



Industria y Comercio

* S U P E R I N T E N D E N C I A

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCION

21 **EXPEDIENTE No.**

04-41831

54 **TÍTULO** Amino-Aquiciclohexanos Insaturados como antagonistas de los receptores NMDA, 5HT3 y Nicotínico Neurales

51 **CLASIFICACIÓN INTERNACIONAL** C07C 211/35, C07D 211/06
B61P 25/28 AGIK 31/13

71 **SOLICITANTE** Merz Pharma GmbH y co KGAR

DOMICILIO Frankfurt main, Alemania

74 **APODERADO** Dilia Maria Rodriguez D' Aleman

22 **BOGOTÁ, D. C.,** Mayo 6, 2004

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE
PCT
ENTRADA EN FASE NACIONAL

1) SOLICITUD DE:			
☒ Patente de invención		☐ Patente de Modelo de Utilidad	
☐ Capítulo I.		☒ Capítulo II.	
2) SOLICITANTE (71)	Nombre: MERZ PHARMA GMBH & Co. KGAA Dirección: Eckenheimer Landstrasse 100, 60318 Frankfurt Main, Alemania Nacionalidad o domicilio: Frankfurt Main, Alemania Lugar de constitución: Alemania		IDENTIFICACIÓN C.C. ☐ NIT: ☐ C.E. ☐ OTRO ☐ Cual _____ NÚMERO _____
	Teléfono: _____ Fax: _____ E. Mail: _____		
3) REPRESENTANTE APODERADO	Nombre: DILIA MARIA RODRIGUEZ D'ALEMAN Dirección: Carrera 11 N°. 93-43 Of. 404 Santafé de Bogotá D.C. Teléfono: 6350835 Fax: 6350824 E. Mail: clarkemodet@clarkemodet.com.co		IDENTIFICACIÓN C.C. ☒ NIT: ☐ C.E. ☐ OTRO ☐ NÚMERO: 41.654.882 TP: 20824 CSJ
4) INVENTOR (ES) (72)	Nombre: 1. PARSONS, Christopher, Graham, Raphael; 2. HENRICH, Markus; 3. DANSYZ, Wojciech; 4. KALVINSH, Ivars; 5. KAUSS, Valerjans; 6. JIRGENSONS, Algars. Dirección: 1. Wartbaumstrasse 38, 61130 Nidderau, Alemania; 2. Bahnhofstrasse 63, 35582 Wetzlar, Alemania; 3. Vor den Gärten 16, 61130 Nidderau, Alemania; 4. Miera 17-8, LV-2169 Salaspils, Lituania; 5. A. Deglava 108/2-36, LV-1082 Riga, Lituania; 6. Hospitalu iela 3-103, LV-1013 Riga, Lituania. Nacionalidad o Domicilio: 1. Inglés; 2. Alemán; 3. Polaco; 4. a 6 Lituanos		
5) PCT (86) Solicitud Internacional No. PCT/GB02/05038 Fecha: Noviembre 7, 2002 Publicación Internacional No. WO 03/040084 A1 Fecha: Mayo 15, 2003			
6) Título (54) <u>1-AMINO-ALQUILCICLOHEXANOS INSATURADOS COMO ANTAGONISTAS DE LOS RECEPTORES NMDA, 5HT3 Y NICOTÍNICO NEURONAL</u>			
7) Clasificación Internacional: C07C 211/40, 211/35, C07D 211/06, A6 1 P 25/28, A61 K 31/13			
8) PRIORIDAD	33) País de Origen	(32) Fecha	(31) Número de Solicitud
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	ESTADOS UNIDOS	NOV. 8, 2001	60/337,858
9) Comprobante de pago N°. 04-32.333 Fecha: Abril 22, 2004			
Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta pagina			

10)

ANEX S

☒ Comprobante de pago de la tasa de presentación de la solicitud
☐ Comprobante de pago por reivindicación de prioridad
☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona Jurídica
☐ Poderes, si fuera el caso
☐ Documento de cesión del inventor al solicitante o a su causante
☐ Declaraciones
☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
☒ Copia del examen preliminar efectuado por la IPEA
☐ De ser el caso, copia del contrato de acceso
☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
☐ De ser el caso, certificado de depósito del material biológico
☐ Arte final 12 x 12 y 6 x 6 cm
☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
☒ Otros
 1. Publicación internacional WO 03/040084 A1
 2. Formulario presentación PCT
 3. Reporte de búsqueda internacional

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA: _____

C.C. 41.654.882 de Bogotá TP 20824 CSJ

Instrucciones para el diligenciamiento del presente formulario. Ver reverso de esta página

SUPERINDUSTRIA Y COMERCIO
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Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTA
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176087-2

RECIBO OFICIAL DE CAJA : 04 - 32,333
FECHA : ABRIL 22 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CLARKE NODET Y CO. COLOMB	CONSIGNACION	BANCO POPULAR	050-00110-6	4944087	22/04/2004	3,990,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRANITES DE SOL. DE PATENTE DE IN	422,000.00
		TOTAL :	\$ 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

UNSATURATED 1-AMINO-ALKYLCYCLOHEXANE NMDA, 5HT₃ AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS**5 BACKGROUND OF THE INVENTION****1. Field of the Invention**

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 therewith, for
10 treating immunomodulatory disorders, and for treating infectious diseases.

2. Prior Art**15 *NMDA Antagonists***

Antagonism of glutamate receptors of the N-methyl-D-aspartate (NMDA) type has a potentially wide range of therapeutic applications [19]. Functional inhibition of NMDA receptors can be achieved through actions at different recognition sites such as the primary transmitter site, strychnine-insensitive glycine site (glycine_B), polyamine site, and phencyclidine site located inside the cation channel. The NMDA receptor channel blockers act in an uncompetitive "use-dependent" manner, meaning that they usually only block the channel in the open state. This use-dependence has been interpreted by many to mean that stronger
20 activation of the receptor should lead to a greater degree of antagonism. Such a mode of action has further been taken to imply that this class of antagonist may be particularly useful when overactivation of NMDA receptors can be expected, such as in epilepsy, ischaemia, and trauma. However, initial clinical experience with the selective, high affinity,
25 strongly use-dependent uncompetitive NMDA receptor antagonist (+)-5-

5 methyl-10,11-dihydro-5H-dibenzocyclohepten-5,10-imine maleate ((+)-MK-801) has been disappointing. Namely, therapeutic efficacy in epilepsy was poor while some psychotropic side effects were apparent at therapeutic doses. These observations, together with the fact that phencyclidine abusers experience similar psychotropic symptoms, has led to the conclusion that uncompetitive antagonism of NMDA receptors may not be a promising therapeutic approach.

However, the use of more elaborate electrophysiological methods indicates that there is no equality between different uncompetitive antagonists since factors such as the speed of receptor blockade (on-off kinetics) and the voltage-dependence of this effect may determine the pharmacodynamic features *in vivo*, i.e., therapeutic safety as well. Paradoxically, agents with low to moderate, rather than high, affinity may be desirable. Such findings triggered a reconsideration of the concept of uncompetitive antagonism of NMDA receptors in drug development [19, 22]. Uncompetitive NMDA receptor antagonists, such as amantadine and memantine - which fulfill the above criteria - have been used clinically for several years in the treatment of Parkinson's disease and dementia respectively, and do indeed rarely produce side effects at the therapeutic doses used in their respective indications.

In view of the above mentioned evidence, we have developed a series of novel uncompetitive NMDA receptor antagonists based on the unsaturated 1-aminoalkylcyclohexane structure. The present study was devoted to compare the NMDA receptor antagonistic properties of these unsaturated 1-aminoalkylcyclohexane derivatives in receptor-binding assays, electrophysiological experiments, one convulsion model and two models of motor impairment. The substitutions of these unsaturated 1-aminoalkylcyclohexanes are detailed in Table 6.

5-HT₃ Receptor Antagonists

5-HT₃ receptors are ligand gated ionotropic receptors permeable for cations. In man 5-HT₃ receptors show the highest density on enterochromaffin cells in the gastrointestinal mucosa, which are
5 innervated by vagal afferents and the area postrema of the brain stem, which forms the chemoreceptor trigger zone.

Since 5-HT₃ receptors not only have a high density in the area postrema but also in the hippocampal and amygdala region of the limbic system, it has been suggested that 5-HT₃ selective antagonists may have
10 psychotropic effects (Greenshaw & Silverstone, 1997).

Indeed, early animal studies suggested that the 5-HT₃ receptor antagonists, in addition to their well recognized anti-emetic use, may well be clinically useful in a number of areas. These include anxiety disorders, schizophrenia, drug and alcohol abuse disorders, depressive disorders,
15 cognitive disorders, Alzheimer's disease, cerebellar tremor, Parkinson's disease treatment-related psychosis, pain (migraine and irritable bowel syndrome), and appetite disorders.

Neuronal nicotinic receptor antagonists

20 At present, ten alpha subunits (alpha 1-10) and four beta (beta 1-4) subunits for nicotinic receptors are known. $\alpha 4\beta 2$ receptors are probably the most common in the CNS, especially in the hippocampus and striatum. They form non-selective cation channels with slowly, incompletely desensitizing currents (type II). Homomeric $\alpha 7$ receptors are
25 both pre- and postsynaptic and are found in the hippocampus, motor cortex and limbic system as well as in the peripheral autonomic nervous system. These receptors are characterized by their high Ca^{2+} permeability and fast, strongly desensitizing responses (type 1A). Changes in nicotinic receptors have been implicated in a number of diseases. These
30 include Alzheimer's disease, Parkinson's disease, Tourette's syndrome,

7

schizophrenia, drug abuse, nicotine abuse, and pain.

Based on the observation that the nicotinic agonist nicotine itself seems to have beneficial effects, drug development so far aimed at the discovery of selective nicotinic agonists.

5 On the other hand, it is unclear whether the effects of nicotinic agonists in, e.g., Tourette's syndrome and schizophrenia, are due to activation or inactivation / desensitization of neuronal nicotinic receptors.

The effects of agonists on neuronal nicotinic receptors is strongly dependent on the exposure period. Rapid reversible desensitization occurs
10 in milliseconds, rundown occurs in seconds, irreversible inactivation of $\alpha 4\beta 2$ and $\alpha 7$ containing receptors occurs in hours and their upregulation occurs within days.

In other words: the effects of nicotinic "agonists" may in fact be due to partial agonism, inactivation and/or desensitization of neuronal
15 nicotinic receptors. In turn, moderate concentrations of neuronal nicotinic receptor channel blockers could produce the same effects as reported for nicotinic agonists in the above mentioned indications.

THE PRESENT INVENTION

20 It has now been found that a range of unsaturated 1-aminoalkylcyclohexanes have pronounced and unexpected NMDA, 5HT₂, and nicotinic receptor antagonistic activity. Owing to the aforementioned property, the substances are suited for the treatment of a wide range of CNS disorders which involve disturbances of glutamatergic,
25 serotonergic, and nicotinic transmission, immunomodulatory effect, and anti-infectious diseases properties. These compounds are preferably in the form of a pharmaceutical composition thereof wherein they are present together with one or more pharmaceutically -acceptable diluents, carriers, or excipients.

30

OBJECTS OF THE INVENTION

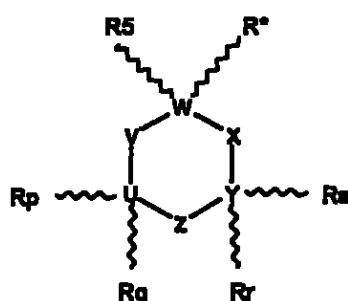
It is an object of the present invention to provide novel pharmaceutical compounds which are unsaturated 1-aminoalkyl -
 cyclohexane NMDA, 5HT₃, and nicotinic receptor antagonists and
 5 pharmaceutical compositions thereof. It is a further object of the invention to provide a novel method of treating, eliminating, alleviating, palliating, or ameliorating undesirable CNS disorders which involve disturbances of glutamatergic, serotonergic, nicotinic transmission, for treating immunomodulatory disorders, and for treating infectious diseases
 10 by employing a compound of the invention or a pharmaceutical composition containing the same. An additional object of the invention is the provision of a process for producing the unsaturated 1-aminoalkyl - cyclohexane active principles. Yet additional objects will become apparent hereinafter, and still further objects will be apparent to one
 15 skilled in the art.

SUMMARY OF THE INVENTION

What we therefore believe to be comprised by our invention may be summarized inter alia in the following words:

20

a compound selected from those of formula I:



25

wherein:

- R' is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ or } 2$,
- 5 - 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),
- 10 - 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),
- 15 - 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-
- 20 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
- 25 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
- 30 or branched lower alkenyl (C_2-C_6), and linear or branched lower

10

alkynyl (C_2-C_9), 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,

5

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

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

15

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,

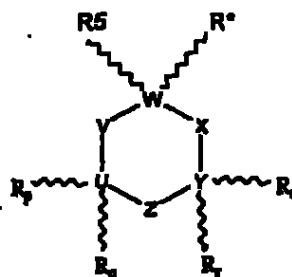
and provided that when U-Z equals cyclohexane, then at least one of
20 $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r , and R_s is linear or branched lower alkenyl (C_2-C_9) or linear or branched lower alkynyl (C_2-C_9),

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

25

a method-of-treating a living animal for alleviation of a condition treatable by a NMDA antagonist comprising the step of administering to the living animal an amount of a compound selected from those of formula I:

11



wherein:

- 5 - R^6 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
10 alkyl (C_1-C_9), linear or branched lower alkenyl (C_2-C_9), and linear or
 branched lower alkynyl (C_2-C_9),
- R^1 and R^2 are independently selected from the group consisting of
15 hydrogen, linear or branched lower alkyl (C_1-C_9), linear or branched
 lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9),
- R^3 and R^4 are independently selected from the group consisting of
20 hydrogen, linear or branched lower alkyl (C_1-C_9), linear or branched
 lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9),
 or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together
 with the N form an optionally C_{1-9} alkyl- and/or C_{2-9} alkenyl-
 substituted 3-7-membered azacycloalkane or azacycloalkene,
- 25 - 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_9), linear
 or branched lower alkenyl (C_2-C_9), and linear or branched lower

alkynyl (C_2-C_9), 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,

5

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

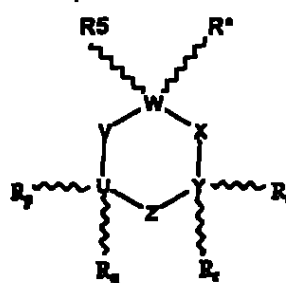
cyclohexane,
cyclohex-1-ene,
10 cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,
cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
15 cyclohexa-2,4-diene, and
cyclohexa-2,5-diene,

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_9) or linear or branched lower alkynyl (C_2-C_9),

20

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

25 a method-of-treating a living animal for alleviation of a condition wherein the compound is selected for its immunomodulatory, anti-malarial, anti-Borna virus, or anti-Hepatitis C, anti-trypanosomal, and anti HSV efficacy, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

- 5 - R^7 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
10 alkyl (C_1-C_8), linear or branched lower alkenyl (C_2-C_8), and linear or
 branched lower alkynyl (C_2-C_8),
- R^1 and R^2 are independently selected from the group consisting of
 hydrogen, linear or branched lower alkyl (C_1-C_8), linear or branched
15 lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8),
- R^3 and R^4 are independently selected from the group consisting of
 hydrogen, linear or branched lower alkyl (C_1-C_8), linear or branched
 lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8),
20 or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together
 with the N form an optionally C_{1-8} alkyl- and/or C_{2-8} alkenyl-
 substituted 3-7-membered azacycloalkane or azacycloalkene,
- R^5 , R_6 , R_7 , R_8 , and R_9 are independently selected from the group
25 consisting of hydrogen, linear or branched lower alkyl (C_1-C_8), linear
 or branched lower alkenyl (C_2-C_8), and linear or branched lower

alkynyl (C_2-C_9), 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,

5

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

cyclohexane,
cyclohex-1-ene,
10 cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,
cyclohexa-1,4-diene,
cyclohexa-1,5-diene,
15 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_9) or linear or branched lower alkynyl (C_2-C_9),

20

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

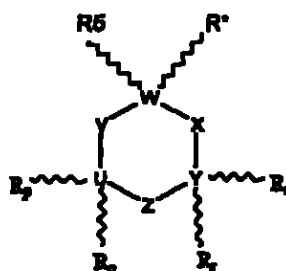
25 a method-of-treating a living animal for alleviation of a condition treatable by an NMDA antagonist selected from the group consisting of excitotoxicity selected from ischaemia during stroke, trauma, hypoxia, hypoglycemia, glaucoma, and hepatic encephalopathy,

chronic neurodegenerative diseases selected from Alzheimer's
30 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,

5 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,
10 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:



15

wherein:

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

20 - $n+m = 0, 1, \text{ or } 2$,

- 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),

25

- 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),

- 5 - 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,
- 10 - 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,
- 15

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

20

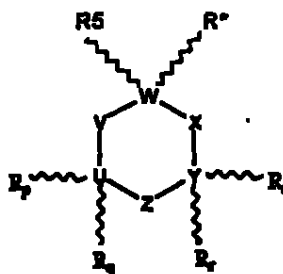
cyclohexane,
 cyclohex-1-ene,
 cyclohex-2-ene,
 cyclohex-3-ene,
 cyclohexa-1,3-diene,
 cyclohexa-1,4-diene,
 cyclohexa-1,5-diene,
 cyclohexa-2,4-diene, and
 cyclohexa-2,5-diene,

30

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),

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

- a method-of-treating a living animal for alleviation of a condition treatable by a $5HT_3$ receptor antagonist, comprising the step of
10 administering to the living animal an amount of a compound selected from those of formula I:



- 15 wherein:

- R^1 is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ or } 2$,
- 20 - 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),
- 25 - 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_9), and linear or branched lower alkynyl (C_2-C_9),

- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-9} alkyl- and/or C_{2-9} 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_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9), 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,

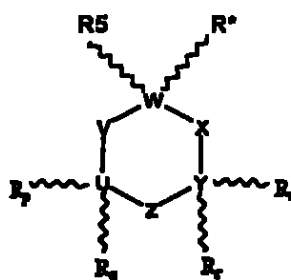
and provided that when U-Z equals cyclohexane, then at least one of

19

$-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_6 , R_7 , R_8 is linear or branched lower alkenyl (C_2-C_8) or linear or branched lower alkynyl (C_2-C_8).

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

a method-of-treating a living animal for alleviation of a condition treatable by a neuronal nicotinic receptor antagonist, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

15

- R^6 is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,

- $n+m = 0, 1, \text{ or } 2$,

20

- A is selected from the group consisting of linear or branched lower alkyl (C_1-C_8), linear or branched lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8),

25

- R^1 and R^2 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_8), linear or branched lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8),

20 20

- R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_8), linear or branched lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-8} alkyl- and/or C_{2-8} 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_8), linear or branched lower alkenyl (C_2-C_8), and linear or branched lower alkynyl (C_2-C_8), 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,

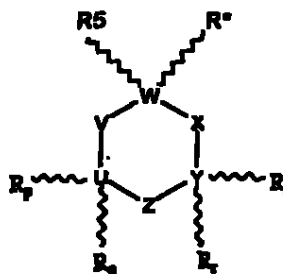
and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl

(C₂-C₆) or linear or branched lower alkynyl (C₂-C₆),

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

5

a method-of-treating a living animal for alleviation of a condition treatable by a 5HT₂ antagonist selected from the group consisting of anxiety disorders, depressive disorders, Schizophrenia and treatment related psychosis, drug and alcohol abuse disorders, cognitive disorders, 10 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:



15

wherein:

- R' is -(A)_n-(CR¹R²)_m-NR³R⁴,

20 - n+m = 0, 1, or 2,

- A is selected from the group consisting of linear or branched lower alkyl (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower alkynyl (C₂-C₆),

25

- R¹ and R² are independently selected from the group consisting of

hydrogen, linear or branched lower alkyl (C_1-C_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9),

- 5 - R^3 and R^4 are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C_1-C_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-9} alkyl- and/or C_{2-9} alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- 10 - 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_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9), or R^5 , R_p , R_q , R_r , and R_s independently may
- 15 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:

20

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

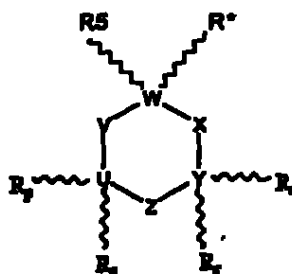
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23
23

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),

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

- 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:
- 15



wherein:

- 20 - R^1 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),
- 25

- 5
- 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,

20

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

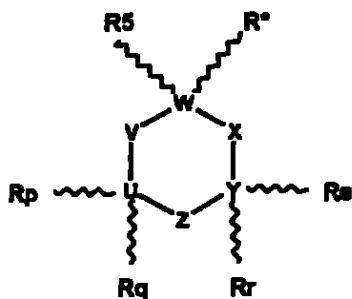
- 25
- cyclohexane,
 - cyclohex-1-ene,
 - cyclohex-2-ene,
 - cyclohex-3-ene,
 - cyclohexa-1,3-diene,
 - cyclohexa-1,4-diene,
 - cyclohexa-1,5-diene,
 - 30 cyclohexa-2,4-diene, and

cyclohexa-2,5-diene,

- and provided that when U-Z equals cyclohexane, then at least one of
 -(A)_n-(CR¹R²)_m-, R³, R⁴, R⁵, R_p, R_q, R_r is linear or branched lower alkenyl
 5 (C₂-C₈) or linear or branched lower alkynyl (C₂-C₈),

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

- 10 use of a compound of Formula I as defined in connection with the
 foregoing methods and its optical isomers and pharmaceutically -
 acceptable acid or base addition salts thereof in the manufacture of a
 medicament for use in any such method; and
- 15 a pharmaceutical composition having a compound selected from
 those of formula I:



- 20 wherein:

- R¹ is -(A)_n-(CR¹R²)_m-NR³R⁴,
- n+m = 0, 1, or 2,

26

- A is selected from the group consisting of linear or branched lower alkyl (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower alkynyl (C₂-C₆),
- 5 - R¹ and R² are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower alkynyl (C₂-C₆),
- R³ and R⁴ are independently selected from the group consisting of
10 hydrogen, linear or branched lower alkyl (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower alkynyl (C₂-C₆), or together form alkylene (C₂-C₁₀) or alkenylene (C₂-C₁₀) or together with the N form an optionally C₁₋₆ alkyl- and/or C₂₋₆ alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- 15 - R⁵ is independently selected from the group consisting of linear or branched lower alkyl (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower alkynyl (C₂-C₆), or R⁵ combines with the carbon to which it is attached and an adjacent carbon to
20 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 (C₁-C₆), linear or branched lower alkenyl (C₂-C₆), and linear or branched lower
25 alkynyl (C₂-C₆), 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,

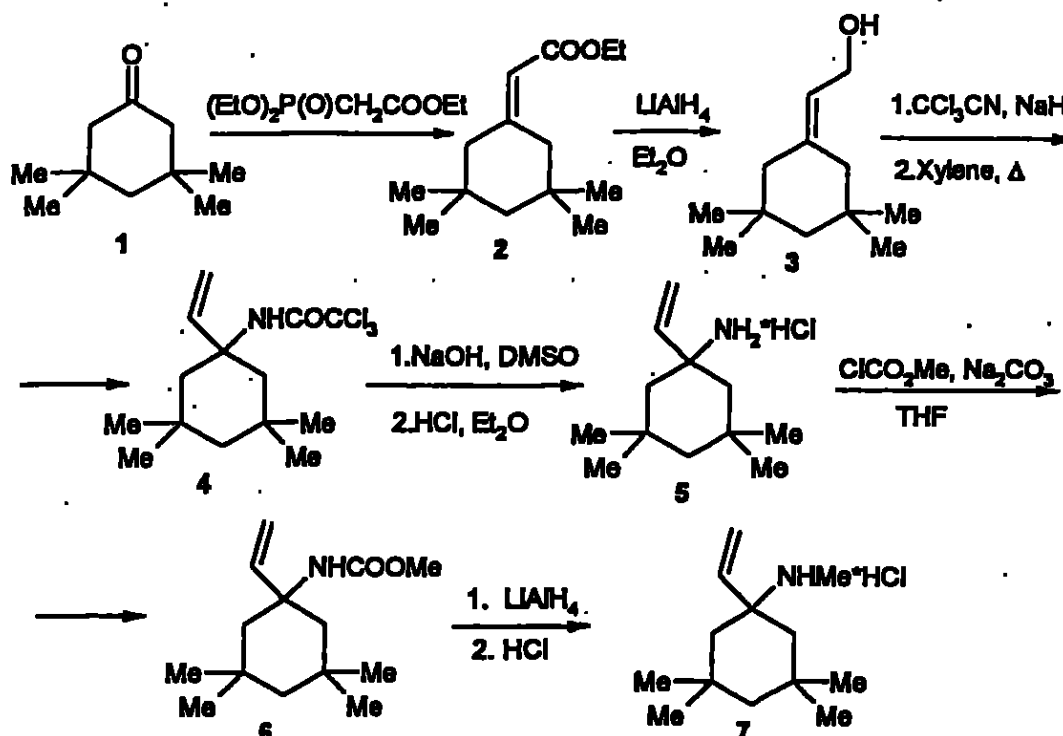
and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r , and R_s is linear or branched lower alkenyl (C_2-C_9) or linear or branched lower alkynyl (C_2-C_9),

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

in combination with one or more pharmaceutically-acceptable diluents, excipients and/or carriers.

DETAILED DESCRIPTION OF THE INVENTION

The following details and detailed Examples are given by way of illustration only, and are not to be construed as limiting.

5 Scheme: Examples 1 and 2**Example 1.**

3,3,5,5-Tetramethyl-1-vinylcyclohexanamine hydrochloride (5).

10 a) Ethyl 2-(3,3,5,5-tetramethylcyclohexylidene)acetate (2).

To a stirred solution of triethyl phosphonoacetate (49.32 g, 222 mmol) in dry THF (180 ml) under argon NaH (8.8 g, 222 mmol, 60% suspension in mineral oil) was added in small portions while cooling with ice water.

Stirring was continued for 1 h at room temperature, then a solution of

15 3,3,5,5-tetramethylcyclohexanone (30.85 g, 200 mmol) was added over 10 min and the resulting mixture was refluxed for 22 h. It was then

29

poured onto ice (400 g) and the product was extracted with diethyl ether (4 150 ml), and the extracts dried over MgSO_4 . After solvent evaporation *in vacuo* an oily residue was distilled at 145 °C (11 mm Hg) to give 36.8 g (86%) of 2 as an oil. ^1H NMR (CDCl_3 , TMS) : 0.96 and 0.98 (total 12H, both s, 3,5- CH_3); 1.27 (3H, t, CH_3 -ethyl); 1.33 (2H, m, 4- CH_2); 1.95 and 2.65 (total 4H, both s, 2,6- CH_2); 4.14 (2H, q, CH_2 -ethyl) and 5.69 ppm (1H, s, =C-H).

b) 2-(3,3,5,5-Tetramethylcyclohexylidene)ethanol (3).

10 To a stirred solution of LiAlH_4 (1.7 g, 45 mmol) in dry ether (60 ml) a solution of acetate 2 (3.2 g, 15 mmol) in ether (20 ml) was added dropwise while cooling with ice water. Stirring was continued for 1 h and the residual LiAlH_4 was destroyed with water. The aqueous layer was separated and twice extracted with ether (30 ml). The combined extracts 15 were washed with brine (50 ml) and dried over MgSO_4 . After concentration *in vacuo* an oily residue was purified by Kugelrohr short path distillation (150-170 °C, 11 mm Hg) to give 3 (2.3 g, 89%) as an oil. ^1H NMR (CDCl_3 , TMS) : 0.92 (6H, s, 3,5- CH_3); 1.10 (1H, br s, OH); 1.28 (2H, s, 4- CH_2); 1.87 and 1.94 (total 4H, both s, 2,6- CH_2); 4.16 (2H, d, 7 Hz, CH_2O) and 5.50 ppm (1H, t, 7 Hz, =C-H).

c) 2,2,2-Trichloro-N-(3,3,5,5-tetramethyl-1-vinylcyclohexyl)acetamide (4).

To a solution of alcohol 3 (0.8 g, 4.7 mmol) in diethyl ether (5 ml) NaH (0.22 g of a 55% dispersion in mineral oil (0.22 mmol)) was added. The 25 reaction mixture was cooled to -10 °C and a solution of trichloroacetonitrile (0.68 g, 4.7 mmol) in diethyl ether (3 ml) was added dropwise. The solution was allowed to warm to room temperature and the solvent evaporated. Pentane (8 ml) containing methanol (0.018 ml) was added to the residue. The resulting mixture was filtered through a pad of celite and evaporated. The residual oil was dissolved in xylene (10 ml) and 30

refluxed for 10 h. Main amount of xylene was distilled off at reduced pressure (11 mm Hg) and the residue purified by flash chromatography on silica gel (hexane, hexane - ethyl acetate, 10:1) to give 4 (0.98 g, 66 %) as an oil. ¹H NMR (CDCl₃, TMS) : 0.95 (6H, s, 3,5-CH₃); 1.18 (6H, s, 3,5-CH₃); 1.1-1.5 (2H, m, 4-CH₂); 1.32 (2H, d, 15 Hz, 2,6-CH₂); 2.15 (2H, d, 15 Hz, 2,6-CH₂); 5.08 (1H, d, 11 Hz, =CH₂); 5.13 (1H, d, 18 Hz, =CH₂); 5.85 (1H, dd, 18 and 11 Hz, -HC=) and 6.7 ppm (1H, br s, NH).

d) 3,3,5,5-Tetramethyl-1-vinylcyclohexanamine hydrochloride (5).

A mixture of amide 4 (0.32 g, 1 mmol) and powdered NaOH (0.4 g, 10 mmol) in DMSO (3 ml) was stirred for 7 days at room temperature. The reaction mixture was diluted with H₂O (20 ml) and stirred overnight at room temperature. The product was extracted with hexane (3 x 10 ml). The combined extracts were washed with brine (20 ml), dried over NaOH and filtered through a pad of celite. To the solution obtained 4 M HCl in dry ethyl ether (0.5 ml) was added and the solvent was evaporated. The residue was treated with acetonitrile (10 ml) and the precipitate was collected on a filter and dried over P₂O₅ *in vacuo* to give 5 (0.12 g, 53%) as a colorless solid. ¹H NMR (CDCl₃, TMS) : 0.98 and 1.01 (total 12H, both s, 3,5-CH₃); 1.19 and 1.29 (total 2H, both d, 14 Hz, 4-CH₂); 1.62 (2H, d, 13.5 Hz, 2,6-CH₂); 1.72 (2H, br s, H₂O); 2.16 (2H, d, 13.5 Hz, 2,6-CH₂); 5.46 and 5.73 (2H, both d, 18 and 11 Hz, =CH₂); 6.16 (1H, dd, 18 and 11 Hz, =CH) and 8.24 ppm (3H, br s, NH₃⁺).

25 Example 2.

N,3,3,5,5-Pentamethyl-1-vinylcyclohexylamine hydrochloride (7).

a) Methyl 3,3,5,5-tetramethyl-1-vinylcyclohexylcarbamate (6).

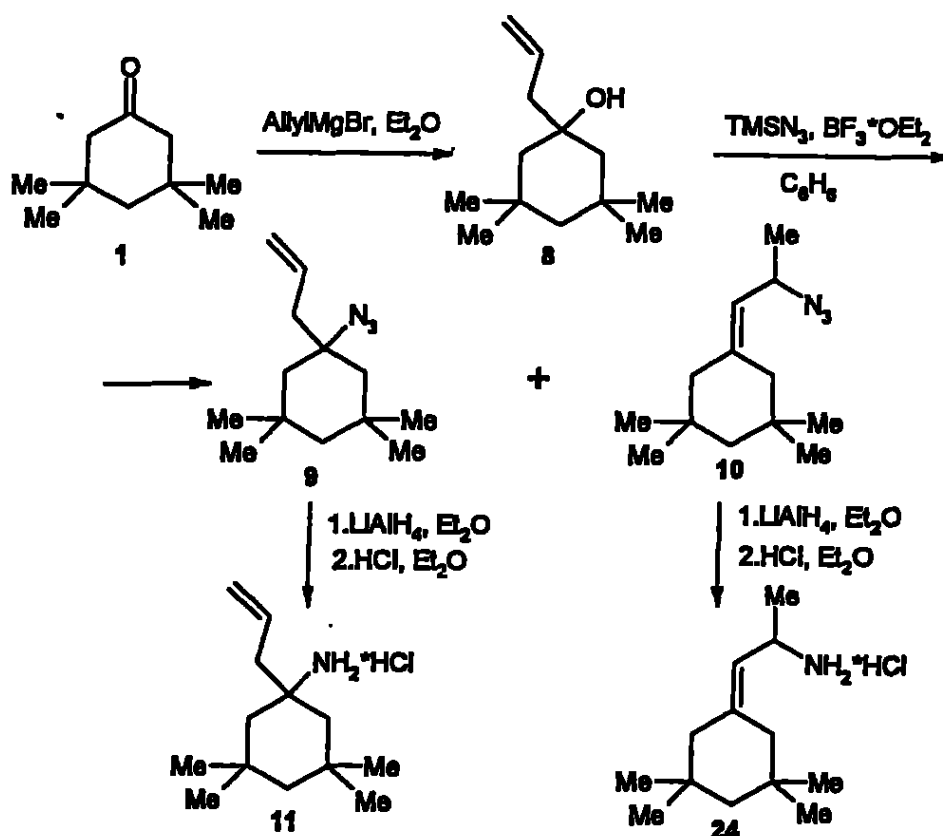
A mixture of amine hydrochloride 5 (0.25 g, 1.2 mmol) and Na₂CO₃ (0.73 g, 6.9 mmol) in THF (6 ml) was stirred at room temperature for 1 h.

Methyl chloroformate (0.27 ml, 3.45 mmol) was added and the reaction mixture was stirred at room temperature for 15 h. The mixture was diluted with diethyl ether (20 ml), filtered and evaporated to the dryness. The crude product was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 10:1) to give 6 (0.24 g, 87%) as a colorless solid with m.p. 61-63 °C. ¹H-NMR (CDCl₃, TMS) : 0.92 and 1.15 (total 12H, both s, 3,5-CH₃); 1.00-1.40 (4H, m, 4-CH₂ and 2,6-CH); 2.00 (2H, d, 14 Hz, 2,6-CH); 3.62 (3H, s, CH₃N); 4.72 (1H, br s, NH); 5.00 and 5.06 (total 2H, both d, 10.5 and 17 Hz, =CH₂) and 5.83 ppm (1H, dd, 10.5 and 17 Hz, =CH).

b) N,3,3,5,5-Pentamethyl-1-vinylcyclohexylamine hydrochloride (7).

A mixture of LiAlH₄ (0.28 g, 7.4 mmol) and carbamate 6 (0.22 g, 0.92 mmol) in THF (22 ml) was refluxed for 12 h. Then it was cooled in an ice bath and water (20 ml) was added dropwise. The resulting suspension was extracted with hexane (3 20 ml) and the combined extracts were washed with brine (20 ml). The extract was dried over NaOH, filtered and treated with 2.4 M HCl solution in diethyl ether (1 ml). The resulting suspension was evaporated to the dryness. The residue was treated with diethyl ether (10 ml) and acetonitrile (1 ml). The precipitate was collected on a filter and dried *in vacuo* over P₂O₅ to give 7 (0.11 g, 52%) as a colorless solid. ¹H-NMR (CDCl₃, TMS) : 1.00 and 1.02 (total 12H, both s, 3,5-CH₃); 1.23 and 1.32 (total 2H, both d, 15 Hz, 4-CH₂); 1.72 (2H, d, 13 Hz, 2,6-CH); 2.15 (2H, d, 13 Hz, 2,6-CH); 2.45 (3H, t, 5 Hz, CH₃N); 5.64 and 5.69 (total 2H, both d, 11 and 17 Hz, =CH₂); 5.98 (1H, dd, 11 and 17 Hz, =CH) and 9.30 ppm (2H, br s, NH₃⁺).

Scheme: Examples 3 and 4

**Example 3.**

1-Allyl-3,3,5,5-tetramethylcyclohexanamine hydrochloride (11).

5

a) 1-Allyl-3,3,5,5-tetramethylcyclohexanol (8).

To a stirred 1 M ethereal solution of allylmagnesium bromide (60 ml, 60 mmol) was added dropwise a solution of 3,3,5,5-tetramethylcyclohexanone (3.86 g, 25 mmol) in dry ether (20 ml). The mixture was stirred for 1 h at ambient temperature and boiled at reflux for 10 min. Then it was cooled with ice water and carefully treated with saturated aqueous NH₄Cl (40 ml). The organic layer was separated and washed with water and brine. After drying over anhydrous MgSO₄, the solution was concentrated *in vacuo*. The residue was fractionally distilled

at reduced pressure to give 3.5 g (72%) of 8 with b.p. 98-100 °C/12 mm Hg. ¹H NMR (CDCl₃, TMS) : 0.88 (6H, s, 3,5-CH₃); 1.20 (6H, s, 3,5-CH₃); 0.95-1.60 (6H, m, 2,4,6-CH₂); 2.15 (2H, d, 7.5 Hz, CH₂C=); 4.95-5.30 (2H, m, =CH₂) and 5.65-6.20 ppm (1H, m, =CH).

5

b) 1-Allyl-1-azido-3,3,5,5-tetramethylcyclohexane (9) and 1-Methyl-2-(3,3,5,5-tetramethylcyclohexylidene)ethyl azide (10).

To a solution of cyclohexanol 8 (1.96 g, 10 mmol) in dry benzene (20 ml) under argon was added azidotrimethylsilane (12 mmol). To this cooled (5°C) solution was slowly added BF₃·OEt₂ (12 mmol) via syringe within 20 min. The mixture was stirred for 6 h, then water was slowly added. The organic layer was separated and washed with saturated aqueous NaHCO₃, and with brine, and dried over MgSO₄. Filtration and evaporation of the solvent keeping the temperature below 25°C gave an oil which was separated by column chromatography on silica gel (light petroleum ether). A fraction with R_f 0.85 (hexane) was collected. Evaporation of the solvent provided 9 as a colorless oil (0.26 g, 11.7%). ¹H NMR (CDCl₃, TMS) : 0.89 (6H, s, 3,5-CH₃); 0.90 (1H, d, 14 Hz, 4-CH₂); 1.05 (2H, d, 14 Hz, 2,6-CH₂); 1.18 (6H, s, 3,5-CH₃); 1.37 (1H, d, 14 Hz, 4-CH₂); 1.60 (2H, d, 14 Hz, 2,6-CH₂), 2.29 (2H, d, 7 Hz, CH₂C=); 4.95-5.25 (2H, m, =CH₂) and 5.65-6.15 ppm (1H, m, =CH).

Evaporation of additional fraction (R_f 0.65 (hexane)) gave 0.425 g (20.3%) of azide 10 as a colorless oil. ¹H NMR (CDCl₃, TMS) : 0.91 (6H, s), 0.94 (3H, s) and 0.96 (3H, s, 3',5'-CH₃); 1.23 (3H, d, 6.5 Hz, 1-CH₃); 1.26 (2H, s, 4'-CH₂); 1.89 (2H, s) and 1.96 (2H, s, 2',6'-CH₂); 4.31 (1H, dq, 6.5 and 9.5 Hz, 1-CH) and 5.21 ppm (1H, dm, 9.5 Hz, =CH).

c) 1-Allyl-3,3,5,5-tetramethylcyclohexanamine hydrochloride (11).

