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Industria y Comercio
SUPERINTENDENCIA

Delegatura de Propiedad Industrial

División de Nuevas Creaciones.

PC
SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No.

04-85290

54 TITULO Derivados Azabicyclicos, Heterociclicos y
Azoespirociclicos de Anniclohexano como antagonistas
de los receptores de 7MDA 5HT₂ y Nicotinicas Neuronales

51 CLASIFICACION INTERNACIONAL A61K 31/40

71 SOLICITANTE Merz Pharma GmbH & Co KGAA

DOMICILIO Frankfurt, Alemania

74 APODERADO Lilia Maria Rodriguez D' Aleman

22 BOGOTA, D.C., Ay 30/2004

SS

PETITORIO

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Fecha (IMP): 2004-08-31 16:59:59
Trámite : 011 PCT-PATENT 1 REGISTRO/ 411 PRESENTAR
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD
PCT
ENTRADA EN FASE NACIO

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Fecha (IMP): 2004-08-31 16:59:59
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Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

1) SOLICITUD DE:

☒ Patente de invención ☐ Patente de Modelo de Utilidad

☐ Capítulo I. ☒ Capítulo II.

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C.E. ☐ OTRO ☐
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Nacionalidad o Domicilio: 1. Inglés, 2. Alemán, 3. Polaco, 4. LV; 5. LV;
6. LV; 7. Alemán; 8. LV

5) PCT (86)

Solicitud Internacional No. PCT/GB03/01236 Fecha: Marzo 21, 2003
Publicación Internacional No. WO 03/080046 A1 Fecha: Octubre 2, 2003

6) Título (54) DERIVADOS AZABICÍCLICOS, AZATRICÍCLICOS Y
AZAESPIROCÍCLICOS DE AMINCICLOHEXANO COMO ANTAGONISTAS DE L S
RECEPTORES DE NMDA, 5HT₂ Y NICOTÍNICOS NEURONALES.

7) Clasificación Internacional: A61K 31/40, C07D 209/02, 221/20, 209/54, 221/22,
487/08, A61P

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Solicitud

60/366,386

9) Comprobante de pago N°. 04-65,502 Fecha: Agosto 19, 2004

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***** CONSIGNACION *****

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CLARKE ROBERT Y CD. COLON	CONSIGNACION	BANCO POPULAR	050-00110-6	73291513	19/08/2004	2,883,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES 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. _____

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. opinión escrita
 - 2. Notificación de la transmisión del reporte de búsqueda
 - 3. Solicitud pct

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRIGUEZ D'ALEMAN

FIRMA:

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C07D 209/03, 221/20, 209/34, 221/22, 487/08, A61P
25/16, 25/18

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(21) International Application Number: PCT/GB03/01236

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ES, FI, FR, GB, GR, HU, IE, IT, LI, MC, NL, PT, RO,
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Published:

— with international search report
before the expiration of the time limit for amending the
claims and to be republished in the event of receipt of
amendments

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: AZABICYCLIC, AZATRICYCLIC AND AZASPIROCYCLIC DERIVATIVES OF AMINOCYCLOHEXANE NMDA,
5HT₃, AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS

(57) Abstract: Azabicyclic, azatricyclic and azaspirocyclic derivatives of aminocyclohexanes of formula I (N, Y, Z, R, R₁-R₅ as
defined in the claims) which are systemically-active as NMDA, 5HT₃, and nicotinic receptor antagonists, pharmaceutical compo-
sitions 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 animalia, antitrypanosomal,
anti-Borna virus, anti-HSV and anti-Hepatitis C virus activity.

WO 03/080046 A1

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 408.80589	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/GB 03/01236	International filing date (day/month/year) 21/03/2003	(Earliest) Priority Date (day/month/year) 21/03/2002
Applicant MERZ PHARMA GMBH & CO. KGAA		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 22.1(b)).

b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search 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.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

**AEABICYCLIC, AEATRICYCLIC AND AEASPIROCICLYC DERIVATIVES OF AMINOCYCLOHEXANE
AS NMDA, 5HT3, AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS**

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 36.2(b), by this Authority as it appears in Box II. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1-2

☐ None of the figures.

**AZABICYCLIC, AZATRICYCLIC AND AZASPIROCICLYC DERIVATIVES OF AMINOCYCLOHEXANES
AS NMDA, 5HT₂, AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS**

1. Field of the Invention

Azabicyclic, azatricyclic and azaspirocyclic derivatives of aminocyclohexanes which are systemically-active as NMDA, 5HT₂, 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 treating immunomodulatory disorders, and for treating infectious diseases.

2. Prior Art

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), polyamine site, and phenocyclidine 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 activation of the receptor should lead to a greater degree of

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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, strongly use-dependent uncompetitive NMDA receptor antagonist (+)-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 azabicyclic, azatricyclic and azaspirocyclic aminocyclohexane structure.

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5-HT₂ Receptor Antagonists

5-HT₂ receptors are ligand gated ionotropic receptors permeable for cations. In man 5-HT₂ receptors show the highest density on enterochromaffin cells in the gastrointestinal mucosa, which are innervated by vagal afferents and the area postrema of the brain stem, which forms the chemoreceptor trigger zone.

Since 5-HT₂ 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-HT₂ selective antagonists may have psychotropic effects (Greenhaw & Silverstone, 1997).

Indeed, early animal studies suggested that the 5-HT₂ 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, 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

At present, ten alpha subunits (alpha 1-10) and four beta subunits (beta 1-4) 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 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

include Alzheimer's disease, Parkinson's disease, Tourette's syndrome, 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 is aimed at the discovery of selective nicotinic agonists.

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 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 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

It has now been found that certain azabicyclic, azatricyclic and azaaprocyclic derivatives of aminocyclohexanes have pronounced and unpredictable 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, 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.

