO_4 . The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over 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 (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°C in CH_2Cl_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 CH_2Cl_2 and saturated aqueous NaHCO_3 . The aqueous layer was

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extracted with CH_2Cl_2 and the combined organics were dried over 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 (M^+)
Calculated for $\text{C}_{22}\text{H}_{34}\text{F}_2\text{N}_2\text{O}_6$: Theory: C, 57.38; H, 7.59; 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))

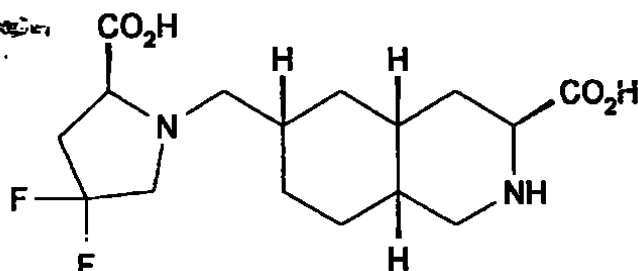
- 15 A solution of the compound of Step D above (3.3 g, 7.10 mmol) dissolved in CH_2Cl_2 (40 mL) was cooled to 0 °C and charged with trimethylsilyl iodide (3.0 mL, 21.3 mmol). The reaction was allowed to warm to room temperature, stirred an additional 4 h, then quenched by the addition of saturated aqueous NaHCO_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with a 1 N solution of sodium thiosulfate, dried over MgSO_4 , filtered, and concentrated in vacuo. The material was chromatographed, (2% MeOH/ CH_2Cl_2), dissolved in 20 mL of Et_2O , and to it was
20 added 50 mL of a HCl/ Et_2O 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 (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}C NMR (D_2O): δ 170.3, 167.7, 125.1 (t, $J_{\text{CF}} = 249.1$ Hz), 65.9, 65.0, 64.1, 63.4, 60.1 (t, $J_{\text{CF}} = 33.9$ Hz), 57.6, 52.8, 42.9, 37.2 (t, $J_{\text{CF}} = 26.4$ 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



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/H₂O and water, then stirred in the presence of 10% pyridine/H₂O for 2 h. After filtration, the resin was washed with water, and the filtrate was concentrated in vacuo to
15 provide the title compound (0.6 g, 97%) as a white foam:

MS(m/e): 347.2 (M⁺)

Calculated for C₁₆H₂₄F₂N₂O₄ 0.1 H₂O: Theory: C, 55.19; H, 7.01; N, 8.05. Found: C, 54.81; H, 6.82; N, 8.13.

¹³C NMR (D₂O): δ 175.1, 171.1, 125.6 (t, J_{CF} = 249.4 Hz), 67.9, 63.0, 59.3 (t, J_{CF} = 34.0 Hz), 54.5, 42.5, 37.5 (t, J_{CF} = 24.9 Hz), 34.3, 32.7, 32.4, 30.6, 28.2, 27.0, 24.3.

EXAMPLE 2

25 To establish that the iGluR₅ receptor subtype is mediating neurogenic protein extravasation, a functional characteristic of migraine, the binding affinity of the panel compounds to the iGluR₅ receptor is first measured using standard methods. For example, the activity of compounds acting at the iGluR₅ receptor antagonists can be
30 determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR₅ 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

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ganglion neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585). The selectivity of compounds acting at the iGluR₅ receptor subtype can then be determined by comparing antagonist activity at the iGluR₅ 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 GluR₁, GluR₂, GluR₃ and GluR₄ receptors (Fletcher et al., 1995, Recept. Channels 3; 21-31); receptor-ligand binding studies and whole-cell voltage clamp electrophysiological recordings of functional activity at human GluR₆ receptors (Hoo et al., Recept. Channels 2; 327-338); and whole-cell voltage clamp electrophysiological recordings of functional activity at AMPA receptors in acutely isolated cerebellar Purkinje neurons (Bleakman et al., 1996, Mol. Pharmacol. 49; 581-585) and other tissues expressing AMPA receptors (Fletcher and Lodge, 1996, Pharmacol. Ther. 70; 65-89).

iGluR₅ antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors were employed. Displacement of ³[H] AMPA by increasing concentrations of antagonist was measured on iGluR₁, iGluR₂, iGluR₃, and iGluR₄ expressing cells, while displacement of ³[H] kainate (KA) was measured on iGluR₅, iGluR₆, iGluR₇, and KA2-expressing cells. Estimated antagonist binding activity (K_i) in μ M was determined for Compounds I - IV. As an indicia of selectivity, the ratio of binding affinity to the iGluR₂ AMPA receptor subtype, versus the binding affinity to iGluR₅ kainate receptor subtype, was also determined. Compounds provided by the present invention displayed a binding affinity of at least 10 fold greater for iGluR₅ than that for iGluR₂, 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.

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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% (ID₅₀) or 100% (ID₁₀₀) was approximated. The respective ID₅₀ and/or ID₁₀₀ values, for each of the panel of compounds employed in the present invention, are summarized in Table I below.

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Table I

Inhibition of Dural Protein Extravasation (ng/Kg)

Compound	Route of administration	ID ₅₀ (ng/Kg)	ID ₁₀₀ (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:

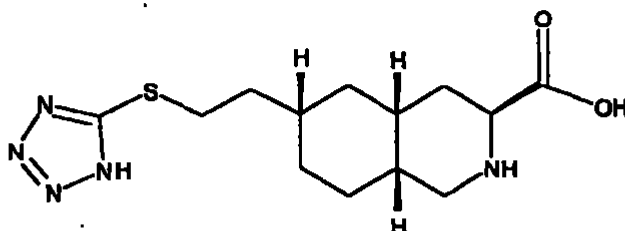
1. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR₅ receptor antagonist or a pharmaceutically acceptable salt thereof.

