



No. 06-099744- -00005-0000

Fecha: 2008-03-31 16:07:42 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 400 OPOSIOBSERVTER Folios: 61

FORMULARIO UNICO DE OPOSICION
2000-12

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OPOSICION A:

- | | |
|---|---|
| ☒ Patente de Invención | ☐ Marca Colectiva |
| ☐ Patente de Modelo de Utilidad | ☐ Marca de Certificación |
| ☐ Diseño Industrial | ☐ Lema Comercial |
| ☐ Esquema de Trazado para Circuitos Integrados | |
| ☐ Marcas de Productos o Servicios | |

2

**SOLICITUD
PUBLICADA**

Número del expediente: 06-099-744
Solicitante: MERZ PHARMA GMBH & CO. KGAA
Apoderado: DILIA MARÍA RODRÍGUEZ D'ALEMÁN
Título de la nueva creación o denominación del signo:
**TERAPIA EN LA QUE SE UTILIZAN DERIVADOS DEL 1-AMINO
CICLOHEXANO PARA EL TRATAMIENTO DE LOS TRASTORNOS DE
CONDUCTA ASOCIADOS CON LA ENFERMEDAD DE ALZHEIMER.**
Gaceta 584 de 28 de diciembre de 2007, número de publicación 1137.

3

OPOSICION PRESENTADA POR:

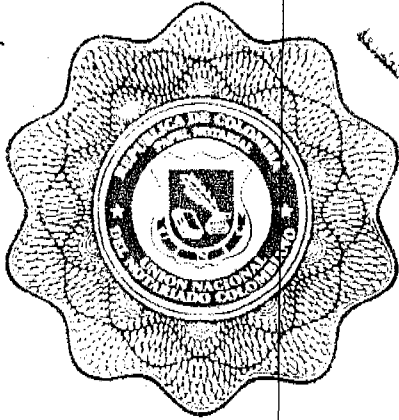
OPOSITOR	Nombre: Lafranco S.A.	IDENTIFICACION	
	Dirección: Carrera 1 No. 46-84	C.C. ☐	NIT ☒
	Teléfono: (092) 449.30.51	C.E. ☐	Otro ☐
	Fax:	Número: 890 301 463 -8	
	Domicilio: Cali - Valle		
REPRESENTANTE O APODERADO (74)	Nombre: José Luis Reyes Villamizar	IDENTIFICACION	
	Dirección: Cra. 17 No. 88-23, Of. 205	C.C. ☒	NIT ☐
	Teléfono: 621.26.31	C.E. ☐	Otro ☐
	E-mail: info@reyes-abogados.com	Número: 79'152.473 de Usaquén	
	Fax: 621.25.42	TP 44655	
	Domicilio: Bogotá, D.C.		

4

FUNDAMENTOS DE LA OPOSICION:

Causal: Incumplimiento de requisitos de patentabilidad (Título II, Capítulo I, Decisión 486 de 2000). Se violan los artículos 14, 16 (las patentes de invención deben ser nuevas, tener nivel inventivo y ser susceptibles de aplicación industrial), 18 (una invención tiene nivel inventivo si no es obvia para una persona versada en la materia) y 20 literal d).

Justificación: VER ANEXO



1658 B

AA 8567146

REPUBLICA DE COLOMBIA

NOTARIA 33 DE BOGOTA D.C.

ESCRITURA PUBLICA NUMERO: 1 6 5 8

- - MIL SEISCIENTOS CINCUENTA Y OCHO - -

FECHA DE OTORGAMIENTO: CUATRO (4) DE

JULIO - - - - -

DEL AÑO DOS MIL DOS (2002). -----

ACTO: -----

1.- PODER ESPECIAL.-----

OTORGADO POR: LAFRANCOL S.A., con Nit. No. - - -

890.301.463-8 - - - - -

a favor de: JOSE LUIS REYES VILLAMIZAR, con C.C.No.

79.152.473 de Usaquén - Bogotá.-----

DIANA BEATRIZ LOPEZ

NOTARIA TREINTA Y TRES (33) DE BOGOTA D.C.

EN LA CIUDAD DE BOGOTA, DISTRITO CAPITAL,

DEPARTAMENTO DE CUNDINAMARCA, REPUBLICA DE COLOMBIA,

ANTE MI, DIANA BEATRIZ LOPEZ, - - - - -

NOTARIA TREINTA Y TRES (33) - - - - -

DE ESTE CIRCULO SE OTORGA LA ESCRITURA PUBLICA QUE

SE CONSIGNA EN LOS SIGUIENTES TERMINOS:-----

COMPARECIO: JUAN MARIA RENDON, mayor de edad,

vecino de Bogotá, D.C, identificado con la cédula de

ciudadanía número 17.125.100 - - - - -

Expedida en Bogotá - - - - -

Y manifestó:-----

PRIMERO: Que obra en su carácter de Representante

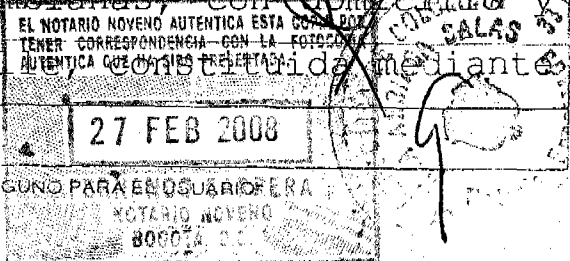
Legal de en nombre y representación de LAFRANCOL

S.A, sociedad comercial organizada y existente

conforme a las leyes colombianas, con domicilio en

sede principal en Cali - Va. constituida mediante

escritura pública número



ESTE PAPEL NO TIENE COSTO ALGUNO PARA EL OTORGANTE

De la Notaría

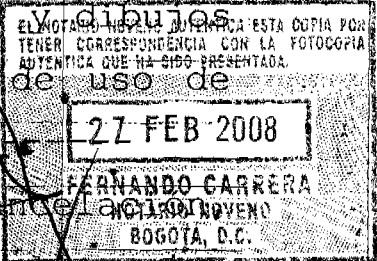
De fecha

Reformada en distintas oportunidades, según consta en el certificado expedido por la Cámara de Comercio de Cali - Valle.-----

SEGUNDO: Que en tal carácter, por este público instrumento, concede PODER ESPECIAL, PERO AMPLIO Y SUFICIENTE a **JOSE LUIS REYES VILLAMIZAR**, mayor de edad, vecino de Bogotá, D.C, identificado con la cédula de ciudadanía número 79.152.473 de Usaquén, abogado en ejercicio, portador de la T.P.No. 446 55 del C.S. de la J., domiciliado en Bogotá, D.C, República de Colombia, con dirección en la carrera 17 No. 88-23, Oficina 205, de la misma ciudad, como su representante con poder especial, amplio y suficiente, para obtener la protección los derechos de propiedad industrial y de libre competencia de Lafrancol S.A., a cuyo efecto lo autorizo, par que nos represente ante cualesquiera entidad o persona, ejerza o no jurisdicción, especialmente ante las el orden administrativo, contencioso, administrativo y judicial, en todo lo concerniente a los siguientes asuntos:-----

a.- Obtención, formulación de observaciones y oposición a patentes de invención, modelos y dibujos industriales y el registro de licencias de uso de esos derechos.-----

b.- Las acciones de oposición, cancelación, nulidad, medidas cautelares, concesión de licencias y en general los procesos civiles, penales, administrativos o contencioso- administrativos relacionados con estos derechos u otros de diferente naturaleza, acciones y procesos que





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AA 8567152

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promueva Lafrancol S.A., o se
promuevan contra esta y.-----

c.- Para que en todos los asuntos
arriba determinados, tanto en
los términos señalados por los
artículos 42 y complementarios

de la decisión 486 de la Comunidad Andina como del
artículo 70 del C.P.C. pueda sustituir este
mandato, transigir, conciliar, admitir los hechos del
proceso, desistir, cancelar, recibir, renunciar y
ratificar los actos de agentes oficiosos y ceder a
título gratuito y/o oneroso, licenciar, inscribir
contratos de cesión y de licencia, inscripción de
prendas, levantamiento de prendas, inscribir
derechos de retención y en general todos los asuntos
que se deban tramitar ante la Superintendencia de
Industria y Comercio.-----

Manifestamos que de la veracidad de las
declaraciones del contenido y autenticidad de los
documentos anexos en éste instrumento público sólo
respondemos los comparecientes.-

EL SUSCRITO NOTARIO NOVENO HACE CONSTAR QUE
LA COPIA FOTOSTÁTICA PROCEDENTE COINCIDE
CON EL ORIGINAL QUE HA SIDO PRESENTADO
QUE FUE LEÍDA Y AUTENTICA.

HASTA AQUI LA MINUTA PRESENTADA

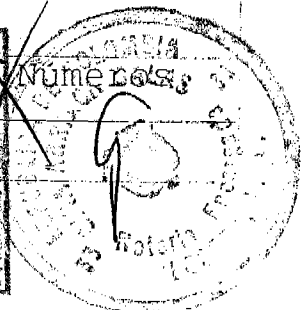
18 MAR 2008

OTORGAMIENTO Y AUTORIZACION: Leído el presente
instrumento Público por los comparecientes y
advertidos de la formalidad de su contenido, dentro
del término legal, lo hallaron conforme con sus
intenciones y lo aprobaron en todas sus partes y
firmaron junto con la Suscrita Notaria quien da fe y
lo autoriza. -----

Se utilizaron las hojas de los números

AA 8567146, 8567152.

EL NOTARIO NOVENO AUTENTICA ESTA COPIA DE
LA ORIGINAL QUE HA SIDO PRESENTADA
27 FEB 2008



ESTE PAPEL NO TIENE COSTO

DERECHOS NOTARIALES: \$ 49.600.00

RESOLUCION No. 4188 del 28 de Diciembre del 2001

Juan Maria Rendon
JUAN MARIA RENDON

C.C. No. 14.125.100 de Bogotá

LAFRANCOL S.A.

Nit. No. 890.301.463-8

TEL: 622-04-66.

ACEPTO :

Jose Luis Reyes Villamizar
JOSE LUIS REYES VILLAMIZAR

C.C. No. 99.152.473

TEL: 621-2631

EL NOTARIO NOVENO AUTENTICA ESTA COPIA POR
TENER CORRESPONDENCIA CON LA FOTOCOPIA
AUTENTICA QUE HA SIDO PRESENTADA.

27 FEB 2008

FERNANDO CARRERA
NOTARIO NOVENO
BOGOTÁ S.C.

Diana Beatriz Lopez
DIANA BEATRIZ LOPEZ

NOTARIA 33 DE BOGOTA D.C.

06 MAR 2008

REPUBLICA DE COLOMBIA
NOTARIO NOVENO
BOGOTÁ D.C.

n.c.a.