A solution of azide 9 (0.221 g, 1.0 mmol) in dry ether (4 ml) was added

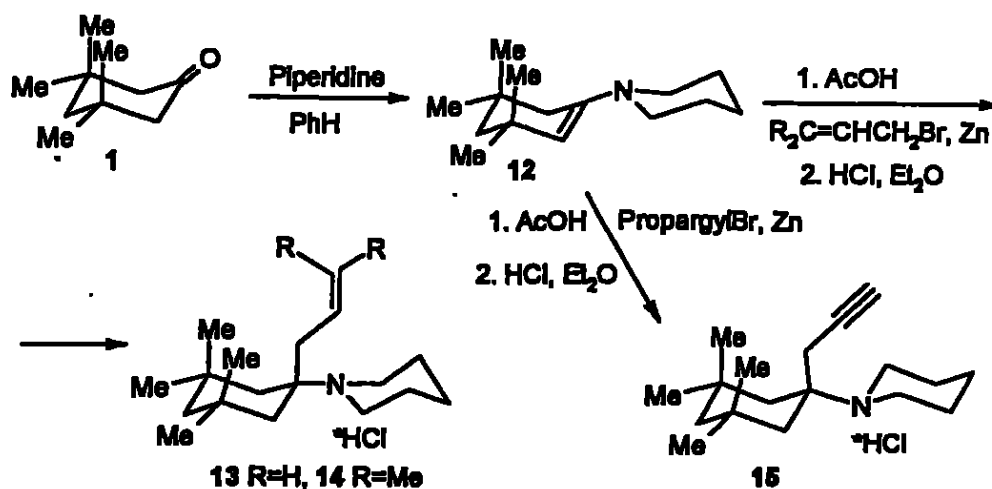
dropwise to a stirred suspension of lithium aluminum hydride (0.152 g , 4 mmol) in ether (10 ml) within 10 min. The mixture was stirred for 4 h, then it was treated with 20% aqueous NaOH (8 ml). The aqueous layer was separated and extracted with diethyl ether (2 15 ml). The combined
6 organic extracts were washed with brine and dried over NaOH. The filtered solution was treated with dry HCl solution in diethyl ether and evaporated. Dry diethyl ether was added to the solid residue and it was collected on filter, and washed with dry ether to give 11 (0.105 g, 47%) as a colorless solid. ¹H NMR (CDCl₃, TMS) : 1.03 (6H, s, 3,5-CH₃); 1.06
10 (6H, s, 3,5-CH₃); 1.29 (2H, s, 4-CH₂); 1.63 (2H, d, 13 Hz, 2,6-CH₂); 1.80 (2H, d, 13 Hz, 2,6-CH₂), 2.71 (2H, d, 7 Hz, CH₂C=); 5.10-5.40 (2H, m, =CH₂); 5.75-6.25 (1H, m, =CH) and 8.25 ppm (3H, br s, NH₃⁺).

Example 4.

15 1-(3,3,5,5-Tetramethylcyclohexylidene)-2-propanamine hydrochloride (24).

A solution of 1-methyl-2-(3,3,5,5-tetramethylcyclohexylidene)ethyl azide (10) (0.33 g, 1.5 mmol) in dry diethyl ether (4 ml) was added dropwise to a stirred suspension of lithium aluminum hydride (0.152 g , 4 mmol) in
20 ether (15 ml) within 10 min. The mixture was stirred for 4 h, then it was treated with 20% aqueous NaOH (8 ml). The aqueous layer was extracted with ether (2*15 ml). The organic extracts were combined, washed with brine and dried over NaOH. The filtered solution was treated with dry HCl solution in ether and evaporated *in vacuo*. Dry ether was added to the
25 solid residue and it was collected on filter and washed with dry ether to give 24 (0.18 g, 54%) as a colorless solid. ¹H NMR (CDCl₃, TMS) : 0.89 (6H, s), 0.92 (3H, s) and 0.98 (3H, s, 3',5'-CH₃); 1.27 (2H, s, 4'-CH₂); 1.47 (3H, d, 6.5 Hz, 3-CH₃); 1.84 (1H, d, 13.5 Hz, 2'-CH); 1.87 (2H, s, 6'-CH₂), 2.06 (1H, d, 13.5 Hz, 2'-CH); 4.17 (1H, dq, 6.5 and 9.5 Hz, 2-
30 CH); 5.35 (1H, d, 9.5 Hz, =CH) and 8.25 ppm (3H, br s, NH₃⁺).

Scheme: Examples 5, 6, and 7

**Example 5.**

5 **1-(1-Allyl-3,3,5,5-tetramethylcyclohexyl)piperidine hydrochloride (13).**

a) **1-(3,3,5,5-Tetramethyl-1-cyclohexenyl-1)piperidine (12).**

Prepared by condensation of piperidine (1.2 equivalents) and 3,3,5,5-tetramethylcyclohexanone by heating in benzene with azeotropic removal
 10 of water. Crude product was obtained by removing starting materials at vacuum distillation conditions (100 °C/ 10 mm Hg). Amber oil. ¹H NMR (CDCl₃, TMS) : 0.94 (6H, s) and 0.97 (6H, s, 3',5'-CH₃); 1.25 (2H, s, 4'-CH₂); 1.40-1.70 (6H, m, piperidine 3,4,5-CH₂); 1.76 (2H, s, 6'-CH₂); 2.60-2.85 (4H, m, piperidine 2,6-CH₂) and 4.40 ppm (1H, s, =CH).

15

b) **1-(1-Allyl-3,3,5,5-tetramethylcyclohexyl)piperidine hydro chloride (13).**

To a solution of enamine 12 (2.1 g, 9 mmol) in THF (20 ml) was added acetic acid 0.675 g, 11.25 mmol). The mixture was stirred for 5 min and zinc powder (0.74 g, 11.25 mgA) was added. Then a solution of
 20 allylbromide (1.63 g, 13.5 mmol) in THF (5 ml) was added dropwise and the mixture was stirred at ambient temperature for 6 h. Aqueous Na₂CO₃

was added and the resulting mixture was extracted with ether. The extract was washed with brine, dried over anhydrous MgSO_4 , and concentrated *in vacuo*. The residue was separated by column chromatography on silica gel (hexane, 5% EtOAc in hexane). The fraction with R_f 0.85 (hexane-EtOAc, 13 : 2) was collected, evaporated and treated with dry HCl solution in ether. The precipitate was filtered and washed with hexane-EtOAc mixture to give 13 (0.79 g, 29%) as a colorless solid. ^1H NMR (CDCl_3 , TMS) : 1.07 (6H, s, 3', 5'- CH_3), 1.10 (6H, s, 3', 5'- CH_3); 1.34 (1H, d, 12.2 Hz) and 1.45 (1H, d, 12.2 Hz, 4'- CH_2); 1.70-1.95 (6H, m, 2', 6'- CH_2 and piperidine 3,5-CH, 4- CH_2); 2.37 (2H, d, 13.4 Hz, 2', 6'- CH_2); 2.40-2.70 (2H, m, piperidine 3,5-CH); 2.76 (2H, d, 7.2 Hz, $\text{CH}_2\text{C}=\text{}$); 2.75-3.00 (2H, m, piperidine 2,6-CH); 3.64 (2H, d, 11.6 Hz, piperidine 2,6-CH); 5.13 (1H, d, 9.6 Hz) and 5.24 (1H, d, 17.8 Hz, $=\text{CH}_2$); 5.85-6.15 (1H, m, $=\text{CH}$) and 10.72 ppm (1H, br s, NH).

Example 6.

1-[3,3,5,5-Tetramethyl-1-(3-methyl-2-butenyl)cyclohexyl]piperidine hydrochloride (14).

Prepared from piperidine 12 according to the procedure for compound 13 (Example 5, b) using 4-bromo-2-methyl-2-butene instead of allylbromide. Yield: 20%. ^1H NMR (CDCl_3 , TMS) : 1.07 and 1.08 (total 12H, both s, 3', 5'- CH_3), 1.32 and 1.44 (2H, both d, 14.2 Hz, 4'- CH_2); 1.69 and 1.76 (6H, both s, $=\text{C}(\text{CH}_3)_2$); 1.68-1.96 (4H, m, 3,5-CH and 4- CH_2); 1.84 (2H, d, 13.4 Hz, , 2', 6'- CH_2); 2.31 (2H, d, 13.4 Hz, , 2', 6'- CH_2); 2.40-2.80 (4H, m, $\text{N}(\text{CH})_2$, 3,5-CH); 2.60 (2H, d, 7.2 Hz, $\text{CH}_2\text{C}=\text{}$); 3.63 (2H, d, 10.4 Hz, $\text{N}(\text{CH})_2$); 5.31 (1H, t, 6.8 Hz, $=\text{CH}$) and 10.55 ppm (1H, br s, NH).

Example 7.

1-[3,3,5,5-Tetramethyl-1-(2-propynyl)cyclohexyl]piperidine hydrochloride (15).

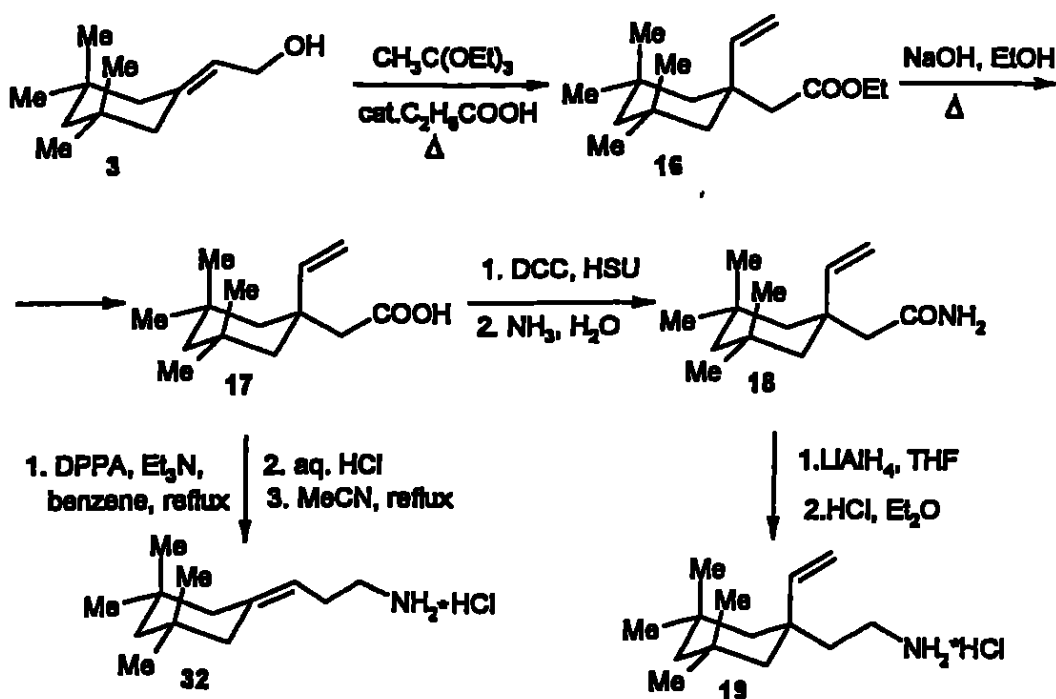
Prepared from piperidine 12 according to the procedure for compound 13

(Example 5, b) using 3-bromopropyne instead of allylbromide. Yield: 6%.

¹H NMR (CDCl₃, TMS) : 1.07 (6H, s, 3'',5''-CH₃), 1.11 (6H, s, 3',3'',5'-CH₃); 1.23 and 1.44 (total 2H, both d, 14.3 Hz, 4'-CH₂); 1.75-2.00 (4H, m, piperidine 3,5-CH, 4-CH₂); 1.91 (2H, d, 13.2 Hz, 2',6'-CH₂); 2.28 (1H, s, HCC); 2.34 (2H, d, 13.2 Hz, 2',6'-CH₂); 2.40-2.70 (2H, m, piperidine 3,5-CH); 2.81 (2H, s, CH₂CC); 2.85-3.10 (2H, m, piperidine 2,6-CH); 3.69 (2H, d, 10.2 Hz, piperidine 2,6-CH) and 11.12 ppm (1H, br s, NH).

Scheme: Examples 8 and 9

15



Example 8.**2-(3,3,5,5-Tetramethyl-1-vinylcyclohexyl)ethanamine hydro chloride (19).****5 a) Ethyl 2-(3,3,5,5-tetramethyl-1-vinylcyclohexyl)acetate (16).**

A mixture of triethyl orthoacetate (18.6 ml, 102 mmol), 2-(3,3,5,5-tetramethyl-cyclohexylidene)ethanol (3) (4.63 g, 25.4 mmol) and propionic acid (0.19 ml, 2.5 mmol) was heated at 145 °C for 10 h.

Ethanol was distilled off from the mixture in the course of reaction. The
10 reaction mixture was cooled and poured into water (100 ml). The aqueous phase was extracted with hexane (2 50 ml) and the combined organic phases were washed with 5 % aqueous KHSO₄ (50 ml) and brine (50 ml). The extract was dried over MgSO₄, filtered and evaporated. The residue
15 was purified by flash chromatography on silica gel (light petroleum ether and light petroleum ether - ethyl acetate, 100: 2) to give 16 (4.64 g, 73 %) as an oil. ¹H-NMR (CDCl₃, TMS) : 0.91 (6H, s, 3,5-CH₃); 1.01 (6H, s, 3,5-CH₃); 1.23 (3H, t, 7 Hz, ethyl CH₃) 1.00-1.30 (4H, m, 4-CH₂ and 2,6-CH); 1.86 (2H, d, 13 Hz, 2,6-CH); 2.22 (2H, s, CH₂C=O); 4.08 (2H, q, 7 Hz, ethyl CH₂); 5.06 and 5.07 (total 2H, both d, 11 and 17.5 Hz, =CH₂)
20 and 5.95 ppm (1H, dd, 11 and 17.5 Hz, -CH=).

b) 2-(3,3,5,5-Tetramethyl-1-vinylcyclohexyl)acetic acid (17).

A solution of NaOH (1.03 g, 25.8 mmol) and acetate 16 (1.3 g, 5.15 mmol) in methanol (26 ml) was refluxed for 3 h. The mixture was cooled
25 to room temperature and poured into water (100 ml). The aqueous phase was acidified by conc. aqueous HCl and extracted with hexane (3 30 ml). The combined organic phases were washed with brine and dried over CaCl₂, filtered and evaporated. The residue was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 10:1)
30 to give 17 (0.7 g, 71 %) as a colorless solid with m.p. 92-94 °C. ¹H-NMR

(CDCl₃, TMS) : 0.92 (6H, s, 3,5-CH₃); 1.02 (6H, s, 3,5-CH₃); 1.00-1.30 (4H, m, 4-CH₂ and 2,6-CH); 1.90 (2H, d, 14 Hz, 2,6-CH); 2.27 (2H, s, CH₂C=O); 5.11 and 5.13 (total 2H, both d, 11 and 18 Hz, =CH₂); 5.99 (1H, dd, 18 and 11 Hz, =CH) and 10.80 ppm (1H, br s, COOH).

5

c) 2-(3,3,5,5-Tetramethyl-1-vinylcyclohexyl)acetamide (18).

N-Hydroxysuccinimide (0.25 g, 2.2 mmol) and N,N'-dicyclohexyl carbodiimide (0.45, 2.2 mmol) was added to a solution of cyclohexylacetic acid 17 (0.45 g, 2 mmol) in THF (5 ml). The mixture was stirred for 18 h at room temperature and cooled in an ice bath. 25 % aqueous NH₄OH (2 ml) was added in one portion and the mixture was stirred at room temperature for 2 h. The precipitate was filtered off and washed with diethyl ether (30 ml). The organic phase of filtrate was separated and washed with 5% aqueous KHSO₄ (10 ml) and brine. The extract was dried over MgSO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 4:1 to 1:1) to give 18 (0.34 g, 76 %) as a colorless solid with m.p. 44-46 °C. ¹H-NMR (CDCl₃, TMS) : 0.91 (6H, s, 3,5-CH₃); 1.02 (6H, s, 3,5-CH₃); 1.00-1.30 (4H, m, 4-CH₂ and 2,6-CH); 1.85 (2H, d, 14 Hz, 2,6-CH); 2.13 (2H, s, CH₂C=O); 5.18 and 5.19 (total 2H, both d, 18 and 11 Hz, =CH₂); 5.40 and 5.60 (total 2H, both br s, NH₂) and 6.03 ppm (1H, dd, 18 and 11 Hz, =CH).

25

d) 2-(3,3,5,5-Tetramethyl-1-vinylcyclohexyl)ethanamine hydrochloride (19).

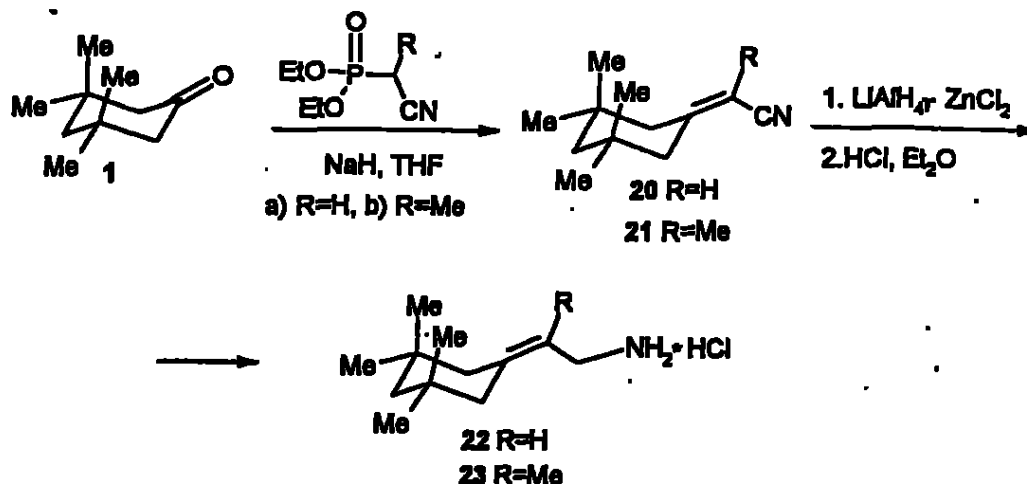
The mixture of LiAlH₄ (0.41 g, 11 mmol) and amide 18 (0.30 g, 1.4 mmol) in THF (18 ml) was refluxed for 17 h. Then it was cooled in an ice bath and water (30 ml) was added dropwise. The resulting suspension was extracted with hexane (3 30 ml) and the combined organic phases were washed with brine. The extract was dried over NaOH, filtered and

concentrated to ~10 ml volume. 4.8 M HCl solution in diethyl ether (1 ml) was added and the resulting suspension was evaporated to the dryness. The residue was treated with acetonitrile (5 ml) and the precipitate was collected on filter and dried *in vacuo* over NaOH to give 19 (0.16 g, 50%) as a colorless solid. ¹H-NMR-(CDCl₃, TMS) : 0.89 (6H, s, 3,5-CH₃); 1.02 (6H, s, 3,5-CH₃); 0.90-1.80 (8H, m, ring protons and ethanamine- 2-CH₂); 2.92 (2H, br s, CH₂N); 5.05 and 5.15 (2H, both d, 18 and 11 Hz, =CH₂); 5.77 (1H, dd, 18 and 11Hz, =CH) and 8.10 ppm (3H, br s, NH₃⁺).

10 **Example 9.**

3-(3,3,5,5-Tetramethylcyclohexylidene)propanamine hydrochloride (32). Triethylamine (0.25 ml, 1.76 mmol) and diphenylphosphoryl azide (0.38 ml, 1.76 mmol) was added to a solution of acid 17 (0.36 g, 1.6 mmol) in benzene (6 ml). The mixture was refluxed for 2 h, cooled to room temperature and evaporated to the dryness. Cold (~5 °C) conc. aqueous HCl (3 ml) was added to the residue. The resulting mixture was stirred at room temperature for 18 h and made strongly alkaline by addition of 10% aqueous NaOH. Hexane (20 ml) was added to the mixture and both phases filtered. The precipitate was washed with hexane (2 5 ml) and water (2 5 ml). The organic phase of the filtrate was separated. The aqueous phase was washed with hexane (2 10 ml). The combined organic phases were washed with brine (10 ml), dried over NaOH and filtered. 4.8 M HCl solution in diethyl ether (1 ml) was added and the resulting suspension was evaporated. The residue was recrystallized from acetonitrile and dried *in vacuo* over P₂O₅ to give 32 (0.1 g, 43%) as a colorless solid. ¹H-NMR: (CDCl₃, TMS) : 0.90 and 0.92 (total 12H, both s, c-Hex-3,5-CH₃); 1.23 (2H, s, c-Hex- 4-CH₂); 1.86 and 1.92 (total 4H, both s, c-Hex- 2,6-CH₂); 2.49 (2H, q, 7 Hz, propanamine- 2-CH₂); 2.98 (2H, t, 7 Hz, propanamine- 1-CH₂); 5.15 (1H, t, 7 Hz, =CH-) and 8.30 ppm (3H, br s, NH₃⁺).

Scheme: Examples 10 and 11

**Example 10.****5 2-(3,3,5,5-Tetramethylcyclohexylidene)ethanamine hydrochloride (22).****a) 3,3,5,5-Tetramethylcyclohexylideneacetonitrile (20).**

60% NaH dispersion in mineral oil (0.96 g, 24 mmol) was added to a solution of diethyl cyanomethylphosphonate (4.25 g, 24 mmol) in THF (30 ml) while cooling with ice water. The mixture was stirred for 30 min and a solution of 3,3,5,5-tetramethylcyclohexanone (3.08 g, 20 mmol) in THF (10 ml) was added dropwise. Cooling bath was removed and the mixture was stirred at room temperature for 72 h. It was poured into ice water (100 ml) and extracted with diethyl ether (3x50 ml). The combined organic phases were washed with brine, dried over MgSO₄, filtered and evaporated. The crude product was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 10:1) to give 20 (2.38 g, 71 %) as a colorless oil. ¹H-NMR (CDCl₃, TMS) δ: 0.97 and 1.01 (total 12H, both s, 3',5'-CH₃); 1.36 (2H, s, 4'-CH₂); 2.01 (2H, s, 2'-CH₂); 2.26 (2H, s, 6'-CH₂) and 5.14 ppm (1H, s, =CH).

b) 2-(3,3,5,5-Tetramethylcyclohexylidene)ethanamine hydrochloride (22).
A suspension of LiAlH_4 (0.68 g, 18 mmol) in diethyl ether (30 ml) was cooled in an ice bath and 1M ZnCl_2 solution in diethyl ether (9 ml, 9 mmol) was added. The resulting mixture was stirred for 15 min and a solution of nitrile 20 (1 g, 6 mmol) in diethyl ether (30 ml) was added dropwise keeping the temperature at 0-5 °C. Ice bath was then removed and the mixture was stirred at room temperature for 24 h. Water (30 ml) and 20% aqueous NaOH (20 ml) was added while cooling with an ice bath. The aqueous phase was extracted with diethyl ether (4 50 ml). The combined organic phases were washed with brine (50 ml) and dried over NaOH, filtered and evaporated. The residue was purified by Kugelrohr short path distillation at 160 °C/ 20 mm Hg. The distillate was diluted with diethyl ether and 4.8M HCl solution in diethyl ether (3 ml) was added. The resulting precipitate was collected on a filter, washed with diethyl ether (3 5 ml) and dried *in vacuo* over NaOH to give 22 as a colorless solid. $^1\text{H-NMR}$ (CDCl_3 , TMS) : 0.91 and 0.92 (total 12H, both s, 3',5'- CH_3); 1.28 (2H, s, 4'- CH_2); 1.89 and 1.93 (total 4H, both s, 2',6'- CH_2); 3.62 (2H, d, 7 Hz, CH_2N); 5.41 (1H, t, 7 Hz, $-\text{C}=\text{CH}$) and 8.3 ppm (3H, br s, NH_3^+).

Example 11.

2-(3,3,5,5-Tetramethylcyclohexylidene)propanamine hydrochloride (23).

a) 2-(3,3,5,5-Tetramethylcyclohexylidene)propionitrile (21).
Prepared according to the procedure for compound 20 (Example 10, a) using diethyl (1-cyanoethyl)phosphonate. Nitrile 21 obtained as a colorless oil with 41% yield. $^1\text{H-NMR}$: (CDCl_3 , TMS) : 0.96 and 1.00 (total 12H, both s, c-Hex-3,5- CH_3); 1.34 (2H, s, c-Hex-4- CH_2); 1.91 (3H, s, propionitrile-3- CH_3); 2.04 and 2.28 ppm (total 4H, both s, c-Hex-2,6-

CH₂).

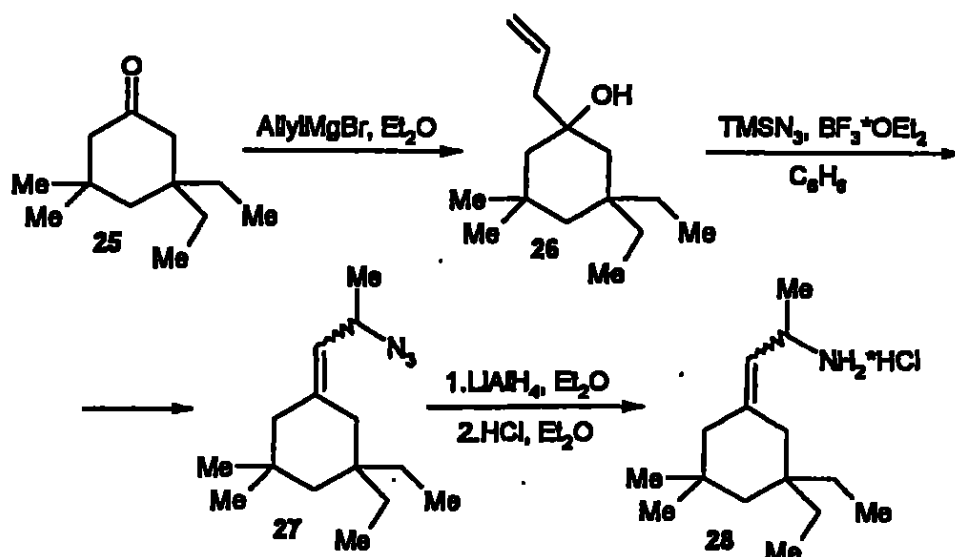
b) 2-(3,3,5,5-Tetramethylcyclohexylidene)propanamine hydrochloride (23).

Prepared from nitrile 21 according to the procedure for compound 22

- 5 (Example 10, b). Amine hydrochloride 23 obtained as a colorless solid. ¹H-NMR: (CDCl₃, TMS) δ: 0.92 and 0.93 (total 12H, both s, c-Hex-3,5-CH₃); 1.27 (2H, s, c-Hex-4-CH₂); 1.89 (3H, s, propanamine-3-CH₃); 1.99 and 2.01 (total 4H, both s, c-Hex-2,6-CH₂); 3.64 (2H, br s, propanamine-1-CH₂) and 8.40 ppm (3H, br s, NH₃⁺).

10

Scheme: Example 12



Example 12.

(*E,Z*)-1-(3,3-Diethyl-5,5-dimethylcyclohexylidene)-2-propanamine hydrochloride (28).

15

a) 1-Allyl-3,3-diethyl-5,5-dimethylcyclohexanol (26).

To a stirred 1 M ethereal solution of allylmagnesium bromide (20 ml, 20 mmol) was added dropwise a solution of 3,3-diethyl-5,5-

44

dimethylcyclohexanone (25) (1.47 g, 8.06 mmol) in dry ether (5 ml). The mixture was stirred for 1 h at ambient temperature and boiled at reflux for 10 min. Then it was cooled with ice water and treated with saturated aqueous NH_4Cl (40 ml). The organic layer was separated and washed with water and brine. After drying over anhydrous MgSO_4 , the solution was concentrated *in vacuo*. The residue was purified by column chromatography on silica gel (light petroleum ether). A fraction with R_f 0.7 (Hexane : EtOAc, 13 : 2) was collected. Evaporation of the solvent afforded 26 (1.35 g, 74%) as a colorless oil. ^1H NMR (CDCl_3 , TMS) : 0.74 (6H, t, 7 Hz, 2CH_3 of ethyl); 0.88 (3H, s, 5-CH_3); 1.19 (3H, s, 5-CH_3); 0.80-2.05 (10H, m, $2,4,6\text{-CH}_2$ and 2CH_2 of ethyl); 2.14 (2H, d, 7 Hz, $\text{CH}_2\text{C}=\text{}$); 4.95-5.30 (2H, m, $=\text{CH}_2$) and 5.65-6.20 ppm (1H, m, $=\text{CH}$).

15 b) (E,Z)-1-Methyl-2-(3,3-diethyl-5,5-dimethylcyclohexylidene)ethyl azide (27).

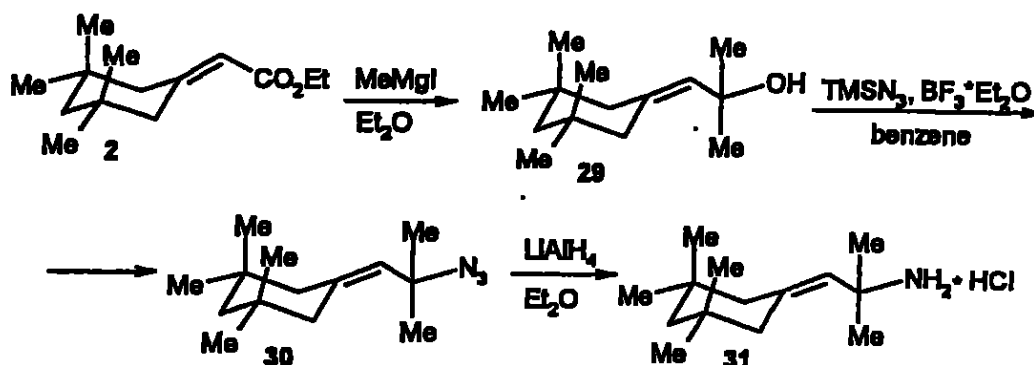
Prepared from cyclohexanol 26 according to the procedure for compounds 9 and 10 (Example 3, b). Azide 27 obtained as a colorless oil with 15% yield. ^1H NMR (CDCl_3 , TMS) : 0.73 and 0.74 (total 6H, both t, 7 Hz, 2CH_3 ethyl); 0.91, 0.94 and 0.97 (total 6H, all s, $5',5''\text{-CH}_3$); 1.10-1.45 (4H, m, 2CH_2 ethyl); 1.22 (3H, d, 6.5 Hz, 1-CH_3); 1.26 (2H, s, $4'\text{-CH}_2$); 1.89 (2H, s) and 1.97 (2H, m, $2'',6''\text{-CH}_2$); 4.08-4.48 (1H, m, 1-CH) and 5.18 ppm (1H, dm, 9.5 Hz, $=\text{CH}$).

25 c) (E,Z)-1-(3,3-Diethyl-5,5-dimethylcyclohexylidene)-2-propanamine hydrochloride (28).

Prepared from azide 27 according to the procedure for compound 24 (Example 4). Amine hydrochloride 28 obtained as a colorless solid in 16% yield. ^1H NMR (CDCl_3 , TMS) : 0.72 (6H, br t, 7 Hz, 2CH_3 ethyl), 0.90, 0.92 and 0.98 (total 6H, all s, $5',5''\text{-CH}_3$); 1.25 (6H, m, $4'\text{-CH}_2$ and

2CH₂ ethyl); 1.47 (3H, d, 6.5 Hz, 2-CH₃); 1.70-2.25 (2H, br AB q, 13 Hz, 2'-CH₂); 1.87 (2H, s, 6'-CH₂), 4.18 (1H, m, 2-CH); 5.34 (1H, br d, 9.5 Hz, =CH) and 8.38 ppm (3H, br s, NH₃⁺).

5 **Scheme: Example 13**



Example 13.

- 10 **2-Methyl-1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanamine hydrochloride (31).**

a) 2-Methyl-1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanol (29).

- A solution of acetate **2** (2.14 g, 10 mmol) in diethyl ether (20 ml) was added to 1.6 M MeLi solution in diethyl ether (26 ml, 40 mmol), while cooling in an ice bath. The reaction mixture was stirred at room temperature for 1 h. It was then cooled in an ice bath and saturated aqueous NH₄Cl (20 ml) was added dropwise. The aqueous phase was extracted with diethyl ether (2 30 ml). The combined organic phases were washed with brine (30 ml), dried over MgSO₄, filtered and evaporated. The residue was purified by Kugelrohr short path distillation (100 °C/ 4 mm Hg) to give **29** (1.86 g, 86%) as a colorless oil. ¹H-NMR: (CDCl₃, TMS) : 0.91 and 0.96 (total 12H, both s, c-Hex-3,5-CH₃); 1.25 (2H, s, c-

Hex- 4-CH₂); 1.38 (6H, s, -C(CH₃)₂O); 1.79 and 2.23 (both 2H, both s, c-Hex- 2,6-CH₂) and 5.39 ppm (1H, s, =CH-).

b) 2-Azido-2-methyl-1-(3,3,5,5-tetramethylcyclohexylidene)propane (30).

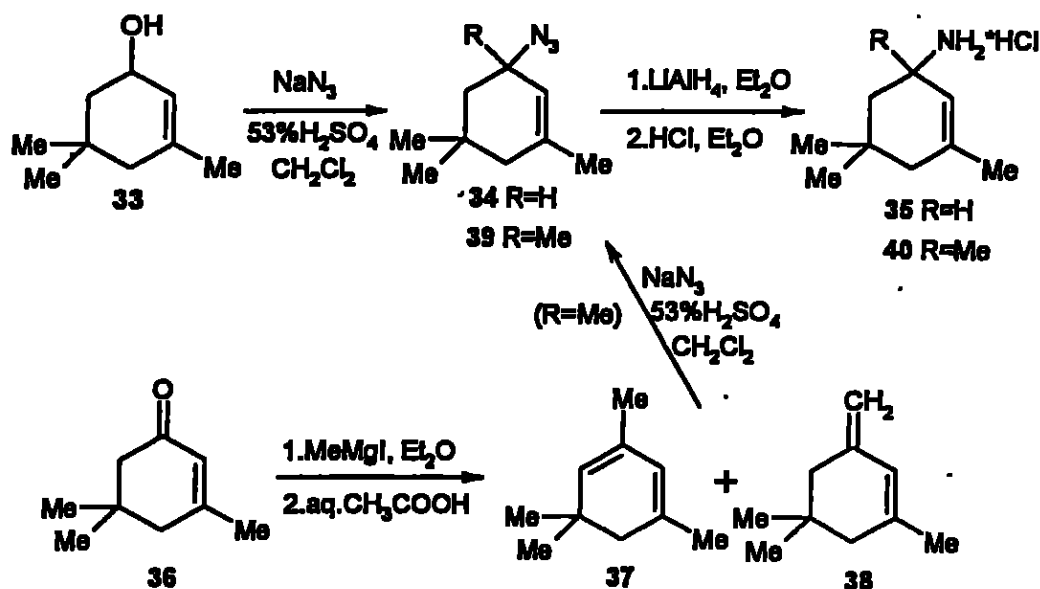
- 5 BF₃Et₂O (0.3 ml, 2.4 mmol) was added to a solution of alcohol 29 (0.42 g, 2 mmol) and TMSN₃ (0.31 ml, 2.4 mmol) in benzene (4.5 ml) during 3 min, while cooling with an ice bath. The reaction mixture was stirred at 5-10 °C for 1 h and filtered through a short silica gel column. The solution was evaporated and the residue was purified by flash chromatography on
10 silica gel (light petroleum ether) to give 30 (0.30 g, 64%) as a colorless oil. ¹H-NMR (CDCl₃, TMS) : 0.92 and 0.98 (total 12H, both s, c-Hex-3,5-CH₃); 1.27 (2H, s, c-Hex- 4-CH₂); 1.40 (6H, s, -C(CH₃)₂N₃); 1.85 and 2.23 (both 2H, both s, c-Hex- 2,6-CH₂) and 5.27 ppm (1H, s, =CH-).

- 15 c) 2-Methyl-1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanamine hydrochloride (31).

Prepared from azide 30 by the same procedure as for amine 24 (Example 4). Amine hydrochloride 31 obtained as a colorless solid in 69% yield. ¹H -
NMR (CDCl₃, TMS) : 0.91 and 0.98 (total 12H, both s, c-Hex-3,5-CH₃);
20 1.26 (2H, s, c-Hex- 4-CH₂); 1.68 (6H, s, -C(CH₃)₂N); 1.84 and 2.10 (both 2H, both s, c-Hex- 2,6-CH₂); 5.15 (1H, s, =CH-) and 8.5 ppm (3H, br s, NH₃⁺).

47

Scheme: Examples 14 and 15

**Example 14.****3,5,5-trimethyl-2-cyclohexen-1-amine hydrochloride (35).**

5

a) 3-Azido-1,5,5-trimethyl-1-cyclohexene (34).

To a cooled (0 °C) suspension of sodium azide (0.81 g, 12.5 mmol) in CH_2Cl_2 (5 ml) was added dropwise 53% aqueous H_2SO_4 (8 ml). The mixture was stirred for 10 min, then a solution of 3,5,5-trimethyl-2-cyclohexanol (33) (0.70 g, 5 mmol) in CH_2Cl_2 (8 ml) was added. The mixture was stirred for 20 h, poured into ice water, neutralized with aqueous NH_4OH and extracted with CH_2Cl_2 . The extract was washed with brine and dried over MgSO_4 . Filtration and evaporation of the solvent keeping the temperature below 25 °C gave an oil which was separated by column chromatography on silica gel (light petroleum ether). A fraction with R_f 0.8 (hexane) was collected. Evaporation of the solvent gave 34 as a colorless oil (0.365 g, 44%). ^1H NMR (CDCl_3 , TMS) : 0.89 and 1.01 (total 6H, both s, 5,5- CH_3); 1.34 (1H, m, c-4-CH); 1.55-1.95 (3H, m, 4-CH, 6- CH_2); 1.71 (3H, s, 1- CH_3); 3.90 (1H, m, 3-CH) and 5.39 ppm (1H,

s, C=CH).

b) 3,5,5-trimethyl-2-cyclohexen-1-amine hydrochloride (35).

Prepared from azide 34 according to the procedure for compound 11

- 5 (Example 3, c). Amine hydrochloride 35 obtained as a colorless solid in 57% yield. ¹H NMR (CDCl₃, TMS) : 0.89 and 1.03 (total 6H, both s, 5,5-CH₃); 1.25-2.15 (4H, m, 4,6-CH₂); 1.72 (3H, s, 3-CH₃); 3.88 (1H, m, 1-CH); 5.41 (1H, s, C=CH) and 8.40 ppm (3H, br s, NH₃⁺).

10 Example 15.

1,3,5,5-Tetramethyl-2-cyclohexen-1-amine hydrochloride (40).

a) 1,3,5,5-Tetramethyl-1,3-cyclohexadiene (37) and 1,5,5-trimethyl-3-methylene-1-cyclohexene (38) mixture.

- 15 To a stirred 2 M ethereal solution of methylmagnesium iodide (15 ml, 30 mmol) was added dropwise a solution of 3,5,5-trimethyl-2-cyclohexen-1-one (36) (1.38 g, 10 mmol) in dry ether (15 ml). The mixture was stirred for 1 h, cooled with ice water and carefully treated with 15% aqueous CH₃COOH (15 ml). The mixture was stirred for an additional hour. The
- 20 organic layer was separated and washed with water and saturated aqueous NaHCO₃. After drying over MgSO₄, the solution was concentrated *in vacuo*. The residue was purified by flash chromatography (light petroleum ether, R_f 0.95 (hexane)) to give a mixture of 37 and 38 (0.955 g, 70%) (7 : 10, based on GC) as an oil. ¹H NMR (CDCl₃, TMS) :
- 25 0.89, 0.98 and 1.03 (total 10.2H, all s, 5,5-CH₃); 1.55-2.20 (total 12.6H, m, CH₂C= and CH₃C=); 4.69 (2H, dm, 4 Hz, =CH₂); 5.06 (0.7H, m, =CH); 5.50 (0.7H, sept, 1.5 Hz, =CH) and 5.92 ppm (1H, m, =CH).

b) 3-Azido-1,5,5,5-tetramethyl-1-cyclohexene (39).