2. A method of treating migraine comprising administering to a patient in need thereof a pharmaceutical composition comprising a selective iGluR₅ receptor antagonist in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

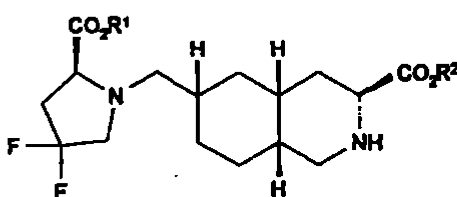
3. The method according to Claim 1 wherein the selective iGluR₅ receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.

4. The method according to Claim 1 wherein the selective iGluR₅ 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 iGluR₅ receptor antagonist is given by the formula



6. The method according to Claim 1 wherein the selective iGluR₅ receptor antagonist is a compound of the formula



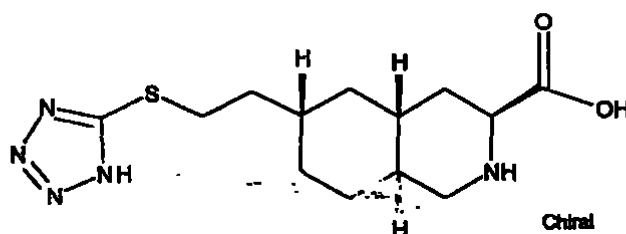
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wherein R^1 and R^2 are each independently H, C_1 - C_{20} alkyl, C_7 - C_6 alkenyl, C_1 - C_6 alkylaryl, C_1 - C_6 alkyl(C_3 - C_{10})cycloalkyl, C_1 - C_6 alkyl-N,N- C_1 - C_6 dialkylamine, C_1 - C_6 alkyl-pyrrolidine, C_1 - C_6 alkyl-piperidine, C_1 - C_6 alkyl-morpholine or a pharmaceutically acceptable salt thereof.

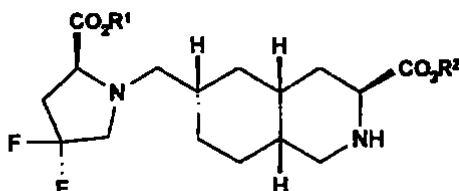
- 5
7. The method according to Claim 6 wherein the selective iGluR₅ receptor antagonist is selected from 3S, 4aR, 6S, 8aR Ethyl 6-(((2S)-2-(Ethoxycarbonyl)-4,4-difluoropyrrolidinyl)methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylate, or 3S, 4aR, 6S, 8aR 6-(((2S)-2-(Carboxylic acid)-4,4-difluoropyrrolidinyl)methyl)-1, 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 iGluR₅ 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 iGluR₅ receptor antagonist.
- 20
10. The use of a selective iGluR₅ receptor antagonist for the manufacture of a medicament for treating migraine.
- 25
11. The use according to Claim 10 wherein the selective iGluR₅ 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 iGluR₅ 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 iGluR₅ receptor antagonist is given by the formula

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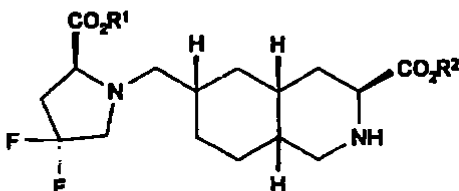
14. The use according to Claim 10 wherein the selective iGluR₅ receptor antagonist is
5 a compound of Formula I



- 10 wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl,
C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-
pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ alkyl-morpholine; or a pharmaceutically
acceptable salt thereof.

- 15 15. The use according to Claim 14 wherein the selective iGluR₅ 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



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wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, C₁-C₆ alkyl-morpholine or a pharmaceutically acceptable salt thereof.

5

17. A compound according to Claim 16 wherein R¹ and R² are each independently H or C₁-C₂₀ alkyl.

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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.

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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 iGluR₅ receptor antagonist in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

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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
5 iGluR₅ receptor antagonist. The present invention further provides novel compounds functional as selective iGluR₅ receptor antagonists as well as compositions and formulations comprising said selective iGluR₅ receptor antagonists.

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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

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Res 541 Febrero de 19.6

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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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R.M. 541 Febrero de 1966

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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)

- | | |
|---|---|
| ☒ [x] ESPECIFICACIONES | ☐ [35] 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.
- ☒ [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, 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.

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ESPAÑOL-INGLES
1 febrero de 1996

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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 Envío 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

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Reg 541 Febrero de 1996

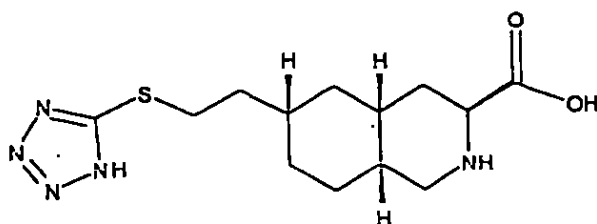
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REIVINDICACIONES:

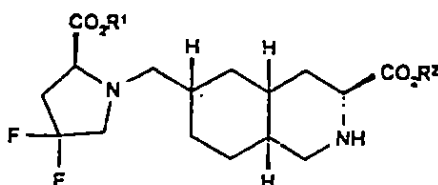
1. Un método para tratar la migraña el cual consiste en administrar a un paciente que necesite dicho tratamiento, una cantidad efectiva con el antagonista selectivo del receptor iGluRs o una sal farmacéuticamente aceptable del mismo.
2. Un método para tratar la migraña el cual consiste en administrar 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.