Es segunda COPIA (FOTOCOPIA)

tomada de su original que se expide conforme al

Artículo 79 del Decreto 960 de 1970 en 06

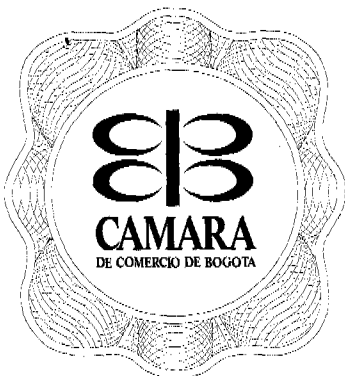
hojas útiles con destino a Jose Luis Reyes

Villamizar BOGOTÁ: Dcto. 1772/79

Santafé de Bogotá D.C. 05 JUL. 2002

Qui Alum





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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331

Hora Certificado 11:13:40

Operacion : 02C160331038

PAGINA No. 1

EN JUNIO DE ESTE AÑO SE ELEGIRÁ JUNTA DIRECTIVA Y REVISOR FISCAL DE LA CAMARA DE COMERCIO. LAS INSCRIPCIONES DE CANDIDATOS DEBEN HACERSE EN LA PRIMERA QUINCENA DE MAYO. PARA INFORMACION DETALLADA DIRIGIRSE A LA SEDE PRINCIPAL O COMUNICARSE AL TELEFONO 8861339.

CERTIFICA:

NOMBRE: LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

DOMICILIO: CALI VALLE

DIRECCION COMERCIAL : ---K 1 46 84

DIRECCION NOTIFICACION JUDICIAL: ---K 1 46 84

CIUDAD: CALI

MATRICULA MERCANTIL NRO. 5233-4 FECHA MATRICULA : 02 DE OCTUBRE DE 1958

DIRECCION ELECTRONICA : esperanzacortes@lafrancol.net

AFILIADO

CERTIFICA:

NIT : 890301463-8

CERTIFICA:

QUE POR ESCRITURA NRO. 1434 DEL 29 DE SEPTIEMBRE DE 1958 NOTARIA CUARTA DE CALI , INSCRITA EN LA CAMARA DE COMERCIO EL 02 DE OCTUBRE DE 1958 BAJO EL NRO. 18319 DEL LIBRO IX , SE CONSTITUYO LA SOCIEDAD DENOMINADA LABORATORIO FRANCO COLOMBIANO LAFRANCOL S.A.

CERTIFICA:

REFORMAS	DOCUMENTO	FECHA.DOC	ORIGEN	FECHA.INS	NRO.
INS LIBRO					
E.P.	1104	30/06/1959	NOTARIA CUARTA DE CALI	07/07/1959	
19467					
E.P.	2309	26/12/1959	NOTARIA CUARTA DE CALI	29/12/1959	
20089					
E.P.	1725	24/07/1962	NOTARIA CUARTA DE CALI	26/07/1962	
24528					
E.P.	1824	31/07/1963	NOTARIA CUARTA DE CALI	14/08/1963	
26360					

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331

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Operacion : 02C160331038

PAGINA No. 2

E.P. 2422	25/10/1963	NOTARIA CUARTA DE CALI	28/10/1963
26717			
E.P. 1720	16/09/1964	NOTARIA CUARTA DE CALI	22/09/1964
28406			
E.P. 101	31/01/1966	NOTARIA CUARTA DE CALI	01/02/1966
31039			
E.P. 552	21/03/1968	NOTARIA CUARTA DE CALI	01/04/1968
35711			
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	16/01/1973
2975 IX			
E.P. 1956	30/05/1973	NOTARIA CUARTA DE CALI	13/06/1973
4337 IX			
E.P. 4964	12/12/1972	NOTARIA CUARTA DE CALI	28/11/1973
5994 IX			
E.P. 5579	12/11/1973	NOTARIA CUARTA DE CALI	28/11/1973
5995 IX			
E.P. 4406	30/09/1974	NOTARIA CUARTA DE CALI	28/11/1974
10887 IX			
E.P. 192	03/02/1978	NOTARIA CUARTA DE CALI	14/02/1978
25355 IX			
E.P. 3479	07/09/1979	NOTARIA CUARTA DE CALI	19/09/1979
34204 IX			
E.P. 4274	12/12/1984	NOTARIA NOVENA DE CALI	19/12/1984
73088 IX			
E.P. 1155	21/05/1985	NOTARIA SEPTIMA DE CALI	03/06/1985
76917 IX			
E.P. 1553	20/06/1986	NOTARIA SEPTIMA DE CALI	08/07/1986
85997 IX			
E.P. 1458	09/06/1987	NOTARIA SEPTIMA DE CALI	24/12/1987
3508 IX			
E.P. 7222	14/12/1988	NOTARIA TERCERA DE CALI	19/12/1988
13847 IX			
E.P. 4530	04/09/1989	NOTARIA TERCERA DE CALI	07/09/1989
21508 IX			
E.P. 3865	02/08/1990	NOTARIA TERCERA DE CALI	13/08/1990
31708 IX			
E.P. 8305	13/12/1995	NOTARIA TERCERA DE CALI	23/01/1996
557 IX			
E.P. 4559	16/11/1999	NOTARIA TERCERA DE CALI	26/11/1999
7911 IX			
E.P. 6.004	02/12/2004	NOTARIA TERCERA DE CALI	14/12/2004
13371 IX			
E.P. 6241	27/12/2006	NOTARIA TERCERA DE CALI	19/01/2007
625 IX			
E.P. 389	07/02/2008	NOTARIA TERCERA DE CALI	19/02/2008
1880 IX			

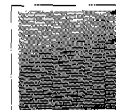
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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331

Hora Certificado 11:13:40

Operacion : 02C160331038

PAGINA No. 3

CERTIFICA:

VIGENCIA: 29 DE SEPTIEMBRE DEL AÑO 2057

CERTIFICA:

OBJETO SOCIAL. SE OCUPA EN: A) FABRICACION, DISTRIBUCION Y VENTA EN EL TERRITORIO DE LA REPUBLICA DE COLOMBIA O EN EL EXTRANJERO DE CUALESQUIERA TIPOS DE VACUNAS, PRODUCTOS QUIMICOS, FARMACEUTICOS ALIMENTICIOS FUNCIONALES, COSMETICOS Y FISIOLOGICOS, REACTIVOS, ANTIBIOTICOS PARA USO HUMANO Y VETERINARIO, PRODUCTOS DIETETICOS, COLORANTES DE PERFUMERIA Y AFINES. B) LA REPRESENTACION DE CASAS FABRICANTES NACIONALES O EXTRANJERAS DE ESTOS MISMOS PRODUCTOS. C) FABRICACION, IMPORTACION, DISTRIBUCION Y VENTA DE CUALESQUIERA TIPOS DE PRODUCTOS VETERINARIOS. D) LA REALIZACION DE TODOS LOS ACTOS, CONTRATOS, CONVENIOS, DIRECTAMENTE RELACIONADOS CON LOS FINES ANTES INDICADOS. EN DESARROLLO DE SU OBJETO SOCIAL PODRA LA SOCIEDAD ADQUIRIR Y VENDER BIENES RAICES Y MUEBLES, DARLOS Y TOMARLOS EN ARRENDAMIENTO, GARANTIZAR CON HIPOTECA SOBRE LOS BIENES RAICES O CON PRENDA SOBRE LOS BIENES MUEBLES, OBLIGACIONES A CARGO DE LA SOCIEDAD; DAR Y RECIBIR A MUTUO COMERCIAL DINERO Y CELEBRAR LOS CONTRATOS COMERCIALES DE CAMBIO EN TODAS SUS MANIFESTACIONES, FUNDAR EMPRESAS QUE TENGAN LA MISMA FINALIDAD SOCIAL O ASOCIARSE CON ELLAS.

CERTIFICA:

ORGANOS DE DIRECCION Y ADMINISTRACION: 1) ASAMBLEA GENERAL DE ACCIONISTAS; 2) JUNTA DIRECTIVA; 3) GERENCIA GENERAL. TAMBIEN TENDRA UN REVISOR FISCAL.

ADMINISTRACION: LA ADMINISTRACION INMEDIATA DE LA SOCIEDAD, SU REPRESENTACION LEGAL Y LA GESTION DE LOS NEGOCIOS SOCIALES ESTARAN A CARGO DE UN GERENTE, DESIGNADO POR LA ASAMBLEA GENERAL DE ACCIONISTAS, PARA PERIODOS DE DE DOS (2) AÑOS REELEGIBLE INDEFINIDAMENTE Y REMOVIBLE LIBREMENTE POR ELLA EN CUALQUIER TIEMPO.

PARAGRAFO PRIMERO. SUPLENTE: EL GERENTE Y REPRESENTANTE LEGAL TENDRA LOS SIGUIENTES SUPLENTE: PRIMERO, SEGUNDO Y TERCERO QUE LO REEMPLAZARAN EN LOS CASOS DE AUSENCIAS ACCIDENTAL, TEMPORAL Y ABSOLUTA CON LAS LIMITACIONES QUE MAS ADELANTE SE ESTABLECEN.

PARAGRAFO SEGUNDO. EL TERCER SUPLENTE DEL GERENTE GENERAL Y REPRESENTANTE LEGAL ESTARA LIMITADO EN SUS FUNCIONES A: COMPROMETER LOS NEGOCIOS SOCIALES EN CUANTIA NO SUPERIOR A CUATRO MIL DOSCIENTOS SALARIOS MINIMOS MENSUALES LEGALES VIGENTES (4.200 SMMMLV); CELEBRAR CONTRATOS COMERCIALES DE COMPRAVENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS, EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS SOCIALES

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IMPRESO EN COLOMBIA CAMARA DE COMERCIO DE BOGOTA

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331

Hora Certificado 11:13:40

Operacion : 02C160331038

PAGINA No. 4

CIVILES Y COMERCIALES, CUALQUIERA QUE SEA SU NATURALEZA CON FACULTADES PARA EXIGIR O SUSCRIBIR LOS DOCUMENTOS Y GARANTIAS NECESARIOS HASTA LA CUANTIA ANTES MENCIONADA.

FUNCIONES DEL GERENTE: A) ... B) EJECUTAR Y HACER CUMPLIR LOS ACUERDOS Y DECISIONES DE LA ASAMBLEA GENERAL DE ACCIONISTAS Y DE LA JUNTA DIRECTIVA Y HACER USO DE LA RAZON SOCIAL. C) REPRESENTAR LEGALMENTE A LA SOCIEDAD CONFORME A LA LEY ANTE TODAS LAS AUTORIDADES CIVILES, JUDICIALES, MILITARES, SANITARIAS, DE POLICIA, ADUANALES, POSTALES, ETC. G) LLEVAR A CABO LA GESTION COMERCIAL Y FINANCIERA. H) TENDRA LA PLENA RESPONSABILIDAD DE LA ACCION ADMINISTRATIVA, LA COORDINACION Y LA SUPERVISION GENERAL DE LA SOCIEDAD, LAS CUALES CUMPLIRA CON ARREGLO A LAS NORMAS DE LOS ESTATUTOS.