- 30 Prepared from 37 and 38 mixture according to the procedure for

compound 34 (Example 14, a). Azide 39 obtained as a colorless oil with 43% yield. ^1H NMR (CDCl_3 , TMS) : 0.93 and 0.99 (total 6H, both s, 5,5- CH_3); 1.31 (3H, s, 1- CH_3); 1.36 and 1.62 (total 2H, both d, 13 Hz, 4- CH_2); 1.72 (5H, s, 1- CH_3 , 6- CH_2); 5.32 (1H, s, $\text{C}=\text{CH}$).

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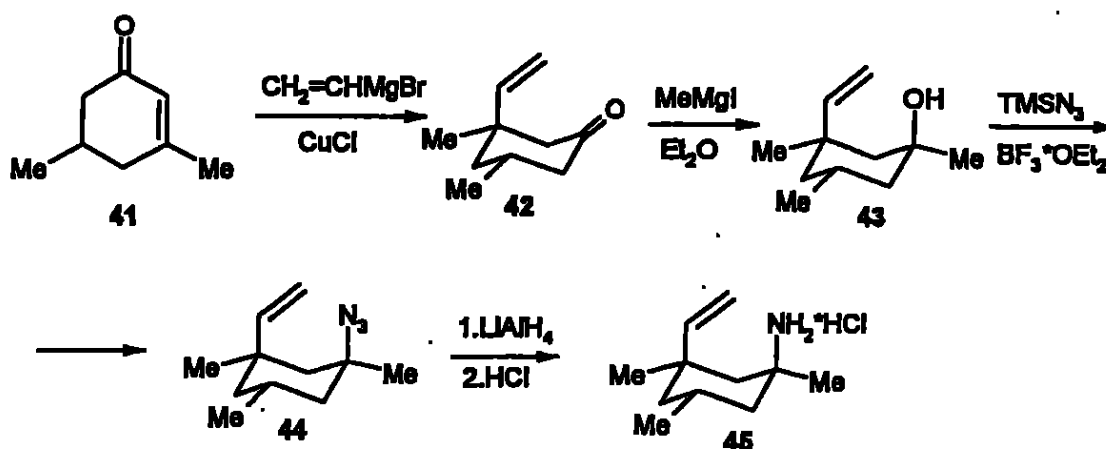
c) 1,3,5,5-Tetramethyl-2-cyclohexan-1-amine hydrochloride (40).

Prepared from azide 39 according to the procedure for compound 11 (Example 3, c). Amine hydrochloride 40 obtained as a colorless solid with 60% yield. ^1H NMR (CDCl_3 , TMS) : 0.96 and 1.07 (total 6H, both s, 5,5- CH_3); 1.56 (3H, s, 1- CH_3); 1.73 (3H, s, 3- CH_3); 1.60-2.06 (4H, m, 4,6- CH_2); 5.49 (1H, s, $\text{C}=\text{CH}$) and 8.27 ppm (3H, br s, NH_3^+).

10

Scheme: Example 16

15



Example 16.

1,3, *trans*-5-trimethyl-*cis*-3-vinylcyclohexanamine hydrochloride (45).

a) 3,5-dimethyl-3-vinylcyclohexanone (42).

20 A 1M solution of vinylmagnesium bromide in THF (90 ml, 90 mmol) was cooled in dry ice-acetone bath to -20°C in an inert atmosphere and CuCl (4.45 g, 45 mmol) was added in one portion. The mixture was stirred for

30 min and a solution of 3,5-dimethyl-2-cyclohexen-1-one (41) (3.73 g, 30 mmol) in THF (40 ml) was added dropwise keeping the reaction temperature at -20°C . The cooling bath was removed and the reaction mixture was allowed to reach room temperature for 2 h. Saturated aqueous NH_4Cl (50 ml) was added thoroughly while cooling with ice bath. Hexane (150 ml) was then added and the aqueous layer was separated and extracted with hexane (2 100 ml). The combined organic extracts were washed with 20% aqueous acetic acid (100 ml) and with saturated aqueous NaHCO_3 (3 200 ml). The extract was dried over MgSO_4 , filtered and evaporated. The crude product was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 20: 1) to give 42 (2.4 g, 52 %) as a colorless oil. $^1\text{H-NMR}$ (CDCl_3 , TMS) : 0.99 (3H, d, 6 Hz, 5- CH_3); 1.11 (3H, s, 3- CH_3); 1.2-2.6 (7H, m, ring protons); 4.94 and 5.01 (total 2H, both d, 17 and 10.5 Hz, $\text{CH}_2=$) and 5.64 ppm (1H, dd, 17 and 11 Hz, =CH).

b) 1,3, trans-5-trimethyl-*cis*-3-vinylcyclohexanol (43).

A solution of ketone 42 (1g, 6.6 mmol) in diethyl ether (10 ml) was added to 1.6M methyl lithium solution in diethyl ether (12 ml, 19.6 mmol) while cooling in an ice bath. The resulting mixture was stirred for 1 h at $0-5^{\circ}\text{C}$ and saturated aqueous NH_4Cl (10 ml) was added thoroughly. The aqueous layer was separated and extracted with diethyl ether (2 15 ml). The combined organic phases were washed with brine (20 ml) and dried over MgSO_4 . The extract was filtered and evaporated. The crude product was purified by flash chromatography on silica gel (3% ethyl acetate in light petroleum ether). Cyclohexanol 43 (0.82 g, 74 %) was obtained as a colorless oil that was used in the next step without characterization.

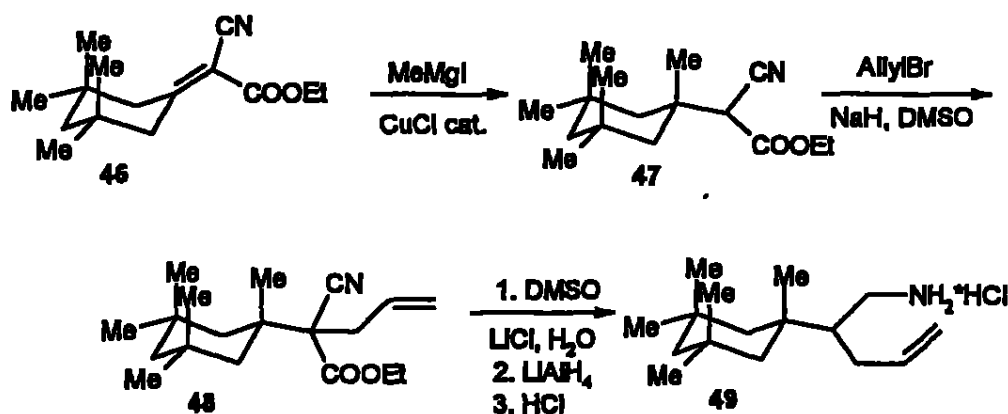
c) 1-Azido-1,3, trans-5-trimethyl-*cis*-3-vinylcyclohexane (44).

Prepared from cyclohexanol 43 according to the procedure for compound

9 (Example 3, b). Azide 44 obtained as a colorless oil with 17% yield. ¹H-NMR (CDCl₃, TMS) : 0.94 (3H, d, 6.5 Hz, 5-CH₃); 0.97 (3H, s, 3-CH₃); 1.27 (3H, s, 1-CH₃); 0.7-2.0 (7H, m, ring protons); 4.95 and 4.97 (total 2H, both d, 18 and 11 Hz, =CH₂) and 5.77 ppm (1H, dd, 18 and 11 Hz, =CH).

d) 1,3, trans-5-trimethyl-clis-3-vinylcyclohexanamine hydrochloride (45). Prepared from azide 44 according to the procedure for compound 11 (Example 3, c). Amine hydrochloride 45 obtained as a colorless solid with 32% yield. ¹H-NMR (CDCl₃, TMS) : 0.92 (3H, d, 6.5 Hz, 5-CH₃); 0.96 (3H, s, 3-CH₃); 1.45 (3H, s, 1-CH₃); 0.8-2.1 (9H, m, 2,4,6-CH₂, 5-CH and H₂O); 4.94 and 4.97 (2H, both d, 18 and 11 Hz, =CH₂); 5.76 (1H, dd, 18 and 11 Hz, =CH) and 8.26 ppm (3H, br s, NH₃⁺).

15 Scheme: Example 17



Example 17.

2-(1,3,3,5,5-Pentamethylcyclohexyl)-4-pentenylamine hydrochloride (49).

20

a) Ethyl 2-cyano-2-(1,3,3,5,5-pentamethylcyclohexyl)acetate (47).

Copper (I) chloride (0.05 g, 0.5 mmol) was added to a cooled (-10 °C) in

argon atmosphere 1M methylmagnesium iodide in ethyl ether (15 ml, 15 mmol) and stirred for 5 min. Then a solution of acetate 46 (2.5 g, 10 mmol) in THF (25 ml) was added dropwise within 20 min, keeping the temperature below 0 °C. The mixture was stirred for 1 h, quenched with saturated aqueous NH₄Cl, and extracted with diethyl ether. The extract was washed with brine, dried over anhydrous MgSO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 20: 1) to give 47 (1.5 g, 56.5 %) as a colorless oil. ¹H NMR (CDCl₃, TMS) : 1.01, 1.07 and 1.09 (total 12H, s, 3',5'-CH₃); 1.00-1.85 (6H, m, ring CH); 1.30 (3H, s, 1'-CH₃); 1.33 (3H, t, 7 Hz, CH₃-ethyl); 3.44 (1H, s, 2-CH) and 4.27 ppm (2H, q, 7 Hz, OCH₂).

b) Ethyl 2-cyano-2-(1,3,3,5,5-pentamethylcyclohexyl)-4-pentenoate (48)

To a solution of cyanoacetate 47 (1.25 g, 4.71 mmol) in anhydrous DMSO (10 ml) was added sodium hydride (0.284 g, 7.09 mmol; 60% mineral oil dispersion). The mixture was stirred for 30 min at 50 °C, and cooled to 20 °C. To this was added allylbromide (0.86 g, 7.1 mmol) and the mixture was stirred for 3 h at room temperature, then for 30 min at 50 °C. The mixture was cooled, treated with water and extracted with diethyl ether. The extract was washed with water and with brine, dried over anhydrous MgSO₄, filtered and evaporated. The residue was purified by flash chromatography on silica gel (light petroleum ether - ethyl acetate, 20: 1) to give 48 (0.92 g, 63.7 %) as a colorless oil. ¹H NMR (CDCl₃, TMS) : 0.98 (6H, s, 3',5'-CH₃); 1.11 (6H, s, 3',5'-CH₃); 1.00-1.85 (6H, m, ring CH); 1.31 (3H, t, 7 Hz, CH₃-ethyl); 1.33 (3H, s, 1'-CH₃); 2.42 and 2.86 (total 2H, both dd, 13 and 7 Hz, 3-CH₂); 4.02 (2H, q, 7 Hz, OCH₂); 5.05-5.37 (2H, m, =CH₂) and 5.55-6.05 ppm (1H, m, =CH).

53

c) 2-(1,3,3,5,5-Pentamethylcyclohexyl)-4-pentenylamine hydrochloride (49)

To a solution of ester 48 (0.9 g, 2.95 mmol) in DMSO (10 ml) was added water (0.53 ml, 2.95 mmol) and lithium chloride (0.25 g, 5.9 mmol). The mixture was stirred for 3 h at 175-180 °C, then it was cooled and water (30 ml) was added. The mixture was extracted with diethyl ether. The extract was washed with water and with brine, dried over anhydrous MgSO₄, filtered and concentrated to 10 ml volume. The solution obtained was added dropwise to a suspension of lithium aluminum hydride (0.25 g, 6.6 mmol) in diethyl ether (15 ml) and stirred at reflux for 3 h. The mixture was cooled and treated with 20% aqueous NaOH, and extracted with diethyl ether. The extract was washed with brine, dried over NaOH, filtered and treated with anhydrous HCl solution in diethyl ether. After evaporation of the solvent, the residue was purified by chromatography on silica gel (chloroform - methanol, 20:1) to give 49 (0.245 g, 31 %) as a colorless solid. ¹H NMR (DMSO-D₆, TMS) : 0.92, 0.96 and 1.04 (total 15H, all s, 3[°], 5[°]-CH₃ and 1[°]-CH₃); 1.00-1.65 (total 6H, m, ring-CH₂); 1.85-2.40 (3H, m, 3-CH₂, 4-CH); 2.60-3.10 (2H, m, CH₂N); 4.90-5.25 (2H, m, =CH₂); 5.62-6.10 (1H, m, =CH) and 7.92 ppm (3H, br s, NH₃⁺).

20

PHARMACEUTICAL COMPOSITIONS

The active ingredients of the invention, together with one or more conventional adjuvants, carriers, or diluents, may be placed into the form of pharmaceutical compositions and unit dosages thereof, and in such form may be employed as solids, such as coated or uncoated tablets or filled capsules, or liquids, such as solutions, suspensions, emulsions, elixirs, or capsules filled with the same, all for oral use; in the form of suppositories or capsules for rectal administration or in the form of sterile injectable solutions for parenteral (including intravenous or subcutaneous) use. Such pharmaceutical compositions and unit dosage forms thereof

may comprise conventional or new ingredients in conventional or special proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed. Tablets containing twenty (20) to one hundred (100) milligrams of active ingredient or, more broadly, ten (10) to two hundred fifty (250) milligrams per tablet, are accordingly suitable representative unit dosage forms.

10

METHOD OF TREATING

Due to their high degree of activity and their low toxicity, together presenting a most favorable therapeutic index, the active principles of the invention may be administered to a subject, e.g., a living animal (including a human) body, in need thereof, for the treatment, alleviation, or amelioration, palliation, or elimination of an indication or condition which is susceptible thereto, or representatively of an indication or condition set forth elsewhere in this application, preferably concurrently, simultaneously, or together with one or more pharmaceutically-acceptable excipients, carriers, or diluents, especially and preferably in the form of a pharmaceutical composition thereof, whether by oral, rectal, or parental (including intravenous and subcutaneous) or in some cases even topical route, in an effective amount. Suitable dosage ranges are 1-1000 milligrams daily, preferably 10-500 milligrams daily, and especially 50-500 milligrams daily, depending as usual upon the exact mode of administration, form in which administered, the indication toward which the administration is directed, the subject involved and the body weight of the subject involved, and the preference and experience of the physician or veterinarian in charge.

55

EXAMPLES OF REPRESENTATIVE PHARMACEUTICAL COMPOSITIONS

With the aid of commonly used solvents, auxillary agents and carriers, the reaction products can be processed into tablets, coated tablets, capsules, drip solutions, suppositories, injection and infusion
5 preparations, and the like and can be therapeutically applied by the oral, rectal, parenteral, and additional routes. Representative pharmaceutical compositions follow.

(a) Tablets suitable for oral administration which contain the active ingredient may be prepared by conventional tableting techniques.

10 (b) For suppositories, any usual suppository base may be employed for incorporation therein by usual procedure of the active ingredient, such as a polyethyleneglycol which is a solid at normal room temperature but which melts at or about body temperature.

(c) For parental (including intravenous and subcutaneous) sterile
15 solutions, the active ingredient together with conventional ingredients in usual amounts are employed, such as for example sodium chloride and double-distilled water q.s., according to conventional procedure, such as filtration, aseptic filling into ampoules or IV-drip bottles, and autoclaving for sterility.

20 Other suitable pharmaceutical compositions will be immediately apparent to one skilled in the art.

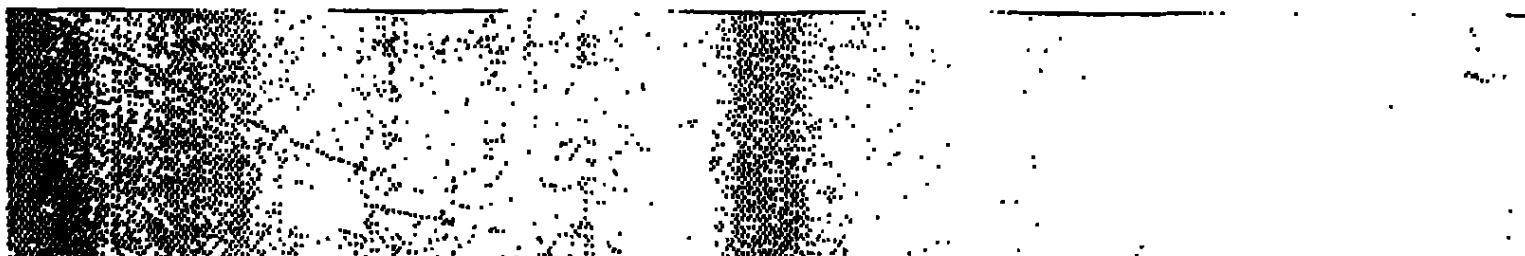
The following examples are again given by way of illustration only and are not to be construed as limiting.

25

EXAMPLE 18

Tablet Formulation

A suitable formulation for a tablet containing 10 milligrams of



active ingredient is as follows:

	Mg.
5 Active Ingredient	10
Lactose	63
Microcrystalline Cellulose	21
Talcum	4
Magnesium stearate	1
10 Colloidal silicon dioxide	1

EXAMPLE 19**Tablet Formulation**

Another suitable formulation for a tablet containing 100 mg is as follows:

5		
		Mg.
	Active Ingredient	100
	Potato starch	20
	Polyvinylpyrrolidone	10
10	Film coated and colored.	
	The film coating material consists of:	
	Lactose	100
	Microcryst. Cellulose	80
	Gelatin	10
15	Polyvinylpyrrolidone, crosslinked	10
	Talcum	10
	Magnesium stearate	2
	Colloidal silicon dioxide	3
	Color pigments	5
20		

EXAMPLE 20**Capsule Formulation**

A suitable formulation for a capsule containing 50 milligrams of active ingredient is as follows:

5

	Mg.
Active ingredient	50
Corn starch	20
10 Dibasic calcium phosphate	50
Talcum	2
Colloidal silicon dioxide	2

filled in a gelatin capsule.

15

EXAMPLE 21**Solution for injection**

A suitable formulation for an injectable solution containing one percent of active ingredient is as follows:

20

Active ingredient	mg	12
Sodium chloride	mg	8
Sterile water to make ml		1

25

EXAMPLE 22**Liquid oral formulation**

A suitable formulation for 1 liter of a liquid mixture containing 2 milligrams of active ingredient in one milli liter of the mixture is as follows:

5		
		G.
	Active Ingredient	2
	Saccharose	250
10	Glucose	300
	Sorbitol	150
	Orange flavor	10
	Sunset yellow.	
	Purified water to make a total	
15	of 1000 ml.	

60

EXAMPLE 23**Liquid oral formulation**

Another suitable formulation for 1 liter of a liquid mixture
containing 20 milligrams of active ingredient in one milli liter of the mixture
is as follows:

5

G.

	Active Ingredient	20.00
10	Tragacanth	7.00
	Glycerol	50.00
	Saccharose	400.00
	Methylparaben	0.50
	Propylparaben	0.05
15	Black currant-flavor	10.00
	Soluble Red color	0.02
	Purified water to make a total of 1000 ml.	

20

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EXAMPLE 24**Liquid oral formulation**

Another suitable formulation for 1 liter of a liquid mixture
containing 2 milligrams of active ingredient in one milli liter of the mixture
5 is as follows:

	G.
Active Ingredient	2
10 Saccharose	400
Bitter orange peel tincture	20
Sweet orange peel tincture	15
Purified water to make a total of 1000 ml.	

16

EXAMPLE 25**Aerosol formulation**

180 g aerosol solution contain:

5

G.

Active Ingredient	10
Oleic acid	5
Ethanol	81
10 Purified Water	9
Tetrafluoroethane	75

15 ml of the solution are filled into aluminum aerosol cans, capped with a dosing valve, purged with 3.0 bar.

15

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EXAMPLE 26**TDS formulation****100 g solution contain:**

5	G.
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
10	Dimethylsulfoxide 5.0
	Hydroxyethylcellulose 0.4
	Purified water 19.6

1.8 ml of the solution are placed on a fleece covered by an adhesive
backing foil. The system is closed by a protective liner which will be
removed before use.

104
64**EXAMPLE 27****Nanoparticle formulation**

10 g of polybutylcyanoacrylate nanoparticles contain:

5		G.
	Active Ingredient	1.00
	Poloxamer	0.10
	Butylcyanoacrylate	8.75
10	Mannitol	0.10
	Sodiumchloride	0.05

Polybutylcyanoacrylate nanoparticles are prepared by emulsion
polymerization in a water/0.1 N HCl/ethanol mixture as polymerization
15 medium. The nanoparticles in the suspension are finally lyophilized under
vacuum.

PHARMACOLOGY - SUMMARY

The active principles of the present invention, and pharmaceutical
20 compositions thereof and method of treating therewith, are characterized
by unique advantageous and unpredictable properties, rendering the
"subject matter as a whole", as claimed herein, unobvious. The
compounds and pharmaceutical compositions thereof have exhibited , in
standard accepted reliable test procedures, the following valuable
25 properties and characteristics:

They are systemically-active, uncompetitive NMDA receptor
antagonists with rapid blocking/unblocking kinetics and strong voltage

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dependency and are, accordingly, of utility in the treatment, elimination, palliation, alleviation, and amelioration of responsive conditions, by application or administration to the living animal host for the treatment of a wide range of CNS disorders which involve disturbances of glutamatergic transmission.

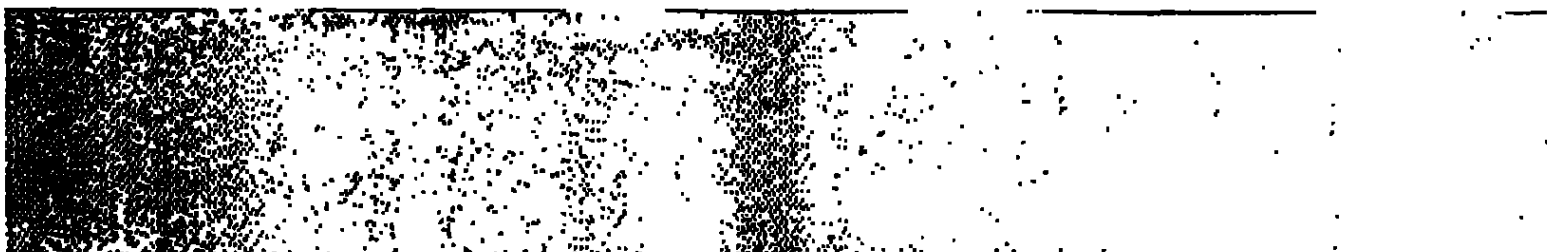
These compounds are also systemically-active, non-competitive 5HT₃ and neuronal nicotinic receptor antagonists and are, accordingly, of utility in the treatment, elimination, palliation, alleviation, and amelioration of responsive conditions, by application or administration to the living animal host for the treatment of a wide range of CNS disorders which involve disturbances of serotonin or nicotinic transmission.

Methods

Receptor Binding Studies

Male Sprague-Dawley rats (200-250g) were decapitated and their brains were removed rapidly. The cortex was dissected and homogenized in 20 volumes of ice-cold 0.32 M sucrose using a glass-Teflon homogenizer. The homogenate was centrifuged at 1000xg for 10 min. The pellet was discarded and the supernatant centrifuged at 20,000xg for 20 min. The resulting pellet was re-suspended in 20 volumes of distilled water and centrifuged for 20 min at 8000xg. Then the supernatant and the buffy coat were centrifuged at 48,000xg for 20 min in the presence of 50 mM Tris-HCl, pH 8.0. The pellet was then re-suspended and centrifuged two to three more times at 48,000xg for 20 min in the presence of 50 mM Tris-HCl, pH 8.0. All centrifugation steps were carried out at 4°C. After resuspension in 5 volumes of 50 mM Tris-HCl, pH 8.0 the membrane suspension was frozen rapidly at -80°C.

On the day of assay the membranes were thawed and washed four times



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by resuspension in 50 mM Tris-HCl, pH 8.0 and centrifugation at 48,000xg for 20 min. and finally re-suspended in 50 mM Tris-HCl, pH 7.4. The amount of protein in the final membrane preparation (250-500 µg/ml) was determined according to the method of Lowry et al. (1951).

5 Incubations were started by adding [³H]-(+)-MK-801 (23.9 Ci/mmol, 5nM, Dupont NEN) to vials with glycine (10 µM), glutamate (10 µM), and 125-250 µg protein (total volume 0.5 ml) and various concentrations of the agents tested (10 concentrations in duplicates). The incubations were continued at room temperature for 120 min (equilibrium was achieved

10 under the conditions used). Non-specific binding was defined by the addition of unlabeled (+)-MK-801 (10 µM). Incubations were terminated using a Millipore filter system. The samples were rinsed twice with 4 ml of ice cold assay buffer over glass fibre filters (Schleicher & Schuell) under a constant vacuum. Following separation and rinse the filters were

15 placed into scintillation liquid (5 ml; Ultima Gold) and radioactivity retained on the filters was determined with a conventional liquid scintillation counter (Hewlett Packard, Liquid Scintillation Analyser). The K_d of [³H]-(+)-MK-801 of 4.6 nM was determined by Scatchard analysis and used according to the Cheng Prussoff relationship to calculate the affinity of

20 displacers as K_d values. Most antagonists were tested in 3 to 7 separate experiments.

NMDA and Neuronal Nicotinic Receptor Subtype Expression in *Xenopus* Oocytes

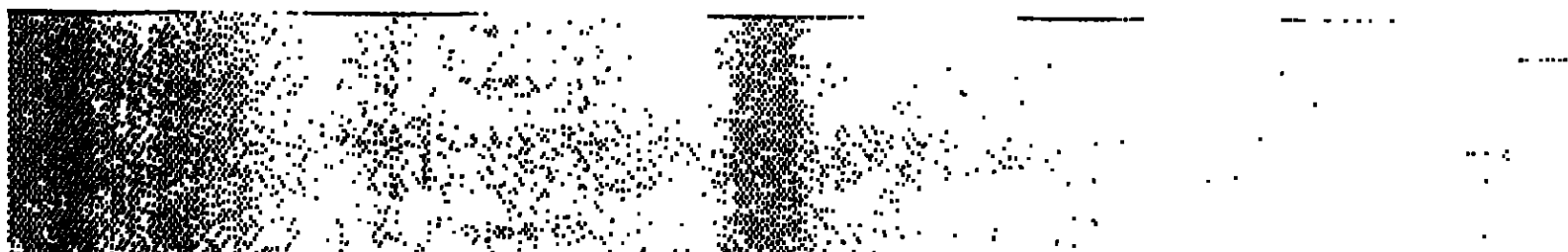
25 Mature female *Xenopus laevis* were anaesthetized in 0.2% Tricaine on ice for 15 min prior to surgery. Oocytes were removed and incubated in 2 mg/ml collagenase (type II) in Ca²⁺-free oocyte Ringer solution (82.5 mM NaCl, 2 mM KCl, 2 mM-MgCl₂, 5 mM HEPES, pH 7.5) for 30 min. at room temperature and washed thoroughly with OR-2 (100 mM NaCl, 2 mM

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KCl, 1 mM MgCl₂, 2 mM CaCl₂, 5 mM HEPES, pH 7.5). The remaining follicle cell layer was removed manually with fine forceps and the oocytes were kept in OR-2. The RNA was dissolved in DEPC-treated, sterile distilled water. RNA for the NMDA NR1a subunit was mixed 1:1 with
5 RNA for the NR2A subunit. Likewise neuronal nicotinic $\alpha 4$ RNA was mixed 1:1 with RNA for the $\beta 2$ subunit. Fifty to 100 nanoliters of each RNA mixture were injected in the oocyte's cytoplasm using a Nanoliter Injector (World Precision Instruments). The oocytes were incubated at 19°C in OR-2 for the following 3 to 6 days.

10 The electrophysiological responses were obtained using the standard two-electrode voltage-clamp method (GeneClamp 500 amplifier), 2-6 days after injection. The electrodes had a resistance between 0.2 and 0.4 M Ω and were filled with 3M KCl. Recordings were made in a custom made chamber with 2 to 3 second exchange times. The bath solution was
15 prepared Ca²⁺-free, to avoid Ca²⁺-induced Cl⁻ currents (100 mM NaCl, 2 mM KCl, 5 mM HEPES, 2 mM BaCl₂, pH 7.35). NMDA receptors were activated by the manual co-application of 1 mM Glutamate and 10 μ M Glycine for 30-40 secs every 2 to 3 mins to oocytes clamped at -70mV. Neuronal nicotinic receptors were activated by application of 100 μ M
20 acetylcholine for 20-30 secs every 2 to 3 mins to oocytes clamped at -70mV. After obtaining stable control responses, full concentration - response curves with antagonists were obtained by preincubating 6-7 different concentrations at log 3 intervals.

Only results from stable cells were accepted for inclusion in the
25 final analysis i.e. showing at least 50% recovery of responses to NMDA following removal of the antagonist tested. Despite this, recovery from drug actions wasn't always 100% because of minor rundown or runup in some cells. When present, this was always compensated by basing the % antagonism at each concentration on both control and recovery and
30 assuming a linear time course for this rundown. All antagonists were

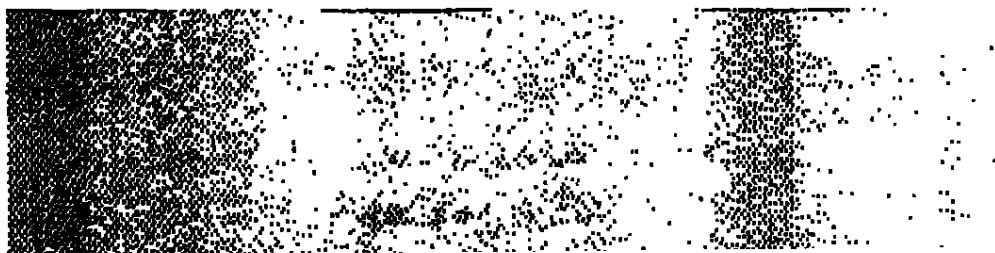


assessed at steady-state blockade with 6 to 7 concentrations on at least 4 cells. Equilibrium blockade was achieved within 1 to 3 agonist applications, depending on antagonist concentration.

Kinetic experiments were performed by applying various concentrations of unsaturated amino-alkyl-cyclohexanes (normally 5 in a log 3 dosing regime) for 10-20 seconds in the continuous presence of glutamate (100 μ M and glycine 10 μ M) for 90-180 seconds in *Xenopus* oocytes expressing NR1a/2A receptors. The perfusion system used for these experiments was a modified oocyte carousel system which allows rapid wash in and wash out of agonist and antagonist with change times less than one second. Exponential fits were made using the program TIDA for windows and most responses were well fitted by a single exponential. This same system was used to access the voltage-dependency of blockade, but the bath solution contained flufenamic acid (100 μ M) to block endogenous voltage-activated and Ca^{2+} activated Cl^- currents. Also, Ba^{2+} (2mM) was replaced by low concentrations of Ca^{2+} (0.2 mM). Following equilibrium blockade by higher concentrations of antagonist (normally around 10 times the IC_{50}), five ramps were driven from -70 mV to +30 mV over two seconds. Similar ramps were driven in bath solutions and for glutamate without antagonist, both before antagonist application and following recovery of responses. The leak currents in the absence of glutamate were subtracted from the glutamate and glutamate plus antagonist curves. Voltage-dependency was then determined by comparing the glutamate and glutamate plus antagonist curves.

Patch Clamp for NMDA and Nicotine

Hippocampi were obtained from rat embryos (E20 to E21) and were then transferred to calcium and magnesium free Hank's buffered salt



69

solution (Gibco) on ice. Cells were mechanically dissociated in 0.05% DNAase / 0.3% ovomucoid (Sigma) following an 8 minute pre-incubation with 0.66% trypsin / 0.1% DNAase (Sigma). The dissociated cells were then centrifuged at 18xg for 10 minutes, re-suspended in minimum essential medium (Gibco) and plated at a density of 150,000 cells cm⁻² onto poly-L-lysine (Sigma)-precoated plastic petri dishes (Falcon). The cells were nourished with NaHCO₃/HEPES-buffered minimum essential medium supplemented with 5% fetal calf serum and 5% horse serum (Gibco) and incubated at 37 C with 5%CO₂ at 95% humidity. The medium was exchanged completely following inhibition of further glial mitosis with cytosine-*-D*-arablnofuranoside (20 M Sigma) after about 7 days in vitro. Thereafter the medium was exchanged partially twice weekly.

Patch clamp recordings were made from these neurones with polished glass electrodes (4-6 m) in the whole cell mode at room temperature (20-22 C) with the aid of an EPC-7 amplifier (List). Test substances were applied by switching channels of a custom-made fast superfusion system with a common outflow (10-20 ms exchange times). The contents of the Intracellular solution were as follows (mM): CsCl (120), TEACl (20), EGTA (10), MgCl₂(1),CaCl₂(0.2), glucose (10), ATP(2), cAMP (0.25); pH was adjusted to 7.3 with CsOH or HCl. The extracellular solutions had the following basic composition (mM): NaCl (140), KCl (3), CaCl₂ (0.2), glucose (10), HEPES (10), sucrose (4.5), tetrodotoxin (TTX 3*10⁻⁴). Glycine (1 M) was present in all solutions: a concentration sufficient to cause around 80-85% activation of glycine_α receptors. Only results from stable cells were accepted for inclusion in the final analysis, i.e., following recovery of responses to NMDA by at least 75% of their depression by the antagonists tested.

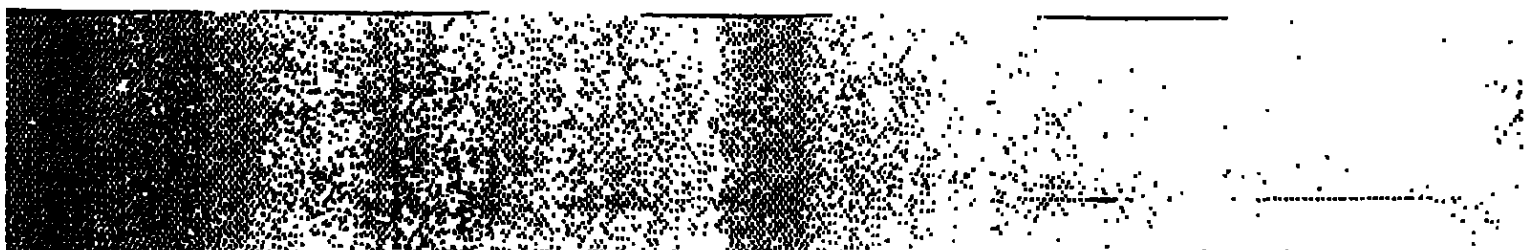
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Patch Clamp for 5-HT3

N1E-115 cells were purchased from the European collection of cell cultures (ECACC, Salisbury, UK) and stored at -80°C until further use. The cells were plated at a density of 100,000 cells cm⁻² onto plastic Petri dishes (Falcon) and were nourished with NaHCO₃/HEPES-buffered minimum essential medium supplemented (MEM) with 15% fetal calf serum (Gibco) and incubated at 37°C with 5%CO₂ at 95% humidity. The medium was exchanged completely daily. Once every three days, cells were reseeded onto fresh Petri dishes following treatment with trypsin - EDTA (1% in PBS), resuspension in MEM and centrifugation at 1000 rpm for four minutes.

Patch clamp recordings at -70 mV were made from lifted cells, 2-3 days following seeding with polished glass electrodes (2-6MΩ) in the whole cell mode at room temperature (20-22°C) with an EPC-7 amplifier (List). The contents of the intracellular solution were as follows (mM): CsCl (130), HEPES (10), EGTA (10), MgCl₂ (2), CaCl₂ (2), K-ATP (2), Tris-GTP (0.2), D-glucose (10); pH was adjusted to 7.3 with CsOH or HCl. The extracellular solutions had the following basic composition (mM): NaCl (124), KCl (2.8), HEPES (10), pH 7.3 adjusted with NaOH or HCl.

After the whole-cell configuration was established, the cells were lifted from the glass substrate and serotonin (10μM), memantine and unsaturated amino-alkyl-cyclohexane derivatives were applied at various concentrations using a fast superfusion device. A piezo translator -driven double-barrelled application pipette was used to expose the lifted cell either to serotonin-free or serotonin-containing solution. A two second serotonin pulse was delivered every 60 seconds. The putative antagonists were dissolved in aqua-bidest and diluted with bath solution to the desired concentration. Only results from stable cells were accepted for inclusion in the final analysis, i.e., showing at least 50%



recovery of responses to serotonin following removal of compounds. Despite this, recovery from drug actions wasn't always 100% because of rundown in some cells ($\leq 10\%$ over 10 minutes). When present, this was always compensated by basing the percent antagonism at each concentration on both control and recovery and assuming a linear time course for this rundown. All antagonists were assessed at steady-state blockade with 3 to 6 concentrations on at least five cells. Equilibrium blockade was achieved within 2 to 5 agonist applications, depending on antagonist concentration.

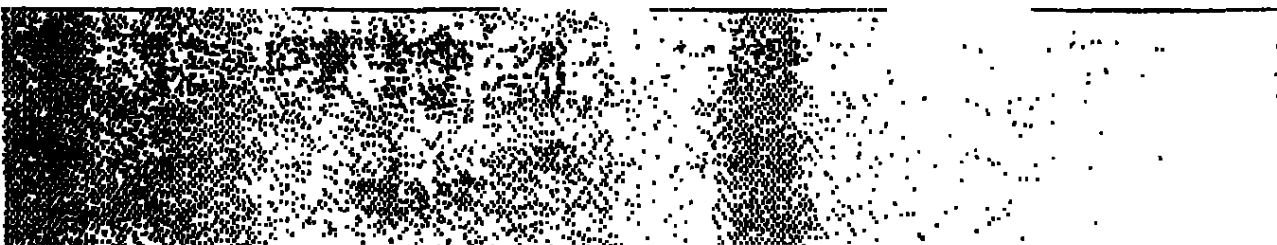
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In vivo

Anticonvulsive activity

NMR female mice (18-28 g) housed 5 per cage were used for the maximal electroshock (MES) and motor impairment tests. All animals were kept with water and food ad libitum under a 12 hour light-dark cycle (light on at 6 a.m.) and at a controlled temperature (20 ± 0.5 C). All experiments were performed between 10 a.m. and 5 p.m. Tested agents were injected 30 min. i.p. before the induction of convulsions if not stated otherwise (see below). All compounds were dissolved in 0.9% saline.

The MES test was performed together with tests for myorelaxant action (traction reflex) and motor coordination (rotarod). For the traction reflex test mice were placed with their forepaws on a horizontal rod and were required to place all 4 paws on the wire within 10 seconds. To test ataxia (motor coordination) mice were placed on an accelerating rotarod and were required to remain on the rod for 1 minute. Only mice not achieving the criteria in all three repetitions of each test were considered to exhibit myorelaxation or ataxia respectively. These tests were followed by MES (100 Hz, 0.5 second shock duration, 50 mA shock intensity, 0.9 ms impulse duration, Ugo Basile) applied through corneal



72

electrodes. The presence of tonic convulsions was scored (tonic extension of hind paws with minimum angle to the body of 90°). The aim was to obtain ED₅₀s for all parameters scored (anticonvulsive activity and motor side effects) with use of the Litchfield Wilcoxon test for quantal dose responses. Division of the ED₅₀ for side effects (ataxia or myorelaxation) by the ED₅₀ for antagonism of electroshock convulsions was used as a therapeutic index (TI).