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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 R¹ y R² son cada cual independientemente H, C₁-C₂₀ ,
alquilo -alquenilo C₂-C₆, alquilarilo C₁-C₆, alquilo C₁-C₆
cicloalquilo(C³ -C¹⁰), alquilo C₁-C¹⁰ -N,N- dialquiloamino C₁-C₆,
alquilo C₁-C₆-pirrolidina, alquilo C₁-C₆-piperidina, alquilo C₁-C₆-
morfolino o una sal farmacéuticamente aceptable del mismo.

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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.

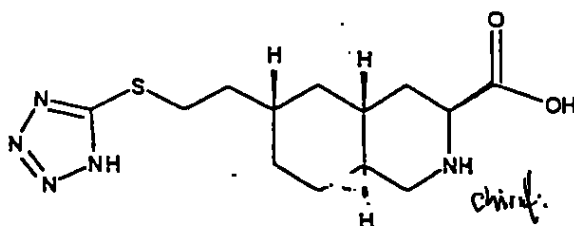
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11. El uso de acuerdo a la Reivindicación 10 en el cual el antagonista selectivo del receptor iGluR5, es el ácido 3S, 4aR, 6S, 8aR-6-(((4-carboxi) fenil) metil) 1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina- carboxílico.

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.

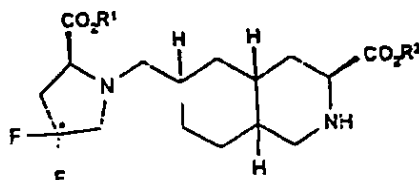
13. El uso de acuerdo a la reivindicación 10, en el cual el antagonista selectivo del receptor iGluR5, se presenta en la formula



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.

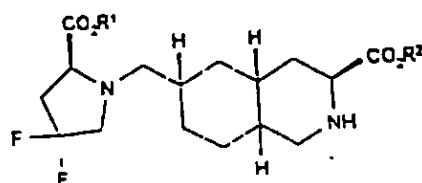
15. El uso para un tratamiento de acuerdo a la Reivindicación 14, en el cual el antagonista selectivo del receptor iGluR5, es seleccionado de 3S, 4aR, 6S, 8aR Etil-6-(((2S)-2-(Etoxicarbonil)- 4, 4-difluoropirrolidino)metil-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahidroisoquinolina-3-carboxilato, o ácido 3S,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

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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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Eduardo Calvo Novara
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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 iGluRs en combinación con un portador, diluyente o excipiente farmacéuticamente aceptable.

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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

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 →	+
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INVENTOR(s)/APPLICANT(s)			
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TITLE OF THE INVENTION (280 characters max)

SELECTIVE iGluR₆ RECEPTOR ANTAGONISTS FOR THE TREATMENT OF MIGRAINE

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ENCLOSED APPLICATION PARTS (check all that apply)

☒ Specification	Number of pages	35	☐ Small Entity Statement
☐ Drawing(s)	Number of Sheets		☐ 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.

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Respectfully submitted,
SIGNATURE

Date 8 / 27 / 99

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REGISTRATION NO. (if appropriate) 36,808

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SELECTIVE iGluR₅ 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), α -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 (GluR₁ - GluR₄), 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 (GluR5, GluR6, and GluR7).

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 tremora, 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

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-HT₁-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-HT₁-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_{1D} 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 α_2 , H₃, 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_{1F} receptor, suggesting a role for the 5-HT_{1F} receptor in migraine (WO93/14201).

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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 GluR₅ and KA2 have been observed: (Sahara *et al.*, *The Journal of Neuroscience*, 17(17), 6611 (1997)). Simmons *et al.* reported that the kainate GluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅

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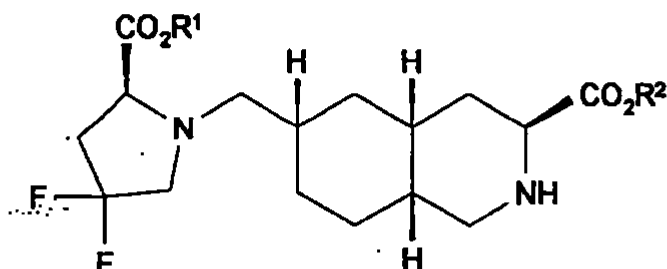
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receptor antagonist or a pharmaceutically acceptable salt thereof. Examples of such neurological disorders, or neurodegenerative conditions, include: cerebral deficits subsequent to cardiac bypass surgery and grafting; stroke; cerebral ischemia; spinal 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^1 and R^2 are each independently H, C_1-C_{20} alkyl, C_2-C_6 alkenyl, C_1-C_6 alkylaryl, C_1-C_6 alkyl(C_3-C_{10})cycloalkyl, C_1-C_6 alkyl-N,N- C_1-C_6 dialkylamine, C_1-C_6 alkyl-pyrrolidine, C_1-C_6 alkyl-piperidine, or C_1-C_6 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.

In addition, the present invention provides pharmaceutical compositions useful for

25 treating or preventing migraine comprising selective iGluR₅ receptor antagonists in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

The present invention also provides the use of a selective iGluR₅ receptor antagonist for the manufacture of a medicament for treating or preventing migraine.