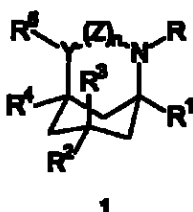
OBJECTS OF THE INVENTION

It is an object of the present invention to provide novel pharmaceutical compounds which are azabicyclic, azatricyclic and azaspirocyclic aminocyclohexane NMDA, 5HT₂, and nicotinic receptor antagonists and 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 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 azabicyclic, azatricyclic and azaspirocyclic aminocyclohexane active principles. Yet additional objects will become apparent hereinafter, and still further objects will be apparent to one 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:

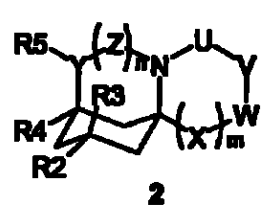
A compound selected from those of formula 1,



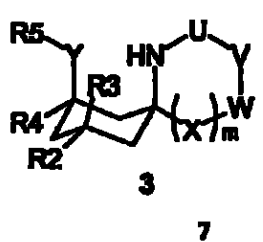
wherein

R and R¹ - R⁶ are each independently selected from straight or branched chain C₁₋₆ alkyl groups (e.g. methyl, ethyl, propyl or butyl groups), straight or branched chain C₂₋₆ alkenyl groups (e.g. ethenyl or propenyl groups), straight or branched chain C₂₋₆ alkynyl groups (e.g. ethynyl or propynyl groups), C₆₋₁₂ aryl groups (e.g. phenyl or naphthyl groups), substituted C₆₋₁₂ aryl groups (e.g. carrying one or more substituents selected from C₁₋₆ alkyl such as methyl or ethyl, C₁₋₆ alkoxy such as methoxy or ethoxy, hydroxy and halo such as chloro or bromo), C₆₋₁₂ aryl-C₁₋₄ alkyl groups (e.g. benzyl or phenethyl groups) and, in the case of R and R² - R⁶, hydrogen atoms;

Z is CH₂;
 N=0 or 1;
 Y=CH;
 and provided that at least one of R² and R³ are not hydrogen and at least one of R⁴ and R⁵ are not hydrogen;
 or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



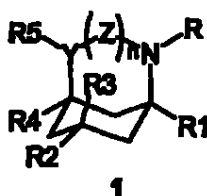
wherein X=CH₂;
 m= 0, 1, 2;
 or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3



wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

such 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 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain

alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R¹ is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R² through R⁵ are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

Z is CH₂;

N=0 or 1;

Y=CH;

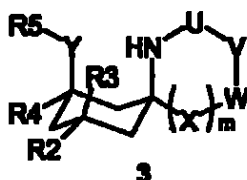
or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



wherein X=CH₂;

$m = 0, 1, 2$;

or those compounds wherein R and R' combine to form a C₂-C₂ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,



wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

which is effective for alleviation of said condition;

such 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,

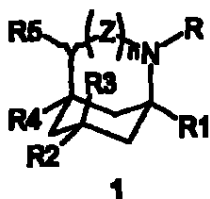
chronic neurodegenerative diseases selected from Alzheimer's disease,

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 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain

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alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R¹ is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

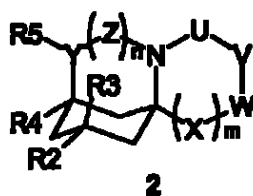
R² through R⁵ are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

Z is CH₂;

N=0 or 1;

Y=CH;

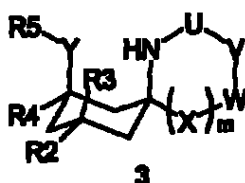
or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



wherein $X = CH_2$;

$m = 0, 1, 2$;

or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,

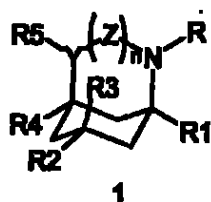


wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

which is effective for alleviation of said condition;

such a method-of-treating a living animal for alleviation of a condition treatable by a 5HT₂ receptor antagonist, comprising the step of administering to the living animal an amount of a compound selected from those of formula 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R¹ is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R² through R⁵ are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

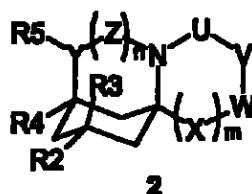
Z is CH₂;

N=0 or 1;

Y=CH;

or those compounds wherein R and R¹ combine to form a C₂-C₆ alkylene or

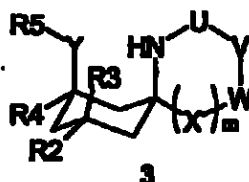
alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



wherein $X = CH_2$;

 $m = 0, 1, 2;$

or those compounds wherein R and R' combine to form a C₆-C₆ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,



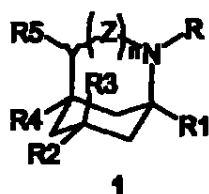
wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

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which is effective for alleviation of said condition;

such 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 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R¹ is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R² through R⁵ are independently selected from the group consisting of hydrogen,

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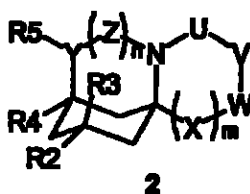
straight or branched chain alkyl (C_1-C_6), straight or branched chain alkenyl (C_2-C_6),
straight or branched chain alkynyl (C_2-C_6), aryl, substituted aryl, and arylalkyl;

Z is CH_2 ;

N=0 or 1;

Y=CH;

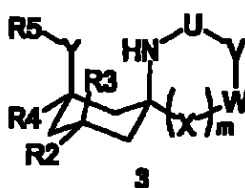
or those compounds wherein R and R¹ combine to form a C_2-C_6 alkenylene or
alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



wherein X=CH₂;

m= 0, 1, 2;

or those compounds wherein R and R¹ combine to form a C_2-C_6 alkenylene or
alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a
bridge, resulting in the basic structure represented by formula 3,

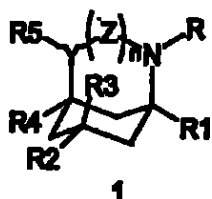


wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

which is effective for alleviation of said condition;

such 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 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R¹ is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R² through R⁵ are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

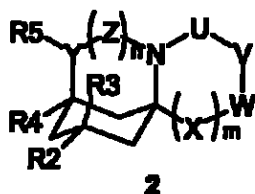
Z is CH₂;

N=0 or 1;

Y=CH;

or those compounds wherein R and R¹ combine to form a C₃-C₆ alkylene or

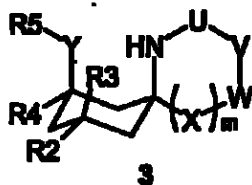
alkenylene bridge U-V-W-X, resulting in the structure represented by formula 2,



wherein $X = CH_3$;

$$m = 0, 1, 2;$$

or those compounds wherein R and R¹ combine to form a C₃-C₃ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,

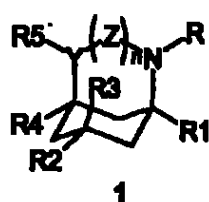


wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

which is effective for alleviation of said condition;

such 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 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

R' is selected from the group consisting of straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

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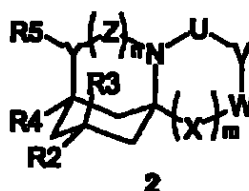
R^2 through R^6 are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C_1-C_6), straight or branched chain alkenyl (C_2-C_6), straight or branched chain alkynyl (C_2-C_6), aryl, substituted aryl, and arylalkyl;

Z is CH_2 ;

$N=0$ or 1 ;

$Y=CH$;