Statistical analysis

10 IC₅₀s in patch clamp and binding studies were calculated according to the four parameter logistic equation using the Grafit computer program (Erithacus Software, England). Ki value for binding studies were then determined according to Cheng and Prusoff. Binding values presented are means ± SEM of 3-5 determinations (each performed in duplicate).

15 4-7 doses of antagonists were tested in each of the in vivo tests (5-8 animals per dose) to allow calculation of graded ED₅₀s according to probit analysis (Litchfield and Wilcoxon) with correction for 0% to 100% effects. ED₅₀s are presented with 95% confidence limits (CI). Pearson product moment correlation analysis (Sigma Stat, Jandel Scientific) was
20 used to compare in vitro potencies and in vivo anticonvulsant activity.

RESULTS

MRZ Numbers

MRZ numbers are used to represent chemical names. The MRZ
25 numbers and their respective chemical names are shown in "MRZ LIST".

MRZ LIST

MRZ	Chemical Name
2/657	1-amino-2,4,4,6,6-pentamethyl-cyclohex-2-en Hydrochloride
2/749	1-(1-Aminoethyl)-3,3,5,5-tetramethylcyclohexene
2/758	1-Ethenyl-3,3,5,5-tetramethylcyclohexylamine
2/1005	1-Amino-3,3,5,5-Tetramethyl-1-cyclohexene
2/1021	2-(3,3,5,5-Tetramethylcyclohexylidene)ethanamine
2/1023	1-Amino-3,3,5-trimethyl-2-cyclohexene
2002	1,3,5,5-Tetramethyl-2-cyclohexen-1-amine
2005	1-Allyl-3,3,5,5-tetramethylcyclohexanamine
2006	1-(3,3,5,5-Tetramethylcyclohexylidene)-2-propanamine
2008	1-(3,3-Diethyl-5,5-dimethylcyclohexylidene)-2-propanamine
2009	de-3-Vinyl-1,3,trans-5-trimethylcyclohexylamine
2010	2-Methyl-1-(3,3,5,5-tetramethyl-1-cyclohexen-1-yl)-2-propanamine
2013	1-(1-Allyl-3,3,5,5-tetramethylcyclohexyl)piperidine
2014	2-(1-Vinyl-3,3,5,5-tetramethylcyclohexyl-1)ethylamine
2015	1-[3,3,5,5-Tetramethyl-1-(3-methyl-2-butenyl)cyclohexyl]piperidine
2016	1-[3,3,5,5-Tetramethyl-1-(2-propynyl)cyclohexyl]piperidine
2017	2-(1,3,3,5,5-Pentamethylcyclohexyl)-4-pentanamine
2018	3-(3,3,5,5-Tetramethylcyclohexylidene)propanamine
2019	2-Methyl-1-(3,3,5,5-tetramethylcyclohexylidene)-2-propanamine
2020	2-(3,3,5,5-Tetramethylcyclohexylidene)propanamine
2021	N-Methyl-1-ethenyl-3,3,5,5-tetramethylcyclohexylamine
2026	N-Allyl-1,3,3,5,5-pentamethylcyclohexanamine

5 Binding MK-80

All compounds displaced [^3H]-(+)-MK-801 with K_i values between 1 and 83 μM (see Table 1).

Table 1

MRZ	Group	[³ H]MK-801 Ki	SEM	n	NMDA IC ₅₀ (μM)	SEM	N
2/657	Ethylene Ring	13.43	1.15	3			
2/749	Ethylene Ring	10.76	1.49	3			
759	Ethylene	1.18	0.20	6	3.28	0.60	6
2/1005	Ethylene Ring	13.63	1.43	4			
2/1021	Ethylene	2.15	0.32	6	0.33	0.05	6
1023	Ethylene Ring	48.60	8.08	6			
2000	Neramexane Sulphate	1.68	0.00	3			
2002	Ethylene Ring	5.70	0.48	3			
2005	Ethylene	9.36	0.12	3	12.60	5.68	6
2006	Ethylene	10.06	0.40	3			
2008	Ethylene	8.07	0.57	3	2.74	0.22	6
2009	Ethylene	22.32	0.88	3	58.17	8.87	6
2013	Ethylene	49.21	11.73	3			
2014	Ethylene	3.12	0.87	3	0.10	0.01	6
2015	Ethylene	63.04	30.66	3			
2016	Ethylene	42.22	13.60	3	71.17	14.66	6
2017	Ethylene	6.79	0.51	3	1.19	0.16	6
2018	Ethylene	20.18	2.60	3	37.06	13.37	6
2019	Ethylene	73.08	8.87	3			
2020	Ethylene	7.45	0.66	3			
2021	Ethylene	6.54	0.72	3	12.73	0.50	6
2010	Ethylene Ring	44.88	13.91	3			
2028	Ethylene				29.58	1.84	6

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The results for representative compounds are reported in Figure 1.

NMDA RECEPTOR SUBTYPE EXPRESSION IN XENOPUS OOCYTES.

NMDA receptor blockade by MRZ 2/759 was determined by applying various concentrations (0.1 to 100 μ M in a log 3 dosing regime) for 10 seconds in the continuous presence of glutamate (100 μ M) and glycine 10 μ M) at -70 mV for 100 seconds in *Xenopus* oocytes expressing NR1a/2A receptors (Figure 2, left). The potency of MRZ 2/759 (IC_{50} = 1.99 μ M, Hill 0.75) was determined by plotting percent blockade against antagonist concentration and then fitting the curve according to the logistic equation (Figure 2, right).

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Patch Clamp

Steady-state inward current responses of freshly dissociated hippocampal neurones to NMDA (200 M with glycine 1 M at -70mV) were antagonized by MRZ 2/759. Peak and steady-state currents were affected to a similar degree making it unlikely that its effects were mediated at the glycine_a site. Strong support for the uncompetitive nature of this antagonism was provided by the clear use- and voltage-dependency of its blockade. See Figure 3.

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Invivo

Anti-Convulsive Activity

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MES and Myorelaxant action results are presented in Table 2.

Table 2

MRZ	MES ED50	MES CL	Myorelocation ED50	Myorelocation CI	Abada ED50	Abada CI	TI Myorelocation	TI Abada
2/857	> 30		> 30		> 30			
2/748	28.68	20.7 - 34.1	36.84	28.6 - 52.1	37.14	30.0 - 48.0	1.5	1.4
2/769	14.84	9.8 - 23.1	12.78	10.3 - 16.9	15.00	11.4 - 19.8	0.9	1.0
2/1005	20.48	9.8 - 43.9	35.88	28.1 - 48.7	28.63	18.1 - 44.8	1.7	1.3
2/1021	28.48	17.8 - 48.9	18.50	10.9 - 25.0	23.08	15.2 - 35.0	0.8	0.8
2/1023	> 50		> 50		> 50			
2002	28.14	21.0 - 32.5	33.98	27.1 - 42.8	52.98	27.8 - 100.8	1.3	2.0
2005	37.34	33.8 - 41.1	38.75	32.6 - 48.4	48.34	37.2 - 85.5	1.1	1.3
2008	57.02	31.4 - 103.4	44.82	38.4 - 50.5	40.88	31.4 - 58.9	0.8	0.7
2008								
2009	> 50		> 50		> 50			
2010	> 50		> 50		> 50			
2013	> 50		> 50		> 50			
2014	47.82	21.5 - 108.5	13.95	8.3 - 31.1	25.83	18.3 - 38.4	0.3	0.5
2015	> 50		> 50		> 50			
2016	> 50		> 50		> 50			
2017	38.88	29.1 - 48.7	35.63	30.0 - 42.3	33.72	25.0 - 45.4	1.0	0.9
2018	78.54	35.0 - 178.3	29.43	23.4 - 37.0	28.70	19.2 - 37.0	0.4	0.3
2019	> 50		> 50		> 50			
2020	28.08	20.4 - 33.3	34.48	28.1 - 40.8	27.57	18.7 - 40.7	1.3	1.1
2021	13.58	21.5 - 20.7	21.42	18.0 - 25.4	24.88	20.1 30.2	1.8	1.8
2023	> 30		> 30		> 30			
2028	25.38	21.1 - 30.5	28.87	23.2 - 30.7	37.84	21.8 - 85.1	1.1	1.5

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In conclusion, from the foregoing, it is apparent that the present invention provides novel, valuable and unexpected applications and uses of the compounds of the present invention, which compounds comprise the active principle according to the present invention, as well as novel pharmaceutical compositions thereof and methods of preparation thereof and of treating therewith, all possessed of the foregoing more specifically -enumerated characteristics and advantages.

The high order of activity of the active agent of the present invention and compositions thereof, as evidenced by the tests reported, is indicative of utility based on its valuable activity in human beings as well as in lower animals. Clinical evaluation in human beings has not been completed, however. It will be clearly understood that the distribution and marketing of any compound or composition falling within the scope of the present invention for use in human beings will of course have to be predicated upon prior approval by governmental agencies, such as the U.S. Federal Food and Drug Administration, which are responsible for and authorized to pass judgment on such questions.

Conclusions

The instant unsaturated 1-amino-alkylcyclohexanes represent a novel class of systemically-active, uncompetitive NMDA receptor antagonists with rapid blocking/unblocking kinetics and strong voltage -dependency. In view of their moderate potency and associated rapid kinetics, they will be useful therapeutics in a wide range of CNS disorders which involve disturbances of glutamatergic transmission.

These compounds accordingly find application in the treatment of the following disorders of a living animal body, especially a human . 1.
Excitotoxicity such as ischaemia during stroke, trauma, hypoxia, hypoglycemia,

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78

glaucoma, and hepatic encephalopathy. 2. Chronic neurodegenerative diseases such as 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, Creutzfeldt-Jakob disease. 3. 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). 4. Epilepsy, tardive dyskinesia, schizophrenia, anxiety, depression, acute pain, spasticity, and tinnitus.

Furthermore, it was found that these compounds are neuronal nicotinic receptor and 5HT₂ receptor antagonists as well. The compounds of the invention thus find application in the treatment of disorders in a living animal body, especially a human, in both nicotinic and 5HT₂ receptor mediated indications for both symptomatic and neuroprotective purposes (e.g. emesis, nicotine abuse, schizophrenia, cerebellar tremor, IBS, migraine, depressive disorders, cognitive disorders, Parkinson's disease treatment-related psychosis and appetite disorders).

In addition, as already stated, due to at least in part to their amine substituent, the compounds of the present invention are also effective in indications not related to the aforementioned mechanism of action, exhibiting immunomodulatory activity, antimalaria and antitrypanosomal potency, anti-Borna virus, anti-HSV and anti-Hepatitis C virus activity.

The method-of-treating a living animal body with a compound of the invention, for the inhibition of progression or alleviation of the selected ailment therein, is as previously stated by any normally-accepted pharmaceutical route, employing the selected dosage which is effective in the alleviation of the particular ailment desired to be alleviated.

Use of the compounds of the present invention in the manufacture of a

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medicament for the treatment of a living animal for inhibition of progression or alleviation of selected ailments or conditions, particularly ailments or conditions susceptible to treatment with an NMDA receptor antagonist, neuronal nicotinic receptor antagonist, 5HT₃ antagonist, or a compound exhibiting

5 immunomodulatory activity, antimalaria and antitrypanosomal potency, anti-Borna virus, and anti-HSV and anti-Hepatitis C virus activity, is carried out in the usual manner comprising the step of admixing an effective amount of a compound of the invention with a pharmaceutically-acceptable diluent, excipient, or carrier, and the method-of-treating, pharmaceutical compositions, and use of a compound of the present invention in the manufacture of a
0 medicament.

Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier, include tablets, capsules, solutions for injection, liquid oral

5 formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

* * * * *

10 It is to be understood that the invention is not to be limited to the exact details of operation, or to the exact compositions, methods, procedures, or embodiments shown and described, as obvious modifications and equivalents will be apparent to one skilled in the art, and the invention is therefore to be limited only by the full scope which can be legally accorded to the appended
15 claims.

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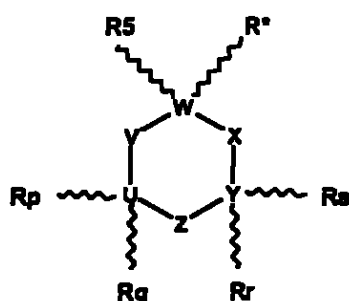
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52

Claims:

1. A compound selected from those of formula I:



wherein:

- 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 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

$-(A)_n-(CR^1R^2)_m-$, 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),

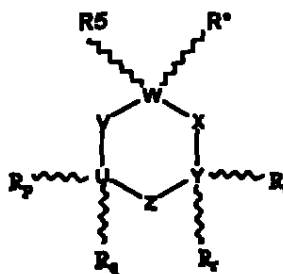
and its optical isomers and pharmaceutically-acceptable acid or base addition salts thereof.

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-1)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.

3. A pharmaceutical composition comprising a compound as claimed in claim 1 or claim 2 in combination with one or more pharmaceutically acceptable diluents, excipients and/or carriers.

4. A method-of-treating a living animal for alleviation of a condition treatable by a NMDA antagonist comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

- R^6 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,
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,

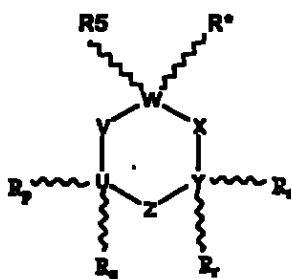
and provided that when U-Z equals cyclohexane, then at least one of $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r is linear or branched lower alkenyl (C_2-C_6) or linear or branched lower alkynyl (C_2-C_6),

its optical isomers and pharmaceutically-acceptable acid or base addition

57

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

5. A method-of-treating a living animal for alleviation of a condition wherein the compound is selected for its immunomodulatory, anti-malarial, anti-Borna virus, or anti-Hepatitis C, anti-trypanosomal, and anti-HSV efficacy, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

- R^1 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_9), and linear or branched lower alkynyl (C_2-C_9), or together form alkylene (C_2-C_{10}) or alkenylene (C_2-C_{10}) or together with the N form an optionally C_{1-9} alkyl- and/or C_{2-9} 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_9), linear or branched lower alkenyl (C_2-C_9), and linear or branched lower alkynyl (C_2-C_9), 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_9) or linear or branched lower alkynyl (C_2-C_9),

its optical isomers and pharmaceutically-acceptable acid or base addition

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

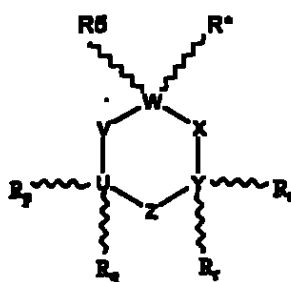
6. A method-of-treating a living animal for alleviation of a condition treatable by an NMDA antagonist selected from the group consisting of excitotoxicity selected from ischaemia during stroke, trauma, hypoxia, hypoglycemia, glaucoma, and hepatic encephalopathy,

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:

- 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,

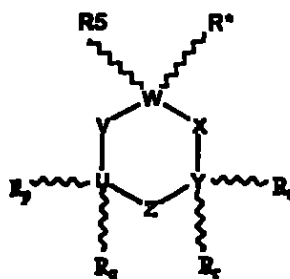
91

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_8) or linear or branched lower alkynyl (C_2-C_8),

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

7. A method-of-treating a living animal for alleviation of a condition treatable by a $5HT_3$ receptor antagonist, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

R^6 is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,

48
92

- $n+m = 0, 1, \text{ or } 2,$
- 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,

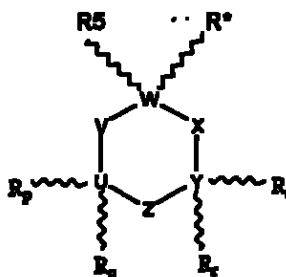
43
93

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_6 , R_7 , R_8 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.

8. A method-of-treating a living animal for alleviation of a condition treatable by a neuronal nicotinic receptor antagonist, comprising the step of administering to the living animal an amount of a compound selected from those of formula I:



wherein:

- R^1 is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ or } 2$,

94

- A is selected from the group consisting of linear or branched lower alkyl (C₁-C₈), linear or branched lower alkenyl (C₂-C₈), and linear or branched lower alkynyl (C₂-C₈),
- R¹ and R² are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C₁-C₈), linear or branched lower alkenyl (C₂-C₈), and linear or branched lower alkynyl (C₂-C₈),
- R³ and R⁴ are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C₁-C₈), linear or branched lower alkenyl (C₂-C₈), and linear or branched lower alkynyl (C₂-C₈), or together form alkylene (C₂-C₁₀) or alkenylene (C₂-C₁₀) or together with the N form an optionally C₁₋₈ alkyl- and/or C₂₋₈ alkenyl-substituted 3-7-membered azacycloalkane or azacycloalkene,
- R⁵, R_p, R_q, R_r, and R_s are independently selected from the group consisting of hydrogen, linear or branched lower alkyl (C₁-C₈), linear or branched lower alkenyl (C₂-C₈), and linear or branched lower alkynyl (C₂-C₈), or R⁵, 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:

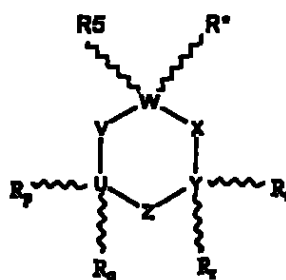
cyclohexane,
cyclohex-1-ene,
cyclohex-2-ene,
cyclohex-3-ene,
cyclohexa-1,3-diene,

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 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 5HT₂ 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^1 is $-(A)_n-(CR^1R^2)_m-NR^3R^4$,

46

- $n+m = 0, 1, \text{ or } 2,$
- 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,

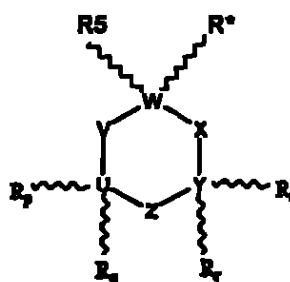
49
97

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:

- R^1 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,

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_8) or linear or branched lower alkynyl (C_2-C_8),

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

11. Use of a compound of formula I as defined in any of claims 4 to 10 and its optical isomers and pharmaceutically-acceptable acid or base addition salts thereof in the manufacture of a medicament for use in a method according to any of said claims 4 to 10.

400
100

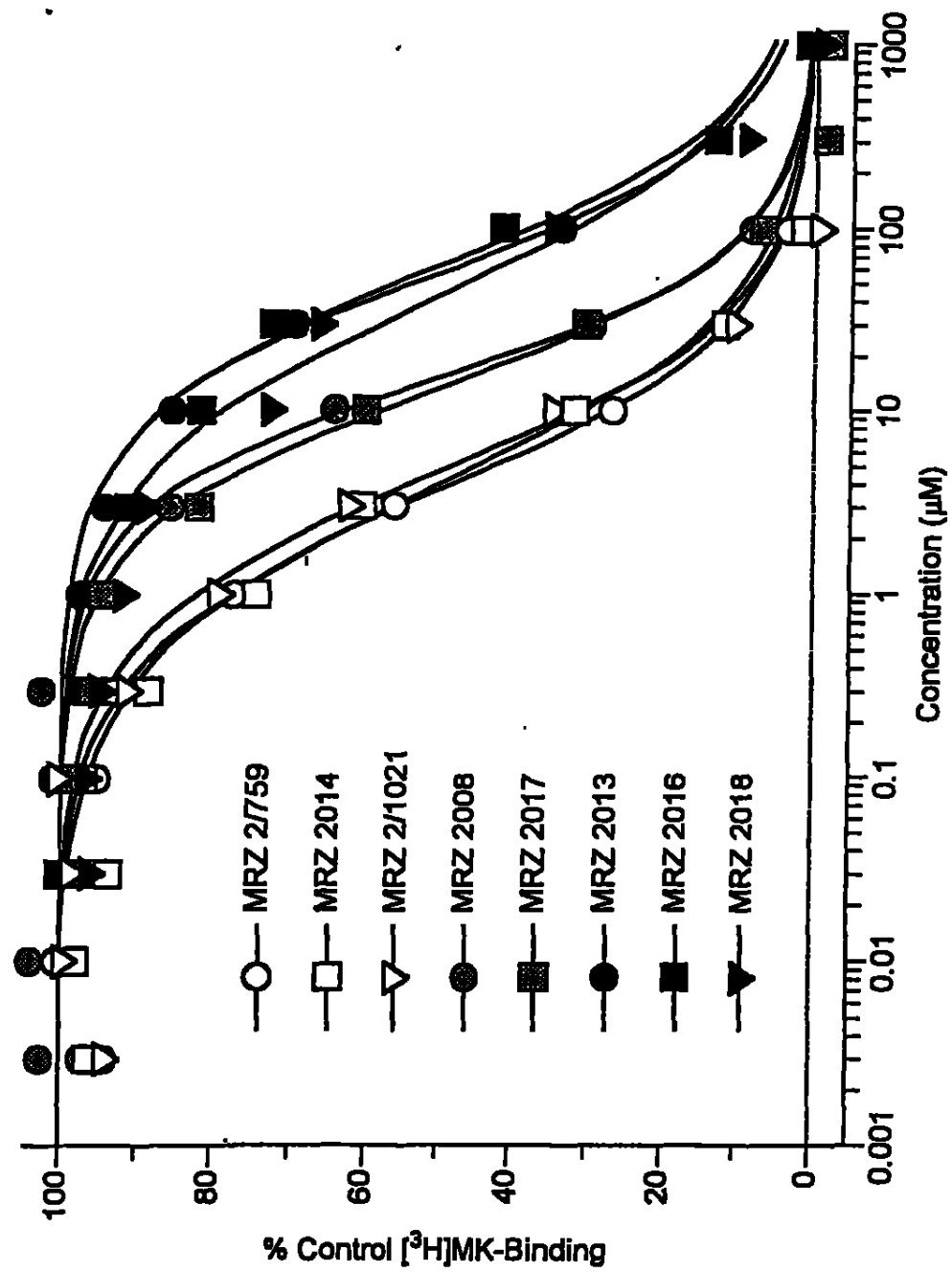


FIG. 1

101

MRZ 2759 on NR1a/2A receptors expressed in *Xenopus* oocytes

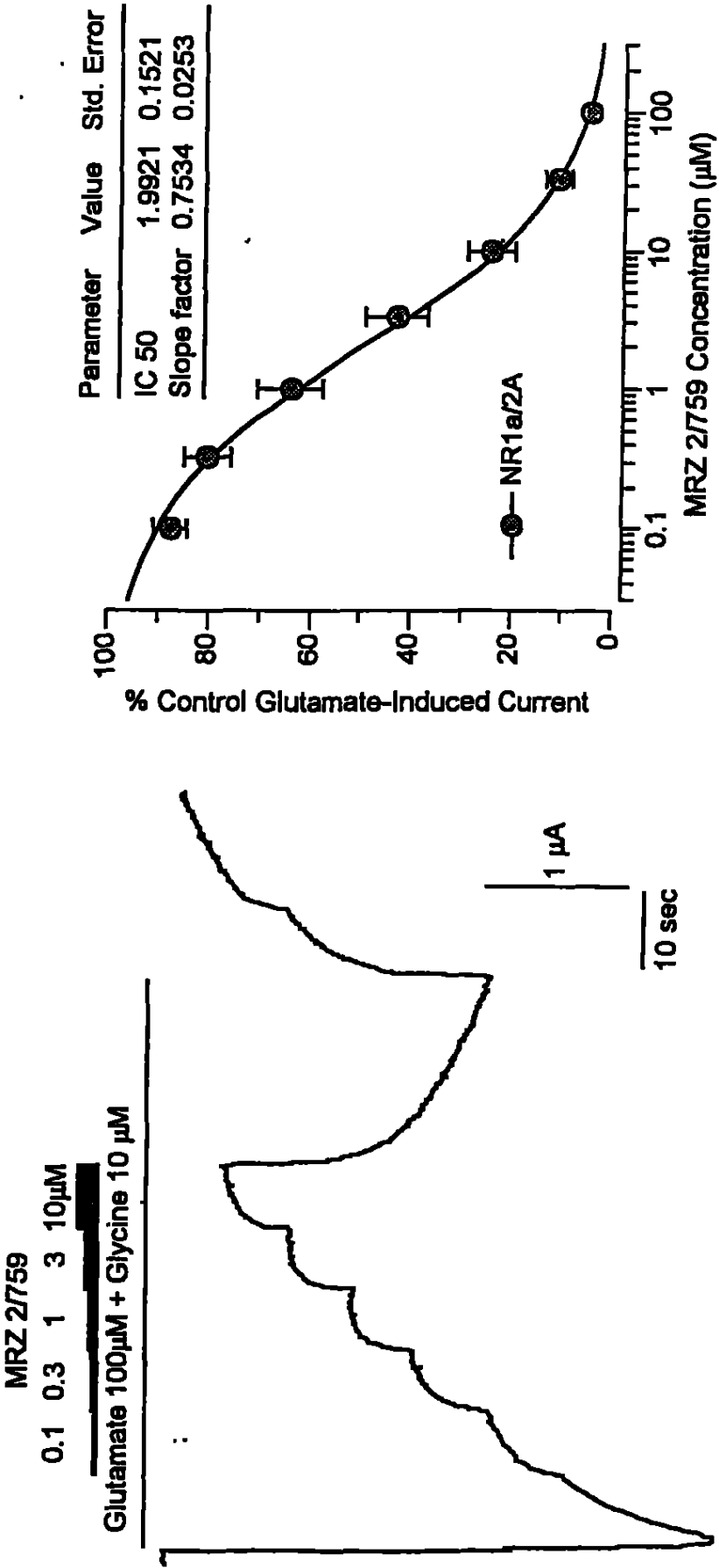


FIG. 2

102

MRZ 2/759 Hippocampus - Patch Clamp

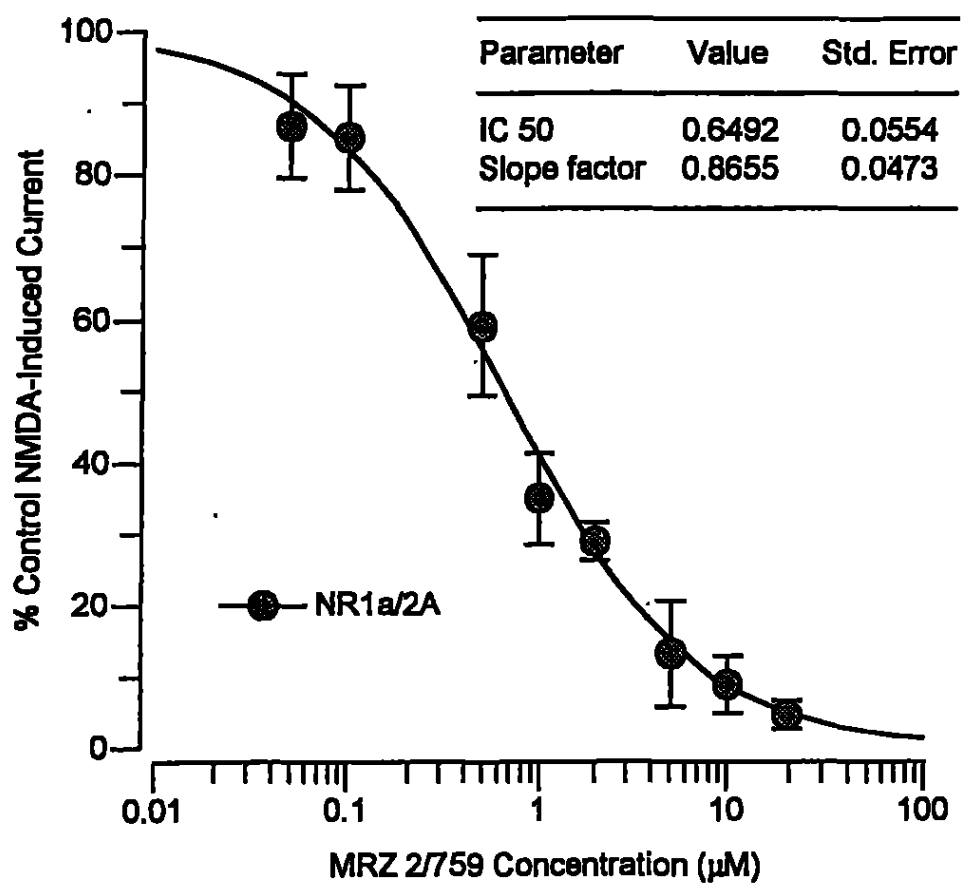


FIG. 3

209
103

**1-AMINO-ALQUILCICLOHEXANOS INSATURADOS COMO
ANTAGONISTAS DE LOS RECEPTORES NMDA, 5HT₃ Y NICOTÍNICO
NEURONAL**

ANTECEDENTES DE LA INVENCION

1. Campo de la invención

Compuestos de 1-amino-alkilciclohexano insaturado que son sistémicamente activos como antagonistas de los receptores NMDA, 5HT₃, y nicotínico, composiciones farmacéuticas que los comprenden, método de preparación de los mismos, y método para tratar trastornos del SNC que incluyen perturbaciones de la transmisión glutamatérgica, serotoninérgica, y nicotínica con los mismos, para tratar trastornos inmunomodulatorios, y para tratar enfermedades infecciosas.

Arte previo

Antagonistas de NMDA

El antagonismo de los receptores de glutamato del tipo N-metil-D-aspartato (NMDA) tiene un rango potencialmente amplio de aplicaciones terapéuticas [19]. Es posible lograr la inhibición funcional de los receptores NMDA mediante acciones sobre diferentes sitios de reconocimiento como por ejemplo el sitio transmisor primario, el sitio glicina insensible a la estricnina (glicina_B), el sitio poliamina, y el sitio fenciclidina que se localizan dentro del canal de cationes. Los bloqueadores del canal del receptor NMDA actúan de una manera no competitiva "dependiente del uso", es decir que usualmente sólo bloquean el canal en el estado abierto. Numerosos investigadores han interpretado que dicha dependencia del uso significa que una activación más fuerte del receptor debería proporcionar un mayor grado de antagonismo.

Además, se ha interpretado que un modo de acción con esas características implica que dicha clase de antagonista puede ser útil en particular cuando se puede esperar una sobreactivación de los receptores NMDA, como por ejemplo en epilepsia, isquemia, y traumatismo. Sin embargo, la experiencia clínica inicial con el antagonista selectivo no competitivo, de alta afinidad y fuertemente dependiente del uso, del receptor NMDA; el maleato de (+)-5-metil-10,11-dihidro-5H-dibenzo-ciclohepten-5,10-imina ((+)-MK-801) ha sido decepcionante. Es decir, que la eficacia terapéutica en epilepsia resultó ser pobre, y además a dosis terapéuticas se hicieron evidentes algunos efectos secundarios psicotrópicos. Dichas observaciones, junto con el hecho de que quienes abusan de la fenciclidina experimentan síntomas psicotrópicos similares, condujeron a la conclusión de que el antagonismo no competitivo de los receptores NMDA no puede ser un enfoque terapéutico prometedor.

Sin embargo, el uso de métodos electrofisiológicos más elaborados indica que no hay equivalencia entre los diferentes antagonistas no competitivos debido a que algunos factores, como por ejemplo la velocidad de bloqueo del receptor (cinética encendido-apagado [*on-off*]) y la dependencia del voltaje de dicho efecto, pueden determinar las características farmacodinámicas *in vivo*, y por lo tanto también la seguridad terapéutica. Es paradójico que puedan ser deseables los agentes con una afinidad baja a moderada, más que alta. Dichos descubrimientos suscitaron una reconsideración sobre el concepto de antagonismo no competitivo de los receptores NMDA en el desarrollo de drogas [19, 22]. Los antagonistas no competitivos del receptor NMDA, como por ejemplo amantadina y memantina - que satisfacen los criterios mencionados anteriormente - se han utilizado

clínicamente durante varios años en el tratamiento de la enfermedad de Parkinson y demencia respectivamente, y por cierto rara vez producen efectos secundarios a las dosis terapéuticas que se utilizan en sus respectivas indicaciones.

En vista de la evidencia mencionada, hemos desarrollado una serie de antagonistas no competitivos del receptor NMDA en base a la estructura del 1-aminoalquilciclohexano insaturado. El presente estudio se concentró en la comparación de las propiedades antagonísticas del receptor NMDA de estos derivados de 1-aminoalquilciclohexano en ensayos de unión al receptor, experimentos electrofisiológicos, un modelo de convulsión y dos modelos de impedimento motor. Las sustituciones de estos 1 -aminoalquilciclohexanos insaturados se detallan en la Tabla 6.

Antagonistas del receptor 5-HT₃

Los receptores 5-HT₃ son receptores ionotrópicos de abertura regulada por ligando, permeables a los cationes. En el ser humano, los receptores 5-HT₃ tienen su densidad más alta en las células enterocromafines de la mucosa gastrointestinal, que están inervadas por aferentes del vago y el área postrema del tronco cerebral, que forma la zona gatillo del quimiorreceptor.

Como los receptores 5-HT₃ no solamente tienen una alta densidad en el área postrema sino también en las regiones del hipocampo y amígdalas del sistema límbico, se ha sugerido que los antagonistas selectivos de 5-HT₃ pueden tener efectos psicotrópicos (Greenshaw & Silverstone, 1997).

Por cierto, los primeros estudios en animales sugirieron que los antagonistas del receptor 5-HT₃, además de su uso antiemético bien reconocido, pueden ser bien útiles clínicamente en varias áreas. Dichas áreas

incluyen trastornos de ansiedad, esquizofrenia, trastornos de abuso de drogas y alcohol, trastornos depresivos, trastornos cognitivos, enfermedad de Alzheimer, tremor cerebeloso, psicosis relacionada con el tratamiento de la enfermedad de Parkinson, dolor (migraña y síndrome del intestino irritable), y trastornos del apetito.

Antagonistas del receptor nicotínico neuronal

Hasta ahora, se conocen diez subunidades alfa (alfa 1-10) y cuatro subunidades beta (beta 1-4) para los receptores nicotínicos. Los receptores $\alpha 4\beta 2$ son probablemente los más comunes en el SNC, especialmente en el hipocampo y el cuerpo estriado. Dichos receptores forman canales de cationes no selectivos con corrientes lenta e incompletamente des-sensibilizantes (tipo II). Los receptores $\alpha 7$ homoméricos son tanto pre- como postsinápticos y se encuentran en el hipocampo, corteza motora y sistema límbico así como en el sistema nervioso autónomo periférico. Dichos receptores se caracterizan por su alta permeabilidad al Ca^{2+} y respuestas rápidas, fuertemente des-sensibilizantes (tipo 1A). Se han relacionado los cambios en los receptores nicotínicos con varias enfermedades. Dichas enfermedades incluyen la enfermedad de Alzheimer, enfermedad de Parkinson, síndrome de Tourette, esquizofrenia, abuso de drogas, abuso de nicotina, y dolor.

Hasta el presente, el desarrollo de drogas se ha dirigido al descubrimiento de agonistas nicotínicos selectivos, sobre la base de la observación que la nicotina en sí, parece tener efectos benéficos como agonista nicotínico.

Por otro lado, no está claro si los efectos, por ejemplo sobre el síndrome de Tourette y la esquizofrenia, de los agonistas nicotínicos se deben a la

activación o inactivación / des-sensibilización de receptores nicotínicos neuronales.

Los efectos de los agonistas sobre el receptor nicotínico neuronal son fuertemente dependientes del período de exposición. La des-sensibilización rápida y reversible ocurre en milisegundos, el agotamiento ocurre en segundos, la inactivación irreversible de receptores que contienen $\alpha 4\beta 2$ y $\alpha 7$ ocurre en horas y su sensibilización ocurre dentro de un período de días.

En otras palabras, de hecho los efectos de "agonistas" nicotínicos pueden deberse a agonismo, inactivación y/o des-sensibilización parciales de receptores nicotínicos neuronales. A su vez, con concentraciones moderadas de bloqueadores del canal de los receptores nicotínicos neuronales se podrían producir los mismos efectos que se informaron para los agonistas nicotínicos en las indicaciones mencionadas anteriormente.

RESUMEN DE LA INVENCION

Ahora se ha descubierto que ciertos derivados de 1 - aminoalquilciclohexanos insaturados tienen una actividad antagonista de los receptores NMDA, 5HT₃, y nicotínico, que es pronunciada y no predecible. Debido a la propiedad anteriormente mencionada, dichas sustancias son apropiadas para el tratamiento de un amplio rango de trastornos del SNC que incluyen perturbaciones de la transmisión glutamatérgica, serotoninérgica, y nicotínica, efecto inmunomodulatorio, y propiedades contra las enfermedades infecciosas. Preferiblemente dichos compuestos están en la forma de una composición farmacéutica de los mismos donde están presentes junto con uno o más diluyentes, vehículos, o excipientes aceptables para uso farmacéutico.

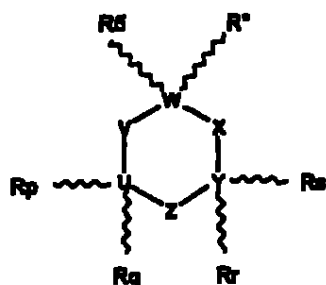
OBJETOS DE LA INVENCION

Un objeto de la presente invención consiste en proporcionar compuestos farmacéuticos novedosos que consisten en 1-aminoalquilciclohexanos insaturados y son antagonistas de los receptores NMDA, 5HT₃, y nicotínico; y composiciones farmacéuticas de los mismos. Un objeto adicional de la invención consiste en proporcionar un método novedoso para tratar, eliminar, aliviar, paliar, o mejorar trastornos no deseables del SNC que incluyen perturbaciones de transmisión glutamatérgica, serotoninérgica, nicotínica, para tratar trastornos inmunomodulatorios, y para tratar enfermedades infecciosas mediante el empleo de un compuesto de la invención o de una composición farmacéutica que lo contiene. Un objeto adicional de la invención consiste en proporcionar un proceso para producir los principios activos de los 1-aminoalquilciclohexanos insaturados. Otros objetivos aún adicionales se harán evidentes a continuación, y otros objetivos aún adicionales serán evidentes para aquellos experimentados en el arte.