30

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 iGluR₅ 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-HT₁-like mediated vasoconstrictive activity of sumatriptan. In addition, the present invention provides compounds functional as selective iGluR₅ 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, α -

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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:

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

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 "C₁-C₄ 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 "C₁-C₆ 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.
15

As used herein the term "C₁-C₁₀ 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.
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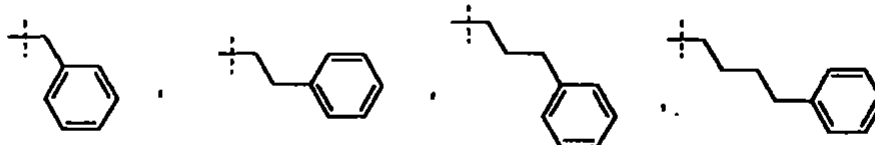
As used herein the term "C₁-C₂₀ alkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 20 carbon atoms and includes, but is not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, isopentyl, hexyl, 3-methylpentyl, 2-ethylbutyl, n-heptyl, n-octyl, 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.
25

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 "C₂-C₆ alkenyl" refers to a straight or branched, monovalent, unsaturated aliphatic chain having from two to six carbon atoms. Typical C₂-C₆ 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.
30

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 "C₁-C₆ 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 "C₁-C₆ alkylaryl" are the following:

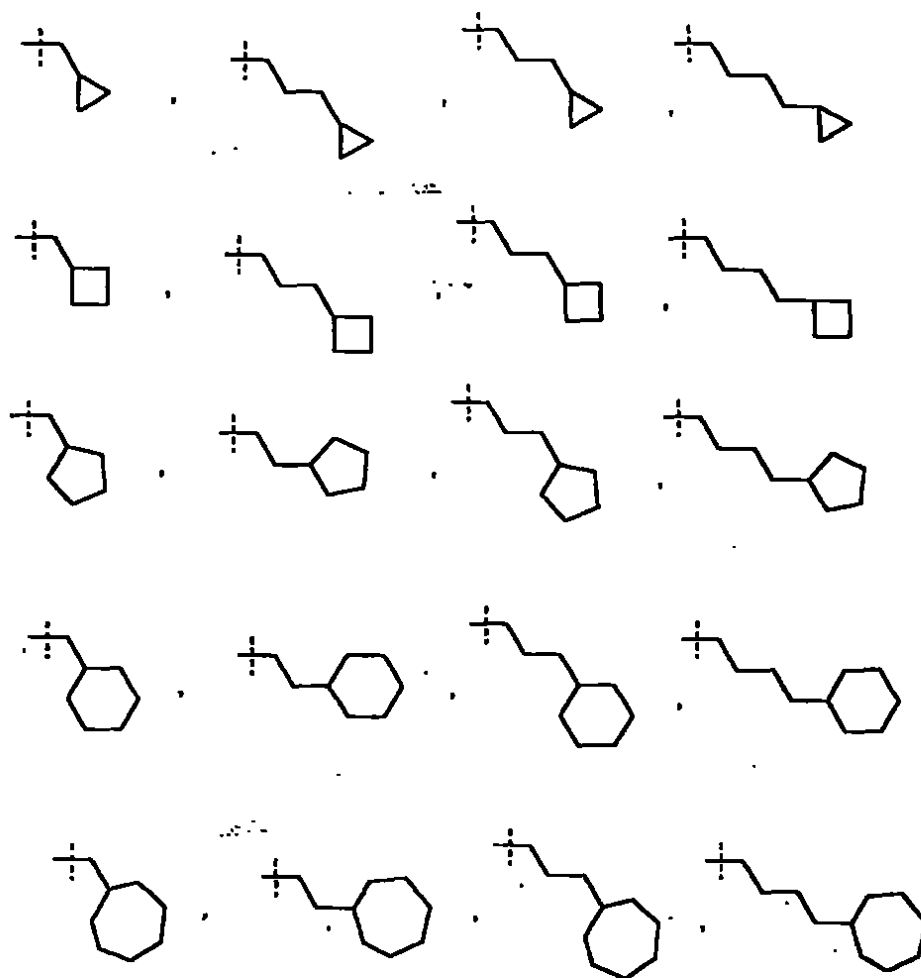


and the like.

- As used herein the term "(C₃-C₁₀)cycloalkyl" refers to a saturated hydrocarbon ring structure containing from three to ten carbon atoms. Typical C₃-C₁₀ cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, and the like. It is understood that "(C₃-C₆)cycloalkyl" and "(C₄-C₆)cycloalkyl" is included within the term "(C₃-C₁₀)cycloalkyl".
- As used herein, the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" refers to a straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has a (C₃-C₁₀)cycloalkyl attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl" are the following:

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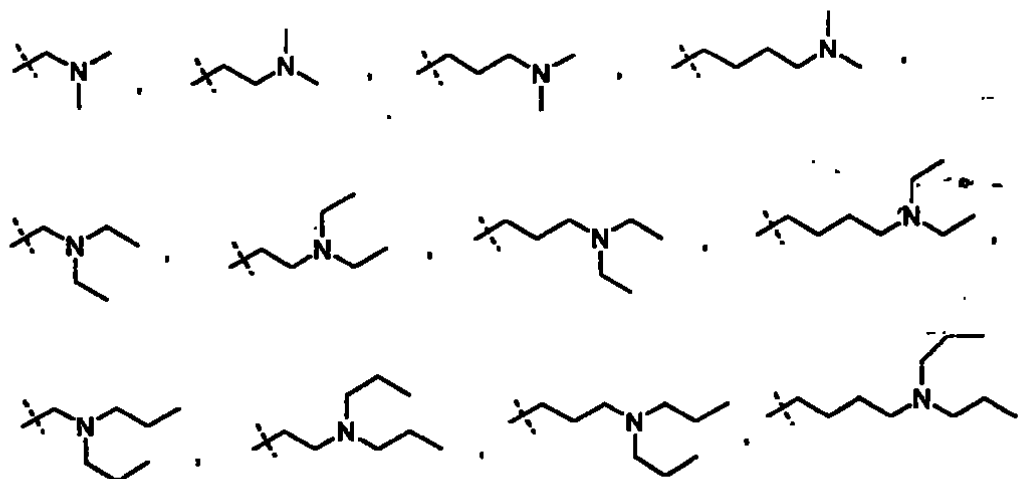
and the like.

As used herein the term "N,N-C₁-C₆ 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-C₁-C₆ dialkylamine" are -N(CH₃)₂, -N(CH₂CH₃)₂, -N(CH₂CH₂CH₃)₂, -N(CH₂CH₂CH₂CH₃)₂, and the like.

As used herein the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" refers to straight or branched, monovalent, saturated aliphatic chain of 1 to 6 carbon atoms which has an N,N-C₁-C₆ dialkylamine attached to the aliphatic chain. Included within the term "C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine" are the following:

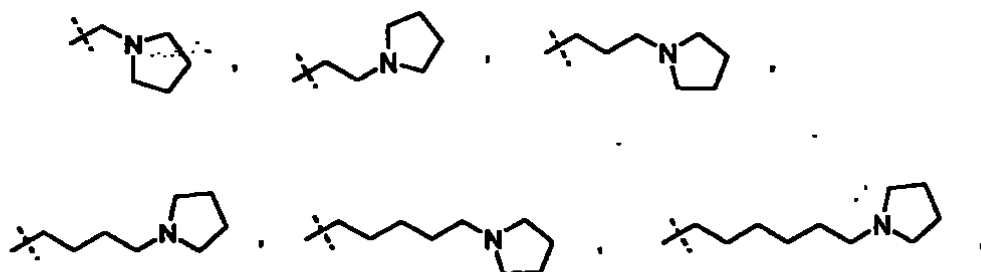
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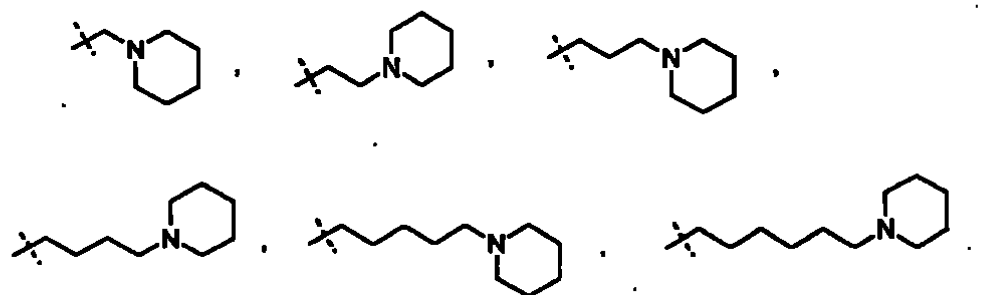
and the like.

- As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-pyrrolidine" are the following:



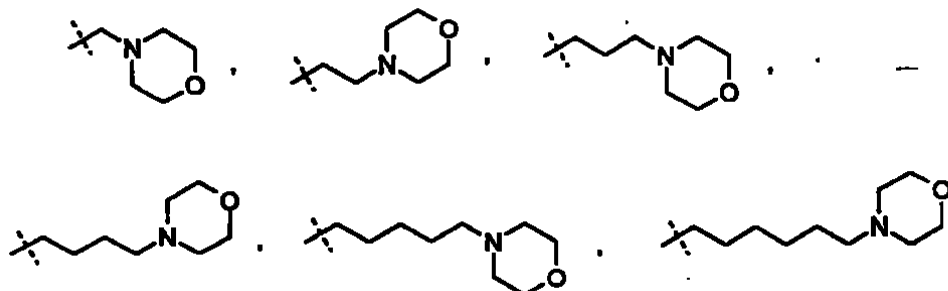
and the like.

- As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-piperidine" are the following:



and the like.

As used herein the term "C₁-C₆ 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 "C₁-C₆ alkyl-morpholine" are the following:



and the like.

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As used herein the term "iGluR₅" 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.

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 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.

25 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.

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It is understood that the term "selective iGluR₅ receptor antagonist" as used herein, includes those excitatory amino acid receptor antagonists which selectively bind to the iGluR₅ kainate receptor subtype, relative to the iGluR₂ AMPA receptor subtype. Preferably the selective iGluR₅ antagonist for use according to the method of the present invention has a binding affinity at least 10 fold greater for iGluR₅ than for iGluR₂, more preferably at least 100 fold greater. It is further understood that any selective iGluR₅ 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 iGluR₅ receptor antagonists are readily available to, or are readily prepared by, one of ordinary skill in the art following recognized procedures. Examples of selective iGluR₅ 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 iGluR₅ 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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The selective iGluR₅ 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 iGluR₅ receptor antagonist. For example, it may be a combination of a compound capable of functioning as an antagonist at the iGluR₅ receptor and one or more other glutamate receptors, in combination with one or more compounds capable of blocking its actions at the iGluR₂ receptor. It is understood, however, that the selective iGluR₅ 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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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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"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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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.