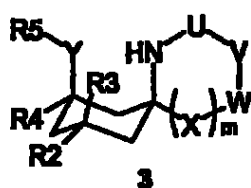
or those compounds wherein R and R^1 combine to form a C_3-C_6 alkylene or alkenylene bridge $U-V-W-X$, resulting in the structure represented by formula 2,



wherein $X=CH_2$;

$m=0, 1, 2$;

or those compounds wherein R and R^1 combine to form a C_3-C_6 alkylene or alkenylene bridge $U-V-W-X$, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,

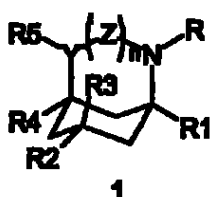


wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

which is effective for alleviation of said condition; and

such a pharmaceutical composition consisting of a compound selected from those of formula 1,



wherein

R is selected from the group consisting of hydrogen, straight or branched chain alkyl (C₁-C₆), straight or branched chain alkenyl (C₂-C₆), straight or branched chain alkynyl (C₂-C₆), aryl, substituted aryl, and arylalkyl;

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R^1 is selected from the group consisting of straight or branched chain alkyl (C_1-C_6), straight or branched chain alkenyl (C_2-C_6), straight or branched chain alkynyl (C_2-C_6), aryl, substituted aryl, and arylalkyl;

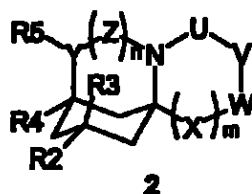
R^2 through R^5 are independently selected from the group consisting of hydrogen, straight or branched chain alkyl (C_1-C_6), straight or branched chain alkenyl (C_2-C_6), straight or branched chain alkynyl (C_2-C_6), aryl, substituted aryl, and arylalkyl;

Z is CH_2 ;

$N=0$ or 1 ;

$Y=CH$;

or those compounds wherein R and R^1 combine to form a C_2-C_6 alkylene or alkenylene bridge $U-V-W-X$, resulting in the structure represented by formula 2,

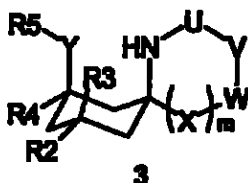


wherein $X=CH_2$;

$m=0, 1, 2$;

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or those compounds wherein R and R' combine to form a C₂-C₂ alkylene or alkenylene bridge U-V-W-X, and ring members N and Y do not connect to form a bridge, resulting in the basic structure represented by formula 3,



wherein ring member N is saturated and ring member Y is saturated or may combine together with R5 to form a carbon-hydrogen bond with the ring carbon to which it is attached;

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

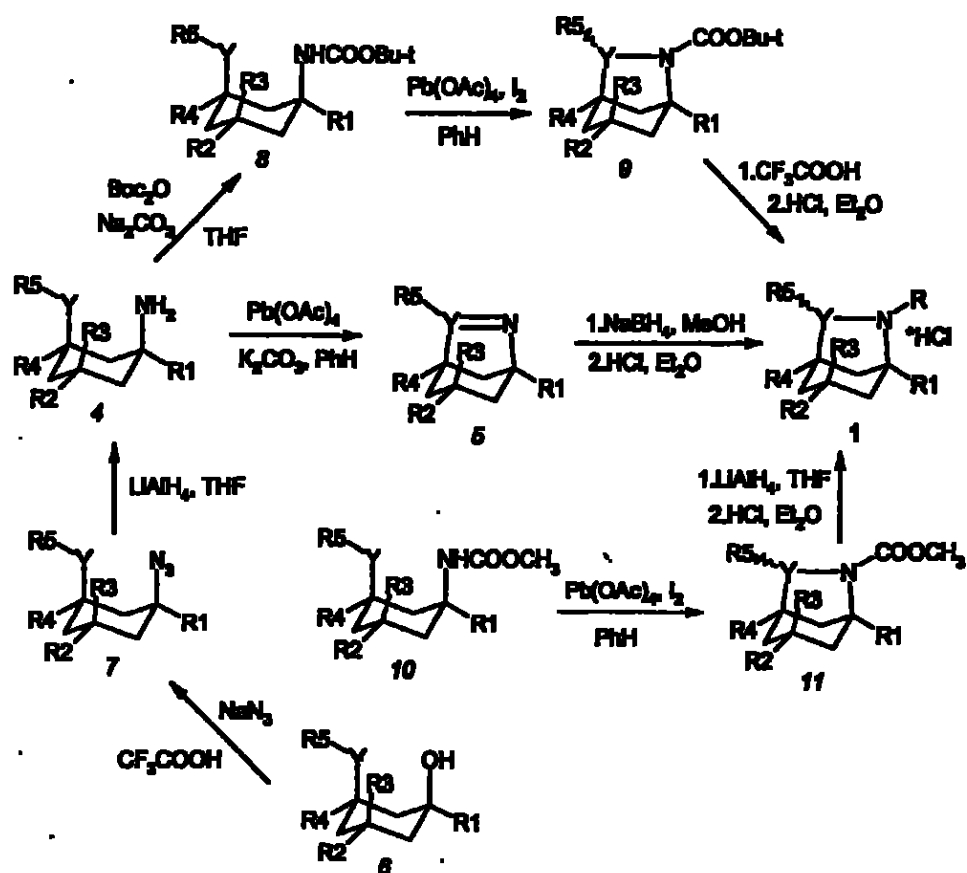
in combination with one or more pharmaceutically-acceptable diluents, excipients, or carriers.

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.

Overall synthetic scheme and table for the 6-Azabicyclo[3.2.1]octanes (belonging to structure of formula 1 of the Summary):

Scheme 1



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Table 1 6-Azabicyclo[3.2.1]octanes 1-1 to 1-8

MRZ number	number in synthetic description	R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n
2011	1-1	H	Me	Me	H	Me	H	CH	0
2023	1-2	H	Et	Me	H	Me	H	CH	0
2007	1-3	H	Me	Et	H	Me	H	CH	0
2/1010	1-4	H	Me	Me	Me	Me	H	CH	0
2/1003	1-5	Me	Me	Me	Me	Me	H	CH	0
2022	1-6	H	Et	Me	Me	Me	H	CH	0
2029	1-7	H	Me	Me	H	Me	Me	CH	0
2028	1-8	H	Me	Me	H	Me	Ph	CH	0

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Example 1.**1, *exo*-3,5-Trimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-1).****a) 1, *exo*-3,5-Trimethyl-6-azabicyclo[3.2.1]oct-6-ene (5-1).**

A mixture of of 1,3,3, *trans*-5-tetramethylcyclohexanamine (4-1) (3.88 g, 25 mmol), K₂CO₃ (28 g, 0.2 mol) and lead tetraacetate (22.2 g, 50 mmol) in dry benzene (125 ml) was stirred for 3 h while boiling at reflux. Then it was cooled with ice water and filtered. The precipitate was washed with diethyl ether and the filtrate evaporated under reduced pressure. The oily residue was separated by column chromatography on silica gel (dichloromethane - *iso*-propyl alcohol, 20 : 1, 10 : 1). A fraction with R_f 0.7 (EtOAc) was collected to give after concentration under reduced pressure 1.0 g (26%) of imine 5-1 as an amber oil.