RESUMEN DE LA INVENCION

Por lo tanto, el objeto de la presente invención se puede resumir, por ejemplo, de la siguiente manera:

un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),
 - R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),
 - R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileno (C_2-C_{10}) o alquenileno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{2-6} alquenilo,
 - R^5 se selecciona en forma independiente entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 se combina con el carbono al cual se encuentra unido y un carbono adyacente para formar una unión doble,
 - R_p, R_q, R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R_p, R_q, R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente

para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre ciclohexano,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

ciclohexa-2,4-dieno, y

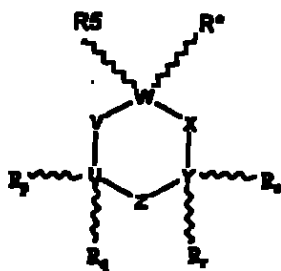
ciclohexa-2,5-dieno,

y con la salvedad de que al menos uno de R_p y R_q no es hidrógeno y al menos uno de R_r y R_s no es hidrógeno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r , y R_s es alquénilo inferior lineal o ramificado (C_2-C_6) o alquínilo inferior lineal o ramificado (C_2-C_6),

y sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos;

un método de tratamiento de un animal vivo para alivio de una condición tratable mediante un antagonista de NMDA que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
 - R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
 - R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_8) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo o C_{2-8} alquenilo,
 - R^5 , R_P , R_Q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o R^5 , R_P , R_Q , R_r , y R_s en forma independiente se pueden

combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

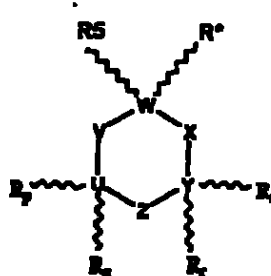
con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

- ciclohexano,
- ciclohex-1-eno,
- ciclohex-2-eno,
- ciclohex-3-eno,
- ciclohexa-1,3-dieno,
- ciclohexa-1,4-dieno,
- ciclohexa-1,5-dieno,
- ciclohexa-2,4-dieno, y
- ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n$ $(CR^1R^2)_m$ -, R^3 , R^4 , R^5 , R_p , R_q , R_r es alquínilo inferior lineal o ramificado (C_2-C_9) o alquínilo inferior lineal o ramificado (C_2-C_9),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición;

un método de tratamiento de un animal vivo para el alivio de una condición donde el compuesto se selecciona por su eficacia inmunomoduladora, anti -malaria, anti-Borna virus, o anti-Hepatitis C, anti-tripanosoma, y anti HSV, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
 - R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
 - R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o juntos forman alquilenilo (C_2-C_{10}) o alquenilenilo (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo o C_{2-8} alquenilo,
- R^5 , R_p , R_q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r , y R_s , en forma independiente se pueden

combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

- ciclohexano,
- ciclohex-1-eno,
- ciclohex-2-eno,
- ciclohex-3-eno,
- ciclohexa-1,3-dieno,
- ciclohexa-1,4-dieno,
- ciclohexa-1,5-dieno,
- ciclohexa-2,4-dieno, y
- ciclohexa-2, 5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición;

un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista de NMDA seleccionada entre el grupo que consiste en excitotoxicidad seleccionada entre isquemia durante accidentes cerebrovasculares, traumatismos, hipoxia, hipoglucemia, glaucoma, y encefalopatía hepática,

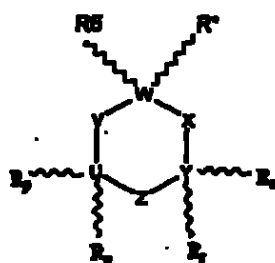
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enfermedades neurodegenerativas crónicas seleccionadas entre enfermedad de Alzheimer, demencia vascular, Mal de Parkinson, Enfermedad de Huntington, esclerosis múltiple, esclerosis lateral amiotrófica, neurodegeneración por SIDA, atrofia olivopontocerebelar, Síndrome de Tourette, enfermedad notora neuronal, disfunción mitocondrial, Síndrome de Korsakoff, y Enfermedad de Creutzfeldt -Jakob,

otros trastornos relacionados con cambios plásticos a largo plazo en el sistema nervioso central seleccionados entre dolor crónico, tolerancia, dependencia y adicción a drogas (por ejemplo, opioides, cocaína, benzodiazepinas, nicotina, y alcohol), y

epilepsia, disquinesia tardía, disquinesia inducida por L-DOPA, esquizofrenia, ansiedad, depresión, dolor agudo, espasticidad, y tinnitus,

que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_mNR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8) y alquino inferior lineal o ramificado (C_2-C_8),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o juntos forman alqueno (C_2-C_{10}) o alqueno (C_2-C_8) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo o C_{2-8} alqueno,

- R^5 , R_p , R_q , R_r y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

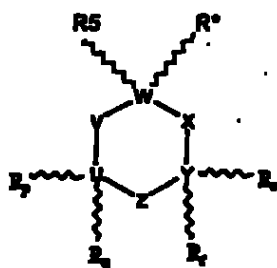
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_8) o alquino inferior lineal o ramificado (C_2-C_8),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición,

un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor $5HT_3$, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o juntos forman alqueno (C_2-C_{10}) o alquino (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo o C_{2-8} alqueno,

- R^5 , R_p , R_q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

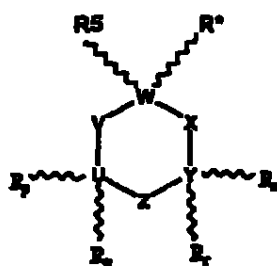
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_6), alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición;

un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor nicotínico neuronal, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^6 es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m=0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alqueno inferior lineal o ramificado (C_2-C_6), y alquino inferior lineal o ramificado (C_2-C_6),
- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alqueno inferior lineal o ramificado (C_2-C_6), y alquino inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma Independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8),

o juntos forman alqueno (C_2-C_{10}) o alqueno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo y/o C_{2-8} alqueno,

- R^5 , R_P , R_Q , R_r y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o R^5 , R_P , R_Q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_r y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

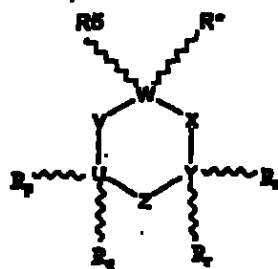
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alquenoilo inferior lineal o ramificado (C_2-C_6) o alquinilo inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición;

un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor $5HT_3$ seleccionado del grupo que consiste en trastornos de ansiedad, trastornos depresivos, esquizofrenia y psicosis relacionadas con tratamientos, trastornos relacionados con el abuso del alcohol y las drogas, trastornos cognitivos, enfermedad de Alzheimer, mal de Parkinson, tremor cerebeloso, migraña, trastornos de la alimentación, síndrome del Intestino irritable (SII), y emesis, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquinilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

122

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{2-6} alquenilo,

- R^5 , R_P , R_Q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_1-C_6), o R^6 , R_P , R_Q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_r y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

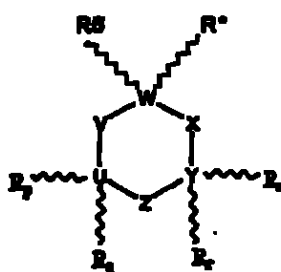
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición,

un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor nicotínico neuronal seleccionado del grupo que consiste en síndrome de Tourette, trastornos de ansiedad, Esquizofrenia, abuso de drogas, abuso de nicotina, abuso de cocaína, disquinesia (Morbus Huntington, inducido por L-DOPA), trastorno de déficit atencional con hiperactividad (ADHD), enfermedad de Alzheimer, mal de Parkinson, y dolor, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,

- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6) y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo o C_{2-6} alquenilo,

- R^5 , R_p , R_q , R_r y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 , R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

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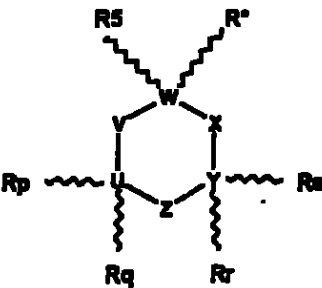
ciclohexa-1,4-dieno,
ciclohexa-1,5-dieno,
ciclohexa-2,4-dieno, y
ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alquínilo inferior lineal o ramificado (C_2-C_6) o alquínilo inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición;

utilización de un compuesto de fórmula I como se define en conexión con los siguientes métodos y sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico del mismo en la fabricación de un medicamento para su utilización en cualquiera de dichos métodos; y

una composición farmacéutica que tiene un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n+m = 0, 1, \text{ o } 2$,

- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileno (C_2-C_{10}) o alquenileno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{2-6} alquenilo,

- R^5 se selecciona en forma independiente entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 se combina con el carbono al cual se encuentra unido y un carbono adyacente para formar una unión doble,

- R_p , R_q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,4dieno,

ciclohexa-1,5-dieno,

ciclohexa-2,4dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que al menos uno de R_p y R_q no es hidrógeno al menos uno de R_r y R_s no es hidrógeno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r , y R_s es alquínilo inferior lineal o ramificado (C_2-C_9) o alquínilo inferior lineal o ramificado (C_2-C_9),

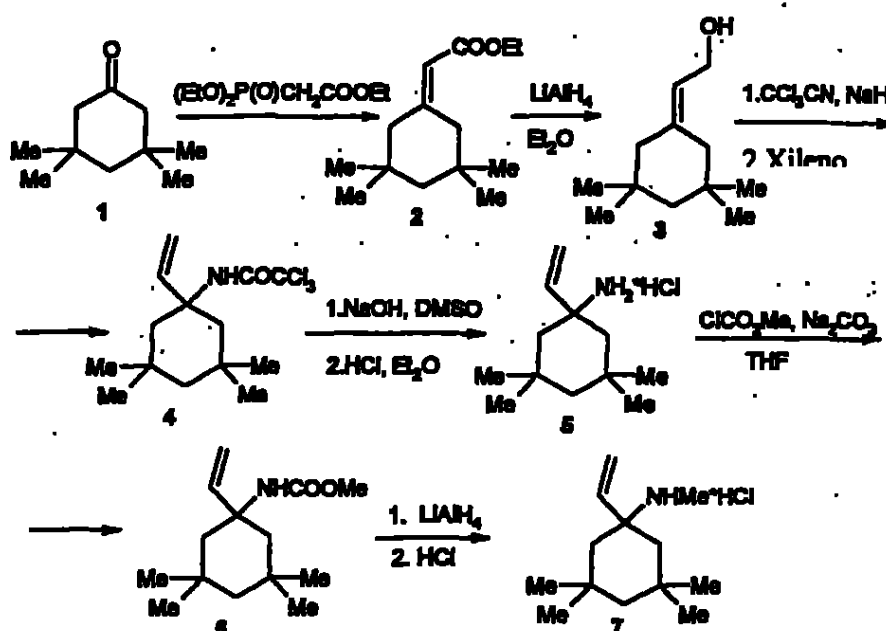
sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos,

en combinación con uno o más diluyentes, excipientes y/o vehículos.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Los siguientes detalles y ejemplos detallados se dan a manera de ilustración solamente, y no deben ser interpretados como limitantes.

Esquema: Ejemplos 1 y 2



Ejemplo 1.

Clorhidrato de 3,3,5,5-tetrametil-1-vinilciclohexanamina (5).

a) 2-(3,3,5,5-tetrametilciclohexiliden)acetato de etilo (2).

A una solución agitada de fosonoacetato de trietilo (49,32 g, 222 mmol) en THF seco (180 ml) bajo argón se agregó NaH (8,8 g, 222 mmol, 60% suspensión en aceite mineral) en pequeñas porciones mientras se enfriaba con agua helada. La agitación se continuó por 1 h a temperatura ambiente, luego se agregó una solución de 3,3,5,5-tetrametilciclohexanona (30,85 g, 200 mmol) durante 10 min y la mezcla resultante se sometió a reflujo por 22 h. Luego se vertió en hielo (400 g) y el producto se extrajo con dietiléter (4 150 ml), y los extractos se secaron sobre MgSO_4 . Luego de la evaporación del solvente al vacío se destiló un residuo oleoso a 145°C (11 mm Hg) para dar 36,8 g (86%) de 2 como un aceite. ^1H NMR (CDCl_3 , TMS) : 0,96 y 0,98 (total 12H, ambos s, 3,5- CH_3); 1,27 (3H, t, CH_3 -etilo); 1,33 (2H, m, 4- CH_2); 1,95 y 2,65 (total 4H, ambos s, 2,6- CH_2); 4,14 (2H, q, CH_2 -etilo) y 5,69 ppm (1H, s, $=\text{C-H}$).

b) 2-(3,3,5,5-Tetrametilciclohexiliden)etanol (3).

A una solución agitada de LiAlH_4 (1,7 g, 45 mmol) en éter seco (60 ml) se agregó una solución de acetato 2 (3,2 g, 15 mmol) en éter (20 ml) por goteo mientras se enfriaba con agua helada. La agitación se continuó por 1h y el LiAlH_4 residual se destruyó con agua. La capa acuosa se separó y se extrajo dos veces con éter (30 ml). Los extractos combinados se lavaron con salmuera (50 ml) y se secaron sobre MgSO_4 . Luego de la concentración al vacío se purificó un residuo oleoso mediante destilación corta de Kugelrohr (150-170 °C, 11 mm Hg) para dar 3 (2,3 g, 89%) como un aceite. ^1H NMR (CDCl_3 , TMS): 0,92 (6H, s, 3,5- CH_3); 1,10 (1H, br s, OH); 1,28 (2H, s, 4- CH_2); 1,87 y 1,94 (total 4H, ambos s, 2,6- CH_2); 4,16 (2H, d, 7 Hz, CH_2O) y 5,50 ppm (1H, t, 7 Hz, =C-H).

c) 2,2,2-Tricloro-N-(3,3,5,5-tetrametil-1-vinilciclohexil)acetamida (4).

A una solución de alcohol 3 (0,8 g, 4,7 mmol) en dietiléter (5 ml) se agregó NaH (0,22 g de una dispersión al 55% en aceite mineral (0,22 mmol)). La mezcla de reacción se enfrió a -10 °C y se agregó una solución de tricloroacetónitrilo (0,68 g, 4,7 mmol) en dietiléter (3 ml) por goteo. La solución se dejó calentar a temperatura ambiente y se evaporó el solvente. Se agregó pentano (8 ml) con metanol (0,018 ml) al residuo. La mezcla resultante se filtró a través de una almohadilla de celite y se evaporó. El aceite residual se disolvió en xileno (10 ml) y se sometió a reflujo por 10 h. La cantidad principal de xileno se eliminó mediante destilación a presión reducida (11mm Hg) y el residuo se purificó mediante cromatografía flash en gel de sílice (hexano, hexano - acetato de etilo, 10:1) para dar 4 (0,98 g, 66 %) como un aceite. ^1H NMR (CDCl_3 , TMS): 0,95 (6H, s, 3,5- CH_3); 1,18 (6 H, s, 3,5- CH_3); 1,1-1,5 (2H, m, 4- CH_2); 1,32 (2H,

d, 15 Hz, 2,6-CH₂); 2,15 (2H, d, 15 Hz, 2, 6-CH₂); 5,08 (1H, d, 11 Hz, =CH₂); 5,13 (1H, d, 18 Hz, =CH₂); 5,85 (1H, dd, 18 y 11 Hz, -HC=) y 6,7 ppm (1H, br s, NH).

d) Clorhidrato de 3,3,5,5-Tetrametil-1-vinilciclohexanamina (5).

Una mezcla de amida 4 (0,32 g, 1 mmol) y NaOH en polvo (0,4 g, 10 mmol) en DMSO (3 ml) se agitó por 7 días a temperatura ambiente. La mezcla de reacción se diluyó con H₂O (20 ml) y se agitó durante la noche a temperatura ambiente. El producto se extrajo con hexano (3 10 ml). Los extractos combinados se lavaron con salmuera (20 ml), se secaron sobre NaOH y se filtraron a través de una almohadilla de celite. A la solución obtenida se agregó HCl 4 M en éter etílico seco (0,5 ml) y el solvente se evaporó. El residuo se trató con acetonitrilo (10 ml) y el precipitado se recogió en un filtro y se secó sobre P₂O₅ al vacío para dar 5 (0,12 g, 53%) como un sólido incoloro. ¹H NMR (CDCl₃, TMS): 0,98 y 1,01 (total 12H, ambos s, 3,5-CH₃); 1,19 y 1,29 (total 2H, ambos d, 14 Hz, 4-CH₂); 1,62 (2H, d, 13,5 Hz, 2,6-CH₂); 1,72 (2H, br s, H₂O); 2,16 (2H, d, 13,5 Hz, 2,6-CH₂); 5,46 y 5,73 (2H, ambos d, 18 y 11 Hz, =CH₂); 6,16 (1H, dd, 18 y 11 Hz, =CH) y 8,24 ppm (3H, br s, NH₃⁺).

Ejemplo 2.

Clorhidrato de N,3,3,5,5-pentametil-1-vinilciclohexilamina (7).

a) 3,3,5,5-tetrametil-1-vinilciclohexilcarbamato de metilo (6).

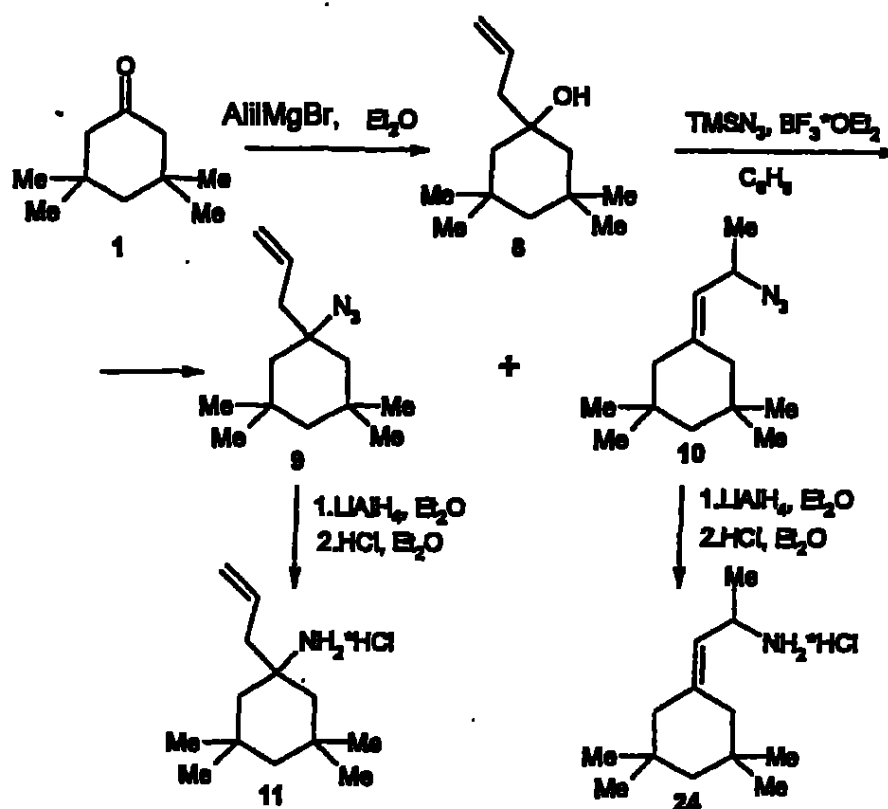
Una mezcla de clorhidrato de amina 5 (0,25 g, 1,2 mmol) y Na₂CO₃ (0,73 g, 6,9 mmol) en THF (6 ml) se agitó a temperatura ambiente por 1h. Se agregó cloroformato de metilo (0,27 ml, 3,45 mmol) y la mezcla de reacción se agitó a temperatura ambiente por 15 h. La mezcla se diluyó con dietiléter (20 ml), se filtró y se evaporó a sequedad. El producto crudo se purificó mediante

cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 10:1) para dar 6 (0,24 g, 87 %) como un sólido incoloro con p.f. 61-63 °C. ^1H -NMR (CDCl_3 , TMS): 0,92 y 1,15 (total 12H, ambos s, 3,5- CH_3); 1,00-1,40 (4H, m, 4- CH_2 y 2,6-CH); 2,00 (2H, d, 14 Hz, 2,6-CH); 3,62 (3H, s, CH_3N); 4,72 (1H, br s, NH); 5,00 y 5,06 (total 2H, ambos d, 10,5 y 17 Hz, $=\text{CH}_2$) y 5,83 ppm (1H, dd, 10,5 y 17 Hz, $=\text{CH}$).

b) Clorhidrato de N,3,3,5,5-Pentametil-1-vinilciclohexilamina (7).

Una mezcla de LiAlH_4 (0,28 g, 7,4 mmol) y carbamato 6 (0,22 g, 0,92 mmol) en THF (22 ml) se sometió a reflujo por 12 h. Luego se enfrió en un baño de hielo y se agregó agua (20 ml) por goteo. La suspensión resultante se extrajo con hexano (3 20 ml) y los extractos combinados se lavaron con salmuera (20 ml). El extracto se secó sobre NaOH, se filtró y se trató con solución 2,4 M de HCl en dietiléter (1 ml). La suspensión resultante se evaporó a sequedad. El residuo se trató con dietiléter (10 ml) y acetonitrilo (1 ml). El precipitado se recogió en un filtro y se secó al vacío sobre P_2O_5 para dar 7 (0,11 g, 52%) como un sólido incoloro. ^1H -NMR (CDCl_3 , TMS): 1,00 y 1,02 (total 12H, ambos s, 3,5- CH_3); 1,23 y 1,32 (total 2H, ambos d, 15 Hz, 4- CH_2); 1,72 (2H, d, 13 Hz, 2,6-CH); 2,15 (2H, d, 13 Hz, 2,6-CH); 2,45 (3H, t, 5 Hz, CH_3N); 5,64 y 5,69 (total 2H, ambos d, 11 y 17 Hz, $=\text{CH}_2$); 5,98 (1H, dd, 11 y 17 Hz, $=\text{CH}$) y 9,30 ppm (2H, br s, NH_3^+).

Esquema: Ejemplos 3 y 4



Ejemplo 3.

Clorhidrato de 1-Alil-3,3,5,5-tetrametilciclohexanamina (11).

a) 1-alil-3,3,5,5-tetrametilciclohexanol (8).

A una solución agitada 1 M en éter de bromuro de alilmagnesio (60 ml, 60 mmol) se agregó por goteo una solución de 3,3,5,5-tetrametilciclohexanona (3,86 g, 25 mmol) en éter seco (20 ml). La mezcla se agitó por 1 h a temperatura ambiente y se hirvió a reflujo por 10 min. Luego se enfrió con agua helada y se trató cuidadosamente con NH_4Cl acuoso saturado (40 ml). La capa orgánica se separó y se lavó con agua y salmuera. Luego de secar sobre MgSO_4 anhidro, la solución se concentró al vacío. El residuo se destiló por fraccionamiento a presión reducida para dar 3,5 g (72%) de **8** con b.p. 98-100

°C/12 mm Hg. ^1H NMR (CDCl_3 , TMS) : 0,88 (6H, s, 3,5- $\text{CH}_{3\text{eq}}$); 1,20 (6H, s, 3,5- $\text{CH}_{3\text{ax}}$); 0,95-1,60 (6H, m, 2,4,6- CH_2); 2,15 (2H, d, 7,5 Hz, $\text{CH}_2\text{C}=\text{}$); 4,95-5,30 (2H, m, $=\text{CH}_2$) y 5,65-6,20 ppm (1H, m, $=\text{CH}$).

b) 1-allyl-1-azido-3,3,5,5-tetrametilciclohexano (9) y azida de 1-metil-2-(3,3,5,5-tetrametilciclohexiliden)etilo (10).

A una solución de ciclohexanol 8 (1,96 g, 10 mmol) en benceno seco (20 ml) bajo argón se agregó azidotrimetilsilano (12 mmol). A esta solución enfriada (5°C) se agregó lentamente $\text{BF}_3 \cdot \text{OEt}_2$ (12 mmol) mediante inyección durante 20 min. La mezcla se agitó por 6 h, luego se agregó lentamente agua. La capa orgánica se separó y se lavó con NaHCO_3 acuoso saturado, y con salmuera, y se secó sobre MgSO_4 . La filtración y evaporación del solvente manteniendo la temperatura por debajo de 25°C dio un aceite el cual se separó mediante cromatografía de columna en gel de sílice (éter de petróleo ligero). Se recogió una fracción con R_f 0,85 (hexano). La evaporación del solvente dio 9 como un aceite incoloro (0,26 g, 11,7%). ^1H NMR (CDCl_3 , TMS): 0,89 (6H, s, 3,5- $\text{CH}_{3\text{eq}}$); 0,90 (1H, d, 14 Hz, 4- CH_{ax}); 1,05 (2H, d, 14 Hz, 2,6- CH_{ax}); 1,18 (6H, s, 3,5- $\text{CH}_{3\text{ax}}$); 1,37 (1H, d, 14 Hz, 4- CH_{eq}); 1,60 (2H, d, 14 Hz, 2,6- CH_{eq}); 2,29 (2H, d, 7 Hz, $\text{CH}_2\text{C}=\text{}$); 4,95-5,25 (2H, m, $=\text{CH}_2$) y 5,65-6,15 ppm (1H, m, $=\text{CH}$).

La evaporación de una fracción adicional (R_f 0,65 (hexano)) dio 0,425 g (20,3 %) de azida 10 como un aceite incoloro. ^1H NMR (CDCl_3 , TMS) : 0,91 (6H, s), 0,94 (3H, s) y 0,96 (3H, s, 3',5'- CH_3); 1,23 (3H, d, 6,5 Hz, 1- CH_3); 1,26 (2H, s, 4'- CH_2); 1,89 (2H, s) y 1,96 (2H, s, 2',6'- CH_2); 4,31 (1H, dq, 6,5 y 9,5 Hz, 1-CH) y 5,21 ppm (1H, dm, 9,5 Hz, $=\text{CH}$).

c) Clorhidrato de 1-Allyl-3,3,5,5-tetrametilciclohexanamina (11).

Una solución de azida 9 (0,221 g, 1,0 mmol) en éter seco (4 ml) se agregó por goteo a una suspensión agitada de hidruro de litio y aluminio (0,152 g, 4 mmol) en éter (10 ml) durante 10 min. La mezcla se agitó por 4 h, luego se trató con NaOH acuoso 20% (8 ml). La capa acuosa se separó y se extrajo con dietiléter (2 15 ml). Los extractos orgánicos combinados se lavaron con salmuera y se secaron sobre NaOH. La solución filtrada se trató con solución de HCl seco en dietiléter y se evaporó. Se agregó dietiléter seco al residuo sólido y se recogió en un filtro, y se lavó con éter seco para dar 11 (0,105 g, 47%) como un sólido incoloro. ^1H NMR (CDCl_3 , TMS): 1,03 (6H, s, 3,5- $\text{CH}_{3\text{eq}}$); 1,06 (6H, s, 3,5- $\text{CH}_{3\text{ax}}$); 1,29 (2H, s, 4- CH_2); 1,63 (2H, d, 13 Hz, 2,6- CH_{ax}); 1,80 (2H, d, 13 Hz, 2,6- CH_{eq}), 2,71 (2H, d, 7 Hz, $\text{CH}_2\text{C}=\text{}$); 5,10-5,40 (2H, m, $=\text{CH}_2$); 5,75-6,25 (1H, m, $=\text{CH}$) y 8,25 ppm (3H, br s, NH_3^+).

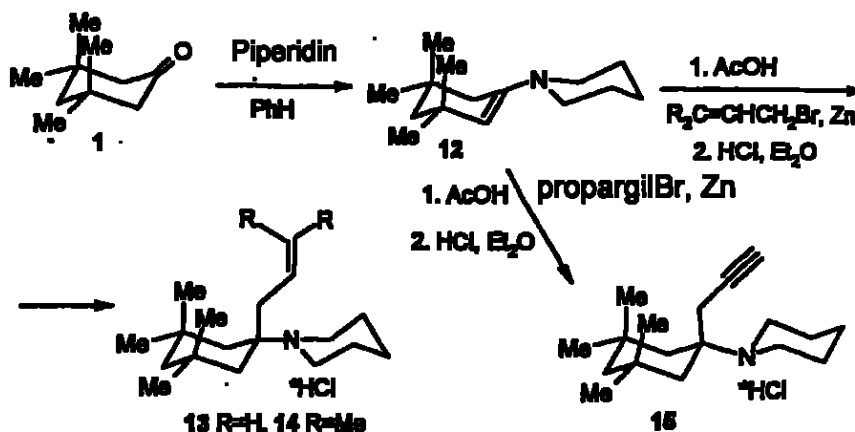
Ejemplo 4.

Clorhidrato de 1-(3,3,5,5-tetrametilciclohexiliden)-2-propanamina (24).

Una solución de azida de 1-metil-2-(3,3,5,5-tetrametilciclohexiliden)etilo (10) (0,33 g, 1,5 mmol) en dietiléter seco (4 ml) se agregó por goteo a una suspensión agitada de hidruro de litio y aluminio (0,152 g, 4 mmol) en éter (15 ml) durante 10 min. La mezcla se agitó por 4 h, luego se trató con NaOH acuoso 20% (8 ml). La capa acuosa se extrajo con éter (2*15 ml). Los extractos orgánicos se combinaron, se lavaron con salmuera y se secaron sobre NaOH. La solución filtrada se trató con solución de HCl seco en éter y se evaporó al vacío. Se agregó éter seco al residuo sólido y se recogió en un filtro y se lavó con éter seco para dar 24 (0,18 g, 54%) como un sólido incoloro. ^1H NMR (CDCl_3 , TMS): 0,89 (6H, s), 0,92 (3H, s) y 0,98 (3H, s, 3',5'- CH_3); 1,27 (2H, s,

4'-CH₂); 1,47 (3H, d, 6,5 Hz, 3-CH₃); 1,84 (1H, d, 13,5 Hz, 2'-CH); 1,87 (2H, s, 6'-CH₂), 2,06 (1H, d, 13,5 Hz, 2'-CH); 4,17 (1H, dq, 6,5 y 9,5 Hz, 2-CH); 5,35 (1H, d, 9,5 Hz, =CH) y 8,25 ppm (3H, br s, NH₃⁺)

Esquema: Ejemplos 5, 6, y 7



Ejemplo 5.

Clorhidrato de 1-(1-allyl-3,3,5,5-tetrametilciclohexil)piperidina (13).

a) 1-(3,3,5,5-tetrametil-1-ciclohexenil-1)piperidina (12).

Se preparó mediante condensación de piperidina (1,2 equivalentes) y 3,3,5,5-tetrametilciclohexanona calentando en benceno con eliminación azeotrópica de agua. El producto crudo se obtuvo mediante la eliminación. El producto crudo se obtuvo mediante la eliminación de los materiales iniciales en condiciones de destilación al vacío (100 °C/ 10 mm Hg). Aceite ámbar. ¹H NMR (CDCl₃, TMS) : 0,94 (6H, s) y 0,97 (6H, s, 3',5'-CH₃); 1,25 (2H, s, 4'-CH₂); 1,40-1,70 (6H, m, piperidina 3,4,5-CH₂); 1,76 (2H, s, 6'-CH₂); 2,60-2,85 (4H, m, piperidina 2,6-CH₂) y 4,40 ppm (1H, s, =CH).

b) Clorhidrato de 1-(1-allyl-3,3,5,5-tetrametilciclohexil)piperidina (13).

A una solución de enamina 12 (2,1 g, 9 mmol) en THF (20 ml) se agregó ácido acético 0,675 g, 11,25 mmol). La mezcla se agitó por 5 min y se agregó polvo

de cinc (0,74 g, 11,25 mgA). Cuando se agregó una solución de alilbromuro (1,63 g, 13,5 mmol) en THF (5 ml) se agregó por goteo y la mezcla se agitó a temperatura ambiente por 6 h. Se agregó Na_2CO_3 acuoso y la mezcla resultante se extrajo con éter. El extracto se lavó con salmuera, se secó sobre MgSO_4 anhidro, y se concentró al vacío. El residuo se separó mediante cromatografía de columna en gel de sílice (hexano, 5% EtOAc en hexano). La fracción con R_f 0,85 (hexano-EtOAc, 13 : 2) se recogió, se evaporó y se trató con solución de HCl seco en éter. El precipitado se filtró y se lavó con una mezcla de hexano-EtOAc para dar 13 (0,79 g, 29%) como un sólido incoloro. ^1H NMR (CDCl_3 , TMS) : 1,07 (6H, s, 3',5'- CH_3 _{eq}), 1,10 (6H, s, 3',5'- CH_3 _{ax}); 1,34 (1H, d, 12,2 Hz) y 1,45 (1H, d, 12,2 Hz, 4'- CH_2); 1,70-1,95 (6H, m, 2',6'- CH_2 _{ax} y piperidina 3,5-CH,-4- CH_2); 2,37 (2H, d, 13,4 Hz, 2',6'- CH_2 _{eq}); 2,40-2,70 (2H, m, piperidina 3,5-CH); 2,76 (2H, d, 7,2Hz, $\text{CH}_2\text{C}=\text{}$); 2,75-3,00 (2H, m, piperidina 2,6-CH); 3,64 (2H, d, 11,6 Hz, piperidina 2,6-CH); 5,13 (1H, d, 9,6 Hz) y 5,24 (1H, d, 17,8 Hz, $=\text{CH}_2$); 5,85-6,15 (1H, m, $=\text{CH}$) y 10,72 ppm (1H, br s, NH).

Ejemplo 6:

Clorhidrato de 1-[3,3,5,5-Tetrametil-1-(3-metil-2-butenil)ciclohexil]piperidina (14).

Se preparó a partir de piperidina 12 de acuerdo con el procedimiento para el compuesto 13 (Ejemplo 5, b) utilizando 4-bromo-2-metil-2-buteno en lugar de alilbromuro. Rendimiento: 20%. ^1H NMR (CDCl_3 , TMS) : 1,07 y 1,08 (total 12H, ambos s, 3',5'- CH_3), 1,32 y 1,44 (2H, ambos d, 14,2 Hz, 4'- CH_2); 1,69 y 1,76 (6H, ambos s, $=\text{C}(\text{CH}_3)_2$); 1,68-1,86 (4H, m, 3,5-CH y 4- CH_2); 1,84 (2H, d, 13,4 Hz, , 2',6'- CH_2 _{ax}); 2,31 (2H, d, 13,4 Hz, , 2',6'- CH_2 _{eq}); 2,40-2,80 (4H,

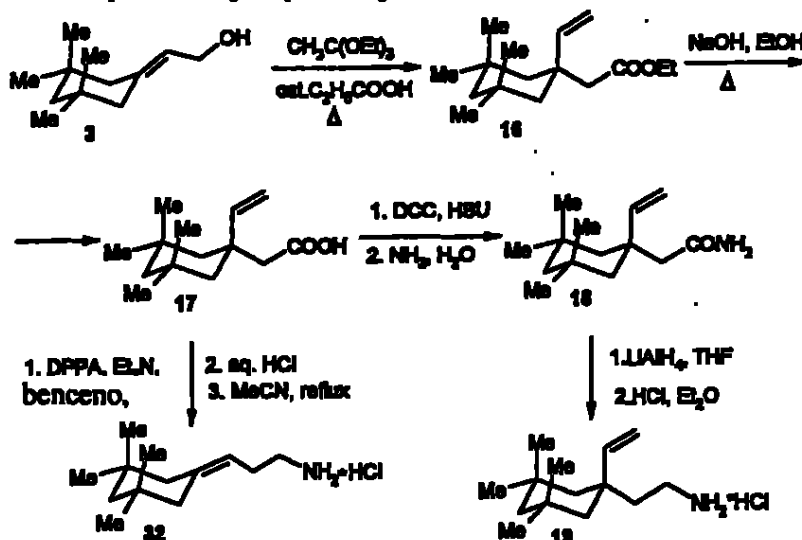
m, $N(CH_2)_2$, 3,5-CH); 2,60 (2H, d, 7,2 Hz, $CH_2C=$); 3,63 (2H, d, 10,4 Hz, $N(CH_2)_2$); 5,31 (1H, t, 6,8 Hz, =CH) y 10,55 ppm (1H, br s, NH).

Ejemplo 7

Clorhidrato de 1-[3,3,5,5-tetrametil-1-(2-propinil)ciclohexil]piperidina (15).

Se preparó a partir de piperidina 12 de acuerdo con el procedimiento para el compuesto 13 (Ejemplo 5, b) utilizando 3-bromopropina en lugar de alilbromuro. Rendimiento: 6%. ^1H NMR ($CDCl_3$, TMS): 1,07 (6H, s, 3',5'- CH_{3eq}), 1,11 (6H, s, 3',5'- CH_{3ax}); 1,23 y 1,44 (total 2H, ambos d, 14,3 Hz, 4'- CH_2); 1,75-2,00 (4H, m, piperidina 3,5-CH, 4- CH_2); 1,91 (2H, d, 13,2 Hz, 2',6'- CH_{ax}); 2,28 (1H, s, HCC); 2,34 (2H, d, 13,2 Hz, 2',6'- CH_{eq}); 2,40-2,70 (2H, m, piperidina 3,5-CH); 2,81 (2H, s, CH_2CC); 2,85-3,10 (2H, m, piperidina 2,6-CH); 3,69 (2H, d, 10,2 Hz, piperidina 2,6-CH) y 11,12 ppm (1H, br s, NH).

Esquema: Ejemplos 8 y 9



Ejemplo 8.

Clorhidrato de 2-(3,3,5,5-Tetrametil-1-vinilciclohexil)etanamina (19).

a) 2-(3,3,5,5-tetrametil-1-vinilciclohexil)acetato de etilo (16).

Una mezcla de ortoacetato de trietilo (18,6 ml, 102 mmol), 2-(3,3,5,5-tetrametil-ciclohexiliden)etanol (3) (4,63 g, 25,4 mmol) y ácido propiónico (0,19 ml, 2,5 mmol) se calentó a 145 °C por 10 h. Se destiló etanol de la mezcla en el curso de la reacción. La mezcla de reacción se enfrió y se vertió en agua (100 ml). La fase acuosa se extrajo con hexano (2 50 ml) y las fases orgánicas combinadas se lavaron con KHSO₄ acuoso 5% (50 ml) y salmuera (50 ml). El extracto se secó sobre MgSO₄, se filtró y se evaporó. El residuo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero y éter de petróleo ligero - acetato de etilo, 100: 2) para dar 16 (4,64 g, 73 %) como un aceite. ¹H-NMR (CDCl₃, TMS) : 0,91 (6H, s, 3,5-CH₃); 1,01 (6H, s, 3,5-CH₃); 1,23 (3H, t, 7 Hz, etilo CH₃) 1,00-1,30 (4H, m, 4-CH₂ y 2,6-CH); 1,86 (2H, d, 13 Hz, 2,6-CH); 2,22 (2H, s, CH₂C = O); 4,08 (2H, q, 7 Hz, etilo CH.); 5,06 y 5,07 (total 2H, ambos d, 11 y 17,5 Hz, =CH₂) y 5,95 ppm (1H, dd, 11 y 17,5 Hz, -CH=).

b) ácido 2-(3,3,5,5-tetrametil-1-vinilciclohexil)acético (17).

Una solución de NaOH (1,03 g, 25,8 mmol) y acetato 16 (1,3 g, 5,15 mmol) en metanol (26 ml) se sometió a reflujo por 3 h. La mezcla se enfrió a temperatura ambiente y se vertió en agua (100 ml). La fase acuosa se acidificó con HCl acuoso concentrado y se extrajo con hexano (3 30 ml). Las fases orgánicas combinadas se lavaron con salmuera y se secaron sobre CaCl₂, se filtraron y se evaporaron. El residuo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 10:1) para dar 17 (0,7 g, 71 %) como un sólido incoloro con p.f. 92-94°C. ¹H-NMR (CDCl₃, TMS) : 0,92 (6H, s, 3,5-CH₃); 1,02 (6H, s, 3,5-CH₃); 1,00-1,30 (4H, m, 4-CH, y 2,6-CH); 1,90

(2H, d, 14 Hz, 2,6-CH); 2,27 (2H, s, CHC=O); 5,11 y 5,13 (total 2H, ambos d, 11 y 18 Hz, =CH₂); 5,99 (1H, dd, 18 y 11 Hz, =CH) y 10,80 ppm (1H, br s, COOH).

c) 2-(3,3,5,5-Tetrametil-1-vinilciclohexil)acetamida (18).

Se agregó N-hidroxisuccinimida (0,25 g, 2,2 mmol) y N,N'-diciclohexilcarbodiimida (0,45, 2,2 mmol) a una solución de ácido ciclohexilacético 17 (0,45 g, 2 mmol) en THF (5 ml). La mezcla se agitó por 18 h a temperatura ambiente y se enfrió en un baño de hielo. Se agregó NH₄OH acuoso al 25% (2 ml) en una porción y la mezcla se agitó a temperatura ambiente por 2 h. El precipitado se eliminó por filtración y se lavó con dietiléter (30 ml). La fase orgánica del filtrado se separó y se lavó con KHSO₄ acuoso 5% (10 ml) y salmuera. El extracto se secó sobre MgSO₄, se filtró y se evaporó. El residuo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 4:1 a 1:1) para dar 18 (0,34 g, 76 %) como un sólido incoloro con p.f. 44-46°C. ¹H-NMR (CDCl₃, TMS) :0,91 (6H, s, 3,5-CH₃); 1,02 (6H, s, 3,5-CH₃); 1,00-1,30 (4H, m, 4-CH₂ y 2,6-CH); 1,85 (2H, d, 14 Hz, 2,6-CH); 2,13 (2H, s, CH₂C=O); 5,18 y 5,19 (total 2H, ambos d, 18 y 11 Hz, =CH₂); 5,40 y 5,60 (total 2H, ambos br s, NH₂) y 6,03 ppm (1H, dd, 18 y 11 Hz, =CH).

d) Clorhidrato de 2-(3,3,5,5-tetrametil-1-vinilciclohexil)etanamina (19).