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 acetate succinate.

15 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.

20 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.

25 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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Formulation 1**Hard gelatin capsules are prepared using the following ingredients:**

5		
		Quantity (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.

20

25

Formulation 2**A tablet is prepared using the ingredients below:**

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

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

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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.

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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**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

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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

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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 iGluR₅ 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 iGluR₅ 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 iGluR₅ 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.

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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

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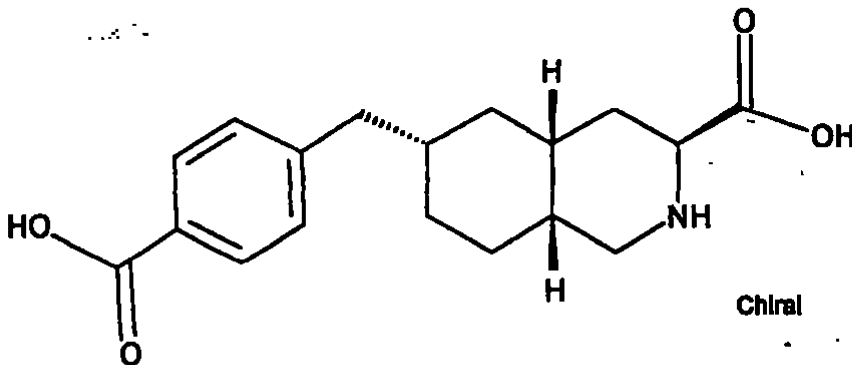
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Hg" refers to millimeters of mercury; "min" refers to minutes; "h" or "hr" refers to hours; "°C" refers to degrees Celsius; "TLC" refers to thin layer chromatography; "HPLC" refers to high performance liquid chromatography; "R_f" refers to retention factor; "R_t" refers to retention time; "δ" refers to part per million down-field from tetramethylsilane; "THF" refers to tetrahydrofuran; "DMF" refers to N,N-dimethylformamide; "DMSO" refers to 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_i" refers to the dissociation constant of an enzyme-antagonist complex and serves as an index of ligand binding; and "ID₅₀" and "ID₁₀₀" 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



20

Those skilled in the art will recognize Compound I as an excitatory amino acid receptor antagonist, selective for the iGluR₅ 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.

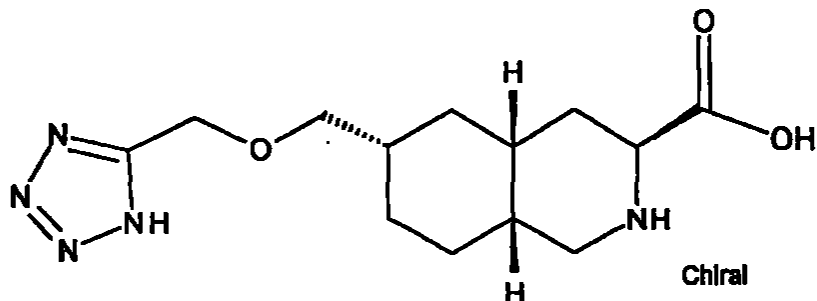
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Compound II

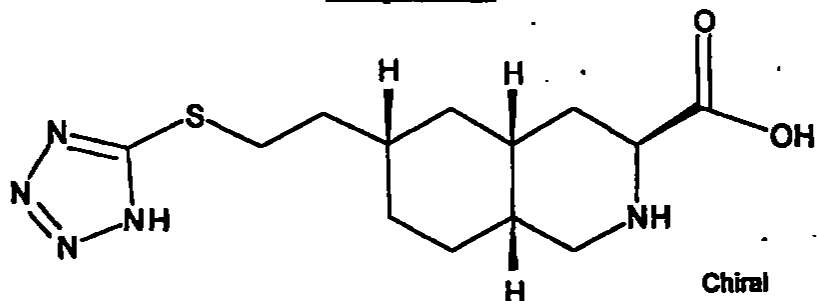
3S, 4aR, 6S, 8aR-6-((((1H-Tetrazole-5-yl) methyl) oxy) methyl) -
1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid



5

Those skilled in the art will recognize Compound II as an excitatory amino acid receptor antagonist, selective for the iGluR₅ 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.

10

Compound III

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Compound III represents a novel compound, functional as a selective iGluR₅ 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.

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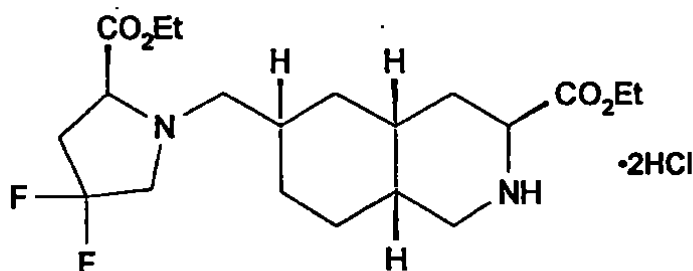
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Compound IV(b)

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 CH₂Cl₂ (100 mL), was added triethylamine (20.9 mL, 150.3 mmol) followed by toluenesulfonyl chloride (19.1 g, 100.2 mmol) dissolved in CH₂Cl₂ (100 mL). The reaction was warmed to room temperature and stirred 16 h, then partitioned between CH₂Cl₂ and 10% aqueous NaHSO₄. The aqueous layer was extracted with CH₂Cl₂ and the combined organics were dried over MgSO₄, 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⁺)
Calculated for C₂₂H₃₁NO₇S 0.1 CH₂Cl₂: Theory: C, 57.45; H, 6.81; N, 3.03. Found: C, 57.76; H, 6.93; N, 3.35.
¹³C NMR (DMSO-d₆): 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.