EN EL EJERCICIO DE SUS FUNCIONES, EL GERENTE PUEDE: 1.- COMPARECER EN LOS JUICIOS, TRANSIGIR Y COMPROMETER LOS NEGOCIOS SOCIALES DE CUALQUIERA NATURALEZA QUE FUEREN, INTERPONER TODO GENERO DE RECURSOS Y CONSTITUIR APODERADOS QUE LO REPRESENTEN JUDICIAL O EXTRAJUDICIALMENTE. 2.- ENAJENAR A CUALQUIER TITULO Y COMPRAR BIENES MUEBLES, CELEBRAR CONTRATOS COMERCIALES DE COMPRA Y VENTA EN GENERAL YA SEA CON LA NACION (MINISTERIOS Y DEPARTAMENTOS ADMINISTRATIVOS), ENTIDADES DESCENTRALIZADAS (ESTABLECIMIENTOS PUBLICOS), EMPRESAS INDUSTRIALES Y COMERCIALES DEL ESTADO, SOCIEDADES DE ECONOMIA MIXTA), EMPRESAS O SOCIEDADES CIVILES Y COMERCIALES CUALQUIERA QUE SEA SU NATURALEZA Y SU CUANTIA, CON AMPLIAS FACULTADES QUE EXIGIR O SUSCRIBIR LOS DOCUMENTOS, Y GARANTIAS NECESARIAS. CONTRATAR PRESTAMOS CUALQUIERA QUE SEA SU CUANTIA, CELEBRAR EL CONTRATO COMERCIAL DE MUTUO EN TODAS SUS MANIFESTACIONES Y SUSCRIBIR LOS DOCUMENTOS Y COMPROMISOS RESPECTIVOS. HACER DEPOSITOS EN BANCOS Y AGENCIAS BANCARIAS, FIRMAR CHEQUES, LETRAS, PAGARES, GIROS, LIBRANZAS Y CUALQUIER OTRO DOCUMENTO, ASI COMO NEGOCIAR ESTOS INSTRUMENTOS, TENERLOS, COBRARLOS, PAGARLOS, DESCARGARLOS, ETC.

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

GERENTE GENERAL Y REPRESENTANTE LEGAL

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

PRIMER SUPLENTE DEL GERENTE

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

*** CONTINUA ***

CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331 Hora Certificado 11:13:40

Operacion : 02C160331038 PAGINA No. 6

PRIMER RENGLON

ESTHER ISABEL VENTURA DE RENDON

C.C.38979831

SEGUNDO RENGLON

ROSA VICTORIA VENTURA DE VISBAL

C.C.38992048

TERCER RENGLON

JUAN PABLO REYES VILLAMIZAR

C.C.80419709

SUPLENTES

PRIMER RENGLON

JUAN MARIA RENDON GUTIERREZ

C.C.17125100

SEGUNDO RENGLON

ROBERTO M. VENTURA CRISPINO

C.C.9086003

TERCER RENGLON

ROBERTO S. VENTURA PAULY

C.C.16697614

CERTIFICA:

DOCUMENTO: ACTA No. 99 DEL 14 DE MARZO DE 2002

ORIGEN: ASAMBLEA GENERAL DE ACCIONISTAS

INSCRIPCION: 09 DE SEPTIEMBRE DE 2002 No. 14675 DEL LIBRO IX

FUE (RON) NOMBRADO(S):

REVISOR FISCAL

ALFREDO LOPEZ & CIA. LTDA

NIT.800026893-5

CERTIFICA:

DOCUMENTO: DOCUMENTO PRIVADO DEL 20 DE OCTUBRE DE 2006

ORIGEN: ALFREDO LOPEZ & CIA LTDA

INSCRIPCION: 07 DE NOVIEMBRE DE 2006 No. 12672 DEL LIBRO IX

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CERTIFICADO NACIONAL

CAMARA DE COMERCIO DE CALI

Fecha : 20080331

Hora Certificado 11:13:40

Operacion : 02C160331038

PAGINA No. 8

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734911- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1B NRO. 46A 121 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734908- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 1A NRO. 46A 28 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008
RENOVO : POR EL AÑO 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.369810- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: --K 1A 46 A 32 DE CALI
FECHA MATRICULA : 29 DE ABRIL DE 1994
RENOVO : POR EL AÑO 2008

CERTIFICA:

QUE A NOMBRE DE LA SOCIEDAD FIGURA MATRICULADO EN LA CAMARA DE COMERCIO BAJO
EL NRO.734913- 2 ESTABLECIMIENTO DE COMERCIO: LABORATORIO FRANCO COLOMBIANO
LAFRANCOL S.A
UBICADO EN: CRA. 3 NRO. 47 25 DE CALI
FECHA MATRICULA : 28 DE MARZO DE 2008

CERTIFICA:

QUE LA SOCIEDAD EFECTUO LA RENOVACION DE SU MATRICULA MERCANTIL EL 28 DE
MARZO DE 2008.

*** CONTINUA ***



Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. 06-089744-00045-0000

RECEIVED BY: [Signature] Date: 2021/03/01
RECEIVED BY: [Signature] Date: 2021/03/01
RECEIVED BY: [Signature] Date: 2021/03/01

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 26,130
FECHA : MARZO 31 DE 2008

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	2662647	31/03/2008	266,000.00
REYES Y REYES ABOGADOS	CONSIGNACION	BANCO DE BOGOTA	062754387	3392255	31/03/2008	266,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-04 PRESENTACION DE OBSERVACIONES	12 MARCAS Y LEMAS COMERCIALES	266,000.00
	TOTAL :	\$ 266,000.00

SON: DOSCIENTOS SESENTA Y SEIS MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No.

Carrera 13 No. 27-00 Pisos 5, 7 y 10
Conmutador 382 0840
Fax 350 5220
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

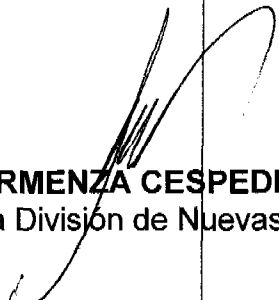
Oficio N°: 5460

ASUNTO:	Radicación PCT N°	06-99744
	Trámite	011
	Evento	379
	Actuación	440
	Folios	011

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por la doctora Eliana Isaura Moreno Bohórquez, en su calidad de apoderada de Gynopharm S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021

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Industria y Comercio
SUPERINTENDENCIA

2020
Bogotá, D.C.,

Doctora:
Dilia María Rodríguez D'Aleman
Apoderada

Oficio N°: 5470

ASUNTO:

Radicación PCT N°	06-99744
Trámite	011
Evento	379
Actuación	440
Folios	055

Con fundamento en lo previsto por el artículo 43 de la Decisión 486 de la Comisión de la Comunidad Andina, se le comunica que la oposición presentada por el doctor José Luis Reyes Villamizar, en su calidad de apoderado de Laboratorio Franco Colombiano Lafrancol S.A., reúne los requisitos formales exigidos por la ley al momento de su presentación.

En cumplimiento de lo dispuesto en la citada norma, se le concede el término de sesenta (60) días hábiles siguientes a la fecha de notificación del presente oficio, para que haga valer sus argumentaciones y presente pruebas.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior oficio fue notificado por fijación en lista de fecha, _____.

202021

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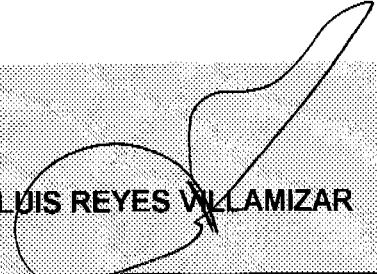
5 Comprobante de pago No. 08-26.130 (Oposición) Fecha Marzo 31 de 2008
(Prórroga) Fecha _____

6 Anexos:

- ☒ Comprobante de pago de la tasa
- ☒ Poderes, si fuere el caso
- ☒ Pruebas de los fundamentos de la oposición
- ☒ Certificado de existencia y representación legal de las partes, cuando sean personas jurídicas
- ☐ Documentos que acrediten el legítimo interés, si fuere el caso
- ☒ Copia de la oposición para el traslado al solicitante.

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NOMBRE: JOSÉ LUIS REYES VILLAMIZAR

FIRMA: 

C.C.No. 79.152.473 T.P. No. 44655

Señor

SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

E.

S.

D.

REF:

Expediente 06-099-744

TÍTULO SOLICITADO: TERAPIA EN LA QUE SE UTILIZAN DERIVADOS DEL 1-AMINO CICLOHEXANO PARA EL TRATAMIENTO DE LOS TRASTORNOS DE CONDUCTA ASOCIADOS CON LA ENFERMEDAD DE ALZHEIMER.

PUBLICACIÓN: Gaceta 584 de 28 de diciembre de 2007, número de publicación 1137.

PRIORIDAD: US 60/550,171 de 03/03/2004

SOLICITANTE: MERZ PHARMA GMBH & CO. KGAA

APODERADO: DILIA MARÍA RODRÍGUEZ D'ALEMÁN

TRÁMITE: PRESENTACIÓN DE OPOSICION ✓

JOSÉ LUIS REYES VILLAMIZAR, mayor de edad, identificado como aparece al pie de mi firma, abogado en ejercicio, titular de la tarjeta profesional número 44655 del Consejo Superior de la Judicatura, actuando como agente oficioso, en nombre de la sociedad LABORATORIO FRANCO-COLOMBIANO, LAFRANCOL S.A., de conformidad con la caución prestada, y estando dentro del plazo establecido por el artículo 42 de la Decisión 486 de 2000, muy respetuosamente me permito formular la siguiente

I. PETICIÓN

Sírvase, señor Superintendente, proceder a negar el beneficio patentario a la solicitud contenida en el expediente **06-099-744**, por incumplir los requisitos materiales de patentabilidad establecidos por el Título II, Capítulo I de la Decisión 486 de 2000. Lo anterior, con base en los argumentos, fundamentos y pruebas

que dentro del término de la prórroga de sesenta días que en la fecha he solicitado, oportunamente presentaré a ese Despacho.

Carrera 17 No. 88-23 Of. 205 Tels.: +57 1 655 7795, +57 1 621 2631, Fax: +57 1 621 2542

info@reyes-angarinos.com - Bogotá, Colombia.

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II. LEGÍTIMO INTERÉS

Asiste a LABORATORIO FRANCO COLOMBIANO S.A. – LAFRANCOL S.A. legítimo interés para presentar esta oposición, pues la eventual concesión de la solicitud restringiría, en forma contraria al Régimen Común Andino de Propiedad Industrial, el empleo de ciertas sustancias y composiciones farmacéuticas, en detrimento de sus legítimos intereses comerciales y de la libre competencia.