¹H NMR (CDCl₃, TMS) δ: 0.86 (3H, d, 6 Hz, 3-CH₃), 0.90-1.80 (7H, m, ring CH); 1.12 (3H, s, 1-CH₃); 1.34 (3H, s, 5-CH₃) and 7.36 ppm (1H, s, HC=).

b) 1, *exo*-3,5-Trimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-1).

A solution of imine 5-1 (0.8 g, 5.3 mmol) in MeOH (2 ml) was added dropwise to a suspension of sodium borohydride (0.4 g, 10.6 mmol) in MeOH (6 ml). The mixture was stirred at room temperature for 24 h, then 10 ml of 5% aqueous NaOH was added. The mixture was extracted with diethyl ether. The organic phase was washed with saturated aqueous NaCl and dried over NaOH pellets. The filtered solution was treated with dry HCl solution in diethyl ether, evaporated under reduced pressure and the residue was recrystallized from dry CH₃CN to give compound 1-1 as a colorless solid (0.33 g, 35%).

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¹H NMR (CDCl₃, TMS) δ: 0.96 (3H, d, 6 Hz, 3-CH₃), 0.95-1.15 (1H, m, 2-CH); 1.11 (3H, s, 1-CH₃); 1.41 (1H, d, 12.4 Hz, 8-CH); 1.55-1.70 (1H, m, 2-CH); 1.57 (3H, s, 5-CH₃); 1.70-1.90 (2H, m, 4-CH and 8-CH); 2.00-2.30 (2H, m, 3-CH and 4-CH); 3.00-3.25 (2H, m, 7-CH₂) and 9.30-9.85 ppm (2H, br s, NH₂⁺).

Example 2.

5-Ethyl-1,exo-3-dimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-2).

a) 1-Azido-1-ethyl-3,3,trans-5-trimethylcyclohexane (7).

A cooled (-0 °C) mixture of 1-ethyl-3,3,trans-5-trimethylcyclohexanol (6) (3.3 g, 18.1 mmol), sodium azide (2.36 g, 36.3 mmol) and trifluoroacetic acid (10.7 ml) in chloroform (50 ml) was stirred for 24 h. Then it was made basic by diluted aqueous ammonia addition. The organic phase was separated, washed with water and dried over K₂CO₃. Filtration and solvent evaporation under reduced pressure gave an oily residue which was separated by flash chromatography on silica gel eluting with light petroleum ether to give azide 7 (2.0 g, 56%) as light colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.64 (1H, d, 14 Hz, ring CH); 0.85-2.15 (8H, m, ring CH and Et-CH₂); 0.90 (3H, d, 7 Hz, 5-CH₃); 0.92 (3H, s, 3-CH₃); 0.97 (3H, t, 7.5 Hz, Et-CH₃) and 1.10 ppm (3H, s, 3-CH₃).

b) 1-Ethyl-3,3,trans-5-trimethylcyclohexanamine (4-2).

Azide 7 (1.97 g, 10 mmol) solution in diethyl ether (10 ml) was added dropwise to a suspension of lithium aluminum hydride (1.13 g, 30 mmol) in diethyl ether (30 ml). The mixture was stirred for 20 h at room temperature. Then it was carefully

quenched with 10% aqueous NaOH. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic phases were washed with saturated aqueous NaCl and dried over NaOH. Filtration and solvent evaporation under reduced pressure gave amine 4-2 (1.36 g, 80%) as an oil.

¹H NMR (CDCl₃, TMS) δ: 0.55-2.15 (9H, m, ring CH and Et-CH₂); 0.88 (3H, s, 3-CH₃); 0.89 (3H, d, 6.5 Hz, 5-CH₃); 0.89 (3H, t, 7 Hz, Et-CH₃) and 1.12 ppm (3H, s, 3-CH₃).

c) 5-Ethyl-1,exo-3-dimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-2).

Prepared in 30% yield from imine 5-2 according to procedure described in Example

1b. Colorless solid.

¹H NMR (CDCl₃, TMS) δ: 0.95-1.16 (7H, m, ring CH, 3-CH₃ and CH₂-Et); 1.12 (3H, s, 1-CH₃); 1.48 (1H, d, 13.6 Hz, 8-CH); 1.55-1.76 (3H, m, ring CH and CH₂-Et); 1.84-2.04 (2H, m, ring CH) and 2.04-2.28 (2H, m, 4,8-CH); 3.14 (2H, m, 7-CH₂) and 9.40 ppm (2H, br s, NH₂⁺).

d) 5-Ethyl-1,exo-3-dimethyl-6-azabicyclo[3.2.1]oct-6-ene (5-2).

Prepared in 32% yield from amine 4-2 according to procedure described in Example

1a. An oil.

¹H NMR (CDCl₃, TMS) δ: 0.82-0.95 (1H, m, ring CH); 0.91 (3H, d, 6 Hz, 3-CH₃), 0.94 (3H, t, 7.5 Hz, Et-CH₃); 1.15-1.75 (6H, m, ring CH); 1.15 (3H, s, 1-CH₃); 1.71 (2H, q, 7.5 Hz, Et-CH₂) and 7.38 ppm (1H, s, HC=).

Example 3.***exo*-3-Ethyl-1,5-dimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-3).****a) *tert*-Butyl *trans*-5-ethyl-1,3,3-trimethylcyclohexylcarbamate (8-1).**

To a solution of 1,3,3-trimethyl-*trans*-5-ethylcyclohexanamine hydrochloride (4-3) (1.54 g, 7.5 mmol) in THF (20 ml) was added Na₂CO₃ (3.18 g, 30 mmol) and the mixture was stirred for 30 min. Then it was cooled with ice water, di-*tert*-butyl dicarbonate (1.7 g, 7.65 mmol) was added and stirring was continued for 20 h. Water was added and the mixture was twice extracted with diethyl ether. The combined extracts were washed with saturated aqueous NaCl, dried over MgSO₄ and evaporated. The solid residue was treated with hexane, filtered and washed with hexane to give carbamate 8-1. Additional amount of 8-1 was isolated after the filtrate was evaporated and treated with acetonitrile. Carbamate 8-1 (1.18 g, 57%) was obtained as a colorless solid with mp 70-71 °C.