La mezcla de LiAlH₄ (0,41 g, 11 mmol) y amida 18 (0,30 g, 1,4 mmol) en THF (18 ml) se sometió a reflujo por 17 h. Luego se enfrió en un baño de hielo y se agregó agua (30 ml) por goteo. La suspensión resultante se extrajo con hexano (3 30 ml) y las fases orgánicas combinadas se lavaron con salmuera. El

extracto se secó sobre NaOH, se filtró y se concentró a ~10 ml volumen. Se agregó solución 4,8 M de HCl en dietiléter (1 ml) y la suspensión resultante se evaporó a sequedad. El residuo se trató con acetonitrilo (5 ml) y el precipitado se recogió en un filtro y se secó al vacío durante NaOH para dar 19 (0,16 g, 50%) como un sólido incoloro. $^1\text{H-NMR}$ (CDCl_3 , TMS) : 0,89 (6H, s, 3,5- CH_3); 1,02 (6H, s, 3,5- CH_3); 0,90-1,80 (8H, m, protones de anillo y etanamina- 2- CH_2); 2,92 (2H, br s, CH_2N); 5,05 y 5,15 (2H, ambos d, 18 y 11 Hz, $=\text{CH}_2$); 5,77 (1H, dd, 18 y 11 Hz, $=\text{CH}$) y 8,10 ppm (3H, br s, NH_3^+).

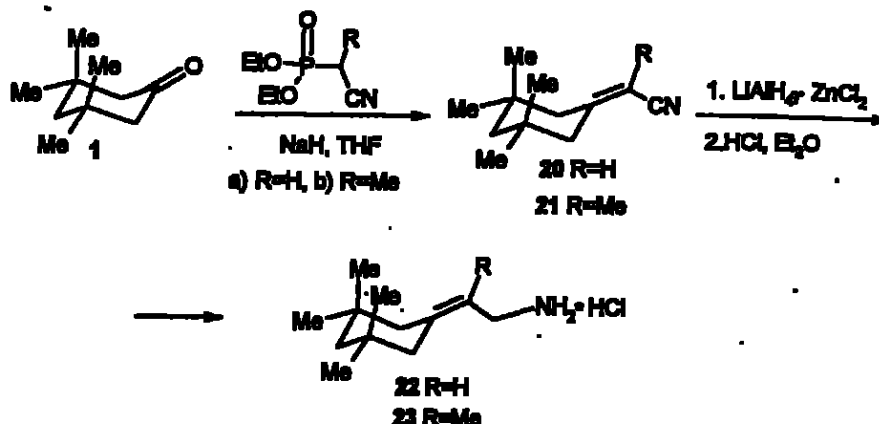
Ejemplo 9.

Clorhidrato 3-(3,3,5,5-tetrametilciclohexiliden)propanamina (32).

Se agregó trietilamina (0,25 ml, 1,76 mmol) y azida de difenilfosforilo (0,38 ml, 1,76 mmol) a una solución de ácido 17 (0,36 g, 1,6 mmol) en benceno (6 ml). La mezcla se sometió a reflujo por 2 h, se enfrió a temperatura ambiente y se evaporó a sequedad. Se agregó HCl acuoso concentrado frío (~5 °C) (3 ml) al residuo. La mezcla resultante se agitó a temperatura ambiente por 18 h y se hizo fuertemente alcalina mediante la adición de NaOH acuoso 10%. Se agregó hexano (20 ml) a la mezcla y ambas fases se filtraron. El precipitado se lavó con hexano (2 5 ml) y agua (2 5 ml). La fase orgánica del filtrado se separó. La fase acuosa se lavó con hexano (2 10 ml). Las fases orgánicas combinadas se lavaron con salmuera (10 ml), se secaron sobre NaOH y se filtraron. Se agregó solución 4,8 M de HCl en dietiléter (1 ml) y la suspensión resultante se evaporó. El residuo se recristalizó a partir de acetonitrilo y se secó al vacío sobre P_2O_5 para dar 32 (0,1 g, 43%) como un sólido incoloro. $^1\text{H-NMR}$: (CDCl_3 , TMS) : 0,90 y 0,92 (total 12H, ambos s, c-Hex-3,5- CH_3); 1,23 (2H, s, c-Hex- 4- CH_2); 1,86 y 1,92 (total 4H, ambos s, c-Hex- 2,6- CH_2) ; 2,49 (2H, q, 7

Hz, propanamina- 2-CH₂); 2,98 (2H, t, 7 Hz, propanamina-1-CH₂); 5,15 (1H, t, 7 Hz, =CH-) y 8,30 ppm (3H, br s, NH₃⁺).

Esquema: Ejemplos 10 y 11



Ejemplo 10.

Clorhidrato de 2-(3,3,5,5-Tetrametilciclohexiliden)etanamina (22).

a) 3,3,5,5-Tetrametilciclohexilidenacetónitrilol (20).

Se agregó una dispersión de NaH al 60% en aceite mineral (0,96 g, 24 mmol) a una solución de cianometilfosfonato de dietilo (4,25 g, 24 mmol) en THF (30 ml) mientras se enfriaba con agua helada. La mezcla se agitó por 30 min y se agregó por goteo una solución de 3,3,5,5-tetrametilciclohexanona (3,08 g, 20 mmol) en THF (10 ml). Se retiró el baño de enfriamiento y la mezcla se agitó a temperatura ambiente por 72 h. Se vertió en agua helada (100 ml) y se extrajo con dietiléter (3,50 ml). Las fases orgánicas combinadas se lavaron con salmuera, se secaron sobre MgSO₄, se filtraron y se evaporaron. El producto crudo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 10:1) para dar 20 (2,38 g, 71 %) como un aceite incoloro. ¹H-NMR (CDCl₃, TMS) b: 0,97 y 1,01 (total 12H, ambos s, 3',5'-

CH₃); 1,36 (2H, s, 4'-CH₂); 2,01 (2H, s, 2'-CH₂); 2,26 (2H, s, 6'-CH₂) y 5,14 ppm (1H, s, =CH).

b) Clorhidrato de 2-(3,3,5,5-tetrametilciclohexiliden)etanamina (22).

Una suspensión de LiAlH₄ (0,68 g, 18 mmol) en dietiléter (30 ml) se enfrió en un baño de hielo y se agregó una solución 1 M de ZnCl₂ en dietiléter (9 ml, 9 mmol). La mezcla resultante se agitó por 15 min y se agregó una solución de nitrilo 20 (1 g, 6 mmol) en dietiléter (30 ml) por goteo manteniendo la temperatura a 0-5 °C. Luego se retiró el baño de hielo y la mezcla se agitó a temperatura ambiente por 24 h. Se agregó agua (30 ml) y NaOH acuoso 20% (20 ml) mientras se enfriaba con un baño de hielo. La fase acuosa se extrajo con dietiléter (4 50 ml). Las fases orgánicas combinadas se lavaron con salmuera (50 ml) y se secaron sobre NaOH, se filtraron y se evaporaron. El residuo se purificó por destilación corta de Kugelrohr a 160 °C/ 20 mm Hg. El destilado se diluyó con dietiléter y se agregó una solución 4,8M de HCl en dietiléter (3 ml). El precipitado resultante se recogió en un filtro, se lavó con dietiléter (3 5 ml) y se secó al vacío sobre NaOH para dar 22 como un sólido incoloro. ¹H-NMR (CDCl₃, TMS) : 0,91 y 0,92 (total 12H, ambos s, 3', 5'-CH₃); 1,28 (2H, s, 4' -CH₂); 1,89 y 1,93 (total 4H, ambos s, 2',6'-CH₂); 3,62 (2H, d, 7 Hz, CH₂N); 5,41 (1H, t, 7 Hz, -C=CH) y 8,3 ppm (3H, br s, NH₃⁺).

Ejemplo 11.

Clorhidrato de 2-(3,3,5,5-tetrametilciclohexiliden)propanamina (23).

a) 2-(3,3,5,5-Tetrametilciclohexiliden)propionitrilo (21).

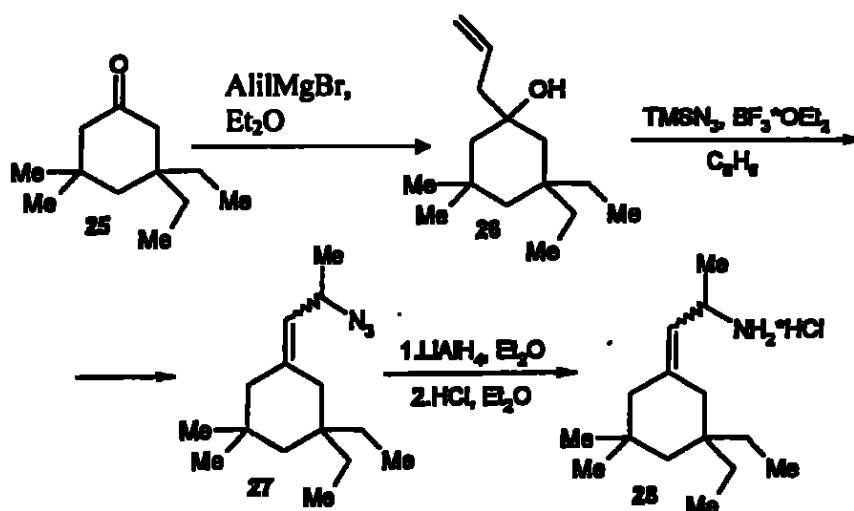
Se preparó de acuerdo con el procedimiento para el compuesto 20 (Ejemplo 10, a) utilizando (1-cianoetil)fosfonato de dietilo. Se obtuvo nitrilo 21 como un aceite incoloro con 41 % rendimiento. ¹H-NMR: (CDCl₃, TMS): 0,96 y

1,00 (total 12H, ambos s, c-Hex-3,5-CH₃); 1,34 (2H, s, c-Hex-4-CH₂); 1,91 (3H, s, propionitrilo-3-CH₃); 2,04 y 2,28 ppm (total 4H, ambos s, c-Hex-2,6-CH₂).

b) Clorhidrato de 2-(3,3,5,5-tetrametilciclohexiliden)propanamina (23).

Se preparó a partir de nitrilo 21 de acuerdo con el procedimiento para el compuesto 22 (Ejemplo 10, b). Se obtuvo clorhidrato de amina 23 como un sólido incoloro. ¹H-NMR: (CDCl₃, TMS) δ: 0,92 y 0,93 (total 12H, ambos s, c-Hex-3,5-CH₃); 1,27 (2H, s, c-Hex-4-CH₂); 1,89 (3H, s, propanamina-3-CH₃); 1,99 y 2,01 (total 4H, ambos s, c-Hex-2,6-CH₂); 3,64 (2H, br s, propanamina-1-CH₂) y 8,40 ppm (3H, br s, NH₃⁺).

Esquema: Ejemplo 12



Ejemplo 12.

Clorhidrato de (E,Z)-1-(3,3-dietil-5,5-dimetilciclohexiliden)-2-propanamina (28).

a) 1-Alil-3,3-dietil-5,5-dimetilciclohexanol (26).

144

144

A una solución agitada 1 M en éter de bromuro de alilmagnesio (20 ml, 20 mmol) se agregó por goteo una solución de 3,3-dietil-5,5-dimetilciclohexanona (25) (1,47 g, 8,06 mmol) en éter seco (5 ml). La mezcla se agitó por 1 h a temperatura ambiente y se calentó a reflujo por 10 min. Luego se enfrió con agua helada y se trató con NH_4Cl acuoso saturado (40 ml). La capa orgánica se separó y se lavó con agua y salmuera. Luego de secar sobre MgSO_4 anhidro, la solución se concentró al vacío. El residuo se purificó mediante cromatografía de columna en gel de sílice (éter de petróleo ligero). Una fracción con R_f 0,7 (Hexano : EtOAc, 13 : 2) se recogió. La evaporación del solvente dio 26 (1,35 g, 74%) como un aceite incoloro. ^1H NMR (CDCl_3 , TMS) 0,74 (6H, t, 7 Hz, 2CH_3 de etilo); 0,88 (3H, s, 5-CH_3); 1,19 (3 H, s, 5-CH_3); 0,80-2,05 (10H, m, $2,4,6\text{-CH}_2$ y 2CH_2 de etilo); 2,14 (2H, d, 7 Hz, $\text{CH}_2\text{C=}$); 4,95-5,30 (2H, m, $=\text{CH}_2$) y 5,65-6,20 ppm (1H, m, $=\text{CH}$).

b) Azida de (E,Z)-1-metil-2-(3,3-dietil-5,5-dimetilciclohexiliden)etilo (27).

Se preparó a partir de ciclohexanol 26 de acuerdo con el procedimiento para los compuestos 9 y 10 (Ejemplo 3, b). Se obtuvo azida 27 como un aceite incoloro con 15% de rendimiento. ^1H NMR (CDCl_3 , TMS) : 0,73 y 0,74 (total 6H, ambos t, 7 Hz, 2CH_3 etilo); 0,91, 0,94 y 0,97 (total 6H, todos los s, $5'$, $5'$ -CH_3); 1,10-1,45 (4H, m, 2CH_2 etilo); 1,22 (3H, d, 6,5 Hz, 1-CH_3); 1,26 (2H, s, $4'\text{-CH}_2$); 1,89 (2H, s) y 1,97 (2H, m, $2',6'\text{-CH}_2$); 4,08-4,48 (1H, m, 1-CH) y 5,18 ppm (1H, dm, 9,5 Hz, $=\text{CH}$).

c) Clorhidrato de (E,Z)-1-(3,3-dietil-5,5-dimetilciclohexiliden)-2-propanamina (28).

145

A una suspensión enfriada (0°C) de azida de sodio (0,81 g, 12,5 mmol) en CH₂Cl₂ (5 ml) se agregó por goteo H₂SO₄ acuoso 53% (8 ml). La mezcla se agitó por 10 min, luego se agregó una solución de 3,5,5-trimetil-2-ciclohexanol (33) (0,70 g, 5 mmol) en CH₂Cl₂ (8 ml). La mezcla se agitó por 20 h, se vertió en agua helada, se neutralizó con NH₄OH acuoso y se extrajo con CH₂Cl₂. El extracto se lavó con salmuera y se secó sobre MgSO₄. La filtración y la evaporación del solvente manteniendo la temperatura por debajo de 25 °C dio un aceite el cual se separó mediante cromatografía de columna en gel de sílice (éter de petróleo ligero). Se recogió una fracción con R_f 0,8 (hexano). La evaporación de el solvente dio 34 como un aceite incoloro (0,365 g, 44%), ¹H NMR (CDCl₃, TMS) : 0,89 y 1,01 (total 6H, ambos s, 5,5-CH₃); 1,34 (1H, m, c-4-CH); 1,55-1,95 (3H, m, 4-CH, 6-CH₂); 1,71 (3H, s; -1-CH₃); 3,90 (1H, m, 3-CH) y 5,39 ppm (1H, s, C=CH).

b) clorhidrato de 3,5,5-trimetil-2-ciclohexen-1-amina (35).

Se preparó a partir de azida 34 de acuerdo con el procedimiento para el compuesto 11 (Ejemplo 3, c). Se obtuvo clorhidrato de amina 35 como un sólido incoloro en rendimiento de 57%. ¹H NMR (CDCl₃, TMS) : 0,89 y 1,03 (total 6H, ambos s, 5,5-CH₃); 1,25-2,15 (4H, m, 4,6-CH₂); 1,72 (3H, s, 3-CH₃); 3,88 (1H, m, 1-CH); 5,41 (1H, s, C=CH) y 8,40 ppm (3H, br s, NH₃⁺).

Ejemplo 15.

Clorhidrato de 1,3,5,5-Tetrametil-2-ciclohexen-1-amina (40).

a) Mezcla de 1,3,5,5-Tetrametil-1,3-ciclohexadieno (37) y 1,5,5-trimetil-3-metilen-1-ciclohexeno (38).

A una solución 2 M en éter de yoduro de metilmagnesio (15 ml, 30 mmol) se agregó por goteo una solución de 3,5,5-trimetil-2-ciclohexen-1-ona

(36) (1,38 g, 10 mmol) en éter seco (15 ml). La mezcla se agitó por 1 h, se enfrió con agua helada y se trató cuidadosamente CH_3COOH acuoso 15% (15 ml). La mezcla se agitó por otra hora. La capa orgánica se separó y se lavó con agua y NaHCO_3 acuoso saturado. Luego de secar sobre MgSO_4 , la solución se concentró al vacío. El residuo se purificó mediante cromatografía flash (éter de petróleo ligero, R_f 0,95 (hexano)) para dar una mezcla de 37 y 38 (0,955 g, 70%) (7:10, en base a GC) como un aceite. ^1H NMR (CDCl_3 , TMS) 0,89, 0,98 y 1,03 (total 10,2H, todos los s, 5,5- CH_3); 1,55-2,20 (total 12,6H, m, $\text{CH}_2\text{C} =$ y $\text{CH}_3\text{C} =$); 4,69 (2H, dm, 4 Hz, $=\text{CH}_2$); 5,06 (0,7H, m, $=\text{CH}$); 5,50 (0,7H, sept, 1,5 Hz, $=\text{CH}$) y 5,92 ppm (1H, m, $=\text{CH}$).

b) 3-Azido-1,5,5,5-tetrametil-1-ciclohexeno (39).

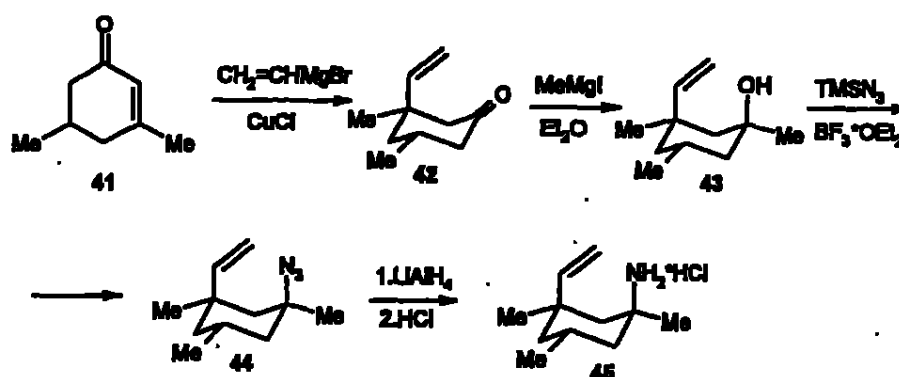
Se preparó a partir de 37 y 38 mixture de acuerdo con el procedimiento para el compuesto 34 (Ejemplo 14, a). Se obtuvo azida 39 como un aceite incoloro con 43% de rendimiento. ^1H NMR (CDCl_3 , TMS) : 0,93 y 0,99 (total 6H, ambos s, 5,5- CH_3); 1,31 (3H, s, 1- CH_3); 1,36 y 1,62 (total 2H, ambos d, 13 Hz, 4- CH_2); 1,72 (5H, s, 1- CH_3 , 6- CH_2); 5,32 (1H, s, $\text{C} = \text{CH}$).

c) clorhidrato de 1,3,5,5-tetrametil-2-ciclohexen-1-amina (40).

Se preparó a partir de azida 39 de acuerdo con el procedimiento para el compuesto 11 (Ejemplo 3, c). Se obtuvo clorhidrato de amina 40 como un sólido incoloro con rendimiento de 60%. ^1H NMR (CDCl_3 , TMS) : 0,96 y 1,07 (total 6H, ambos s, 5,5- CH_3); 1,56 (3H, s, 1- CH_3); 1,73 (3H, s, 3- CH_3); 1,60-2,05 (4H, m, 4,6- CH_2); 5,49 (1H, s, $\text{C} = \text{CH}$) y 8,27 ppm (3H, br s, NH_3^+).

Esquema: Ejemplo 16

147



Ejemplo 16.

Clorhidrato de 1,3,trans-5-trimetil-cis-3-vinilciclohexanamina (45).

a) 3,5-dimetil-3-vinilciclohexanona (42).

Una solución 1M de bromuro de vinilmagnesio en THF (90 ml, 90 mmol) se enfrió en un baño de acetona helada seco a -20°C en una atmósfera inerte y se agregó CuCl (4,45 g, 45 mmol) en una porción. La mezcla se agitó por 30 min y se agregó por goteo una solución de 3,5-dimetil-2-ciclohexen-1-ona (41) (3,73 g, 30 mmol) en THF (40 ml) manteniendo la temperatura de la reacción a -20°C . Se retiró el baño de enfriamiento y la mezcla de reacción se dejó alcanzar la temperatura ambiente por 2 h. Se agregó NH_4Cl acuoso saturado (50 ml) a fondo mientras se enfriaba con un baño de hielo. Luego se agregó hexano (150 ml) y la capa acuosa se separó y se extrajo con hexano (2 100 ml). Los extractos orgánicos combinados se lavaron con ácido acético acuoso 20% (100 ml) y con NaHCO_3 acuoso saturado (3 200 ml). El extracto se secó sobre MgSO_4 , se filtró y se evaporó. El producto crudo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 20: 1) para dar 42 (2,4 g, 52 %) como un aceite incoloro. $^1\text{H-NMR}$ (CDCl_3 , TMS) : 0,99 (3H, d, 6 Hz, 5- CH_3); 1,11 (3H, s, 3- CH_3); 1,2-2,6 (7H, m, protones de

anillo); 4,94 y 5,01 (total 2H, ambos d, 17 y 10,5 Hz, CH₂ =) y 5,64 ppm (1H, dd, 17 y 11 Hz, =CH).

b) 1,3, trans-5-trimetil-clis-3-vinilciclohexanol (43).

Una solución de acetona 42 (1 g, 6,6 mmol) en dietiléter (10 ml) se agregó a una solución 1,6M de metil-litio en dietiléter (12 ml, 19,6 mmol) mientras se enfriaba en un baño de hielo. La mezcla resultante se agitó bien por 1h a 0-5°C y se agregó NH₄Cl acuoso saturado (10 ml). La capa acuosa se separó y se extrajo con dietiléter (2 15 ml). Las fases orgánicas combinadas se lavaron con salmuera (20 ml) y se secaron sobre MgSO₄. El extracto se filtró y se evaporó. El producto crudo se purificó mediante cromatografía flash en gel de sílice (acetato de etilo 3% en éter de petróleo ligero). Se obtuvo ciclohexanol 43 (0,82 g, 74 %) como un aceite incoloro que se utilizó en el siguiente paso sin caracterización.

c) 1-Azido-1,3, trans-5-trimetil-clis-3-vinilciclohexano (44).

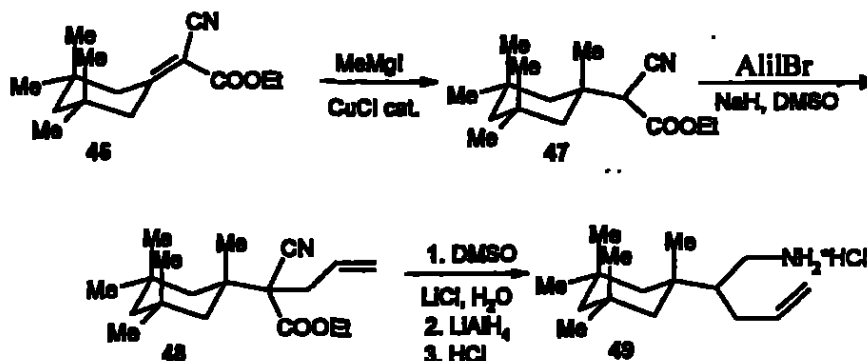
Se preparó a partir de ciclohexanol 43 de acuerdo con el procedimiento para el compuesto 9 (Ejemplo 3, b). Se obtuvo azida 44 como un aceite incoloro con un rendimiento de 17%. ¹H-NMR (CDCl₃, TMS) : 0,94 (3H, d, 6,5 Hz, 5-CH₃); 0,97 (3H, s, 3-CH₃); 1,27 (3H, s, 1-CH₃); 0,7-2,0 (7H, m, protones de anillo); 4,95 y 4,97 (total 2H, ambos d, 18 y 11 Hz, =CH₂) y 5,77 ppm (1H, dd, 18 y 11 Hz, =CH).

d) Clorhidrato de 1,3,trans-5-trimetil-clis-3-vinilciclohexanamina (45).

Se preparó a partir de azida 44 de acuerdo con el procedimiento para el compuesto 11 (Ejemplo 3, c). Se obtuvo clorhidrato de amina 45 como un sólido incoloro con un rendimiento de 32%. ¹H-NMR (CDCl₃, TMS) :0,92 (3H, d, 6,5 Hz, 5-CH₃); 0,96 (3H, s, 3-CH₃); 1,45 (3H, s, 1-CH₃); 0,8-2,1 (9H, m, 2,4,6-

CH₂, 5-CH y H₂O); 4,94 y 4,97 (2H, ambos d, 18 y 11 Hz, =CH₂); 5,76 (1H, dd, 18 y 11 Hz, =CH) y 8,26 ppm (3H, br s, NH₃⁺).

Esquema: Ejemplo 17



Ejemplo 17.

Clorhidrato de 2-(1,3,3,5,5-pentametilciclohexil)-4-pentenilamina (49).

a) 2-ciano-2-(1,3,3,5,5-pentametilciclohexil)acetato de etilo(47).

Se agregó cloruro de cobre (I) (0,05 g, 0,5 mmol) a una solución de yoduro de metilmagnesio 1 M en éter etílico enfriada (-10 °C) en una atmósfera de argón (15 ml, 15 mmol) y se agitó por 5 min. Luego se agregó por goteo una solución de acetato 46 (2,5 g, 10 mmol) en THF (25 ml) durante 20 min, manteniendo la temperatura por debajo de 0°C. La mezcla se agitó por 1h, se fraguó con NH₄Cl acuoso saturado, y se extrajo con dietiléter. El extracto se lavó con salmuera, se secó sobre MgSO₄ anhidro, se filtró y se evaporó. El residuo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 20: 1) para dar 47 (1,5 g, 56,5 %) como un aceite incoloro. ¹H NMR (CDCl₃, TMS) : 1,01, 1,07 y 1,09 (total 12H, s, 3' , 5' -CH₃); 1,00-1,85 (6H, m,

150

anillo CH); 1,30 (3H, s, 1' -CH₃); 1,33 (3H, t, 7 Hz, CH₃-etil); 3,44 (1H, s, 2-CH) y 4,27 ppm (2H, q, 7 Hz, OCH₂).

b) 2-clano-2-(1,3,3,5,5-pentametilciclohexil)-4-pentenoato de etilo (48)

A una solución de cianoacetato 47 (1,25 g, 4,71 mmol) en DMSO anhidro (10 ml) se agregó hidruro de sodio (0,284 g, 7,09 mmol; dispersión 60% en aceite mineral). La mezcla se agitó por 30 min a 50°C, y se enfrió a 20°C. A esto se agregó alilbromuro (0,86 g, 7,1 mmol) y la mezcla se agitó por 3 h a temperatura ambiente, luego por 30 min a 50 °C. La mezcla se enfrió, se trató con agua y se extrajo con dietiléter. El extracto se lavó con agua y con salmuera, se secó sobre MgSO₄ anhidro, se filtró y se evaporó. El residuo se purificó mediante cromatografía flash en gel de sílice (éter de petróleo ligero - acetato de etilo, 20: 1) para dar 48 (0,92 g, 63,7 %) como un aceite incoloro. ¹H NMR (CDCl₃, TMS) : 0,98 (6H, s, 3',5'-CH₃eq); 1,11 (6H, s, 3',5'-CH₃ax); 1,00-1,85 (6H, m, anillo CH); 1,31 (3H, t, 7 Hz, CH₃-etil); 1,33 (3H, s, 1'-CH₃); 2,42 y 2,86 (total 2H, ambos dd, 13 y 7 Hz, 3-CH₂); 4,02 (2H; q, 7Hz, OCH₂); 5,05-5,37 (2H, m, =CH₂) y 5,55-6,05 ppm (1H, m, =CH).

c) Clorhidrato de 2-(1,3,3,5,5-Pentametilciclohexil)-4-pentenilamina (49)

A una solución de éster 48 (0,9 g, 2,95 mmol) en DMSO (10 ml) se agregó agua (0,53 ml, 2,95 mmol) y cloruro de litio (0,25 g, 5,9 mmol). La mezcla se agitó por 3 h a 175-180 °C, luego se enfrió y se agregó agua (30 ml). La mezcla se extrajo con dietiléter. El extracto se lavó con agua y con salmuera, se secó sobre MgSO₄ anhidro, se filtró y se concentró a un volumen de 10 ml. La solución obtenida se agregó por goteo a una suspensión de

151

hidruro de litio y aluminio (0,25 g, 6,6 mmol) en dietiléter (15 ml) y se agitó a reflujo por 3 h. La mezcla se enfrió y se trató con NaOH acuoso 20%, y se extrajo con dietiléter. El extracto se lavó con salmuera, se secó sobre NaOH, se filtró y se trató con solución de HCl anhidro en dietiléter. Luego de la evaporación del solvente, el residuo se purificó mediante cromatografía en gel de sílice (cloroformo - metanol, 20:1) para dar 49 (0,245 g, 31 %) como un sólido incoloro. ^1H NMR (DMSO- D_6 , TMS) : 0,92, 0,96 y 1,04 (total 15H, todos los s, 3' , 5' - CH_3 y 1'- CH_3), 1,00-1,65 (total 6H, m, anillo- CH_2); 1,85-2,40 (3H, m, 3- CH_2 , 4-CH); 2,80-3,10 (2H, m, CH_2N); 4,90-5,25 (2H, m, = CH_2); 5,62-6,10 (1H, m, =CH) y 7,92 ppm (3H, br s, NH_3^+).

COMPOSICIONES FARMACÉUTICAS

Los ingredientes activos de la invención, junto con uno o más coadyuvantes, vehículos, o diluyentes convencionales, se pueden poner en la forma de composiciones farmacéuticas y unidades de dosificación de las mismas, y en dicha forma se pueden emplear como sólidos, por ejemplo tabletas recubiertas o sin recubrir o cápsulas rellenas, o líquidos, como por ejemplo soluciones, suspensiones, emulsiones, elixires, o rellenas cápsulas con los mismos, todos para uso oral; en la forma de supositorios o cápsulas para administración rectal o en la forma de soluciones estériles inyectables para uso parenteral (incluyendo intravenoso o subcutáneo). Dichas composiciones farmacéuticas y formas de dosificación unitarias de los mismos pueden comprender ingredientes convencionales o nuevos en proporciones convencionales o especiales, con compuestos o principios activos adicionales o sin los mismos, y dichas formas de dosificación unitarias pueden contener cualquier cantidad efectiva apropiada del ingrediente activo en medida

correspondiente al rango de dosificación diaria que se intenta aplicar. Por lo tanto, las tabletas que contienen entre veinte (20) y cien (100) miligramos de ingrediente activo o, más ampliamente, entre diez (10) y doscientos cincuenta (250) miligramos por tableta, son formas de dosificación unitaria representativas apropiadas.

MÉTODO DE TRATAMIENTO

Debido a su alto grado de actividad y a su baja toxicidad, además de un índice terapéutico más favorable, los principios activos de la invención se pueden administrar a un sujeto, por ejemplo, al cuerpo de un animal vivo (incluyendo un humano), que necesita los mismos, para el tratamiento, para aliviar, o para mejorar, paliar, o eliminar una indicación o condición que es susceptible de eso, o en forma representativa de una indicación o condición establecida en cualquier parte de la presente solicitud, preferiblemente en forma concurrente, simultánea, o junto con uno o más excipientes, vehículos, o diluyentes aceptables para uso farmacéutico, especial y preferiblemente en la forma de una composición farmacéutica de los mismos, si se aplica por ruta oral, rectal, o parenteral (incluyendo intravenosa y subcutánea) o en algunos casos aún tópica, en una cantidad efectiva. Los rangos de dosificación apropiados son 1-1000 miligramos diariamente, preferiblemente 10-500 miligramos diariamente, y especialmente 50-500 miligramos diariamente, dependiendo como es usual del modo exacto de administración, de la forma en que se administra, la indicación hacia donde se dirige la administración, del sujeto y del peso corporal de dicho sujeto, y de la preferencia y experiencia del médico o veterinario a cargo.

EJEMPLOS DE COMPOSICIONES FARMACÉUTICAS REPRESENTATIVAS

Se pueden procesar los productos de reacción en forma de tabletas, tabletas recubiertas, cápsulas, soluciones de goteo, supositorios, preparaciones para inyección e infusión, etcétera, con el auxilio de los solventes, agentes auxiliares y vehículos que se utilizan comúnmente; y se pueden aplicar en forma terapéutica por las rutas oral, rectal, parenteral, y rutas adicionales. A continuación, se presentan las composiciones farmacéuticas representativas.

(a) Se pueden preparar tabletas apropiadas para administración oral que contienen el ingrediente activo por técnicas convencionales de fabricación de tabletas.

(b) Para hacer supositorios, se puede emplear cualquier base usual para supositorios, como por ejemplo un polietilenglicol que es sólido a la temperatura ambiente normal pero que se funde aproximadamente a la temperatura corporal e incorporar el ingrediente activo a la misma mediante los procedimientos usuales.

(c) Para soluciones estériles parenterales (incluyendo intravenosas y subcutáneas), el ingrediente activo se emplea junto con ingredientes convencionales como por ejemplo cloruro de sodio y agua bidestilada c.s.p. en las cantidades usuales, de acuerdo con el procedimiento convencional, como por ejemplo filtración, rellenado aséptico de ampollas o botellas para goteo IV, y pasando por autoclave para esterilizar.

Otras composiciones farmacéuticas apropiadas serán inmediatamente evidentes para aquellos experimentados en el arte.

Nuevamente, los siguientes ejemplos se dan solamente como ilustración y no se deben entender como limitantes.

EJEMPLO 18

Formulación en tabletas

Una formulación apropiada para una tableta que contiene 10 miligramos de ingrediente activo es la siguiente:

	Mg
Ingrediente activo	10
Lactosa	63
Celulosa microcristalina	21
Talco	4
Estearato de magnesio	1
Dióxido de silicio coloidal	1

EJEMPLO 19

Formulación en tabletas

Otra formulación apropiada para una tableta que contiene 100mg es la siguiente:

	Mg
Ingrediente activo	100
Almidón de papa	20
Polivinilpirrolidona	10

Se recubren con película y se colorean.

El material de la película de recubrimiento consiste en:

Lactosa	100
Celulosa microcristalina	80
Gelatina	10
Povidón, reticulada	10
Talco	10
Estearato de magnesio	2
Dióxido de silicio coloidal	3
Pigmentos colorantes	5

EJEMPLO 20

Formulación de cápsulas

Una formulación apropiada para una cápsula que contiene 50 miligramos de ingrediente activo es la siguiente:

	Mg
Ingrediente activo	50
Almidón de maíz	20
Fosfato dibásico de calcio	50
Talco	2
Dióxido de silicio coloidal	2

Se utilizó como relleno para una cápsula de gelatina.

EJEMPLO 21

Solución para inyección

156

Una formulación apropiada para una solución inyectable que contiene un porcentaje de ingrediente activo es la siguiente:

Ingrediente activo	mg	12
Cloruro de sodio	mg	8
Agua estéril para hacer	ml	1

EJEMPLO 22

Formulación líquida oral

Una formulación apropiada para 1 litro de una mezcla líquida que contiene 2 miligramos de ingrediente activo en un mililitro de la mezcla es la siguiente:

	G.
Ingrediente activo	2
Sacarosa	250
Glucosa	300
Sorbitol	150
Sabor naranja	10
Amarillo ocaso.	
Agua purificada para hacer un total de 1000 ml.	

EJEMPLO 23

Formulación líquida oral

Otra formulación apropiada para 1 litro de una mezcla líquida que contienen 20 miligramos de ingrediente activo en un mililitro de la mezcla es la siguiente:

157

	G.
Ingrediente activo	20,00
Goma tragacanto	7,00
Glicerol	50,00
Sacarosa	400,00
Metilparabeno	0,50
Propilparabeno	0,05
Sabor cassis	10,00
Color rojo soluble	0,02
Agua purificada para hacer un total de 1000 ml.	

EJEMPLO 24

Formulación líquida oral

Otra formulación apropiada para 1 litro de una mezcla líquida que contiene 2 miligramos de ingrediente activo en un mili-litro de la mezcla es la siguiente:

	G.
Ingrediente activo	2
Sacarosa	400
Tintura de cáscara de naranja amarga	20
Tintura de cáscara de naranja dulce	15
Agua purificada para hacer un total de 1000 ml.	

158

EJEMPLO 25

Formulación en aerosol

180g de solución de aerosol contienen:

	G.
Ingrediente activo	10
Ácido oleico	5
Etanol	81
Agua purificada	9
Tetrafluoroetano	75

Se utilizaron 15ml de la solución como relleno de latas de aerosol de aluminio, tapadas con una válvula dosificadora, purgada con 3,0bar.

EJEMPLO 26

Formulación TDS

100g de solución contienen:

	G.
Ingrediente activo	10,0
Etanol	57,5
propilenglicol	7,5
Dimetilsulfóxido	5,0

154
159

Hidroxietilcelulosa	0,4
Agua purificada	19,6

Se pusieron 1,8ml de la solución en un fieltro cubierto con una hoja adhesiva. El sistema se cierra mediante un revestimiento protector que se quitará antes del uso.

EJEMPLO 27

Formulación de nanopartículas

10g de nanopartículas de polibutílcianoacrilato contienen:

G.

Ingrediente activo	1,00
Poloxámero	0,10
cianoacrilato de butilo	8,75
Manitol	0,10
cloruro de sodio	0,05

Se prepararon nanopartículas de polibutílcianoacrilato por polimerización de una emulsión en una mezcla agua/ HCl 0,1N/etanol as medio de polimerización. Finalmente, las nanopartículas en la suspensión se liofilizan al vacío.

FARMACOLOGÍA - RESUMEN

Los principios activos de la presente invención, y composiciones farmacéuticas de los mismos y los métodos para tratar con los mismos, se

caracterizan por propiedades únicas, ventajosas y no predecibles, que hacen que "la materia sujeta como un todo", según se reivindica aquí, no sea obvia. En procedimientos de prueba estándar aceptados y confiable, los compuestos y composiciones farmacéuticas de los mismos han mostrado las siguientes propiedades y características valiosas:

Los mismos son antagonistas no competitivos del receptor NMDA sistémicamente activos, con una rápida cinética de bloqueo/desbloqueo y una fuerte dependencia del voltaje y por lo tanto son de utilidad para el tratamiento, para eliminación, para paliar, aliviar, y mejorar condiciones sensibles, mediante la aplicación o administración al huésped animal vivo para el tratamiento de un amplio rango de trastornos del SNC que incluyen perturbaciones de transmisión glutamatérgica.

Dichos compuestos también son sistémicamente activos, antagonistas no competitivos del receptor nicotínico neuronal 5-HT₃ y por lo tanto, son de utilidad para el tratamiento, para eliminación, para paliar, aliviar, y mejorar condiciones sensibles, mediante la aplicación o administración al huésped animal vivo para el tratamiento de un amplio rango de trastornos del SNC que incluyen perturbaciones de la transmisión de serotonina o nicotínica.