III. FUNDAMENTOS DE LA OPOSICIÓN

La solicitud colombiana de la referencia, que se encuentra actualmente en trámite y que se refiere a un método para tratar un trastorno de conducta asociado a la enfermedad de Alzheimer que comprende administrar una cantidad efectiva de un 1-aminociclohexano (memantina o neramexano) en combinación con una cantidad efectiva de un inhibidor de acetilcolinesterasa (Donepezil) o un antipsicótico atípico, incumple con los requisitos necesarios para otorgársele el privilegio de patente de invención, tal y como se demuestra con los siguientes argumentos:

3.1 Primero que todo, la solicitud colombiana en trámite anteriormente referenciada incurre claramente en una improcedencia de patentabilidad, ya que como se puede observar en lo expuesto en su capítulo reivindicatorio, dicha solicitud se refiere específicamente en todas sus 20 reivindicaciones, a un método de tratamiento que involucra una combinación de principios activos, lo cual es inadmisibles por lo contenido en el artículo 20 literal d) del título II capítulo I de la decisión 486 de 2000 de la Comunidad Andina de Naciones en la cual se expone claramente que *“No serán patentables: los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales.”*

3.2 En segundo lugar, y por si no fuera suficiente con que la solicitud en trámite incurra directamente en una improcedencia de patentabilidad como se expuso anteriormente, existen diversos documentos que pueden desvirtuar tanto la novedad como el nivel inventivo de lo reivindicado por dicha solicitud en trámite, veamos:

- La Publicación internacional WO 03/101458 publicada el 11 de diciembre de 2003 y titulada “A COMBINATION OF AN NMDA-ANTAGONIST AND ACETYLCHOLINE ESTERASE INHIBITORS FOR THE TREATMENT OF

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ALZHEIMER'S DISEASE" revela un tratamiento para el deterioro cognitivo leve o (MCI) y para demencia de diferentes tipos tales como la demencia tipo Alzheimer, demencia vascular, demencia con cuerpos de Lewy, demencia-SIDA y demencia frontotemporal por administración de medicamentos que tienen mecanismo de acción dual.

Uno de los grupos de medicamentos allí mencionados son los inhibidores de acetilcolinesterasa entre los que se encuentran **Donepezil**, Rivastigmina, Galantamina y tacrina y, que han sido aprobados en muchos países para el tratamiento de la enfermedad de Alzheimer leve a moderada.

Otro grupo de medicamentos revelados en la anterioridad mencionada son los antagonistas de NMDA de los cuales Memantina es el más representativo y que recientemente fue aprobado en estados Unidos para el tratamiento de la Enfermedad de Alzheimer moderada a severa.

En el documento encontramos además que, la combinación revelada en la solicitud colombiana en trámite ya había sido sugerida, así como el régimen de dosificación de Memantina y Donepezil, veamos:

The invention thus provides the combined treatment of a patient suffering from a dementia syndrome with a first component which is an acetylcholinesterase inhibitor(s) and a second component which is an NMDA antagonist. (...)

While all combinations of first and second group compounds are useful the following combinations are considered as the preferred combinations:

Memantine/Donepezil, Memantine/Galantamine, Memantine/Rivastigmine and Memantine/Tacrine. (...)

The dosage ranges for the NMDA antagonist, Memantine are 0.1mg -500mg of active ingredient pr. dosage. More preferred are 1- 50 mg and most preferred are 2 - 25 mg. Presently the preferred dosage administered is 20mg.

Presently, the dosage regime for the available acetylcholinesterase inhibitor are the following:

Tacrine 10-40 mg four times a day

Donepezil 5-10 mg per day

Rivastigmine 3-12 mg per day

Galantamine 4-24 mg per day

Además reivindica:

3. The composition according to claim 2 wherein component (a) is Donepezil.
4. The composition according to claim 1 wherein component (b) is Memantine.

Como se puede observar, esta anterioridad revela la combinación farmacéutica entre inhibidores de la acetilcolinesterasa (explícitamente donepezil) y antagonistas del receptor de NMDA (explícitamente memantina) en el tratamiento de trastornos asociados a la enfermedad de Alzheimer.; del mismo modo, se encuentra suficiente información que infiere las razones de dicha combinación, así como una descripción detallada de los rangos de dosificación de los estos principios activos dentro de la misma.

De esta manera, e irrefutablemente, puede afirmarse que la solicitud colombiana en trámite carece totalmente de novedad, puesto que toda la información y las características del método terapéutico que se reivindica, se encuentran absolutamente contenidas y descritas en el estado de la técnica.

- La publicación científica "No Interaction Of Memantine With Acetylcholinesterase Inhibitors Approved For Clinical Use¹" revela:

Abstract:

The loss of cholinergic neurons within the basal forebrain of patients with Alzheimer's disease (AD) may underlie aspects of the dementia. Excessive activation of N-methyl-D-aspartate (NMDA) receptors may underlie the degeneration of cholinergic cells. New drug therapies have been designed to either enhance cholinergic function by inhibition acetylcholinesterase (AChE), e.g. galanthamine, tetrahydroaminoacridine or donepezil, or by attenuation of NMDA receptor function, e.g. memantine. A combination of these two therapeutic approaches may be more beneficial at slowing the progression of the AD. The current study investigated whether memantine would attenuate the inhibition of AChE produced by these three drugs. The results indicate that these AChE inhibitors do not lose their therapeutic efficacy in combination with memantine. Our in vitro data suggest that the clinical combination of memantine with a reversible AChE inhibitor should be a valuable pharmacotherapeutic approach to dementia.

¹ No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use.
Autores: Wenk GL Fuente: Quack G, Moebius HJ, Danysz W, Life Sciences [Life Sci], ISSN: 0024-3205, 2000 Feb 11; Vol. 66 (12), pp. 1079-83; En: Medline - EBSCO.

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- La publicación científica "Tolerability Of Memantine In Combination With Cholinesterase Inhibitors In Dementia Therapy²" revela:

Abstract:

Memantine, a moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in dementia, including Alzheimer disease (AD). Therefore, its combination with acetylcholinesterase inhibitors (AChEIs) is anticipated. We report a postmarketing surveillance study conducted among German physicians who, during routine clinical practice, treated demented patients with memantine in combination with an AChEI. Most of the 158 surveyed patients (mean age, 74 years) were diagnosed with AD but other dementias were included. Memantine was prescribed at a wide range of daily doses (median, 20 mg/day) and was combined with donepezil for most patients (84%). Combination therapy was well tolerated for nearly all patients (98%) for an average observation period of 4 months at stable doses of both antidementia agents. No serious adverse drug reaction (ADR) was reported. No ADR or change in blood chemistry was experienced by most patients (96% and 81%, respectively); the six reported ADRs resolved without sequelae and without drug discontinuation. Global clinical status of most patients was judged as improved (54%) or stable (39%) over the observation period. These findings particularly suggest that memantine in combination with AChEIs is safe and well tolerated.

- La publicación científica "Memantine For The Treatment Of Dementia³" revela:

Abstract:

BACKGROUND: The use of cholinesterase inhibitors to correct the cholinergic deficit in patients with mild to moderate Alzheimer's disease (AD) is well established. However, the treatment is only effective in about half of the patients for whom it is prescribed. Vascular dementia may respond, at least to some extent, to these drugs (T Erkinjuntti and colleagues, Lancet 2002; 359: 1283-90). In 2002, the Committee of Proprietary Medicinal Products recommended that memantine-a drug that acts on the glutamatergic system rather than the cholinergic system-be approved by the European Commission for the treatment of moderately severe to severe AD. Clinical trials have shown some effectiveness of memantine in the treatment of vascular dementia, although it has not been approved for use in this disorder.

RECENT DEVELOPMENTS: The results of a study of the effects of memantine on moderate to severe AD have recently been published (B

² Título: Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy. Autores: Hartmann S Fuente: Möbius HJ, International Clinical Psychopharmacology [Int Clin Psychopharmacol], ISSN: 0268-1315, 2003 Mar; Vol. 18 (2), pp. 81-5; En: Medline - EBSCO

³ Título: Memantine for the treatment of dementia. Autores: Wilcock GK Fuente: Lancet Neurology [Lancet Neurol], ISSN: 1474-5442, 2003 Aug; Vol. 2 (8), pp. 503-5; En: Medline - EBSCO.

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Reisberg and colleagues, N Engl J Med 2003; 348: 1333-41). Reisberg and colleagues treated their patients for 28 weeks, assessed several outcome variables, and found that memantine reduced clinical deterioration without significant adverse effects. This study is important as memantine is the only treatment licensed for patients with more advanced AD. WHERE NEXT? Several questions about the use of memantine as a treatment for AD remain to be answered. How beneficial is memantine treatment in routine clinical practice compared with clinical trials? What is the best way to assess treatment effects? How long do the beneficial effects last? Does memantine have neuroprotective, rather than just symptomatic, effects? In addition, we need to know when to switch from cholinesterase inhibitors to memantine or when to co-prescribe memantine with cholinesterase inhibitors. The efficacy of memantine in vascular dementia also requires further investigation.

Como se puede observar, existen diversas publicaciones de carácter científico que contienen argumentos que sustentan la combinación farmacológica entre memantina e inhibidores de la acetilcolinesterasa (como donepezil), lo cual desvirtúa sin más el nivel inventivo de lo contenido en el capítulo reivindicatorio de la solicitud colombiana en trámite, específicamente lo contenido en sus reivindicaciones 1 a 3, 5 y 6.

Vale la pena aclarar que los artículos científicos aquí expuestos, representan tan solo una pequeña parte de la inmensa cantidad de información de carácter científico que se puede conseguir acerca de la relación farmacológica entre antagonistas del receptor NMDA e inhibidores de la acetilcolinesterasa para el tratamiento de enfermedades relacionadas al mismo tipo del síndrome de Alzheimer. Así mismo, es importante resaltar que si se tiene en cuenta que por separado dichos tipos de fármacos tienen a su vez un sustento científico que explica su utilidad en el tratamiento de dichos padecimientos neurodegenerativos^{4,5,6,7}, cualquier persona medianamente versada en la materia buscaría asociar en una formulación farmacéutica, cantidades terapéuticamente efectivas de dichos fármacos para el tratamiento de este tipo de trastornos.

⁴ Título: Donepezil improved the clinical state and quality of life in moderate-to-severe Alzheimer disease Fuente: ACP Journal Club. v136(2):59, March/April, 2002. AN: 00021607-200203000-00019 Reviewed SourceFeldman H, Gauthier S, Hecker J, et al., and the Donepezil MSAD Study Investigators Group. A 24-week, randomized, double-blind study of donepezil in moderate to severe Alzheimer's disease. Neurology. 2001 Aug 28;57:613-20. AbstractComplete ReferenceTable of Contents En: Evidence Based Medicine Review - EBMR.

⁵ Título: Is memantine safe and effective for Alzheimer disease? Fuente: Ebell M Evidence-Based Practice, 2003 Jul; 6 (7): 6-7, 2. (6-7, 2p) (journal article - abstract, CEU, commentary, exam questions) ISSN: 1095-4120 CINAHL AN: 2004014048 En: CINAHL Plus with Full Text

⁶ Título: Neramexane. Fuente: (eng), Drugs In R&D [Drugs R D], ISSN: 1174-5886, 2002; Vol. 3 (1), pp. 19-20; PMID: 11881523 En: Medline - EBSCO.