¹H NMR (CDCl₃, TMS) δ: 0.65-1.65 (7H, m, CH₂-Et and ring CH); 0.88 (3H, t, 6.5 Hz, CH₂-Et); 0.88 and 0.99 (both 3H, s, 3,3-CH₃); 1.42 (9H, s, t-Bu); 1.85 (1H, dq, 13.5 and 2.5 Hz, 6-CH₃); 2.24 (1H, d, 14 Hz, 2-CH₃) and 4.30 ppm (1H, br s, NH).

b) *tert*-Butyl *exo*-3-ethyl-1,5-dimethyl-6-azabicyclo[3.2.1]octane-6-carboxylate (9-1).

To a mixture of carbamate 8-1 (1.05 g, 3.85 mmol) and iodine (1.95 g, 7.7 mmol) in dry benzene (35 ml) was added lead tetraacetate (3.92 g, 8.85 mmol) in one

portion. The mixture was stirred while boiling at reflux for 4 h then cooled with ice water and filtered. The precipitate was washed with diethyl ether and the filtrate carefully washed with saturated aqueous potassium metabisulfite followed by saturated aqueous NaHCO_3 . The organic phase was washed with saturated aqueous NaCl , dried over MgSO_4 and evaporated. The residue was purified by flash chromatography on silica gel (light petroleum ether – ethyl acetate, 20:1) to give compound 9-1 (0.76 g, 73%) as a colorless oil.

^1H NMR (CDCl_3 , TMS) δ : 0.86 (3H, t, 6.5 Hz, $\text{CH}_3\text{-Et}$); 1.00 (3H, s, 1- CH_3); 1.00-1.80 (7H, m, $\text{CH}_2\text{-Et}$ and ring CH); 1.46 (12H, s, t-Bu and 5- CH_3); 1.95-2.45 (2H, m, ring-CH); 3.06 and 3.36 ppm (both 1H, d, 11 Hz, 7- CH_2).

c) *exo*-3-Ethyl-1,5-dimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-3).

Carbamate 9-1 (0.73 g, 2.7 mmol) was added to a solution of trifluoroacetic acid (3 ml) in dichloromethane (15 ml) and the mixture was stirred at room temperature for 10 h. The solution was evaporated under reduced pressure and the residue was treated with 10% aqueous NaOH (5 ml) and extracted with diethyl ether. The extract was washed with saturated aqueous NaCl and dried over NaOH . The filtered solution was treated with dry HCl solution in diethyl ether. The solvent was evaporated under reduced pressure and the residue was treated with dry acetonitrile to give amine hydrochloride 1-3 as colorless solid (0.34 g, 62%).

^1H NMR (CDCl_3 , TMS) δ : 0.85-2.45 (9H, m, 2, 4, 8- CH_2 , 3-CH and $\text{CH}_2\text{-Et}$); 0.90 (3H, t, 7 Hz, $\text{CH}_3\text{-Et}$); 1.12 (3H, s, 1- CH_3); 1.59 (3H, s, 5- CH_3); 3.13 (2H, t, 6 Hz, 7- CH_2) and 9.55 ppm (2H, br s, NH_2^+).

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Example 4.**1,3,3,5-Tetramethyl-6-azabicyclo [3.2.1]octane hydrochloride (1-4).****a) *tert*-Butyl 1,3,3,5,5-pentamethylcyclohexylcarbamate (8-2).**

Prepared in 70% yield from 1,3,3,5,5-pentamethylcyclohexanamine hydrochloride (4-4) according to the procedure described in Example 3a. Purified by flash chromatography on silica gel (light petroleum ether – ethyl acetate, 20:1). A colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.87 (6H, s, 3,5-CH₃); 0.90-1.45 (4H, m, 4-CH₂ and 2,6-CH₂); 1.12 (6H, s, 3,5-CH₃); 1.27 (3H, s, 1-CH₃); 1.42 (9H, s, *t*-Bu); 2.24 (2H, d, 15 Hz, 2,6-CH₂) and 4.30 ppm (1H, br s, NH).

b) *tert*-Butyl 1,3,3,5-tetramethyl-6-azabicyclo[3.2.1]octane-6-carboxylate (9-2).

Prepared in 48% yield from carbamate 8-2 according to the procedure described in Example 3b. A colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.91, 0.94 and 0.99 (total 9H, all s, 1,3,3-CH₃); 0.80-1.75 (5H, m, ring CH); 1.34 and 1.52 (total 3H, both s, 5-CH₃); 1.41 and 1.44 (total 9H, both s, *t*-Bu); 1.91 and 2.09 (total 1H, both d, 14.5 Hz, 6-CH); 3.00 and 3.28 (one rotamer); and 3.03 and 3.33 (another rotamer; total 2H, all dd, 11 and 2 Hz, 7-CH₂).

c) 1,3,3,5-Tetramethyl-6-azabicyclo [3.2.1]octane hydrochloride (1-4).

Prepared in 68% yield from carbamate 9-2 according to the procedure described in Example 3c. Colorless solid. ¹H NMR (CDCl₃, TMS) δ: 1.00, 1.13 and 1.29 (total 9H, s, 1,3,3-CH₃); 1.25-1.65 (4H, m, 2-CH₂ and 4,8-CH); 1.64 (3H, s, 5-CH₃);

1.81 (1H, dt, 12.4 and 2.3 Hz, 4-CH); 2.21 (1H, d, 14.5 Hz, 8-CH); 3.10-3.40 (2H, m, 7-CH₂); 9.10 and 9.90 ppm (total 2H, both br s, NH₂⁺).

Example 5.

1,3,3,5,6-Pentamethyl-6-azabicyclo [3.2.1]octane hydrochloride (1-5).

a) Methyl 1,3,3,5-tetramethyl-6-azabicyclo[3.2.1]octane-6-carboxylate (11).

Prepared in 50% yield from methyl 1,3,3,5,5-pentamethylcyclohexylcarbamate (10) according to the procedure described in Example 3b. A colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.87 and 0.96 (total 9H, both s, 1,3,3-CH₃); 1.00-1.70 (4H, m, 2-CH₂ and 4,8-CH); 1.33 and 1.46 (total 3H, both s, 1-CH₃); 1.70-1.20 (2H, m, 4,8-CH); 3.04 and 3.34 (major rotamer) and 3.10 and 3.39 (minor rotamer; total 2H, all dd, 11.5 and 1.5 Hz, 7-CH₂); 3.59 (major) and 3.64 (total 3H, both s, OCH₃).

b) 1,3,3,5,6-Pentamethyl-6-azabicyclo [3.2.1]octane hydrochloride (1-5).