- 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

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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 CH_2Cl_2 and water. The aqueous layer was extracted two times with CH_2Cl_2 and the combined organics were dried over MgSO_4 , filtered, and concentrated in vacuo. Column chromatography (50% EtOAc/hexane followed by 5% MeOH/ CH_2Cl_2) gave 9.2 g (95%) of the desired intermediate title compound as a colorless oil:

MS(m/e): 441.3 (M^+)
Calculated for $\text{C}_{22}\text{H}_{36}\text{N}_2\text{O}_5\text{S}$: 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°C in CH_2Cl_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 CH_2Cl_2 was added. Upon stirring for 45 min at -78°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 NaHSO_4 . The aqueous layer was extracted with CH_2Cl_2 and the combined organics were dried over 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 (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°C in CH_2Cl_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 CH_2Cl_2 and saturated aqueous NaHCO_3 . The aqueous layer was

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extracted with CH_2Cl_2 and the combined organics were dried over 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:

5.4.4

MS(m/e): 461.2 (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 CH_2Cl_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 NaHCO_3 (50 mL). The aqueous layer was extracted with CH_2Cl_2 and the combined organics washed with a 1 N solution of sodium thiosulfate, dried over MgSO_4 , filtered, and concentrated in vacuo. The material was chromatographed, (2% MeOH/ CH_2Cl_2), dissolved in 20 mL of Et_2O , and to it was
20 added 50 mL of a $\text{HCl}/\text{Et}_2\text{O}$ 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 (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}C NMR (D_2O): δ 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.

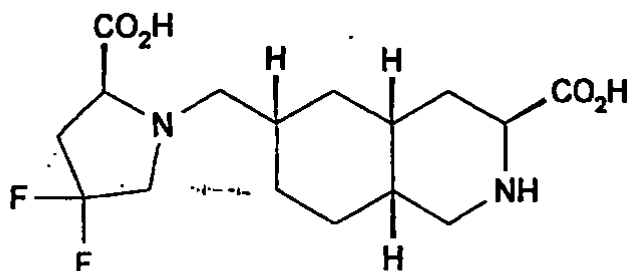
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Compound IV(a)

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

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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 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/H₂O and water, then stirred in the presence of 10% pyridine/H₂O for 2 h. After 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⁺)

Calculated for C₁₆H₂₄F₂N₂O₄ 0.1 H₂O: Theory: C, 55.19; H, 7.01; N, 8.05. Found: C, 54.81; H, 6.82; N, 8.13.

¹³C NMR (D₂O): δ 175.1, 171.1, 125.6 (t, J_{C-F} = 249.4 Hz), 67.9, 63.0, 59.3 (t, J_{C-F} = 34.0 Hz), 54.5, 42.5, 37.5 (t, J_{C-F} = 24.9 Hz), 34.3, 32.7, 32.4, 30.6, 28.2, 27.0, 24.3.

EXAMPLE 2

To establish that the iGluR₅ receptor subtype is mediating neurogenic protein extravasation, a functional characteristic of migraine, the binding affinity of the panel compounds to the iGluR₅ receptor is first measured using standard methods. For example, the activity of compounds acting at the iGluR₅ receptor antagonists can be determined by radiolabelled ligand binding studies at the cloned and expressed human iGluR₅ 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 iGluR₅ receptor subtype can then be determined by comparing antagonist activity at the iGluR₅ receptor with antagonist activity at other AMPA and kainate receptors. Methods useful for such comparison studies include: receptor-ligand

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

10 iGluR5 antagonist binding affinity profiles

Cell lines (HEK293 cells) stably transfected with human iGluR receptors were employed. Displacement of ³[H] AMPA by increasing concentrations of antagonist was measured on iGluR₁, iGluR₂, iGluR₃, and iGluR₄ expressing cells, while displacement of ³[H] kainate (KA) was measured on iGluR₅, iGluR₆, iGluR₇, and KA2-expressing cells.

15 Estimated antagonist binding activity (K_i) in μ M was determined for Compounds I - IV. As an indicia of selectivity, the ratio of binding affinity to the iGluR₂ AMPA receptor subtype, versus the binding affinity to iGluR₅ kainate receptor subtype, was also determined. Compounds provided by the present invention displayed a binding affinity of at least 10 fold greater for iGluR₅ than that for iGluR₂, more preferably at least 100 fold.

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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.

25 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

30 (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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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% (ID₅₀) or 100% (ID₁₀₀) was approximated. The respective ID₅₀ and/or ID₁₀₀ values, for each of the panel of compounds employed in the present invention, are summarized in Table I below.

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Table I

Inhibition of Dural Protein Extravasation (ng/Kg)

Compound	Route of administration	ID ₅₀ (ng/Kg)	ID ₁₀₀ (ng/Kg)
I	iv	6.5 (rat),	—
—	—	4.0 (Gpug)	—
II	iv	15 (rat)	—
III	iv	0.053 (rat)	0.10
IV(b)	po	—	0.01

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What is claimed is:

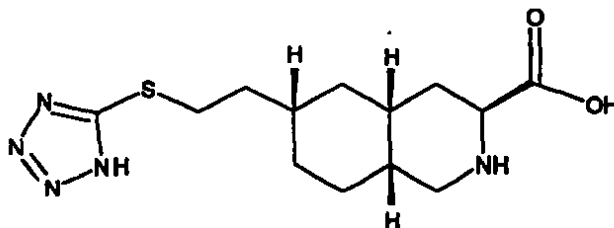
1. A method of treating migraine comprising administering to a patient in need thereof an effective amount of a selective iGluR₅ receptor antagonist or a pharmaceutically acceptable salt thereof.