⁷ Título: Memantine and the amino-alkyl-cyclohexane MRZ 2/579 are moderate affinity uncompetitive NMDA receptor antagonists--in vitro characterisation. Autores: Parsons CG Fuente: Danysz W, Quack G, Amino Acids [Amino Acids], ISSN: 0939-4451, 2000; Vol. 19 (1), pp. 157-66; En: Medline - EBSCO

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- Además de lo expuesto hasta aquí, es importante resaltar que existen otras publicaciones que al igual que los artículos científicos antes expuestos, desvirtúan tanto la novedad como el nivel inventivo de la solicitud colombiana, entre ellos pueden mencionarse:
- ✓ La patente americana US 5,334,618 publicada el 02 de agosto de 1994 de título "Method of preventing NMDA receptor-mediated neuronal damage", revela el uso de memantina y antagonistas NMDA relacionados en el tratamiento de la degeneración neuronal mediada por el receptor de NMDA, en donde se incluye la enfermedad de Huntington y de Alzheimer, y desórdenes neurodegenerativos agudos y crónicos.
 - ✓ La publicación internacional WO 03/040084 publicada el 15 de mayo de 2003 de título "Unsaturated 1-amino-alkylcyclohexane NMDA, 5HT3 and neuronal nicotinic receptor antagonists", revela el uso de derivados de 1-aminoalquilciclohexano en el tratamiento de desórdenes de la ansiedad y enfermedades de Alzheimer y Parkinson;
 - ✓ La publicación internacional WO 01/98253 publicada el 27 de diciembre de 2001 de título "1-amino-alkylcyclohexanes as 5-HT3 and neuronal nicotinic receptor antagonists" revela el uso de derivados de 1-aminoalquilciclohexano en el tratamiento de la ansiedad, esquizofrenia, emesis, desórdenes de abuso de drogas y alcohol, desórdenes del apetito y depresión y enfermedad de Alzheimer y Parkinson y síndrome de Tourette.
 - ✓ La patente americana 2003/207881 publicada el 06 de noviembre de 2003 de título "2-adamantylethylamines and their use in the treatment of conditions generally associated with abnormalities in glutamatergic transmisión" revela compuestos tipo adamantanaminas útiles en el tratamiento de la enfermedad de Alzheimer, Parkinson, Huntington, demencia senil, dependencia a las drogas, demencia vascular, depresión, desorden bipolar, esquizofrenia, psicosis, desórdenes del comportamiento, entre otros.
 - ✓ La publicación internacional WO 03/039468 publicada el 15 de mayo de 2003 de título "Antimnemonic therapy for hypermemory syndromes" revela, entre otros compuestos a Memantina en dosis entre 0,1 y 5mg/día en el tratamiento de desórdenes como adicción a drogas, desorden bipolar, depresión, esquizofrenia, desórdenes de ansiedad y de personalidad.

En conclusión, la solicitud colombiana en trámite incurre, en una directa improcedencia de patentabilidad al reivindicar un método de tratamiento para trastornos del tipo Alzheimer, además carece totalmente de novedad y nivel

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inventivo, puesto que se revelan composiciones que comprenden compuestos 1-aminoalquilciclohexano (como memantina o pertenecientes a esa familia) y dicha asociación farmacológica que sustenta el método terapéutico reivindicado, ya que se había descrito de manera idéntica en el estado de la técnica, y además, existe suficiente información anterior a la solicitud colombiana, que puede conducir de manera obvia a lo contenido en el capítulo reivindicatorio de dicha solicitud en trámite.

Así las cosas, y con fundamento en los argumentos expuestos a lo largo del presente escrito, respetuosamente reitero la solicitud para que el despacho se abstenga de conceder el privilegio de patente solicitado, y ordene en consecuencia el archivo del expediente respectivo.

IV. FUNDAMENTOS DE DERECHO

Son fundamentos de derecho el Capítulo I, artículos 14, 16, 18 y 20 literal d) (Requisitos de Patentabilidad) y el artículo 42 (Oposiciones) de la Decisión 486 de 2000.

V. PRUEBAS

Ruego que se tenga como tal, sin perjuicio de las que puedan presentarse al vencimiento de la prórroga solicitada, y de aquellas que el Despacho considere oficiosamente, las siguientes:

- La Publicación internacional WO 03/101458 publicada el 11 de diciembre de 2003 y titulada "A COMBINATION OF AN NMDA-ANTAGONIST AND ACETYLCHOLINE ESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE" paginas 1 a 3, 7 y capítulo reivindicatorio.
- Abstracts de las publicaciones científicas "No Interaction Of Memantine With Acetylcholinesterase Inhibitors Approved For Clinical Use"; "Tolerability Of Memantine In Combination With Cholinesterase Inhibitors In Dementia Therapy" y "Memantine For The Treatment Of Dementia".
- La publicación internacional WO 03/040084 publicada el 15 de mayo de 2003 de título "Unsaturated 1-amino-alkylcyclohexane NMDA, 5HT3 and neuronal nicotinic receptor antagonists", portada y capítulo reivindicatorio.

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- La publicación internacional WO 01/98253 publicada el 27 de diciembre de 2001 de título "1-amino-alkylcyclohexanes as 5-HT3 and neuronal nicotinic receptor antagonists", portada y capítulo reivindicatorio.
- La patente americana 2003/207881 publicada el 06 de noviembre de 2003 de título "2-adamantylethylamines and their use in the treatment of conditions generally associated with abnormalities in glutamatergic transmission", portada y capítulo reivindicatorio.
- La publicación internacional WO 03/039468 publicada el 15 de mayo de 2003 de título "Antimnemonic therapy for hypermemory syndromes" portada y capítulo reivindicatorio.

VI. ANEXOS

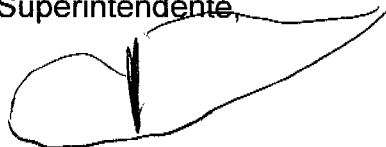
Para efectos del trámite correspondiente, me permito anexar al presente escrito los siguientes anexos:

1. Certificado de existencia y representación legal de Lafrancol S.A.
2. Poder para actuar.
3. Constancia de pago de las tasas de tramitación de oposición.
4. Copia para correr traslado al solicitante.
5. El mencionado en el acápite de pruebas.

VII. NOTIFICACIONES

El suscrito recibirá notificaciones en la secretaría de su Despacho o en mi oficina localizada en la Carrera 17 No. 88-23, Oficina 205, Fax (1) 621.25.42 de esta ciudad. Lafrancol S.A., las recibirá en sus oficinas localizadas en la Carrera 1 N° 46-84 de Cali.

Señor Superintendente,



JOSÉ LUIS REYES VILLAMIZAR

C.C. 79.152.473 de Usaquén

T.P.A. 44.655 de C.S.J.

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
11 December 2003 (11.12.2003)

PCT

(10) International Publication Number
WO 03/101458 A1

(51) International Patent Classification⁷: A61K 31/55, 31/13, A61P 25/28

(21) International Application Number: PCT/DK03/00342

(22) International Filing Date: 22 May 2003 (22.05.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
PA 2002 00844 31 May 2002 (31.05.2002) DK
60/384,467 31 May 2002 (31.05.2002) US

(71) Applicant (for all designated States except US): **H. LUNDBECK A/S** [DK/DK]; Ottiliavej 9, DK-2500 Valby-Copenhagen (DK).

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For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 03/101458 A1

(54) Title: A COMBINATION OF AN NMDA-ANTAGONIST AND ACETYLCHOLINE ESTERASE INHIBITORS FOR THE TREATMENT OF ALZHEIMER'S DISEASE

(57) Abstract: A pharmaceutical composition comprising (a) an effective amount of one or more of acetylcholinesterase inhibitor(s) or a pharmaceutically effective salt thereof and (b) an effective amount of one or more NMDA-antagonist(s).

A combination of an NMDA-antagonist and acetylcholine esterase inhibitors for the treatment of Alzheimer's disease.

- 5 The present invention provides a treatment for mild cognitive impairment (MCI) and for dementia of different types such as dementia of Alzheimer's type, vascular dementia, Lewy body dementia, AIDS dementia and frontotemporal dementia by administration of medicaments having dual mechanisms of action.
- 10 Dementia of different origin are a growing problem in the world. Among the elderly, Alzheimer's disease is the most common type of dementia. The prevalence of the disease raises from 2% of the people aged 65-70 to as high as 20% of the people aged 80 and older. Though perhaps not the only contributing factor, the increased life expectancy and the increased elderly population explains the raise in the frequency of
- 15 the disease.

Alzheimer's disease is a slowly progressing neurodegenerative disease characterised by significant loss of function in more than one cognitive domain. Associated diseases such as psychiatric illness and change in behaviour or personality are common.

20

- Presently, the disease cannot be cured. Current treatment gives for some patients a delay in the symptoms, for others a modest cognitive improvement and a dramatic improvement in only a small number of patients. A slower progression of the disease is also desirable for improving the life quality for the patient and the patient's
- 25 relatives. However, experience with the current treatment with Alzheimer's therapy, still 30% of the patients do not respond to the treatment. Consequently, a great need for improvement in the treatment of Alzheimer's disease exists.

- The mechanisms behind the different types of dementia, including Alzheimer's
- 30 disease, are not fully understood. Of medicaments available for treatment, which presently is only slowing the progression of the disease, they represent different mechanisms of action in the central nervous system.

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One group of medicaments are represented by the acetylcholinesterase inhibitors, of which medicaments like Donepezil, Rivastigmine, Galantamine and Tacrine are pharmaceuticals having this particular activity. The acetylcholinesterase inhibitors are presently approved in many countries for treatment of mild to moderate Alzheimer's disease.

Another group of medicaments are the NMDA antagonist of which Memantine is a representative. Memantine was recently approved in the EU for treatment of moderate severe to severe Alzheimer's disease.

Though of very different mechanisms of action, both types of medicaments are useful in the treatment of Alzheimer's disease, though in different stages of the disease progression.

The invention thus provides the combined treatment of a patient suffering from a dementia syndrome with a first component which is an acetylcholinesterase inhibitor(s) and a second component which is an NMDA antagonist.

The invention also provides a pharmaceutical composition which comprises a first component which is an acetylcholinesterase inhibitor(s) and a second component which is an NMDA antagonist.

The acetylcholinesterase inhibitors include, but are not limited to:

Donepezil, a known compound described in EP 296560 and US 4895841.

Galantamines use in the treatment of Alzheimer's disease is described in EP236684 and US 4663318.

Rivastigmine as described in national applications corresponding to US 5602176 and GB 2203040.

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Tacrine as used in the treatment of cholinergic deficit state, such as Alzheimer's disease, is described in EP 328535 and US 4816456.