A solution of carbamate 11 (1.0 g, 4.44 mmol) in diethyl ether (10 ml) was added to a suspension of lithium aluminum hydride (0.34 g, 9 mmol) in diethyl ether (25 ml). The mixture was stirred for 20 h at room temperature. Then it was cooled with ice water and carefully quenched with 10% aqueous NaOH. The organic phase was separated and the aqueous phase extracted with diethyl ether. The combined organic phases were washed with saturated aqueous NaCl and dried over NaOH. Filtered solution was treated with an excess amount of dry HCl solution in diethyl ether. The solvent was evaporated under reduced pressure and the residue was treated with dry acetonitrile and diethyl ether (2:1), and cooled in refrigerator for

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24 h. The precipitate was filtered and washed with diethyl ether to give amine hydrochloride 1-5 (0.25 g, 26%) as a colorless solid.

¹H NMR (CDCl₃, TMS) δ: 1.03, 1.09, 1.16 and 1.22 (total 9H, all s, 1, 3,3-CH₃); 1.44 (3H, s, 5-CH₃); 1.50-2.50 (6H, m, 2, 4, 8-CH₂); 2.73 (d, 5 Hz) and 2.80 (total 3H, d, 5.5 Hz, N-CH₃); 2.55 (m) and 2.94 (total 1H, dd, 12 and 6 Hz, 7-CH); 3.73 (dd, 12 and 8.5 Hz) and 4.07 (total 1H, dd, 13 and 7 Hz, 7-CH); 9.50 and 10.80 ppm (total 1H, br s, NH⁺).

Example 6.

5-Ethyl-1,3,3-trimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-6).

a) 5-Ethyl-1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-ene (5-3).

Prepared in 28% yield from 1-ethyl-3,3,5,5-tetramethylcyclohexanamine (4-5) according to the procedure described in Example 1a. An oil.

¹H NMR (CDCl₃, TMS) δ: 0.93 (3H, s, 3-CH₃); 0.94 (3H, t, 7.4 Hz, Et-CH₃); 0.98 (3H, s, 3-CH₃); 1.15 (3H, s, 1-CH₃); 1.20-1.50 (5H, m, ring CH); 1.57 (1H, dt, 12.4 and 2 Hz, ring CH); 1.89 (2H, dq, 7.5 and 2.8 Hz, Et-CH₂) and 7.47 ppm (1H, s, HC=).

b) 5-Ethyl-1,3,3-trimethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-6).

Prepared in 33% yield from imine 5-3 according to the procedure described in Example 1b.

Colorless solid.

¹H NMR (CDCl₃, TMS) δ: 1.01 (3H, s, 3-CH₃); 1.03 (3H, t, 7.5 Hz, CH₃-Et); 1.13 and 1.31 (both 3H, s, 1,3-CH₃); 1.25-1.35 (1H, m, ring CH); 1.35-1.65 (4H, m,

CH₂-Et and ring CH); 1.89 (1H, d, 12 Hz, 2-CH); 1.92-2.12 (2H, m, 4,8-CH); 3.05-3.45 (2H, m, 7-CH₂); 9.05 and 9.65 ppm (both 1H, br s, NH₂⁺).

Example 7.

1, *exo*-3,5, *exo,endo*-7-Tetramethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-7).

a) *tert*-Butyl *cis*-3-ethyl-1,3,*trans*-5-trimethylcyclohexylcarbamate (8-3).

Prepared in 81% yield from 1,3,5-trimethyl-*cis*-3-ethylcyclohexanamine hydrochloride (4-6) according to the procedure described in Example 3a. Purified by flash chromatography on silica gel (light petroleum ether – ethyl acetate, 20:1). A colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.63 (1H, d, 12.5 Hz, ring CH); 0.70-0.90 (1H, m, ring CH); 0.79 (3H, t, 7.5 Hz, CH₃-Et); 0.86 (3H, d, 6.4 Hz, 5-CH₃); 1.28 (3H, s, 3-CH₃); 1.25-1.85 (6H, m, ring CH and CH₂-Et); 1.41 (9H, s, *t*-Bu); 1.52 (3H, s, 1-CH₃); 2.35 (1H, d, 12.5 Hz, 2-CH) and 4.31 ppm (1H, br s, NH).

***tert*-Butyl 1, *exo*-3,5, *exo,endo*-7-tetramethyl 6-azabicyclo[3.2.1]octane-6-carboxylate (9-3).**

Prepared in 57% yield from carbamate 8-3 according to the procedure described in Example 3b. A colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.60-1.85 (6H, m, ring CH); 0.85-1.15 (6H, m, 1,3-CH₃); 1.35-1.55 (6H, m, 5,7-CH₃); 1.45 (9H, s, *t*-Bu); 2.06 and 2.27 (total 1H, m, ring CH); 3.36 and 3.51 ppm (total 1H, m, 7-CH).

1, *exo*-3,5, *exo,endo*-7-Tetramethyl-6-azabicyclo[3.2.1]octane hydrochloride (1-7).

Prepared in 70% yield from carbamate 9-3 according to the procedure described in Example 3c. A colorless solid.

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¹H NMR (CDCl₃, TMS) δ: 0.96 (3H, d, 5.8 Hz, 3-CH₃); 1.00 (3H, s, 1-CH₃); 1.00–1.15 (1H, m, 2-CH); 1.36 (1H, d, 12 Hz, 8-CH); 1.43 (3H, d, 7.4 Hz, 7-CH₃); 1.55–1.75 (2H, m, 2-CH and 4-CH); 1.62 (3H, s, 5-CH₃); 1.90 (1H, d, 12.6 Hz, 8-CH); 2.15–2.35 (2H, m, 3-CH and 4-CH); 3.65 (1H, m, 7-CH); 9.00 and 9.95 ppm (total 2H, both br s, NH₂⁺).

Example 8.

1, *exo*-3,5-Trimethyl-*exo,endo*-7-phenyl-6-azabicyclo[3.2.1]octane hydrochloride (1-8).

a) 3-Benzyl-3,5-dimethylcyclohexanone (13).

To a cooled (-20 °C) 1M benzylmagnesium bromide solution in diethyl ether (50 ml) under argon was added CuCl (0.52 g, 5.3 mmol) and the mixture was stirred for 5 min. Then a solution of 3,5-dimethyl-2-cyclohexen-1-one (12) (4.4 g, 35.1 mmol) in diethyl ether (15 ml) was added dropwise keeping the temperature below -10 °C. The mixture was stirred for 2 h and quenched with 10% aqueous acetic acid (40 ml). The organic layer was separated, washed with water, saturated aqueous NaHCO₃ and saturated aqueous NaCl, and dried over MgSO₄. Filtration and concentration *in vacuo* afforded oily residue what was separated by flash chromatography on silica gel (light petroleum ether – ethyl acetate, 10:1). Cyclohexanone 13 (4.0 g, 53%) was obtained as a colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.92 (3H, s, 3-CH₃); 1.06 (3H, d, 6 Hz, 5-CH₃), 1.10–2.45

k3

(7H, m, ring CH); 2.42 and 2.58 (total 2H, both d, 13 Hz, CH₂Ph) and 7.05-7.35 ppm (5H, m, Ph).

b) *cis*-3-Benzyl-1,3,*trans*-5-trimethylcyclohexanol (14).