Métodos

Estudios de unión al receptor

Se decapitaron ratas Sprague-Dawley de sexo masculino (200-250g) y se extrajeron inmediatamente sus cerebros. Se disecó la corteza y se homogeneizó en 20 volúmenes de sacarosa 0,32M enfriada con hielo utilizando un homogeneizador de vidrio-Teflon. Se centrifugó el homogenato a 1,000xG durante 10 min. Se descartó el gránulo y el sobrenadante se centrifugó a

20,000xG durante 20 min. El gránulo resultante se resuspendió en 20 volúmenes de agua destilada y se centrifugó durante 20 minutos a 8,000xG. luego el sobrenadante y la capa de plasma coagulado se centrifugó a 48,000xG durante 20 minutos en presencia de Tris-HCl 50mM, a pH 8,0. Luego se resuspendió el gránulo y se centrifugó entre dos y tres veces más a 48,000xG durante 20 minutos en presencia de Tris-HCl 50mM, a pH 8,0. Todos los pasos de centrifugado se llevaron a cabo a 4°C. Después de resuspender en 5 volúmenes de Tris-HCl 50mM, a pH 8,0; se congeló rápidamente la suspensión de membrana a -80°C.

El día del ensayo se descongelaron las membranas y se lavó cuatro veces por resuspensión en Tris-HCl 50mM, a pH 8,0 y se centrifugó a 48,000xg durante 20 minutos y finalmente se resuspendió en Tris-HCl 50mM, a pH 7,4. Se determinó la cantidad de proteína en la preparación final de membrana (250-500µg/ml) de acuerdo con el método de Lowry et al. (1951). Las incubaciones se comenzaron agregando [³H]-(+)-MK-801 (23,9 Ci/mmol, 5nM, Dupont NEN) a ampollitas con glicina (10µM), glutamato (10µM), y 125-250µg de proteína (volumen total 0,5ml) y diferentes concentraciones de los agentes que se probaron (10 concentraciones por duplicado). Las incubaciones se continuaron a temperatura ambiente durante 120 minutos (bajo las condiciones que se utilizaron se llegó al equilibrio). Se definió la unión no específica por la adición de (+)-MK-801 sin marcar (10µM). Se terminaron las incubaciones utilizando un sistema de filtro Millipore. Las muestras se enjuagaron dos veces con 4ml de solución amortiguadora de pH de ensayo enfriada con hielo, sobre filtros de fibra de vidrio (Schleicher & Schuell) a un vacío constante. Después de la separación y el enjuague se pusieron los filtros en líquido de centelleo

(5ml; Ultima Gold) y se determinó la radioactividad retenida en los filtros con un contador de centelleo líquido convencional (Hewlett Packard, Liquid Scintillation Analyser). Se determinó la K_d de [^3H]-(+)-MK-801 de 4,6nM mediante análisis Scatchard y se utilizó de acuerdo con la relación de Cheng Prussoff para calcular la afinidad de los desplazadores como valores de K_d . Se probaron más antagonistas en entre 3 y 7 experimentos por separado.

Expresión del subtipo de receptores neuronales NMDA y nicotínico en oocitos de *Xenopus*

Se anestesiaron hembras maduras de *Xenopus laevis* en Tricaina al 0,2% en hielo durante 15 minutos antes de la cirugía. Se extrajeron los oocitos y se incubaron en 2mg/ml de colagenasa (tipo II) en solución de Ringer para oocitos libre de Ca^{2+} (NaCl 82,5mM, KCl 2mM, $MgCl_2$ 2mM, HEPES 5mM, pH 7,5) durante 30 minutos a temperatura ambiente y se lavó completamente con OR-2 (NaCl 100mM, KCl 2mM, $MgCl_2$ 1mM, $CaCl_2$ 2mM, HEPES 5mM, pH 7,5). La capa restante de células de folículo se extrajo en forma manual con un fórceps fino y los oocitos se mantuvieron en OR-2. El ARN se disolvió en agua destilada estéril tratada con DEPC. El ARN para la subunidad NR1A NMDA se mezcló 1:1 con ARN para la subunidad NR ^{2} A. De la misma manera, el ARN nicotínico neuronal $\alpha 4$ se mezcló 1:1 con ARN para la subunidad $\beta 2$. Se inyectaron entre 50 y 100 nanolitros de cada mezcla de ARN en el citoplasma de los oocitos utilizando un inyector Nanoliter Injector (World Precision Instruments). Los oocitos se incubaron a 19°C en OR-2 durante los siguientes 3 a 6 días.

Las respuestas electrofisiológicas se obtuvieron utilizando el método estándar de pinzamiento de voltaje de dos electrodos (amplificador GeneClamp

169
163

500), 2-6 días después de la inyección. Los electrodos tenían una resistencia entre 0,2 y 0,4M Ω y se rellenaron con KCl 3M. Se hicieron registros en una cámara hecha especialmente con tiempos de intercambio de entre 2 y 3 segundos. La solución de baño se preparó libre de Ca²⁺, para evitar las corrientes de Ca²⁺ inducidas por Cl⁻ (NaCl 100mM, KCl 2mM, HEPES 5mM, 2mM BaCl₂, pH 7,35). Se activaron los receptores NMDA mediante co-aplicación manual de glutamato 1mM y glicina 10 μ M durante 30-40 segundos cada entre 2 y 3 minutos a oocitos pinzados a -70mV. Los receptores nicotínicos neuronales se activaron por aplicación de acetilcolina 100 μ M durante 20-30 segundos cada entre 2 y 3 minutos a oocitos pinzados a -70mV. Después de obtener respuestas estables de control, se obtuvieron curvas completas de concentración-respuesta con antagonistas preincubando 6-7 concentraciones diferentes a intervalos log 3.

En el análisis final se incluyeron se aceptaron solamente resultados de células estables, es decir que mostraban una recuperación de por lo menos 50% en las respuestas a NMDA después de la eliminación del antagonista que se estaba probando. A pesar de esto, la recuperación de las acciones de la droga no fue siempre del 100% debido a un agotamiento o recuperación minoritarios en algunas células. Cuando sucedió esto, se compensó siempre basando el antagonismo porcentual a cada concentración tanto en el control como en el recuperado y asumiendo un transcurso lineal en el tiempo para dicho agotamiento. Todos los antagonistas se evaluaron en el bloqueo de estado estacionario con entre 6 y 7 concentraciones sobre por lo menos 4 células. Se consiguió el equilibrio de bloqueo dentro de 1 a 3 aplicaciones de agonista, dependiendo de la concentración de antagonista.

Los experimentos de cinética se llevaron a cabo aplicando diferentes concentraciones de amino-alkil-ciclohexanos insaturados (normalmente 5 en un régimen de dosificación log 3) durante 10-20 segundos en presencia continua de glutamato (100 μ M y glicina 10 μ M) durante 90-180 segundos en oocitos de *Xenopus* que expresaban receptores NR1a/2A. El sistema de perfusión que se utilizó para dichos experimentos era un modificado sistema carrusel para oocitos que permitía una rápida entrada y salida del agonista y antagonista con tiempos de recambio menores de un segundo. Se realizaron ajustes exponenciales utilizando el programa TIDA para Windows y la mayor parte de las respuestas se ajustaron a una única exponencial. El mismo sistema se utilizó para acceder a la dependencia del voltaje de bloqueo, pero la solución de baño contenía ácido flufenámico (100 μ M) para bloquear las corrientes endógenas activadas por el voltaje y las corrientes de Cl⁻ activadas por Ca²⁺. También se reemplazó el Ba²⁺ (2mM) por bajas concentraciones de Ca²⁺ (0,2 mM). Después del bloqueo de equilibrio por concentraciones más altas de antagonista (normalmente alrededor de 10 veces la IC₅₀), se impulsaron cinco rampas entre -70mV y +30mV durante dos segundos. Se impulsaron rampas similares en soluciones de baño y para glutamato sin antagonista, ambos antes de la aplicación de antagonista y después de la recuperación de las respuestas. Las corrientes filtración en ausencia de glutamato se sustrajeron de las curvas de glutamato y de glutamato más antagonista. Luego se determinó la dependencia del voltaje por comparación de las curvas de glutamato y de glutamato más antagonista.

Pinzamiento zonal para NMDA y Nicotina

Se obtuvieron hipocampos de embriones de rata (E20 a E21) y luego se

165

transfirieron a una solución salina de Hank de pH amortiguado libre de calcio y magnesio (Gibco) sobre hielo. Se disociaron las células en forma mecánica en ADNasa al 0,05% / ovomucoide al 0,3% (Sigma) seguido de una preincubación de 8 minutos con tripsina al 0,66% / ADNasa al 0,1% (Sigma). Luego se centrifugaron las células disociadas a 18xG durante 10 minutos, se resuspendió en medio esencial mínimo (Gibco) y se puso en placas a una densidad de 150,000 células cm⁻² sobre placas de Petri plásticas (Falcon) pre-recubiertas con poli-L-lisina (Sigma). Las células se nutrieron con medio esencial mínimo NaHCO₃/amortiguador de pH HEPES suplementado con suero fetal bovino al 5% y suero de caballo al 5% (Gibco) y se incubaron a 37°C con CO₂ al 5% a una humedad del 95%. El medio se intercambió completamente después de la inhibición de la mitosis adicional de la glía con citosina-R-D-arabinofuranósido (20µM Sigma) después de aproximadamente 7 días *in vitro*. Después, el medio se intercambió parcialmente dos veces por semana.

Se hicieron registros de pinzamiento zonal de aquellas neuronas con electrodos de vidrio pulido (4-8m) en el modo de célula completa a temperatura ambiente (20-22°C) con la ayuda de un amplificador EPC-7 (List). Las sustancias de prueba se aplicaron intercambiando los canales de un sistema de superfusión rápida hecho a medida con un flujo en común (tiempos de intercambio de 10-20ms). Los contenidos de la solución intracelular fueron según sigue (mM): CaCl (120), TEACl (20), EGTA (10), MgCl₂(1), CaCl₂(0,2), glucosa (10), ATP(2), cAMP (0,25); se ajustó el pH a 7,3 con CsOH o HCl. Las soluciones extracelulares tenían las siguientes composición básica (mM): NaCl (140), KCl (3), CaCl₂ (0,2), glucosa (10), HEPES (10), sacarosa (4,5), tetrodotoxina (TTX 3*10⁻⁴). Hubo glicina (1µM) presente en todas las

soluciones: una concentración suficiente como para causar alrededor de 80-85% activación de los receptores de glicina_B. En el análisis final se incluyeron se aceptaron solamente los resultados de células estables, es decir, después de la recuperación de respuestas a la NMDA por lo menos en un 75% de su depresión por los antagonistas que se probaron.

Pinzamiento zonal para 5-HT₃

Se adquirieron células N1E-115 de la Colección Europea de cultivos de células (ECACC, Salisbury, UK) y se almacenaron a -80°C hasta su uso. Las células se pusieron en placas a una densidad de 100,000 células cm⁻² sobre placas de Petri plásticas (Falcon) y se nutrieron con medio esencial mínimo NaHCO₃/amortiguador de pH HEPES suplementado (MEM) con suero fetal bovino (Gibco) al 15% y se incubaron a 37°C con CO₂ al 5% a una humedad del 95%. El medio se intercambiaba completamente todos los días. Una vez cada tres días, se repicaron las células sobre Placas de Petri frescas después del tratamiento con tripsina-EDTA (1% en PBS), se resuspendieron en MEM y se centrifugaron a 1,000 rpm durante cuatro minutos.

2-3 Días después de la siembra se hicieron registros de pinzamiento zonal a -70mV en las células que se levantaron, con electrodos de vidrio pulido (2-6MΩ) en el modo de célula completa a temperatura ambiente (20-22°C) con un amplificador EPC-7 (List). Los contenidos de la solución intracelular fueron los siguientes (mM): CsCl(130), HEPES (10), EGTA (10), MgCl₂ (2), CaCl₂ (2), K-ATP (2), Tris-GTP (0,2), D-glucosa (10); se ajustó el pH a 7,3 con CsOH o HCl. Las soluciones extracelulares tenían la siguiente composición básica (mM): NaCl (124), KCl (2,8), HEPES (10), se ajustó el pH a 7,3 con NaOH o HCl.

Después de establecer la configuración de célula completa, se tomaron las células del sustrato de vidrio y se aplicaron serotonina (10 μ M), memantina y derivados de amino-alkil-ciclohexano insaturado a diferentes concentraciones utilizando un dispositivo de superfusión rápida. Se utilizó una pipeta de aplicación manejada mediante un transductor piezoeléctrico de tubo doble para exponer la célula cosechada tanto a solución libre de serotonina como a solución que contiene serotonina. Se aplicó un pulso de serotonina de dos segundos cada 60 segundos. Se disolvieron los antagonistas putativos en agua bidestilada y se diluyeron con solución de baño a la concentración deseada. En el análisis final se incluyeron solamente los resultados de las células estables, es decir, los que mostraron una recuperación de por lo menos 50% de respuestas a la serotonina después de la eliminación de los compuestos. A pesar de esto, la recuperación de las acciones de la droga no fue siempre del 100% debido al agotamiento en algunas células ($\leq 10\%$ durante el transcurso de 10 minutos). Cuando hubo agotamiento, se compensó siempre basando el antagonismo porcentual a cada concentración tanto en el control como en la recuperación y asumiendo un transcurso lineal en el tiempo para dicho agotamiento. Todos los antagonistas se evaluaron al bloqueo de estado estacionario con entre 3 y 6 concentraciones sobre por lo menos cinco células. El bloqueo de equilibrio se consiguió dentro de las 2 a 5 aplicaciones de agonista, dependiendo de la concentración de antagonista.

In vivo

Actividad anticonvulsiva

Se utilizaron ratones hembra RMN (18-28 g) alojados de a 5 por jaula para las pruebas de máximo electroshock (MES) y deterioro motor. Todos los

animales se mantuvieron con agua y alimento a voluntad bajo un ciclo luz y oscuridad de 12 horas (se encendieron las luces a las 6 a.m.) y a una temperatura controlada ($20 \pm 0,5^{\circ}\text{C}$). Todos los experimentos se llevaron a cabo entre las 10 a.m. y las 5 p.m. A menos que se especifique de otra manera, los agentes que se probaron se inyectaron por vía i.p. 30 minutos antes de la inducción de convulsiones (véase a continuación). Todos los compuestos se disolvieron en solución salina al 0,9%.

La prueba MES se llevó a cabo junto con pruebas de la acción miorelajante (reflejo de tracción) y coordinación motriz (varilla giratoria). Para la prueba del reflejo de tracción se pusieron ratones con sus patas delanteras sobre una varilla horizontal y se requirió que pusieran sus 4 patas sobre el cable dentro de los 10 segundos. Para probar la ataxia (coordinación motriz) se pusieron ratones sobre una varilla giratoria acelerada y se requirió que permanecieran sobre la varilla durante 1 minuto. Se consideró que solamente los ratones que no satisficieron los criterios en tres repeticiones de cada prueba mostraban miorelajación o ataxia respectivamente. Dichas pruebas fueron seguidas de MES (100Hz, duración del shock de 0,5 segundos, intensidad del shock de 50mA, duración del impulso de 0,9ms, Ugo Basile) que se aplicaron a través de electrodos en la córnea. Se clasificó la presencia de convulsiones tónicas (extensión tónica de patas traseras con un ángulo mínimo respecto del cuerpo de 90°). El objetivo fue obtener las ED_{50} para todos los parámetros que se clasificaron (actividad anticonvulsiva y efectos motores secundarios) utilizando la prueba de Litchfield Wilcoxon para respuestas cuánticas a las dosis. Se utilizó la división de las ED_{50} para efectos secundarios (ataxia o

miorrelajación) por los ED₅₀ para antagonismo de convulsiones por electroshock como un índice terapéutico (TI).

Análisis estadístico

Los IC₅₀ para pinzamiento zonal y estudios de unión se calcularon de acuerdo con la ecuación logística de cuatro parámetros utilizando el programa Grafit de computadora (Erith-acus Software, Inglaterra). Luego determinaron los valores de K_i para los estudios de unión de acuerdo con Cheng y Prusoff. Los valores de unión presentados son las medias ± SEM de 3-5 determinaciones (cada una se llevó a cabo por duplicado).

Se probaron 4-7 dosis de antagonistas en cada una de las pruebas in vivo (5-8 animales por dosis) para permitir el cálculo de las ED₅₀ graduadas de acuerdo con el análisis probit (Litchfield y Wilcoxon) con corrección para efectos entre 0% y 100%. Las ED₅₀ se presentan con límites de confianza del 95% (CI). Se utilizó un análisis de correlación del momento de los productos, de Pearson (Sigma Stat, Jandel Scientific) para comparar las potencias in vitro y la actividad anticonvulsiva in vivo.

RESULTADOS

Números MRZ

Se utilizaron números MRZ para representar nombres químicos. Los números MRZ y sus respectivos nombres químicos se muestran en "LISTA MRZ"

LISTA DE MRZ

MRZ	Nombre químico
2/657	Clorhidrato de 1-amino-2,4,4,6,6-pentametil-ciclohex-2-en
2/749	1-(1-Aminoetil)-3,3,5,5-tetrametilciclohexeno
2/759	1-Etenil-3,3,5,5-tetrametilciclohexilamina

2/1005	1-Amino-3,3,5,5-Tetrametil-1-ciclohexeno
2/1021	2-(3,3,5,5-Tetrametilciclohexiliden)etanamina
2/1023	1-Amino-3,3,5-trimetil-2-ciclohexeno
2002	1,3,5,5-Tetrametil-2-ciclohexen-1-amina
2005	1-Alil-3,3,5,5-tetrametilciclohexanamina
2006	1-(3,3,5,5-Tetrametilciclohexiliden)-2-propanamina
2008	1-(3,3-Dietil-5,5-dimetilciclohexiliden)-2-propanamina
2009	cis-3-Vinil-1,3,trans-5-trimetilciclohexilamina
2010	2-Metil-1-(3,3,5,5-Tetrametil-1-ciclohexen-1-il)2-propanamina
2013	1-(1-Alil-3,3,5,5-tetrametilciclohexil)piperidina
2014	2-(1-Vinil-3,3,5,5 tetrametilciclohexil-1)etilamina
2015	1-[3,3,5,5-Tetrametil-1-(3-metil-2-butenil)ciclohexil]piperidina
2016	1-[3,3,5,5-Tetrametil-1-(2-propinil)ciclohexil]piperidina
2017	2-(1,3,3,5,5-Pentameticiclohexil)-4-pentenilamina
2018	3-(3,3,5,5-Tetrametilciclohexiliden)propanamina
2019	2-Metil-1-(3,3,5,5-tetrametilciclohexiliden)-2-propanamina
2020	2-(3,3,5,5-Tetrametilciclohexiliden)propanamina
2021	N-Metil-1-etenil-3,3,5,5-tetrametilciclohexilamina
2026	N-Alil-1,3,3,5,5-pentametilciclohexanamina

MK-80 de unión

Todos los compuestos se desplazaron [³H]- (+)-MK-801 con valores Ki entre 1 y 83 pM (ver Tabla 1).

Tabla 1

MRZ	Grupo	[³ H]MK-801 Ki	SEM	n	NMDA IC ₅₀ (μM)	SEM	N
2/657	Anillo etileno	13,43	1,15	3			
2/749	Anillo etileno	10,76	1,49	3			
759	Etileno	1,18	0,20	6	328	0,60	6
2/1005	Anillo etileno	13,63	1,43	4			
2/1021	Etileno	2,15	0,32	6	0,33	0,05	6
1023	Anillo etileno	49,60	8,09	6			
2000	Neramexansulf	1,68	0,00	3			

	ato						
2002	Anillo etileno	5,70	0,48	3			
2005	Etileno	9,35	0,12	3	12,60	5,68	6
2006	Etileno	10,06	0,40	3			
2008	Etileno	8,07	0,57	3	2,74	0,22	6
2009	Etileno	22,32	0,88	3	58,17	8,87	6
2013	Etileno	49,21	11,73	3			
2014	Etileno	3,12	0,67	3	0,10	0,01	6
2015	Etileno	83,04	30,98	3			
2016	Etileno	42,22	13,60	3	71,17	14,66	6
2017	Etileno	6,79	0,51	3	1,19	0,16	6
2018	Etileno	20,18	2,80	3	37,06	13,37	6
2019	Etileno	73,06	8,67	3			
2020	Etileno	7,45	0,69	3			
2021	Etileno	6,54	0,72	3	12,73	0,50	6
2010	Anillo etileno	44,88	13,91	3			
2026	Etileno				29,56	1,64	6

Los resultados de compuestos representativos se informan en la Figura 1.

EXPRESIÓN DEL SUBTIPO DE RECEPTOR NMDA EN XENOPUS OOCYTES.

El bloqueo del receptor NMDA por MRZ 2/759 se determinó aplicando diversas concentraciones (entre 0,1 y 100 μ M en un régimen de dosificación log) durante 10 segundos en la presencia continua de glutamato (100 μ M) y glicina 10 p.M) a -70 mV durante 100 segundos en Xenopus oocytes expresando receptores NR1a/2A (Figura 2, izq). La potencia de MRZ 2/759 (IC_{50} = 1,99 μ M, Hill 0,75) se determinó comparando el porcentaje de bloqueo contra la concentración del antagonista y luego ajustando la curva de acuerdo con la ecuación lógica (Figura 2, der).

Parche de membrana (Patch Clamp)

Las respuestas de corriente entrante en estado estacionario de neuronas hipocámpicas a NMDA (200 M con glicina 1M a -70mV) se antagonizaron con MRZ 2/759. Las corrientes de pico y estado estacionario fueron afectadas en grado similar imposibilitando que sus efectos fueran mediados en el sitio glicina_B. Se obtuvo una fuerte evidencia de la naturaleza no competitiva de este antagonismo por el uso claro y la dependencia del voltaje de su bloqueo. Ver Figura 3.

Actividad anti convulsiva In vivo

En la Tabla 2 se presentan los resultados de la acción de MES y Miorelajantes.

MRZ	MES ED50	MES CL	Miorelajación ED50	Miorelajación CI	Ataxia ED50	Ataxia CI	TI Miorelajación	TI Ataxia
2/657	> 30		> 30		> 30			
2/749	26,58	20,7-34,1	38,64	28,6-52,1	37,14	30,0-48,0	1,5	1,4
2/759	14,84	9,6-23,1	12,76	10,3 - 15,9	15,00	11,4-19,8	0,9	1,0
2/1005	20,48	9,6-43,9	35,68	26,1-48,7	26,83	16,1-44,8	1,7	1,3
2/1021	29,46	17,8-48,9	16,50	10,9-25,0	23,09	15,2 - 35,0	0,6	0,8
2/1023	> 50		> 50		> 50			
2002	26,14	21,0-32,5	33,96	27,1 -42,6	52,98	27,8-100,8	1,3	2,0
2005	37,34	33,9-41,1	38,75	32,6-48,4	49,34	37,2-65,5	1,1	1,3
2006	57,02	31,4-103,4	44,62	39,4-50,5	40,88	31,4-58,9	0,8	0,7
2008		-						
2009	> 50		> 50		> 50			
2010	>50		>50		>50			
2013	> 50		> 50		> 50			
2014	47,82	21,5-106,5	13,95	6,3 - 31,1	25,83	18,3-36,4	0,3	0,5
2015	> 50		> 50		> 50			
2016	> 50		> 50		> 50			
2017	36,88	29,1-46,7	35,63	30,0-42,3	33,72	25,0-45,4	1,0	0,9
2018	78,54	35,0-176,3	29,43	23,4-37,0	26,70	19,2-37,0	0,4	0,3
2019	> 50		> 50		> 50			
2020	26,06	20,4-33,3	34,48	29,1 -40,8	27,57	18,7-40,7	1,3	1,1
2021	13,58	21,5-20,7	21,42	18,0-25,4	24,68	20,1 30,2	1,6	1,8

122

2023	>30		>30		>30			
2028	25,38	21,1-30,5	26,67	23,2-30,7	37,64	21,8-65,1	1,1	1,5

174

En conclusión, en base a lo anteriormente expuesto, es evidente que la presente invención proporciona aplicaciones y usos novedosos, valiosos, y no predecibles de los compuestos de la presente invención, así como novedosas composiciones farmacéuticas de los mismos y métodos de preparación de los mismos y de tratamiento que utilizan los mismos, donde dichos compuestos comprenden el principio activo de acuerdo con la presente invención y poseen todos ellos las características y ventajas enumeradas anteriormente en forma más específica.

El alto orden de actividad del agente activo de la presente invención y de las composiciones del mismo, según lo evidencian las pruebas que se informaron, es indicativo de utilidad en base a su valiosa actividad en seres humanos así como en animales inferiores. Sin embargo, la evaluación clínica en seres humanos no se ha completado. Se comprenderá claramente que por supuesto la distribución y comercialización de cualquier compuesto o composición abarcada por el alcance de la presente invención para utilizar en seres humanos se deberá subordinar a la previa aprobación por las agencias gubernamentales, como por ejemplo la U.S. Federal Food and Drug Administration (FDA), que son responsable de emitir un juicio sobre dichas cuestiones, y están autorizadas para hacerlo.

Conclusiones

El 1-amino-alquilciclohexano insaturado de la invención representa una novedosa clase de antagonista no competitivo del receptor NMDA sistémicamente activo, con una rápida cinética de bloqueo/desbloqueo y una fuerte dependencia del voltaje. Debido a su moderada potencia y su rápida cinética asociada, los mismos serán compuestos terapéuticos útiles en un

amplio rango de trastornos del SNC que incluyen perturbaciones de transmisión glutamatérgica.

Por lo tanto dichos compuestos encuentran aplicación en el tratamiento de los siguientes trastornos de un cuerpo animal vivo, especialmente un humano.

1. Excitotoxicidad como por ejemplo Isquemia durante apoplejía, trauma, hipoxia, hipoglicemia, glaucoma, y encefalopatía hepática.

2. Enfermedades neurodegenerativas crónicas como por ejemplo enfermedad de Alzheimer, demencia vascular, enfermedad de Parkinson, enfermedad de Huntington, esclerosis múltiple, esclerosis lateral amiotrófica, SIDA-neurodegeneración, atrofia del núcleo dentado, síndrome de Tourette, enfermedad de las neuronas motoras, disfunción de las mitocondrias, síndrome Korsakoff, enfermedad de Creutzfeldt-Jakob.

3. Otros trastornos relacionados con cambios plásticos a largo plazo en el sistema nervioso central que se selecciona entre: dolor crónico, tolerancia, dependencia y adicción a drogas (por ejemplo, opioides, cocaína, benzodiazepinas, nicotina, y alcohol).

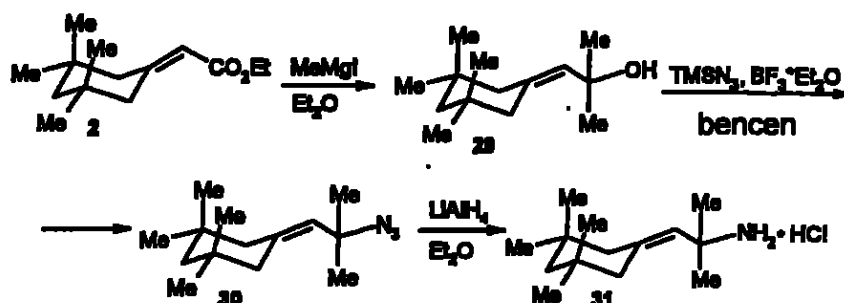
4. Epilepsia, discinesia tardía, esquizofrenia, ansiedad, depresión, dolor agudo, espasticidad, y tinnitus.

Además, se ha descubierto que dichos compuestos son receptores nicotínicos neuronales y también antagonistas del receptor 5-HT₃. Por lo tanto, los compuestos de la invención encuentran aplicación en el tratamiento de trastornos en un cuerpo animal vivo, especialmente un humano, en indicaciones mediadas por los receptores tanto nicotínicos como 5-HT₃ para propósitos tanto sintomáticos como neuroprotectores (por ejemplo emesis,

197

Se preparó a partir de azida 27 de acuerdo con el procedimiento para el compuesto 24 (Ejemplo 4). Se obtuvo clorhidrato de amina 28 como un sólido incoloro en 16% de rendimiento. ^1H NMR (CDCl_3 , TMS) : 0,72 (6H, br t, 7 Hz, 2CH_3 etil), 0,90, 0,92 y 0,98 (total 6H, todos los s, $5',5'$ - CH_3); 1,25 (6H, m, $4'$ - CH_2 y 2CH_2 etil); 1,47 (3H, d, 6,5 Hz, 2-CH_3); 1,70-2,25 (2H, br AB q, 13 Hz, $2'$ - CH_2); 1,87 (2H, s, $6'$ - CH_2), 4,18 (1H, m, 2-CH); 5,34 (1H, br d, 9,5 Hz, $=\text{CH}$) y 8,38 ppm (3H, br s, NH_3^+).

Esquema: Ejemplo 13



Ejemplo 13.

Clorhidrato de 2-metil-1-(3,3,5,5-tetrametilciclohexiliden)-2-propanamina (31).

a) 2-Metil-1-(3,3,5,5-tetrametilciclohexiliden)-2-propanol (29).

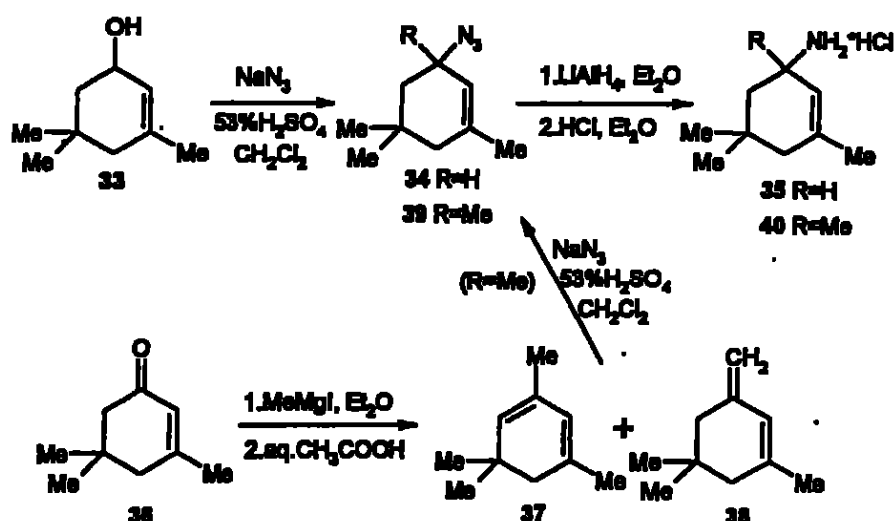
Se agregó una solución de acetato 2 (2,14 g, 10 mmol) en dietiléter (20 ml) a una solución 1,6 M de MeLi en dietiléter (26 ml, 40 mmol), mientras se enfriaba en un baño de hielo. La mezcla de reacción se agitó a temperatura ambiente por 1h. Luego se enfrió en un baño de hielo y se agregó NH_4Cl acuoso saturado (20 ml) por goteo. La fase acuosa se extrajo con dietiléter (2 30 ml). Las fases orgánicas combinadas se lavaron con salmuera (30 ml), se secaron sobre MgSO_4 , se filtraron y se evaporaron. El residuo se purificó por

destilación corta de Kugelrohr (100 °C/ 4 mm Hg) para dar 29 (1,86 g, 88%) como un aceite incoloro. ¹H-NMR: (CDCl₃, TMS) : 0,91 y 0,96 (total 12H, ambos s, c-Hex-3,5-CH₃); 1,25 (2H, s, c-Hex- 4-CH₂); 1,38 (6H, s, -C(CH₃)₂O); 1,79 y 2,23 (ambos 2H, ambos s, c-Hex- 2,6-CH₂) y 5,39 ppm (1H, s, =CH-).

c) Clorhidrato de 2-metil-1-(3,3,5,5-tetrametilciclohexiliden)-2-propanamina (31).

Se preparó a partir de azida 30 mediante el mismo procedimiento que para amina 24 (Ejemplo 4). Se obtuvo clorhidrato de amina 31 como un sólido incoloro en rendimiento de 69%. ¹H-NMR (CDCl₃, TMS) : 0,91 y 0,98 (total 12H, ambos s, c-Hex-3,5-CH₃); 1,26 (2H, s, c-Hex- 4-CH₂); 1,68 (6H, s, -C(CH₃)₂N); 1,84 y 2,10 (ambos 2H, ambos s, c-Hex- 2,6-CH₂); 5,15 (1H, s, =CH-) y 8,5 ppm (3H, br s, NH₃⁺).

Esquema: Ejemplos 14 y 15



Ejemplo 14.

Clorhidrato de 3,5,5-trimetil-2-ciclohexen-1-amina (35).

a) 3-Azido-1,5,5-trimetil-1-ciclohexeno (34).

abuso de nicotina, esquizofrenia, temblor cerebeloso, IBS, migraña, trastornos depresivos, trastornos cognitivos, psicosis relacionada con el tratamiento de la enfermedad de Parkinson y trastornos del apetito).

Además, según ya se estableció, debido por lo menos en parte a su sustituyente amina, los compuestos de la presente invención también son efectivos en indicaciones no relacionadas con el mecanismo de acción mencionado anteriormente, mostrando actividad inmunomoduladora, antimalaria y potencia antitripanosomas, actividad anti-virus Borna, anti-HSV y anti-virus de Hepatitis C.

El método para tratar a un cuerpo animal vivo con un compuesto de la invención, para la inhibición del progreso o para el alivio de los seleccionados dolencias en particular, se puede realizar según se estableció anteriormente mediante cualquier ruta farmacéutica normalmente aceptada, mediante el empleo de la dosificación seleccionada que es efectiva para el alivio de las dolencias en particular que se desean aliviar.

El uso de los compuestos de la presente invención en la fabricación de un medicamento para el tratamiento de un animal vivo para la inhibición del progreso o para el alivio de las dolencias o condiciones seleccionadas, en particular de dolencias o condiciones susceptibles de tratamiento con un antagonista del receptor NMDA, antagonista de un receptor nicotínico neuronal, antagonista de 5-HT₃, o un compuesto que muestra actividad inmunomoduladora, antimalaria y potencia antitripanosoma, actividad anti-virus Borna, y anti-HSV y anti-virus de Hepatitis C y el método para tratar, composiciones farmacéuticas, y uso de un compuesto de la presente invención en la fabricación de un medicamento; se llevan a cabo de la manera usual, que

comprende el paso de mezclar una cantidad efectiva de un compuesto de la invención con un diluyente, excipiente, o vehículo aceptable para uso farmacéutico.

Las composiciones farmacéuticas representativas se preparan mezclando el ingrediente activo con un excipiente, diluyente, o vehículo aceptable para uso farmacéutico apropiado; incluyen tabletas, cápsulas, soluciones para inyección, formulaciones líquidas orales, formulaciones en aerosol, formulaciones TDS, y formulaciones en nanopartículas, para producir así medicamentos para uso oral, inyectable, o uso dérmico, también de acuerdo con lo anterior.

Queda entendido que la invención no está limitada a los detalles específicos de operación, o a las composiciones, métodos, procedimientos o realizaciones exactos a los que se muestran y describen en la presente, ya que los especialistas podrán vislumbrar modificaciones obvias de los mismos y, por lo tanto, la invención estará limitada solamente por el pleno alcance que se pueda asignar a las reivindicaciones adjuntas.

Referencias

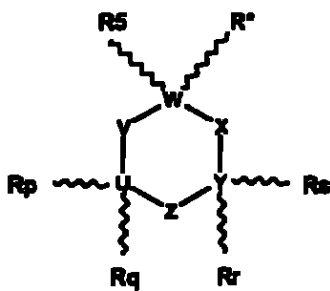
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182
182

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REIVINDICACIONES

1. Un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),
- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),
- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileno (C_2-C_{10}) o alquenileno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{2-6} alquenilo,
- R^5 se selecciona en forma independiente entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o

ramificado (C_2-C_8), y alquínilo inferior lineal o ramificado (C_2-C_8), o R^5 se combina con el carbono al cual se encuentra unido y un carbono adyacente para formar una unión doble,

- R_P , R_Q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquénilo inferior lineal o ramificado (C_2-C_8), y alquínilo inferior lineal o ramificado (C_2-C_8), o R_P , R_Q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se seleccionan entre ciclohexano, ciclohex-2-eno, ciclohex-3-eno, ciclohexa-1,4dieno, ciclohexa-1,5-dieno, ciclohexa-2,4dieno, y ciclohexa-2,5-dieno,

y con la salvedad de que al menos uno de R_P y R_Q no es hidrógeno y al menos uno de R_r y R_s no es hidrógeno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_P , R_Q , R_r , y R_s es alquénilo inferior lineal o ramificado (C_2-C_8) o alquínilo inferior lineal o ramificado (C_2-C_8),

y sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos.

2. Un compuesto como se reivindica en la reivindicación 1 seleccionado entre el grupo que consiste en:

1-etenil-3,3,5,5-tetrametilciclohexilamina;

2-(3,3,5,5-tetrametilciclohexiliden)etanamina;

1-amino-3, 3, 5-trimetil-2-ciclohexeno;

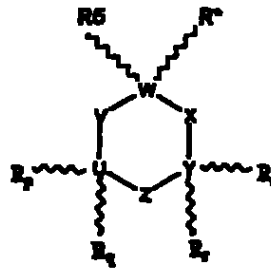
185

1,3,5,5-tetrametil-2-ciclohexen-1-amina;
 1-alil-3,3,5,5-tetrametilciclohexanamina;
 1-(3,3, 5,5-tetrametilciclohexiliden)-2 -propanamina;
 1-(3,3-dietil-5,5-dimetilciclohexiliden)-2-propanamina;
 cis-3-vinil-1,3,trans-5-trimetilciclohexilamina;
 2-metil-1-(3,3,5,5-tetrametil-1-ciclohexen-1-il)-2-propanamina;
 1-(1-alil-3,3, 5, 5-tetrametilciclohexil)piperidina;
 2-(1-vinil-3,3,5,5-tetrametilciclohexil-1)etilamina;
 1-[3,3,5,5-tetrametil-1-(3-metil-2-butenil)ciclohexil]piperidina;
 1-[3, 3,5, 5-tetrametil-1-(2-propinil) ciclohexil]piperidina;
 2-(1,3,3,5,5-pentametilciclohexil) -4-pentenilamina;
 3-(3,3,5,5-tetrametilciclohexiliden)propanamina;
 2-metil-1-(3,3,5,5-tetrametilciclohexiliden)-2-propanamina;
 2-(3,3,5,5-tetrametilciclohexiliden)propanamina;
 N-metil-1-etenil-3,3, 5, 5-tetrametilciclohexilamina;
 N-alil-1,3,3,5,5-pentametilciclohexanamina;
 y los isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos.

3. Una composición farmacéutica que comprende un compuesto como se reivindica en la reivindicación 1 o reivindicación 2 en combinación con uno o más diluyentes, excipientes y/o vehículos aceptables para uso farmacéutico.