Similarly, when the invention is regarded in its broadest sense, the second component is a compound which functions as an NMDA antagonist or partial antagonist of which
5 assays like Ebert et. al *European Journal of Pharmacology* **1997**, 333, 99-104 exists for determining this activity. Other compounds than the compounds mentioned here have the desired effect. It is intended to include compounds which show antagonism in the assay described above.

10 In the present invention, the combination of one compound of the group of acetylcholinesterase inhibitors with one compound of the group of NMDA antagonist is included. Likewise, the combination of two compounds of the first group with one or two or the compounds selected from the second group is also within the present invention and *vice versa*.

15 While all combinations of first and second group compounds are useful the following combinations are considered as the preferred combinations:

Memantine/Donepezil, Memantine/Galantamine, Memantine/Rivastigmine and
20 Memantine/Tacrine.

Where the compounds exists as different polymorphs, isomers, enantiomers or tautomers the present invention also embraces these variations as well as different salts or solvates etc.

25 Active metabolites of the compounds described are also embraced by the invention.

Alzheimer's Disease

30 Characteristics of Alzheimer's Disease are some of the following symptoms occurring:

- Dementia

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Title:

Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy.

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MeSH Terms:

Phenylcarbamates*
Cholinesterase Inhibitors/*therapeutic use
Dementia/*drug therapy
Excitatory Amino Acid Antagonists/*adverse effects
Memantine/*adverse effects
Adult; Aged; Aged, 80 and over; Carbamates/administration & dosage; Carbamates/therapeutic use; Cholinesterase Inhibitors/administration & dosage; Dose-Response Relationship, Drug; Drug Therapy, Combination; Excitatory Amino Acid Antagonists/administration & dosage; Excitatory Amino Acid Antagonists/therapeutic use; Humans; Indans/administration & dosage; Indans/therapeutic use; Memantine/administration & dosage; Memantine/therapeutic use; Middle Aged; Piperidines/administration & dosage; Piperidines/therapeutic use; Product Surveillance, Postmarketing; Questionnaires; Tacrine/administration & dosage; Tacrine/therapeutic use; Treatment Outcome

Abstract:

Memantine, a moderate-affinity, uncompetitive N-methyl-D-aspartate (NMDA) receptor antagonist, has been shown to be effective in dementia, including Alzheimer disease (AD).

Therefore, its combination with acetylcholinesterase inhibitors (AChEIs) is anticipated. We report a postmarketing surveillance study conducted among German physicians who, during routine clinical practice, treated demented patients with memantine in combination with an AChEI. Most of the 158 surveyed patients (mean age, 74 years) were diagnosed with AD but other dementias were included. Memantine was prescribed at a wide range of daily doses (median, 20 mg/day) and was combined with donepezil for most patients (84%). Combination therapy was well tolerated for nearly all patients (98%) for an average observation period of 4 months at stable doses of both antidementia agents. No serious adverse drug reaction (ADR) was reported. No ADR or change in blood chemistry was experienced by most patients (96% and 81%, respectively); the six reported ADRs resolved without sequelae and without drug discontinuation. Global clinical status of most patients was judged as improved (54%) or stable (39%) over the observation period. These findings particularly suggest that memantine in combination with AChEIs is safe and well tolerated.

CAS Registry Number:

0 (Carbamates)
0 (Cholinesterase Inhibitors)
0 (Excitatory Amino Acid Antagonists)
0 (Indans)
0 (Phenylcarbamates)
0 (Piperidines)
120011-70-3 (donepezil)
123441-03-2 (rivastigmine)
19982-08-2 (Memantine)
321-64-2 (Tacrine)

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direct=true&db=cmedm&AN=12598818&site=ehost-live](http://www.sinab.unal.edu.co:2109/login.aspx?direct=true&db=cmedm&AN=12598818&site=ehost-live)

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Tolerability of memantine in combination with cholinesterase inhibitors in dementia therapy.

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1: Life Sci. 2000 Feb 11;66(12):1079-83.

[RETRACTED] Links

No interaction of memantine with acetylcholinesterase inhibitors approved for clinical use.

Wenk GL, Quack G, Moebius HJ, Danysz W.

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The loss of cholinergic neurons within the basal forebrain of patients with Alzheimer's disease (AD) may underlie aspects of the dementia. Excessive activation of N-methyl-D-aspartate (NMDA) receptors may underlie the degeneration of cholinergic cells. New drug therapies have been designed to either enhance cholinergic function by inhibition acetylcholinesterase (AChE), e.g. galanthamine, tetrahydroaminoacridine or donepezil, or by attenuation of NMDA receptor function, e.g. memantine. A combination of these two therapeutic approaches may be more beneficial at slowing the progression of the AD. The current study investigated whether memantine would attenuate the inhibition of AChE produced by these three drugs. The results indicate that these AChE inhibitors do not lose their therapeutic efficacy in combination with memantine. Our in vitro data suggest that the clinical combination of memantine with a reversible AChE inhibitor should be a valuable pharmacotherapeutic approach to dementia.

PMID: 10737358 [PubMed - indexed for MEDLINE]

Related Links

- Co-administration of memantine has no effect on the in vitro or ex vivo determined acetylcholinesterase inhibition of donepezil in *Neuropharmacology* 2004
- Preliminary investigation of the functional effects of memantine and memantine combined with galanthamine or donepezil in *Neuropharmacology* 2007
- In vitro galanthamine-memantine co-application mechanism of beneficial effects in *Neuropharmacology* 2006
- Lack of pharmacokinetic or pharmacodynamic interaction between memantine and donepezil in *Neuropharmacology* 2007
- Changes in cerebral neurotransmitter and metabolite concentrations by acute donepezil and memantine administrations: a microdialysis study in *Neuropharmacology* 2006

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Patient Drug Information

- Memantine (Symmetrel®, Symmetrel® Syrup)**
Amantadine is used to treat Parkinson's disease and conditions similar to those of Parkinson's disease. It also is used to prevent and treat respiratory infections caused by influenza A virus.
- Donepezil (Aricept®)** Donepezil is used to treat the symptoms of Alzheimer's disease, but it does not cure the disease.
- Galantamine (Razadyne®) (formerly available as Reminyl®) (Razadyne 6ER)** Galantamine is used to treat the symptoms of Alzheimer's disease (AD), a brain disease that slowly destroys the memory and the ability to think, learn, communicate and handle daily activities. Galantamine is in a class of...

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1: Lancet Neurol. 2003 Aug;2(8):503-5.

Lancet Neurol. 2003 Aug;2(8):503-5. Links

Memantine for the treatment of dementia.**Wilcock GK.**

Department of Care of the Elderly, University of Bristol, UK. gordon.wilcock@bris.ac.uk

BACKGROUND: The use of cholinesterase inhibitors to correct the cholinergic deficit in patients with mild to moderate Alzheimer's disease (AD) is well established. However, the treatment is only effective in about half of the patients for whom it is prescribed. Vascular dementia may respond, at least to some extent, to these drugs (T Erkinjuntti and colleagues, Lancet 2002; 359: 1283-90). In 2002, the Committee of Proprietary Medicinal Products recommended that memantine—a drug that acts on the glutamatergic system rather than the cholinergic system—be approved by the European Commission for the treatment of moderately severe to severe AD. Clinical trials have shown some effectiveness of memantine in the treatment of vascular dementia, although it has not been approved for use in this disorder. **RECENT DEVELOPMENTS:** The results of a study of the effects of memantine on moderate to severe AD have recently been published (B Reisberg and colleagues, N Engl J Med 2003; 348: 1333-41). Reisberg and colleagues treated their patients for 28 weeks, assessed several outcome variables, and found that memantine reduced clinical deterioration without significant adverse effects. This study is important as memantine is the only treatment licensed for patients with more advanced AD. **WHERE NEXT?** Several questions about the use of memantine as a treatment for AD remain to be answered. How beneficial is memantine treatment in routine clinical practice compared with clinical trials? What is the best way to assess treatment effects? How long do the beneficial effects last? Does memantine have neuroprotective, rather than just symptomatic, effects? In addition, we need to know when to switch from cholinesterase inhibitors to memantine or when to co-prescribe memantine with cholinesterase inhibitors. The efficacy of memantine in vascular dementia also requires further investigation.

PMID: 12878438 [PubMed - indexed for MEDLINE]

Related Links

- Memantine for dementia.
[Cochrane Database Syst Rev. 2003]
- Efficacy and adverse effects of cholinesterase inhibitors and memantine in vascular dementia: a meta-analysis of randomised controlled trials.
- Memantine for dementia.
[Cochrane Database Syst Rev. 2004]
- The molecular basis of memantine action in Alzheimer's disease and other neurologic disorders: low-affinity, uncompetitive antagonism.
[Curr Alzheimer Res. 2005]
- Paradigm shift in NMDA receptor antagonist drug development: molecular mechanism of uncompetitive inhibition by memantine in the treatment of Alzheimer's disease and other neurologic disorders.
[Alzheimer Dis. 2004]

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Patient Drug Information

- Amantadine (Symmetrel®, Symmetrel® Syrup)
Amantadine is used to treat Parkinson's disease and conditions similar to those of Parkinson's disease. It also is used to prevent and treat respiratory infections caused by influenza A virus.
- Memantine (Namenda®, Namenda® Roche® Pak)
Memantine is used to treat the symptoms of Alzheimer's disease. Memantine is in a class of medications called NMDA receptor antagonists. It works by decreasing abnormal excitement in the brain. Memantine can help people ...

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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: UNSATURATED 1-AMINO-ALKYLCYCLOHEXANE NMDA, 5HT₃ AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS

(57) Abstract: Unsaturated 1-amino-alkylcyclohexane compounds which are systemically-active as NMDA, 5HT₃ and nicotinic receptor antagonists, pharmaceutical compositions comprising the same, method of preparation thereof, and method of treating CNS disorders which involve disturbances of glutamatergic, serotonergic, and nicotinic transmission, treating immunomodulatory disorders, and antimalaria, antitrypanosomal, anti-Borna virus, anti-HSV and anti-Hepatitis C virus activity.

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substituted 3-7-membered azacycloalkane or azacycloalkene,

- R^5 is independently selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 combines with the carbon to which it is attached and an adjacent carbon to form a double bond,
- R_p, R_q, R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R_p, R_q, R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p, R_q, R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from

cyclohexane,
cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
cyclohexa-2,4-diene, and
cyclohexa-2,5-diene,

and provided that at least one of R_p and R_q is not hydrogen and at least one of R_r and R_s is not hydrogen,

and provided that when U-Z equals cyclohexane, then at least one of

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$-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r , and R_s is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

and its optical isomers and pharmaceutically-acceptable acid or base addition salts thereof.