A solution of ketone 13 (3.9 g, 18.1 mmol) in diethyl ether (10 ml) was added dropwise to 1M MeMgI in diethyl ether (40 ml). The mixture was stirred for 1 h at room temperature. Etheral extract obtained after traditional workup for Grignard reactions was dried over Na₂SO₄, filtered and evaporated to give an oily residue what was purified by flash chromatography on silica gel (light petroleum ether – ethyl acetate). Cyclohexanol 14 (3.2 g, 76%) was obtained as a colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.75 (3H, s, 3-CH₃); 0.95-1.25 (3H, m, ring CH); 0.92 (3H, d, 6.6 Hz, 5-CH₃), 1.23 (3H, s, 1-CH₃); 1.45-1.75 (3H, m, ring CH); 2.05-2.25 (1H, m, 5-CH); 2.77 and 3.04 (both 1H, d, 13 Hz, CH₂Ph) and 7.05-7.35 ppm (5H, m, aryl CH).

c) N-(*cis*-3-Benzyl-1,3,*trans*-5-trimethylcyclohexyl)-2-chloroacetamide (15).

Sulfuric acid (2.1 ml, 3.83 g, 39 mmol) was added dropwise to a stirred solution of cyclohexanol 14 (3.0 g, 13 mmol) and chloroacetonitrile (4.0 g, 52 mmol) in acetic acid (2.1 ml) while cooling with ice water. The mixture was stirred for 24 h at room temperature then poured into ice water (10 ml). The mixture was neutralised with 20% aqueous NaOH and extracted with diethyl ether (3×15 ml). The combined organic phases were washed with saturated aqueous NaCl and dried over MgSO₄. The extract was filtered and the solvent evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of light petroleum ether

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and ethyl acetate (10: 1) to give amide 15 (1.32 g, 33%) as a colorless oil.

¹H NMR (CDCl₃, TMS) δ: 0.73 (3H, s, 3-CH₃); 0.90-1.40 (3H, m, ring CH); 0.98 (3H, d, 6.6 Hz, 5-CH₃), 1.42 (3H, s, 1-CH₃); 1.63 (1H, m, ring CH); 1.80-2.05 (1H, m, 5-CH); 2.12 (1H, dq, 13.8 and 3 Hz, 6-CH); 2.33 (1H, d, 12.7 Hz, CH₂Ph); 2.51 (1H, dt, 15 and 2.2 Hz, 2-CH); 3.17 (1H, d, 12.7 Hz, CH₂Ph); 3.95 and 3.96 (total 2H, both s, CH₂CO); 6.52 (1H, br s, NH) and 7.00-7.35 ppm (6H, m, aryl CH).

d) *cis*-3-Benzyl-1,3,*trans*-5-trimethylcyclohexanamine hydrochloride (4-7).

A solution of amide 15 (0.62 g, 2 mmol) and thiourea (0.18 g, 2.4 mmol) in a mixture of ethanol (5 ml) and acetic acid (1 ml) was refluxed for 10 h. The reaction mixture was cooled to room temperature and 20 ml of 10% aqueous NaOH was added while stirring. The resulting mixture was extracted with diethyl ether (3x 10 ml). The combined extracts were washed with saturated aqueous NaCl, dried over NaOH, filtered and treated with dry HCl solution in diethyl ether. The solvent was evaporated under reduced pressure and the residue treated with dry diethyl ether to give amine hydrochloride 4-7 (0.33 g, 35%) as a colorless solid.

¹H NMR (CDCl₃, TMS) δ: 0.88 (3H, d, 6.5 Hz, 5-CH₃); 0.70-1.30 (3H, m, ring CH); 0.73 (3H, s, 3-CH₃); 1.28 (3H, s, 1-CH₃); 1.50 (1H, d, 15.4 Hz, ring CH); 1.60-1.85 (1H, m, ring CH); 2.05 (1H, d, 16 Hz, ring CH); 2.15-2.50 (1H, m, 5-CH); 2.47 and 3.33 (both 1H, d, 12.8 Hz, CH₂Ph); 7.00-7.35 (5H, m, aryl CH) and 8.42 ppm (3H, br s, NH₃⁺).

e) 1, *exo*-3,5-Trimethyl-7-phenyl-6-azabicyclo[3.2.1]oct-6-ene (5-4).

Prepared in 40% yield from free amine 4-7 according to the procedure described in

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Example 1a. An oil.

¹H NMR (CDCl₃, TMS) δ: 0.94 (3H, d, 6.6 Hz, 3-CH₃); 0.90-1.15 (2H, m, ring CH); 1.26 (3H, s, 1-CH₃); 1.30-1.90 (5H, m, ring CH); 1.43 (3H, s, 5-CH₃) and 7.30-7.65 ppm (5H, m, aryl CH).

f) 1, *exo*-3,5-Trimethyl-*exo,endo*-7-phenyl-6-azabicyclo[3.2.1]octane hydrochloride (1-8).

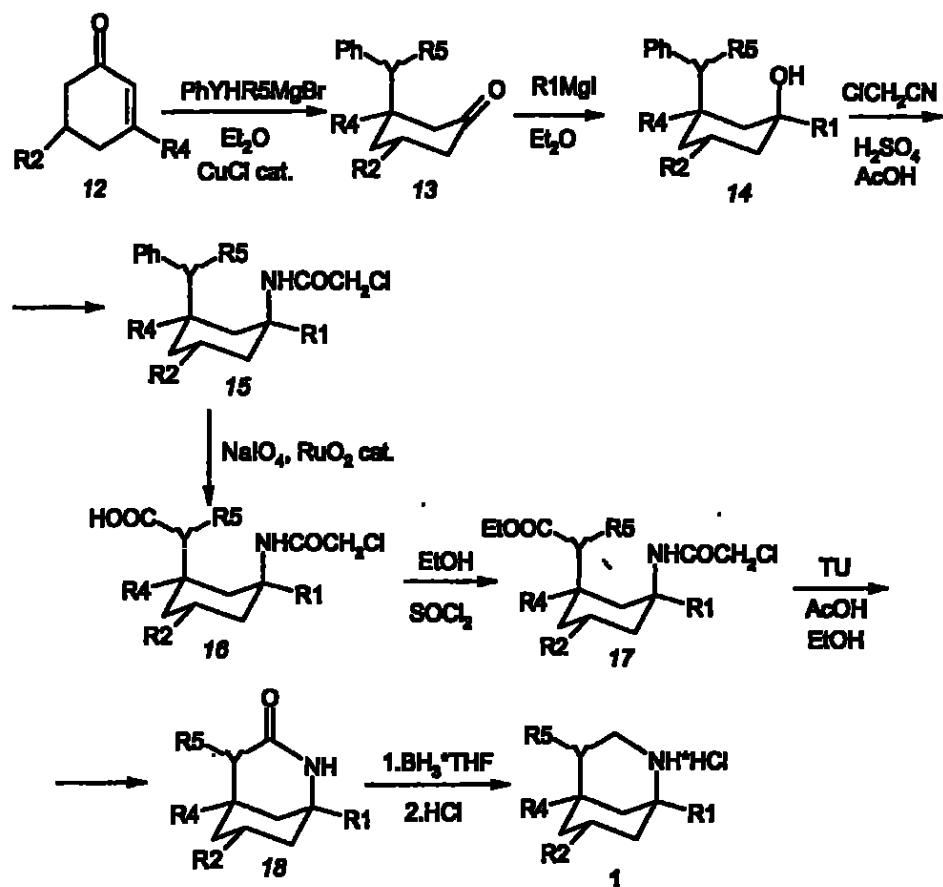
Prepared in 33% yield from imine 5-4 according to the procedure described in Example 1b.