2. A method of treating migraine comprising administering to a patient in need thereof a pharmaceutical composition comprising a selective iGluR₅ receptor antagonist in combination with one or more pharmaceutically acceptable carriers, diluents, or excipients.

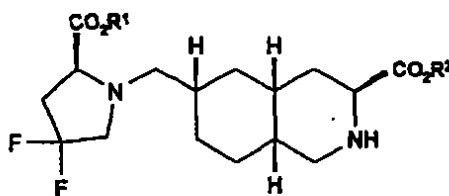
3. The method according to Claim 1 wherein the selective iGluR₅ receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((4-carboxy) phenyl) methyl) -1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a - decahydroisoquinoline-3-carboxylic acid.

4. The method according to Claim 1 wherein the selective iGluR₅ 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 iGluR₅ receptor antagonist is given by the formula



6. The method according to Claim 1 wherein the selective iGluR₅ receptor antagonist is a compound of the formula



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wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, C₁-C₆ alkyl-morpholine or a pharmaceutically acceptable salt thereof.

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7. The method according to Claim 6 wherein the selective iGluR₅ 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

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8. A method of treating dural protein extravasation comprising administering to a patient in need thereof an effective amount of a selective iGluR₅ receptor antagonist.

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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 iGluR₅ receptor antagonist.

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10. The use of a selective iGluR₅ receptor antagonist for the manufacture of a medicament for treating migraine.

11. The use according to Claim 10 wherein the selective iGluR₅ 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.

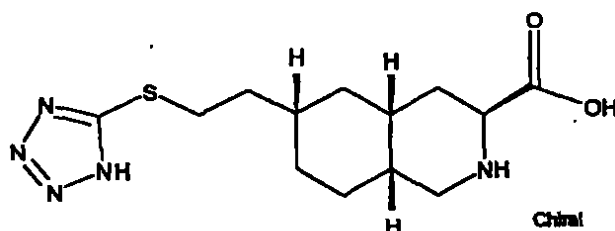
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12. The use according to Claim 10 wherein the selective iGluR₅ receptor antagonist is 3S, 4aR, 6S, 8aR-6-(((1H-Tetrazole-5-yl) methyl) oxy) methyl)-1, 2, 3, 4, 4a, 5, 6, 7, 8, 8a-decahydroisoquinoline-3-carboxylic acid.

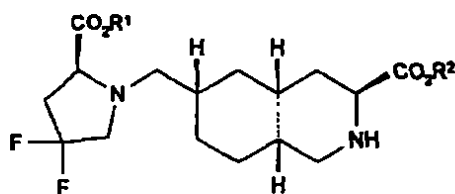
13. The use according to Claim 10 wherein the selective iGluR₅ receptor antagonist is given by the formula

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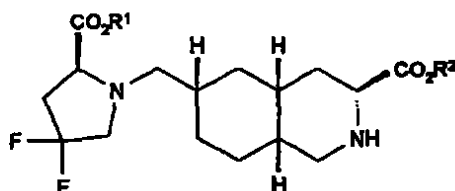
14. The use according to Claim 10 wherein the selective iGluR₅ receptor antagonist is
5 a compound of Formula I



- 10 wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, or C₁-C₆ alkyl-morpholine; or a pharmaceutically acceptable salt thereof.

- 15 15. The use according to Claim 14 wherein the selective iGluR₅ 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
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16. A compound of the formula



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wherein R¹ and R² are each independently H, C₁-C₂₀ alkyl, C₂-C₆ alkenyl, C₁-C₆ alkylaryl, C₁-C₆ alkyl(C₃-C₁₀)cycloalkyl, C₁-C₆ alkyl-N,N-C₁-C₆ dialkylamine, C₁-C₆ alkyl-pyrrolidine, C₁-C₆ alkyl-piperidine, C₁-C₆ alkyl-morpholine or a pharmaceutically acceptable salt thereof.

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17. A compound according to Claim 16 wherein R¹ and R² are each independently H or C₁-C₂₀ alkyl.

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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 iGluR₅ receptor antagonist in combination with a pharmaceutically acceptable carrier, diluent, or excipient.

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 iGluR₅ receptor antagonist. The present invention further provides novel compounds functional as selective iGluR₅ receptor antagonists as well as compositions and formulations comprising said selective iGluR₅ receptor antagonists.

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 auténtica de la solicitud estadinense número 60/142.485 de Julio de 1999 y copia auténtica 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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Conmutador: 334 12 21-2-3-4
Fax: 281 31 25 e-mail: info@slc.gov.co
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Folio ~~259~~

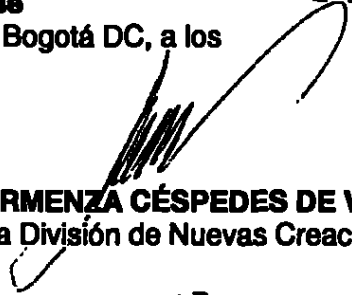
2020
Bogotá DC

Doctor
JOSE ANTONIO LLOREDA
Apoderado

REFERENCIA:	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 02 D.C. 2002


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

Bogotá, DC, 01-03-07 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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