2. A compound as claimed in claim 1 selected from the group consisting of:

- 1-ethenyl-3,3,5,5-tetramethylcyclohexylamine;
- 2-(3,3,5,5-tetramethylcyclohexylidene)ethanamine;
- 1-amino-3,3,5-trimethyl-2-cyclohexene;
- 1,3,5,5-tetramethyl-2-cyclohexen-1-amine;
- 1-allyl-3,3,5,5-tetramethylcyclohexylamine;
- 1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanamine;
- 1-(3,3-diethyl-5,5-dimethylcyclohexylidene)-2-propanamine;
- cis*-3-vinyl-1,3,*trans*-5-trimethylcyclohexylamine;
- 2-methyl-1-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-2-propanamine;
- 1-(1-allyl-3,3,5,5-tetramethylcyclohexyl)piperidine;
- 2-(1-vinyl-3,3,5,5-tetramethylcyclohexyl)ethylamine;
- 1-[3,3,5,5-tetramethyl-1-(3-methyl-2-butenyl)cyclohexyl]piperidine;
- 1-[3,3,5,5-tetramethyl-1-(2-propynyl)cyclohexyl]piperidine;
- 2-(1,3,3,5,5-pentamethylcyclohexyl)-4-pentenylamine;
- 3-(3,3,5,5-tetramethylcyclohexylidene)propanamine;
- 2-methyl-1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanamine;
- 2-(3,3,5,5-tetramethylcyclohexylidene)propanamine;
- N-methyl-1-ethenyl-3,3,5,5-tetramethylcyclohexylamine;
- N-allyl-1,3,3,5,5-pentamethylcyclohexylamine;

and the optical isomers and pharmaceutically-acceptable acid or base addition salts thereof.

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lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,

- R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,
cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
cyclohexa-2,4-diene, and
cyclohexa-2,5-diene,

and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

its optical isomers and pharmaceutically-acceptable acid or base addition

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lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,

R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,
cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
cyclohexa-2,4-diene, and
cyclohexa-2,5-diene,

and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

its optical isomers and pharmaceutically-acceptable acid or base addition

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salts thereof, which is effective for alleviation of said condition.

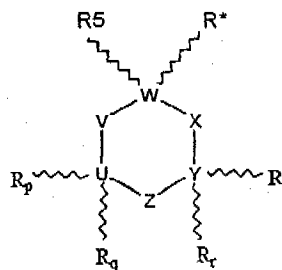
6. A method-of-treating a living animal for alleviation of a condition treatable by an NMDA antagonist selected from the group consisting of excitotoxicity selected from ischaemia during stroke, trauma, hypoxia, hypoglycemia, glaucoma, and hepatic encephalopathy,

chronic neurodegenerative diseases selected from Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-neurodegeneration, olivopontocerebellar atrophy, Tourette's syndrome, motor neurone disease, mitochondrial dysfunction, Korsakoff syndrome, and Creutzfeldt-Jakob disease,

other disorders related to long term plastic changes in the central nervous system selected from chronic pain, drug tolerance, dependence and addiction (e.g., opioids, cocaine, benzodiazepines, nicotine, and alcohol), and

epilepsy, tardive dyskinesia, L-DOPA-induced dyskinesia, schizophrenia, anxiety, depression, acute pain, spasticity, and tinnitus,

comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

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- R^* is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ or } 2$,
- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,

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- $n+m = 0, 1, \text{ or } 2,$
- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,

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- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,

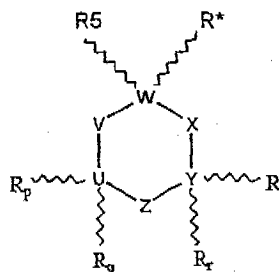
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cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
cyclohexa-2,4-diene, and
cyclohexa-2,5-diene,

and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

its optical isomers and pharmaceutically-acceptable acid or base addition salts thereof, which is effective for alleviation of said condition.

9. A method-of-treating a living animal for alleviation of a condition treatable by a $5HT_3$ antagonist selected from the group consisting of anxiety disorders, depressive disorders, Schizophrenia and treatment related psychosis, drug and alcohol abuse disorders, cognitive disorders, Alzheimer's disease, Parkinson's disease, cerebellar tremor, migraine, appetite disorders, inflammatory bowel syndrome (IBS), and emesis, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

- R^* is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,

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- $n + m = 0, 1, \text{ or } 2,$
- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5 , R_p , R_q , R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5 , R_p , R_q , R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p , R_q , R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,

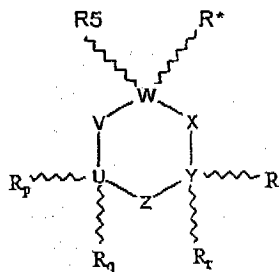
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cyclohex-3-ene,
 cyclohexa-1,3-diene,
 cyclohexa-1,4-diene,
 cyclohexa-1,5-diene,
 cyclohexa-2,4-diene, and
 cyclohexa-2,5-diene,

and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

its optical isomers and pharmaceutically-acceptable acid or base addition salts thereof, which is effective for alleviation of said condition.

10. A method-of-treating a living animal for alleviation of a condition treatable by a neuronal nicotinic receptor antagonist selected from the group consisting of Tourette's syndrome, anxiety disorders, Schizophrenia, drug abuse, nicotine abuse, cocaine abuse, dyskinesia (Morbus Huntington, L-DOPA-induced), attention deficit hyperactivity disorder (ADHD), Alzheimer's disease, Parkinson's disease, and pain, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

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- R^* is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ or } 2$,
- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6),
- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-6} alkyl- and/or C_{2-6} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5, R_p, R_q, R_r , and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_6), linear or branched lower alkenyl (C_2-C_6), and linear or branched lower alkynyl (C_2-C_6), or R^5, R_p, R_q, R_r , and R_s independently may combine with the carbon to which it is attached and an adjacent carbon to form a double bond, or R_p, R_q, R_r , and R_s independently may form a double bond with U or with Y to which it is attached,

provided that U-V-W-X-Y-Z is selected from:

cyclohexane,

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(54) Title: 1-AMINO-ALKYLCYCLOHEXANES AS 5-HT₃ AND NEURONAL NICOTINICRECEPTOR ANTAGONISTS

(57) Abstract: Certain 1-aminoalkylcyclohexanes are systematically-active 5HT₃ and nicotinic receptor antagonists and are useful in the inhibition of progression of or alleviation of conditions resulting from disturbances of serotonergic or nicotinic transmission giving them a wide range of utility in the treatment of CNS-disorders. Pharmaceutical compositions thereof for such purpose and method of making same, as well as a method-of-treating conditions which are alleviated by the employment of a 5HT₃ or neuronal nicotinic receptor antagonist.

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R⁵, R⁶ and R⁷ is ethyl.

5. A method of claim 1 wherein R⁵ is propyl.

5 6. A method of any one of claims 1 to 3 wherein R⁶ or R⁷ is methyl.

7. A method of any one of claims 2 to 6 wherein R⁸ and R⁹ together represent a C₄ or C₅ alkylene group.

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8. A method of claim 1 wherein the compound is selected from

- 1-Amino-1,3,3,5,5-pentamethylcyclohexane,
15 1-Amino-1-propyl-3,3,5,5-tetramethylcyclohexane,
1-Amino-1,3,3,5(trans)-tetramethylcyclohexane (axial amino group),
1-Amino-1,3,5,5-tetramethyl-3-ethylcyclohexane (mixture of diastereomers),
20 1-Amino-1,3,5-trimethylcyclohexane (mixture of diastereomers),
1-Amino-1,3-dimethyl-3-propylcyclohexane (mixture of diastereomers),
1-Amino-1,3(trans),5(trans)-trimethyl-3(cis)-propyl-
25 cyclohexane,
1-Amino-1,3-dimethyl-3-ethylcyclohexane,
1-Amino-1,3,3-trimethylcyclohexane,
1-Amino-1,3(trans)-dimethylcyclohexane,
1-Amino-1-methyl-3(trans)propylcyclohexane,
30 1-Amino-1-methyl-3(trans)ethylcyclohexane,
1-Amino-1,3,3-trimethyl-5(cis)ethylcyclohexane,
1-Amino-1,3,3-trimethyl-5(trans)ethylcyclohexane,
N-methyl-1-Amino-1,3,3,5,5-pentamethylcyclohexane,
1-Amino-1-methylcyclohexane,
35 N, N-dimethyl-1-amino-1,3,3,5,5-pentamethylcyclohexane,
1-Amino-1,5,5-trimethyl-3(cis)-isopropyl-cyclohexane,
1-Amino-1,5,5-trimethyl-3(trans)-isopropyl-cyclohexane,

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1-Amino-1-methyl-3(cis)-ethyl-cyclohexane,
1-Amino-1-methyl-3(cis)-methyl-cyclohexane,
1-Amino-5,5-diethyl-1,3,3-trimethyl-cyclohexane, and
N-(1,3,3,5,5-pentamethylcyclohexyl) pyrrolidine, and
5 optical isomers, enantiomers, hydrates and
pharmaceutically acceptable salts of any of the
foregoing.

9. A method of any one of claims 1 to 8 wherein the
10 condition alleviated or inhibited is selected from
emesis, anxiety disorders, schizophrenia, drug and
alcohol abuse disorders, depressive disorders, cognitive
disorders, Alzheimer's disease, cerebella tremor,
Parkinson's disease, Tourette's syndrome, pain and
15 appetite disorders.

10. A method of any one of claims 1 to 9 wherein the
compound is administered in the form of a pharmaceutical
composition comprising the compound in combination with
20 one or more pharmaceutically acceptable diluents,
excipients or carriers.

11. Use of a 1-aminoalkylcyclohexane as defined in any
one of claims 1 to 8, including the optical isomers,
25 enantiomers, hydrates thereof, and pharmaceutically
acceptable salts in the manufacture of a medicament to
treat a living animal for inhibition of progression of
or for alleviation of a condition which is alleviated by
a 5HT₂ or neuronal nicotinic receptor antagonist.

12. A 1-aminoalkylcyclohexane as defined in any one of
claims 1 to 8, including the optical isomers,
enantiomers, hydrates thereof, and pharmaceutically
acceptable salts for use in treating a condition which
35 is alleviated by a 5HT₂ or neuronal nicotinic receptor
antagonist.

the percentage of animals in groups of $n=8$ animals showing PCP related behaviours scored.

[0183] FIG. 2 shows the behavioural profile of Example 1. The compound of Example 1 was administered intraperitoneally at doses of 10, 20, 40 and 80 mg/kg 20 min prior to test and the percentage of animals in groups of $n=8$ animals showing PCP related behaviours scored.

[0184] FIG. 3 shows the behavioural profile of ketamine. Ketamine was administered intraperitoneally at doses of 10, 20, 40 and 80 mg/kg twenty minutes prior to test and the percentage of animals in groups of $n=8$ animals showing PCP related behaviours scored.

[0185] The data in FIG. 2 show that surprisingly, despite having similar in vitro binding potency to memantine, the compound of Example 1 shows no tendency to elicit "PCP syndrome" (see FIG. 2).

[0186] Comparisons of side effect liability were made using these behavioural ratings after the administration of doses of compound that were equally effective as analgesics (see FIGS. 4 to 6).