4. Un método de tratamiento de un animal vivo para alivio de una condición tratable mediante un antagonista de NMDA que comprende el paso

de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8),
 - R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8),
 - R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o ramificado (C_2-C_8), o juntos forman alqueno (C_2-C_{10}) o alqueno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo y/o C_{2-8} alqueno,
 - $R^5, R^6, R^7, R^8, \text{ y } R^9$ se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquino inferior lineal o

187

ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

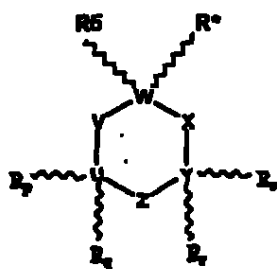
con la salvedad de que U-V-W-X-Y-Z se seleccionan entre: .

ciclohexano,
 ciclohex-1-eno,
 ciclohex-2-eno,
 ciclohex-3-eno,
 ciclohexa-1,3-dieno,
 ciclohexa-1,4-dieno,
 ciclohexa-1,5-dieno,
 ciclohexa-2,4-dieno, y
 ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n$, $(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_8) o alqueno inferior lineal o ramificado (C_2-C_8),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

5. Un método de tratamiento de un animal vivo para el alivio de una condición donde el compuesto se selecciona por su eficacia inmunomoduladora, anti-malaria, anti-Borna virus, o anti-Hepatitis C, anti-tripanosomal, y anti-HSV, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n (CR^1R^2)_m -NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),
- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo y/o C_{2-8} alquenilo,
- R^5, R_P, R_Q, R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o R^5, R_P, R_Q, R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente

para formar una unión doble, o R_P , R_Q , R_T , y R_S en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,
 ciclohex-1-eno,
 ciclohex-2-eno,
 ciclohex-3-eno,
 ciclohexa-1,3-dieno,
 ciclohexa-1,4-dieno,
 ciclohexa-1,5-dieno
 ciclohexa-2,4-dieno, y
 ciclohexa-2, 5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n(CR^1R^2)_m$ -, R^3 , R^4 , R^5 , R_P , R_Q , R_T es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

6. Un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista de NMDA seleccionado entre el grupo que consiste en excitotoxicidad seleccionada entre isquemia durante un accidente cerebrovascular, traumatismo, hipoxia, hipoglicemia, glaucoma, y encefalopatía de origen hepático,

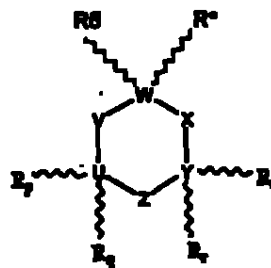
enfermedades neurodegenerativas crónicas seleccionadas entre enfermedad de Alzheimer, demencia vascular, mal de Parkinson, enfermedad

de Huntington, esclerosis múltiple, esclerosis lateral amiotrófica, neurodegeneración por SIDA, atrofia olivopontocerebelar, síndrome de Tourette, enfermedades de las neuronas motoras, disfunción mitocondrial, síndrome de Korsakoff, y enfermedad de Creutzfeldt-Jakob,

otros trastornos relacionados con cambios plásticos de largo plazo en el sistema nervioso central seleccionados entre dolor crónico, tolerancia, dependencia y adicción a drogas (p. ej., opioides, cocaína, benzodiazepinas, nicotina, y alcohol), epilepsia, disquinesia tardía, disquinesia inducida por L-DOPA, esquizofrenia, ansiedad, depresión, dolor agudo, espasticidad, y tinnitus,

que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre

los compuestos de fórmula I:



donde:

- R^* es $-(A)_n (CR^1R^2)_m NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alqueno inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8).

191

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileo (C_2-C_{10}) o alquencileno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{1-6} alquenilo,

- R^5 , R_P , R_Q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 , R_P , R_Q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

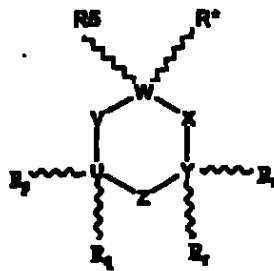
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n$ $(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_P , R_Q , R_r es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

7. Un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor 5HT₃, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

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

- $n + m = 0, 1, \text{ o } 2$,

- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alqueno inferior lineal o ramificado (C_2-C_6), y alquino inferior lineal o ramificado (C_2-C_6),

193

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{1-6} alquenilo,

- R^5 , R_P , R_Q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 , R_P , R_Q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

ciclohexa-2,4-dieno, y

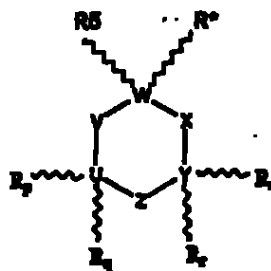
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194

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alquénilo inferior lineal o ramificado (C_2-C_6) o alquinilo inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

8. Un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor nicotínico neuronal, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n(CR^1R^2)_m NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,
- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquénilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),
- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquénilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

145
195

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo y/o C_{1-8} alquenilo,

- R^5 , R_p , R_q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

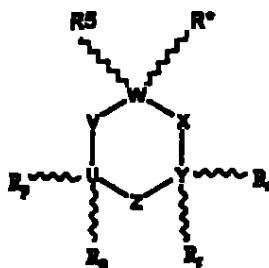
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m-$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6).

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

9. Un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor $5HT_3$ seleccionado del grupo que consiste en trastornos de ansiedad, trastornos depresivos, esquizofrenia y psicosis relacionadas con tratamientos, desórdenes de abuso de drogas y alcohol, desórdenes cognitivos, enfermedad de Alzheimer, mal de Parkinson, temblor cerebeloso, migraña, trastornos de la alimentación, síndrome del intestino irritable (SII), y emesis, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n-(CR^1R^2)_m-NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,

- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o juntos forman alquileno (C_2-C_{10}) o alquenileno (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-8} alquilo y/o C_{2-8} alquenilo,

- R^5 , R_p , R_q , R_r , y R_s se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_8), alquenilo inferior lineal o ramificado (C_2-C_8), y alquinilo inferior lineal o ramificado (C_2-C_8), o R^5 , R_p , R_q , R_r , y R_s en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_p , R_q , R_r , y R_s en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno;

ciclohexa-1,3-dieno,

ciclohexa-1,4-dieno,

ciclohexa-1,5-dieno,

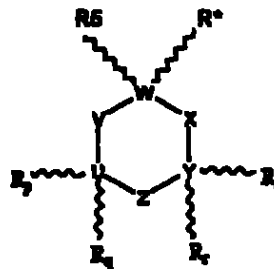
ciclohexa-2,4-dieno, y

ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_p , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_9) o alquino inferior lineal o ramificado (C_2-C_9).

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

10. Un método de tratamiento de un animal vivo para el alivio de una condición tratable mediante un antagonista del receptor nicotínico neuronal seleccionado del grupo que consiste en síndrome de Tourette, trastornos de ansiedad, esquizofrenia, abuso de drogas, abuso de nicotina, abuso de cocaína, disquinesia (Morbus Huntington, inducido por L-DOPA), trastorno de déficit atencional con hiperactividad (ADHD), enfermedad de Alzheimer, mal de Parkinson, y dolor, que comprende el paso de administrar al animal vivo una cantidad de un compuesto seleccionado entre los compuestos de fórmula I:



donde:

- R^* es $-(A)_n(CR^1R^2)_m NR^3R^4$,
- $n + m = 0, 1, \text{ o } 2$,

- A se selecciona entre el grupo que consiste en alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^1 y R^2 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6),

- R^3 y R^4 se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6), y alquinilo inferior lineal o ramificado (C_2-C_6), o juntos forman alquileo (C_2-C_{10}) o alquenileo (C_2-C_{10}) o junto con el N forman un azacicloalcano o azacicloalqueno de 3-7 miembros opcionalmente sustituido por C_{1-6} alquilo y/o C_{2-6} alquenilo,

- R^5 , R_P , R_Q , R_R , y R_S se seleccionan en forma independiente entre el grupo que consiste en hidrógeno, alquilo inferior lineal o ramificado (C_1-C_6), alquenilo inferior lineal o ramificado (C_2-C_6); y alquinilo inferior lineal o ramificado (C_2-C_6), o R^5 , R_P , R_Q , R_R , y R_S en forma independiente se pueden combinar con el carbono al cual se encuentran unidos y un carbono adyacente para formar una unión doble, o R_P , R_Q , R_R , y R_S en forma independiente pueden formar una unión doble con U o con Y al cual se encuentran unidos,

con la salvedad de que U-V-W-X-Y-Z se selecciona entre:

ciclohexano,

ciclohex-1-eno,

ciclohex-2-eno,

ciclohex-3-eno,

ciclohexa-1,3-dieno,

200

ciclohexa-1,4-dieno,
ciclohexa-1,5-dieno,
ciclohexa-2,4-dieno, y
ciclohexa-2,5-dieno,

y con la salvedad de que cuando U-Z es igual a ciclohexano, luego al menos uno de $-(A)_n-(CR^1R^2)_m$, R^3 , R^4 , R^5 , R_P , R_q , R_r es alqueno inferior lineal o ramificado (C_2-C_6) o alquino inferior lineal o ramificado (C_2-C_6),

sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos, el cual es efectivo para el alivio de dicha condición.

11. Utilización de un compuesto de fórmula I como se define en cualquiera de las reivindicaciones 4 a 10 y sus isómeros ópticos y sales de adición ácidas o básicas aceptables para uso farmacéutico de los mismos en la fabricación de un medicamento para su utilización en un método de acuerdo con cualquiera de las reivindicaciones 4 a 10.

Resumen:

Compuestos de 1-amino-alkilciclohexano insaturado que son sistémicamente-activos como antagonistas del receptor NMDA, 5HT; y nicotínico, composiciones farmacéuticas que comprenden a los mismos, método de preparación de los mismos, y método de tratamiento de trastornos del CNS que incluyen trastornos de la transmisión glutamatérgica, serotoninérgica, y nicotínica, tratamiento de trastornos de inmunomoduladores y actividad antimalaria, anti tripanosomal, anti-Borna virus, anti-HSV y anti-virus de la Hepatitis C.

201
202

Leyendas de las figuras

figura 1

substitute sheet (rule 26)	hoja de reemplazo (Regla 26)
% Control [³ H]MK-Binding	% Unión [³ H]MK control
Concentration (μM)	Concentración (μM)

figura 2

MRZ 2/759 on NR1a/2 ^a receptors expressed in oocitos de <i>Xenopus</i>	MRZ 2/759 sobre receptores NR1a/2A expresados en oocitos de <i>Xenopus</i>
Glutamate 100μM + Glycine 10 μM	Glutamato 100 μM + Glicina 10 μM
substitute sheet (rule 26)	hoja de reemplazo (Regla 26)
% control glutamate-induced current	% de corriente inducida por glutamato control
Parameter	Parámetro
Value	Valor
std. Error	Error estándar
IC 50	IC ₅₀
slope factor	Factor de la pendiente
MRZ 2/759 concentration (μM)	Concentración de MRZ 2/759 (μM)

figura 3

MRZ 2/759 hipocampo – patch clamp	MRZ 2/759 de hipocampo – <i>patch clamp</i>
parameter	Parámetro

203
203

value	Valor
std. error	Error estándar
% control NMDA-induced current	% de corriente inducida por NMDA control
IC 50	IC ₅₀
slope factor	Factor de la pendiente
MRZ 2/759 concentration (μM)	Concentración de MRZ 2/759 (μM)

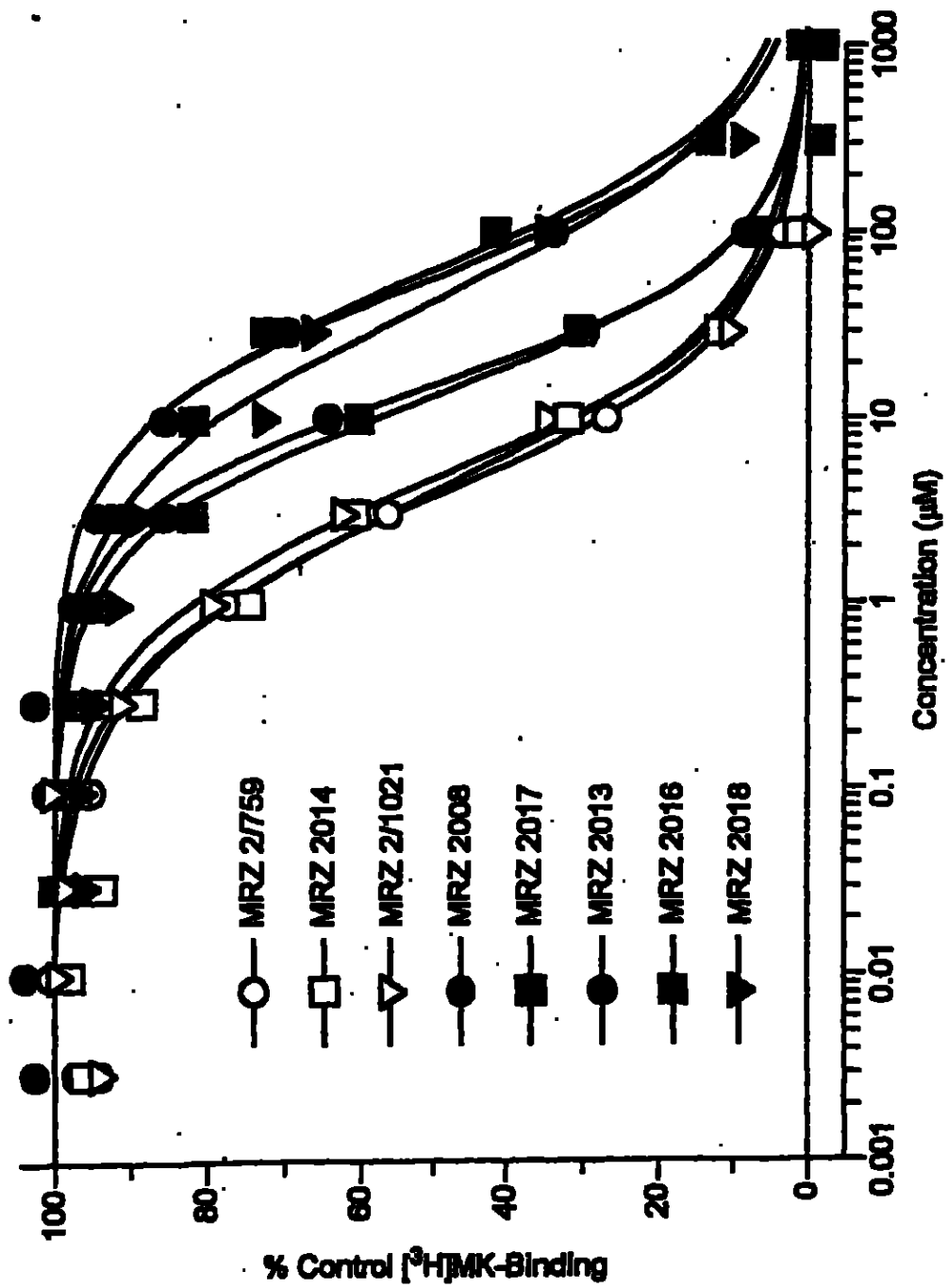


FIG. 1

205
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MRZ 2/759 on NR1a/2A receptors expressed in *Xenopus* oocytes

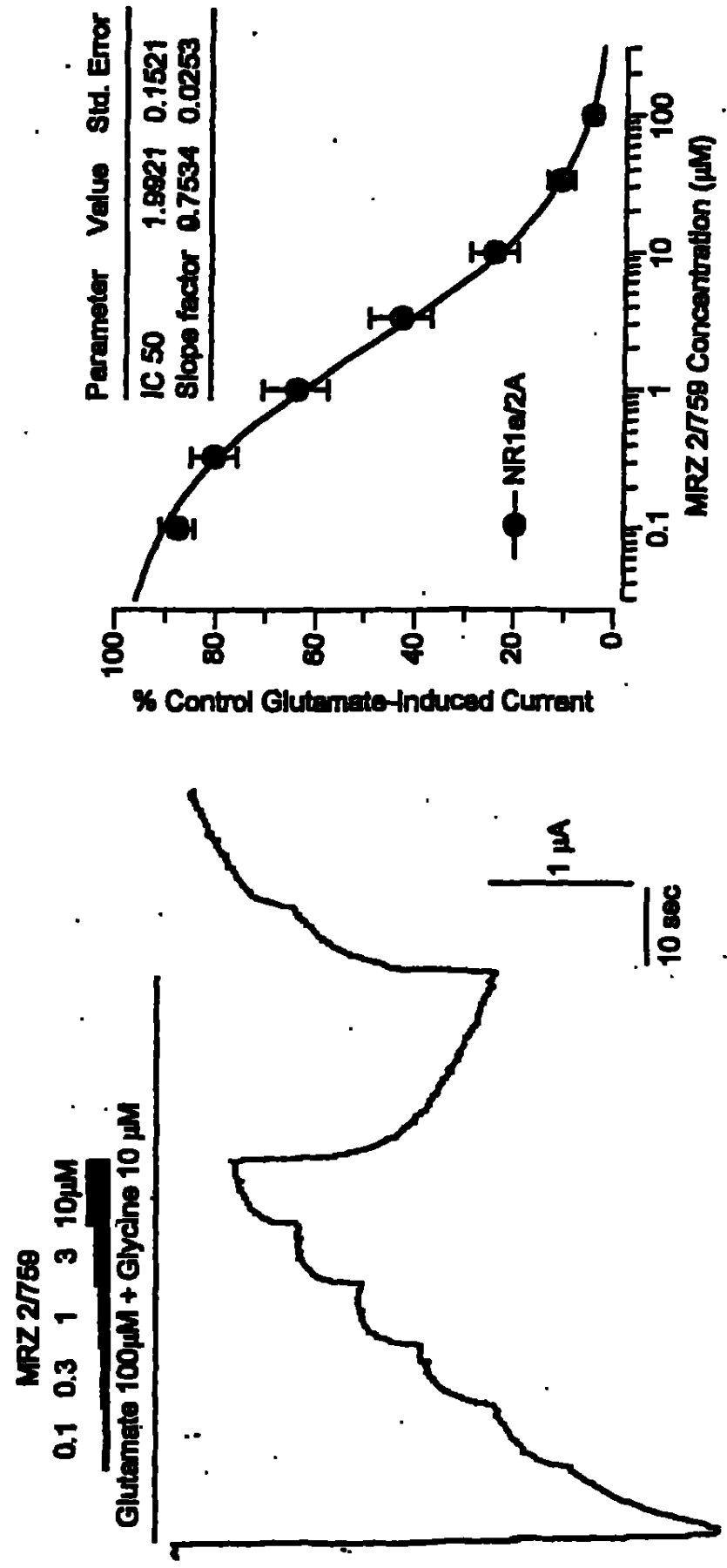


FIG. 2

MRZ 2/759 Hippocampus - Patch Clamp

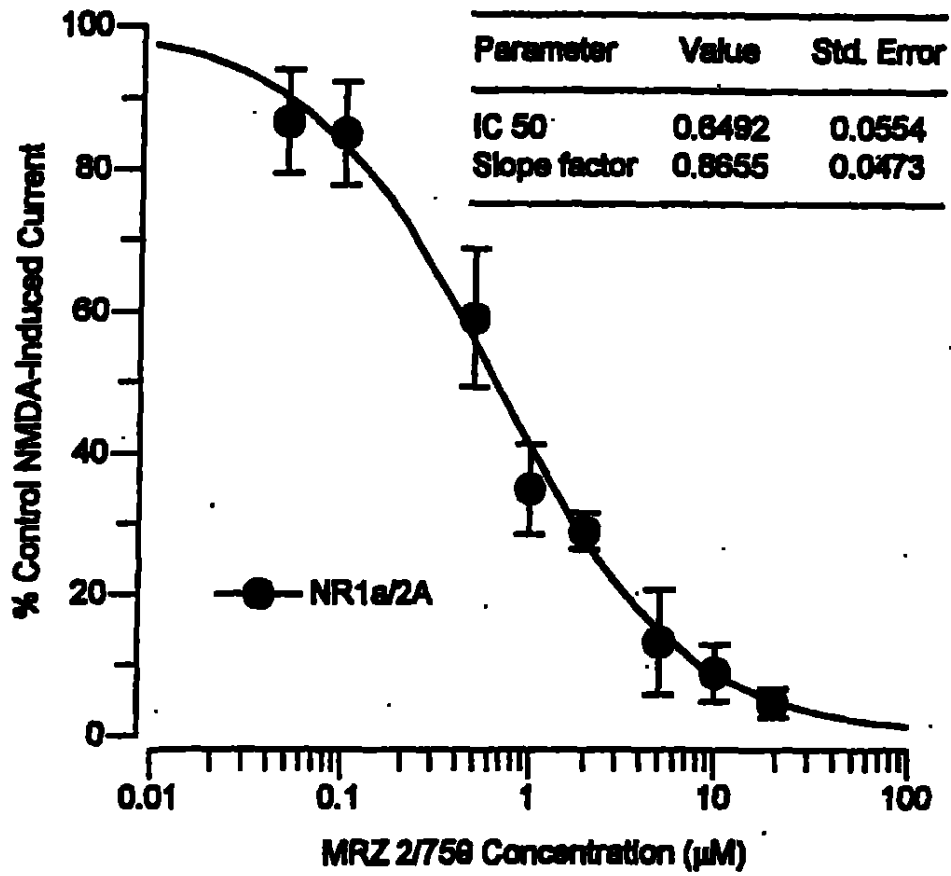


FIG. 3

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: Marsden, John C. FRANK B. DEHN & CO. 179 Queen Victoria Street London EC4V 4EL GRANDE BRETAGNE	File <u>408-79723</u> 28 JAN 2004 Frank B. Dehn & Co. RECEIVED ANSD	NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)
		Date of mailing (day/month/year) 26.01.2004
Applicant's or agent's file reference 408.79723		IMPORTANT NOTIFICATION
International application No. PCT/GB 02/05038	International filing date (day/month/year) 07.11.2002	Priority date (day/month/year) 07.11.2001
Applicant MERZ PHARMA GMBH & CO. KGAA		

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.
2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.
3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.
4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed invention is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the International preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523856 apmu d Fax +49 89 2399 - 4465	Authorized Officer Roche, S Tel. +49 89 2399-8031
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PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 408.79723	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA/18)	
International application No. PCT/GB 02/05038	International filing date (day/month/year) 07.11.2002	Priority date (day/month/year) 07.11.2001
International Patent Classification (IPC) or both national classification and IPC C07C211/40		
Applicant MERZ PHARMA GMBH & CO. KGAA		
1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36. 2. This REPORT consists of a total of 4 sheets, including this cover sheet. ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.18 and Section 807 of the Administrative Instructions under the PCT). These annexes consist of a total of sheets.		
3. This report contains indications relating to the following items: I ☒ Basis of the opinion II ☐ Priority III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV ☐ Lack of unity of invention V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI ☐ Certain documents cited VII ☐ Certain defects in the international application VIII ☐ Certain observations on the international application		
Date of submission of the demand 04.06.2003	Date of completion of this report 28.01.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 823658 apmu d Fax: +49 89 2399 - 4485	Authorized Officer Kleidermigg, O Telephone No. +49 89 2399-2143 	

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 02/05038**

I. Basis of the report

1. With regard to the elements of the International application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

Description, Pages

1-78 as originally filed

Claims, Numbers

1-11 as originally filed

Drawings, Sheets

1/3-3/3 received on 20.01.2003 with letter of 18.01.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the International application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the International search (under Rule 23.1(b)).
- ☐ the language of publication of the International application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of International preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the International application, the International preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the International application in written form.
- ☐ filed together with the International application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the International application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 02/05038**

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-11
	No: Claims	
Inventive step (IS)	Yes: Claims	1-11
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-11
	No: Claims	

2. Citations and explanations

see separate sheet

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT - SEPARATE SHEET**

International application No. PCT/GB02/05038

Section V**D1: US-A-6034134**

The present application relates to compounds according to formula (I) (cf. claim 1). D1 represents the closest prior art and differs from the subject matter of the present application insofar that compounds in D1 show no unsaturation.

The closest compounds disclosed in D1 show substituents $R_p=R_q=R_r=R_s = \text{Me}$, $R^* = \text{NH}_2$, $R_5 = \text{ethyl, propyl}$ (cf. table 6, entries 600 and 601). The present application claims compounds with $R_5 = \text{allyl or vinyl}$. With the letter dated 5.12.2003 the applicant presented comparative data showing that the unsaturated compounds according to the present application exhibit similar binding to $[^3\text{H}]\text{-MK-801}$ as the corresponding saturated species of D1. This effect is not obvious for the skilled person from D1 due to the fact that the compared compounds show a different electron density distribution and geometry, which could disturb the compound-receptor interaction.

Thus, the subject matter of present claims 1-11 fulfils the requirements of Article 33(2) and (3) PCT.

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

Marsden, John C.
FRANK B. DEHN & CO.
179 Queen Victoria Street
LONDON EC4V 4EL
GRANDE BRETAGNE

File 408-79723

- 7 AUG 2003

Frank B. Dehn & Co.
RECEIVED

ANSD

WRITTEN OPINION
(PCT Rule 66)Date of mailing
(day/month/year)

05.08.2003

Applicant's or agent's file reference
408.79723

REPLY DUE

within 3 month(s)
from the above date of mailingInternational application No.
PCT/GB02/05038International filing date (day/month/year)
07.11.2002Priority date (day/month/year)
07.11.2001International Patent Classification (IPC) or both national classification and IPC
C07C211A0Applicant
MERZ PHARMA GMBH & CO. KGAA

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.
2. This opinion contains indications relating to the following items:
 - I ☒ Basis of the opinion
 - II ☐ Priority
 - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application
3. The applicant is hereby invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.
4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 07.03.2004

DUE DATES
NOTEDName and mailing address of the international
preliminary examining authority:European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tlx 523858 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer

Kleidemigg, O

Formalities officer (incl. extension of time limits)

Roche, S

Telephone No. +49 89 2399-8031



I. Basis of the opinion

1. With regard to the elements of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed"*),

Description, Pages

1-78

as originally filed

Claims, Numbers

1-11

as originally filed

Drawings, Sheets

1/3-3/3

received on 20.01.2003 with letter of 18.01.2003

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

34
214

WRITTEN OPINION

International application No. **PCT/GB02/05038**

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).
- (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this opinion.)*

6. Additional observations, if necessary:

V. Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	
Inventive step (IS)	Claims	1-11
Industrial applicability (IA)	Claims	

2. Citations and explanations

see separate sheet

25
25

Section V

D1: US-A-6034134

The present application relates to compounds according to formula (I) (cf. claim 1). D1 represents the closest prior art and differs from the subject matter of the present application insofar that compounds in D1 show no unsaturation.

However, the closest compounds disclosed in D1 show substituents $R_p=R_q=R_r=R_s = \text{Me}$, $R^*=\text{NH}_2$, $R_5=\text{ethyl, propyl}$ (cf. table 6, entries 600 and 601). The present application, however, claims compounds with $R_5=\text{ally or vinyl}$. The close structural relationship of those compounds and the same application, leads, in absence of any comparative biological data, to the conclusion, that the present application does not involve an inventive step.

Thus, the subject matter of present claims 1-11 does not fulfil the requirements of Article 33(3) PCT.

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
15 May 2003 (15.05.2003)

PCT

(10) International Publication Number
WO 03/040084 A1

(51) International Patent Classification: C07C 211/40,
211/35, C07D 211/06, A61P 25/28, A61K 31/13

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(21) International Application Number: PCT/GB02/05038

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Dehn & Co., 179 Queen Victoria Street, London EC4V 4EL,
(GB).

(22) International Filing Date:

7 November 2002 (07.11.2002)

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(81) Designated States (*national*): AE, AG, AL, AM, AT (util-
ity model), AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA,
CH, CN, CO, CR, CU, CZ (utility model), CZ, DE (util-
ity model), DE, DK (utility model), DK, DM, DZ, EC, EE
(utility model), EE, ES, FI (utility model), FI, GB, GD, GE,
GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ,
LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN,
MW, MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC,
SD, SE, SG, SI, SK (utility model), SK, SL, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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(72) Inventors; and

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(DE). KALVINSH, Ivars [LV/LV]; Miera 17-8, LV-2169
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(84) Designated States (*regional*): ARIPO patent (GH, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

Published:

— with international search report

*For two-letter codes and other abbreviations, refer to the "Guid-
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, anti-trypansomal, anti-Borna virus, anti-HSV and anti-Hepatitis C virus activity.

WO 03/040084 A1

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference
(if desired) (12 characters maximum) 408.79723

Box No. I TITLE OF INVENTION UNSATURATED 1-AMINO-ALKYLCYCLOHEXANE NMDA, 5HT3 AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS	
Box No. II APPLICANT ☐ This person is also inventor	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) MERZ PHARMA GMBH & CO. KGAA Eckanelmer Landstrasse 100 D-80318 Frankfurt Main DE	
Telephone No.	
Facsimile No.	
Teleprinter No.	
Applicant's registration No. with the Office	
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence (if no State of residence is indicated below.) PARSONS, Christopher Graham Raphael Wartbaumstrasse 38 D-61130 Nidderau DE	
This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only (If this check-box is marked, do not fill in below.)	
Applicant's registration No. with the Office	
State (that is, country) of nationality: GB	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.	
Box No. IV AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE	
The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as: ☒ agent ☐ common representative	
Name and address: (Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country.) MARSDEN, John Christopher et al. Frank B. Dehn & Co. 179 Queen Victoria Street London EC4V 4EL GB	
Telephone No. +44 20 7206 0600	
Facsimile No. +44 20 7206 0700	
Teleprinter No.	
Agent's registration No. with the Office	
☐ Address for correspondence: Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.	

218

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> HENRICH, Markus Bahnhofstrasse 63 35582 Wetzlar DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: DE	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> DANSYZ, Wojciech Vor den Gärten 16 D-61130 Nidderau DE	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: PL	State (that is, country) of residence: DE
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> KALVINSH, Ivars Miera 17-8 Salaspils LV-2169 LV	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: LV	State (that is, country) of residence: LV
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> KAUSS, Valerjans A. Deglava 108/2-36 Riga LV-1082 LV	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: LV	State (that is, country) of residence: LV
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S) <i>If none of the following sub-boxes is used, this sheet should not be included in the request.</i>	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> JIRGENSONS, Algars Hospitalu iela 3-103 Riga LV-1013 LV	This person is: ☐ applicant only ☒ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality: LV	State (that is, country) of residence: LV
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
Name and address: <i>(Family name followed by given name; for a legal entity, full official designation. The address must include postal code and name of country. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)</i> 	This person is: ☐ applicant only ☐ applicant and inventor ☐ inventor only <i>(If this check-box is marked, do not fill in below.)</i> Applicant's registration No. with the Office
State (that is, country) of nationality:	State (that is, country) of residence:
This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

Box No. V DESIGNATION OF STATES

Mark the applicable check-boxes below; at least one must be marked.

The following designations are hereby made under Rule 4.9(a):

Regional Patent

- ☐ AP ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT (if other kind of protection or treatment desired, specify on dotted line)
- ☐ EA Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT
- ☐ EP European Patent: AT Austria, BE Belgium, BG Bulgaria, CH & LI Switzerland and Liechtenstein, CY Cyprus, CZ Czech Republic, DE Germany, DK Denmark, EE Estonia, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, SK Slovakia, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT
- ☐ OA OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT (if other kind of protection or treatment desired, specify on dotted line)

National Patent (if other kind of protection or treatment desired, specify on dotted line):

- | | | |
|--|---|---|
| ☐ AE United Arab Emirates | ☐ GM Gambia | ☐ NZ New Zealand |
| ☐ AG Antigua and Barbuda | ☐ HR Croatia | ☐ OM Oman |
| ☐ AL Albania | ☐ HU Hungary | ☐ PH Philippines |
| ☐ AM Armenia | ☐ ID Indonesia | ☐ PL Poland |
| ☐ AT Austria and utility model | ☐ IL Israel | ☐ PT Portugal |
| ☐ AU Australia | ☐ IN India | ☐ RO Romania |
| ☐ AZ Azerbaijan | ☐ IS Iceland | ☐ RU Russian Federation |
| ☐ BA Bosnia and Herzegovina | ☐ JP Japan | |
| ☐ BB Barbados | ☐ KE Kenya | ☐ SD Sudan |
| ☐ BG Bulgaria | ☐ KG Kyrgyzstan | ☐ SE Sweden |
| ☐ BR Brazil | ☐ KP Democratic People's Republic of Korea | ☐ SG Singapore |
| ☐ BY Belarus | ☐ KR Republic of Korea | ☐ SI Slovenia |
| ☐ BZ Belize | ☐ KZ Kazakhstan | ☐ SK Slovakia and utility model |
| ☐ CA Canada | ☐ LC Saint Lucia | ☐ SL Sierra Leone |
| ☐ CH & LI Switzerland and Liechtenstein | ☐ LK Sri Lanka | ☐ TJ Tajikistan |
| ☐ CN China | ☐ LR Liberia | ☐ TM Turkmenistan |
| ☐ CO Colombia | ☐ LS Lesotho | ☐ TN Tunisia |
| ☐ CR Costa Rica | ☐ LT Lithuania | ☐ TR Turkey |
| ☐ CU Cuba | ☐ LU Luxembourg | ☐ TT Trinidad and Tobago |
| ☐ CZ Czech Republic and utility model | ☐ LV Latvia | |
| ☐ DE Germany and utility model | ☐ MA Morocco | ☐ TZ United Republic of Tanzania |
| ☐ DK Denmark and utility model | ☐ MD Republic of Moldova | ☐ UA Ukraine |
| ☐ DM Dominica | | ☐ UG Uganda |
| ☐ DZ Algeria | ☐ MG Madagascar | ☐ US United States of America |
| ☐ EC Ecuador | ☐ MK The former Yugoslav Republic of Macedonia | |
| ☐ EE Estonia and utility model | ☐ MN Mongolia | ☐ UZ Uzbekistan |
| ☐ ES Spain | ☐ MW Malawi | ☐ VN Viet Nam |
| ☐ FI Finland and utility model | ☐ MX Mexico | ☐ YU Yugoslavia |
| ☐ GB United Kingdom | ☐ MZ Mozambique | ☐ ZA South Africa |
| ☐ GD Grenada | ☐ NO Norway | ☐ ZM Zambia |
| ☐ GE Georgia | | ☐ ZW Zimbabwe |
| ☐ GH Ghana | | |

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

- ☐ VC St. Vincent and the Grenadines ☐
- ☐ SC Seychelles ☐

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit. (Confirmation (including fees) must reach the receiving Office within the 15-month time limit.)

Box No. VI PRIORITY CLAIM				
The priority of the following earlier application(s) is hereby claimed:				
Filing date of earlier application (day/month/year)	Number of earlier application	Where earlier application is:		
		national application: country or Member of WTO	regional application:* regional Office	international application: receiving Office
item (1) 7 November 2001 (07.11.01)	60/350,974	US		
item (2) 8 November 2001 (08.11.01)	60/337,858	US		
item (3)				
item (4)				
item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) (only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office) identified above as:

☐ all items ☐ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

* Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(h)(U)):

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) (If two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used):

ISA / EP

Request to use results of earlier search; reference to that search (If an earlier search has been carried out by or requested from the International Searching Authority):

Date (day/month/year) Number Country (or regional Office)

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) (mark the applicable check-boxes below and indicate in the right column the number of each type of declaration):

		Number of declarations
☐ Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐ Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐ Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐ Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐ Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

For receiving Office use only	
1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid
For International Bureau use only	
Date of receipt of the record copy by the International Bureau:	

INTERNATIONAL SEARCH REPORT

Internat Application No
PCT/Gb 02/05038

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C211/40 C07C211/35 C07D211/06 A61P25/28 A61K31/13

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data bases consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, BEILSTEIN Data, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 6 071 966 A (GOLD MARKUS ET AL) 6 June 2000 (2000-06-06) column 2, lines 23-37; table 6; column 19, line 35 - column 21, line 17; claims 1-12	1-11
Y	US 6 034 134 A (GOLD MARKUS ET AL) 7 March 2000 (2000-03-07) column 2, line 37 - column 6, line 3; table 6; column 26, line 55 - column 28, line 60	1-11

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"S" document member of the same patent family

Date of the actual completion of the international search

13 February 2003

Date of mailing of the international search report

26/02/2003

Name and mailing address of the ISA

European Patent Office, P.O. 5818 Patentkan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Kleidermigg, O

INTERNATIONAL SEARCH REPORT

Inter-
national application No.
PCT/GB 02/05038

Box I Observations where certain claims were found unsearchable (Continuation of Item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: —
because they relate to subject matter not required to be searched by this Authority, namely:
see FURTHER INFORMATION sheet PCT/ISA/210
2. ☐ Claims Nos.: —
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.: —
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of Item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

275

FURTHER INFORMATION CONTINUED FROM PCT/SA/ 210

Continuation of Box I.1

Although claims 4-10 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box I.1

Rule 39.1(iv) PCT - Method for treatment of the human or animal body by therapy

226

INTERNATIONAL SEARCH REPORT

International application No
PCT/GB 02/05038

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 6071966 A	06-06-2000	AU 724974 B2	05-10-2000
		AU 8804298 A	25-01-1999
		CN 1266423 T	13-09-2000
		EA 2254 B1	28-02-2002
		WO 9901416 A2	14-01-1999
		EP 1009732 A2	21-06-2000
		FI 992801 A	29-12-1999
		HU 0100266 A2	29-05-2002
		JP 2002511873 T	16-04-2002
		NO 996548 A	28-02-2000
		PL 337809 A1	11-09-2000
		US 6034134 A	07-03-2000
		ZA 9805678 A	10-01-2000
US 6034134 A	07-03-2000	AU 724974 B2	05-10-2000
		AU 8804298 A	25-01-1999
		CN 1266423 T	13-09-2000
		EA 2254 B1	28-02-2002
		WO 9901416 A2	14-01-1999
		EP 1009732 A2	21-06-2000
		FI 992801 A	29-12-1999
		HU 0100266 A2	29-05-2002
		JP 2002511873 T	16-04-2002
		NO 996548 A	28-02-2000
		PL 337809 A1	11-09-2000
		US 6071966 A	06-06-2000
		ZA 9805678 A	10-01-2000

SUPERINDUSTRIA Y COMERCIO

Radicación : 04041831 00000000 Folios: 226
Fecha (MIB): 2004-05-06 15:51:25
Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCION ✓		
MODELO DE UTILIDAD	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		
DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()
- Comprobante de pago de las tasas establecidas	()	()
COMPLETA ()		
INCOMPLETA ()		
ESQUEMA DE TRAZADO ()		
- Indicación de que solicita el registro de un Esquema de trazado.	()	()
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	()	()
- Representación gráfica del esquema de trazado	()	()
- Comprobante de pago de las tasas establecidas.	()	()
COMPLETA ()		
INCOMPLETA ()		

Firma Responsable: *Claudia M. Neva*

Fecha:

228

2020
Bogotá D C

Doctor(a)
DILIA MARIA RODRIGUEZ D'ALEMAN
Apoderado
MERZ PHARMA GMBH & Co..

Oficio N°

65556

ASUNTO:

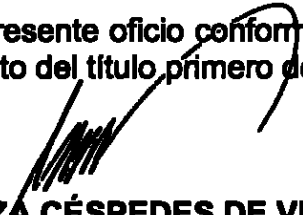
Radicación N°	04-041831
Solicitud internacional	PCT/GB02/05038
Fecha inicio fase nacional	07/06/2004
Trámite	011
Evento	379
Actuación	416
Folios	001

Como resultado del examen de forma, realizado con fundamento en el artículo 38 de la Decisión 486 de la Comisión de la Comunidad Andina, artículo 27 del Tratado de Cooperación en Materia de Patentes (PCT), regla 51 bis del Reglamento y Circular Única de la Superintendencia de Industria y Comercio, se le comunica que:

- La solicitud no contiene copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando éste fuere una persona jurídica.

En cumplimiento de lo dispuesto por el artículo 39 de la Decisión 486, se le requiere para que dentro del término de dos meses siguientes a la fecha de notificación del presente oficio, complete los requisitos anteriormente enunciados. En caso de no dar cumplimiento al presente requerimiento, la solicitud se considerará abandonada y perderá su prelación.

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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 13/11/2004

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