[0187] IV. Assessment of Analgesia

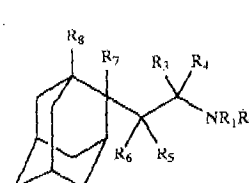
[0188] Analgesia testing was performed in male Sprague Dawley rats weighing 200-250 g. Drugs were administered 20 minutes prior to a sub-plantar injection of formalin into the right hind paw. The characteristic nociceptive behavioural responses elicited by this injection were rated on a scale from "0"=no effect through to "3"=effect of maximal intensity. As with side effect ratings, all observations were made blind to treatment condition. Ratings of nociception related behaviours were made in two time periods, one from the time of injection for a further five minutes ($t=0$ to $t=5$ min), and a second from $t=5$ min to $t=30$ min. The response to formalin injection in this model is biphasic, the first phase occurring during the first five minutes consists of a primary inflammation related response. The second phase, occurring over the subsequent 30 minutes is a delayed phase in which the phenomenon of "wind up" or neurally mediated hyperalgesia, is thought to occur. It is the second phase of response that has relevance to sciatica, diabetic neuropathy and other neuropathic chronic pain states. Responses to test compounds were assessed during this second phase from $t=5$ min to $t=30$ min. Data were analysed by means of Median tests followed by post hoc Bonferroni corrected Mann-Whitney U-tests. Data for test compounds are presented in FIGS. 4-6.

[0189] FIG. 4 shows the effect of memantine (5, 10 and 20 mg/kg) on the nociception related behaviours associated with sub-plantar injection of formalin into the rat hind paw. Memantine was effective over a dose range of 10 to 20 mg/kg, with a minimum effective dose of 10 mg/kg.

[0190] FIG. 5 shows the effect of Example 1 (10, 20 and 40 mg/kg) on the nociception related behaviours associated with sub-plantar injection of formalin into the rat hind paw. Example 1 was effective over a dose range of 20 to 40 mg/kg, with a minimum effective dose of 20 mg/kg.

[0191] FIG. 6 shows the effect of ketamine (5, 10 and 20 mg/kg) on the nociception related behaviours associated with sub-plantar injection of formalin into the rat hind paw. Ketamine showed a minimum effective dose of 20 mg/kg.

1. The use of a compound of formula (1):



wherein

R_1, R_2, R_3, R_4, R_5 and R_6 are independently selected from hydrogen, alkyl, aryl and non-aromatic heterocyclic groups, or each of one or more pair(s) of the substituent groups R_1 to R_6 may together form a 3, 4, 5, 6, 7 or 8-membered ring containing 0, 1 or 2 heteroatom(s);

R_7 is selected from alkyl, aryl and non-aromatic heterocyclic groups; and

R_8 is selected from hydrogen, halogen, alkyl, aryl and non-aromatic heterocyclic groups;

and pharmaceutically acceptable salts and prodrugs thereof, in the manufacture of a medicament for use in the treatment of a condition generally associated with abnormalities in glutamatergic transmission.

2. A use according to claim 1 wherein R_8 is selected from hydrogen, alkyl, aryl and non-aromatic heterocyclic groups.

3. A use according to claim 1 wherein R_1, R_2, R_3, R_4, R_5 and R_6 are independently selected from hydrogen, alkyl and aryl, or each of one or more pair(s) of the substituent groups R_1 to R_6 may together form a 3, 4, 5, 6, 7 or 8-membered ring containing 0, 1 or 2 heteroatom(s);

R_7 is selected from alkyl and aryl; and

R_8 is selected from hydrogen, halogen, alkyl and aryl.

4. A use according to claim 3 wherein R_8 is selected from hydrogen, alkyl and aryl.

5. A use according to claim 1 wherein R_1 to R_6 and R_8 are independently selected from hydrogen and alkyl.

6. A use according to claim 1 wherein R_1 to R_6 and R_8 are independently selected from lower alkyl.

7. A use according to claim 1 wherein R_1 to R_6 and R_8 are independently selected from acyclic lower alkyl.

8. A use according to any preceding claim wherein one or both of R_1 and R_2 is selected from hydrogen and methyl.

9. A use according to any preceding claim wherein one or both of R_3 and R_4 is selected from hydrogen and methyl.

10. A use according to any preceding claim wherein one or both of R_5 and R_6 is selected from hydrogen and methyl.

11. A use according to claim 1 wherein a ring formed by a pair of the substituent groups R_1 to R_6 contains 0 or 1 heteroatom(s).

12. A use according to claim 1 wherein a ring formed by a pair of the substituent groups R_1 to R_6 is saturated or partially unsaturated.

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13. A use according to claim 1 wherein a ring formed by a pair of the substituent groups R_1 to R_6 is saturated.

14. A use according to any preceding claim wherein R_7 is selected from cycloalkyl, unsubstituted acyclic alkyl, acyclic alkyl substituted by a non-aromatic heterocyclic group, aryl-substituted acyclic alkyl, aryl and non-aromatic heterocyclic groups

15. A use according to any preceding claim wherein R_7 is selected from unsubstituted acyclic alkyl, aryl-substituted acyclic alkyl and aryl.

16. A use according to any of claims 1 to 13 wherein R_7 is selected from carbocyclic aromatic group.

17. A use according to any of claims 1 to 13 where R_7 is selected from 5 and 6-membered non-aromatic heterocyclic groups.

18. A use according to any of claims 1 to 13 and 17 wherein R_7 is selected from non-aromatic heterocyclic groups containing 1 or 2 heteroatoms selected from N, O and S.

19. A use according to any of claims 1 to 13 wherein R_7 is tolyl, phenyl, methoxyphenyl or thienyl.

20. A use according to any preceding claim wherein R_8 is hydrogen.

21. A use according to claim 1 wherein the compound is selected from the group consisting of:

2-[2-(2-phenyl)adamantyl]ethylamine,

2-[2-[2-(2-thienyl)]adamantyl]ethylamine,

4-[2-[2-[2-(2-thienyl)]adamantyl]]ethylmorpholine,

1-[2-[2-[2-(2-thienyl)]adamantyl]]ethylpyrrolidine,

1-[2-[2-[2-(2-thienyl)]adamantyl]]ethylpiperidine,

N-(2-methylpropyl)-2-[2-[2-(2-thienyl)]adamantyl]ethylamine,

N-(4-methylbenzyl)-2-[2-[2-(2-thienyl)]adamantyl]ethylamine,

2-[2-[2-(4-methylphenyl)]adamantyl]ethylamine,

N-methyl-2-[2-[2-(4-methylphenyl)]adamantyl]ethylamine,

N,N-dimethyl-2-[2-[2-(4-methylphenyl)]adamantyl]ethylamine,

2-[2-(2-methyl)adamantyl]ethylamine,

2-[2-(2-benzyl)adamantyl]ethylamine,

2-[2-(2-(3-methoxyphenyl))adamantyl]ethylamine, and

1-[2-[2-(4-methylphenyl)]adamantyl]-2-propylamine.

22. A use according to claim 1 wherein the compound is 2-[2-(2-phenyl)adamantyl]ethylamine.

23. A method of treatment of a condition generally associated with abnormalities in glutamatergic transmission comprising administration to a patient in need of such treatment of a pharmaceutically effective dose of a compound of formula (1) or a pharmaceutically acceptable salt thereof as defined in any one of claims 1 to 22.

24. A use or method according to any preceding claim wherein said condition generally associated with abnormalities in glutamatergic transmission is a condition treatable by blockade of the N-methyl-D-aspartate (NMDA) receptor.

25. A use or method according to any preceding claim wherein said condition generally associated with abnormali-

ties in glutamatergic transmission is a condition in which administration of an NMDA receptor antagonist would be beneficial.

26. A use or method according to any preceding claim wherein said condition generally associated with abnormalities in glutamatergic transmission is a condition selected from ischaemic stroke, haemorrhagic stroke, subarachnoid haemorrhage, subdural haematoma, coronary artery bypass surgery, neurosurgery, traumatic brain injury, traumatic spinal injury, Alzheimer's disease, Parkinson's disease, Huntington's disease, Pick's disease, Lewy body disease, senile dementia, spongiform encephalopathies, prion-protein induced neurotoxicity, peri-natal asphyxia, demyelinating disease, multiinfarct dementia, vascular dementia, dementia pugilans, drug dependence, alcohol withdrawal, opiate withdrawal, motor neurone disease, multiple sclerosis, acute and chronic pain, cancer pain, trigeminal neuralgia, migraine, pain caused by excessive vasodilation, cluster headache, primary and secondary hyperalgesia, inflammatory pain, nociceptive pain, tabes dorsalis, phantom limb pain, spinal cord injury pain, central pain, post herpetic pain, HIV pain and diabetic neuropathy.

27. A use or method according to any of claims 1 to 25 wherein said condition generally associated with abnormalities in glutamatergic transmission is a condition selected from epilepsy, AIDS dementia, multiple system atrophy, progressive supra-nuclear palsy, Friedrich's ataxia, autism, fragile X syndrome, tuberous sclerosis, attention deficit disorder, olivio-ponto-cerebellar atrophy, cerebral palsy, drug-induced optic neuritis, peripheral neuropathy, myelopathy, ischaemic retinopathy, glaucoma, cardiac arrest, meningitis, encephalitis, depression, bi-polar disorder, schizophrenia, psychosis, behaviour disorders, impulse control disorders, pre-eclampsia, neuroleptic malignant syndrome, chronic fatigue syndrome, anorexia nervosa, anxiety disorders, generalised anxiety disorder, panic disorder, phobias, fresh water drowning and decompression.

28. A use or method according to any of claims 1 to 25 wherein said condition is neuropathic pain or vasodilatory headache.

29. A use or method according to any of claims 1 to 28 wherein said treatment is the reduction or prevention of the progression of said condition.

30. A use or method according to claim 29 wherein said condition is a neurodegenerative disorder.

31. Per se, a compound as set out in any one of claims 1 to 22 and pharmaceutically acceptable salts and prodrugs thereof, other than compounds wherein R_7 is 3-aminopropyl.

32. A compound as defined in claim 31 other than compounds wherein R_7 is an alkyl group substituted by a substituent other than one selected from aryl and non-aromatic heterocycles.

33. A compound as defined in claim 31 or 32 wherein R_7 is selected from cycloalkyl, unsubstituted acyclic alkyl, acyclic alkyl substituted by a non-aromatic heterocyclic group, acyclic alkyl substituted by aryl, aryl and a non-aromatic heterocyclic group.

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(54) Title: ANTIMNEMONIC THERAPY FOR HYPERMEMORY SYNDROMES

(57) Abstract: The present invention relates to antimnemonic therapy for the treatment of behavioral disorders such as addiction, ob-
sessive-compulsive disorder, Tourette's Syndrome, post-traumatic stress disorder (PTSD), bipolar disorder, depression, schizophre-
nia, anxiety disorders and personality disorders. Antimnemonic therapy may involve cue- or psychotherapy-induced reactivation of
memories in combination with the administration of antimnemonic drugs.