Colorless solid.

¹H NMR (CDCl₃, TMS) δ: 0.75-1.95 (4H, m, ring CH); 0.86 (3H, d, 5.8 Hz, 3-CH₃); 1.20 (3H, s, 1-CH₃); 1.56 (3H, s, 5-CH₃); 1.99 (1H, d, 14.4 Hz, 8-CH); 2.05-2.15 (1H, m, ring CH); 2.20-2.30 (1H, m, ring CH); 4.57 (1H, m, 7-CH); 7.24 and 7.65 (total 5H, both br s, Ph); 9.15 and 10.40 ppm (total 2H, both br s, NH₂⁺).

Overall synthetic scheme and table for 6-Azabicyclo[3.2.1]nonanes (belonging to the structure of formula 1 of the Summary).

Scheme 2



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Table 2 6-Azabicyclo[3.2.1]nonane 1-9

MRZ numb er	number in synthetic descriptio n	R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n
2046	1-9	H	Me	Me	H	Me	H	CH	1

Example 9.

1,5,exo-7-Trimethyl-2-azabicyclo[3.3.1]nonane hydrochloride (1-9).

a) 2-{*cis*-3-[(2-Chloroacetyl)amino]-1,3,*trans*-5-trimethylcyclohexyl}acetic acid (16).

To a solution of 1.5 g (4.9 mmol) of N-(*cis*-3-Benzyl-1,3,*trans*-5-trimethylcyclohexyl)-2-chloroacetamide (obtained from a fraction with R_f 0.7-0.8 (Hexanes-EtOAc, 2:1) separated after the synthesis of compound 15, Example 8c) in a mixture of acetonitrile (16 ml), tetrachloromethane (16 ml) and water (23 ml) was added sodium periodate (10.5 g, 49 mmol) and ruthenium dioxide (7 mg, 0.06 mmol). The mixture was stirred at room temperature for 72 h, then it was filtered and the filter cake was washed with dichloromethane. The organic phase of the filtrate was separated and the aqueous phase was extracted with dichloromethane. The combined organic phases were dried over CaCl₂, filtered and evaporated. The

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residue was purified by flash chromatography on silica gel eluting with chloroform to give acid 16 (0.55 g, 41%) as an oil.

¹H NMR (DMSO-d₆, TMS) δ: 0.8-2.6 (7H, m, ring CH); 0.84 and 0.85 (total 3H, d, 6 Hz, 5-CH₃); 0.92 and 1.01 (total 3H, s, 1-CH₃); 1.21 and 1.22 (total 3H, s, 3-CH₃); 2.19 and 2.39 (total 2H, both d, 13.5 Hz, CH₂CO); 3.97 ppm (2H, s, CH₂Cl); 7.57 and 7.70 (total 1H, both br s, NH) and 12.05 ppm (1H, br s, COOH).

b) Ethyl 2-{*cis*-3-[(2-chloroacetyl)amino]-1,3,*trans*-5-trimethylcyclohexyl}acetate (17).

Thionyl chloride (0.73 ml, 10 mmol) was added dropwise to a solution of acid 16 (0.55 g, 1.99 mmol) in dry ethanol (5 ml), while cooling with ice water. The resulting solution was stirred for 15 h at room temperature then evaporated under reduced pressure. The residue was purified by flash chromatography on silica gel eluting with a mixture of light petroleum ether and ethyl acetate (8: 1) to give ethyl ester 17 (0.32 g, 54%) as an oil.

¹H NMR (CDCl₃, TMS) δ: 0.7-1.6 (4H, m, ring CH); 0.88-0.94 (3H, m, 5-CH₃); 1.04 and 1.14 (total 3H, s, 1-CH₃); 1.25 (2H, t, 7 Hz, CH₃-ethyl); 1.36 and 1.38 (total 3H, s, 3-CH₃); 1.6-1.8 (1H, m, 5-CH); 2.05-2.35 (2H, m, ring CH); 2.16 and 2.79 (total 2H, d, 13 Hz, CH₂CO); 3.92 and 3.95 (total 2H, s, CH₂Cl); 4.12 (2H, q, 7 Hz, CH₂O); 6.42 and 7.28 ppm (total 1H, br s, NH).

c) 1,5,*exo*-7-Trimethyl-2-azabicyclo[3.3.1]nonan-3-one (18).

A solution of ethyl ester 17 (0.32 g, 1.07 mmol) and thiourea (0.098g, 1.3 mmol) in a mixture of ethanol (5 ml) and acetic acid (1.2 ml) was refluxed for 20 h. The

reaction mixture was cooled to room temperature and the solvents evaporated. 10% aqueous NaOH was added and the mixture was extracted with chloroform (3x 10 ml). The combined organic extracts were dried over CaCl₂, filtered and evaporated. The residue was purified by flash chromatography on silica gel eluting with a mixture of light petroleum ether and ethyl acetate (6:1, 3:1). A fraction with R_f 0.4 (Hexane-EtOAc, 2:1) was collected to give lactam 18 (0.12 g, 39%) as a colorless solid with mp 176-177 °C.

¹H NMR (CDCl₃, TMS) δ: 0.89 (3H, d, 5.8 Hz, 7-CH₃); 0.75-1.05 (3H, m, ring CH); 0.99 (3H, s, 5-CH₃); 1.20 (3H, s, 1-CH₃); 1.24-1.36 (1H, m, ring CH); 1.45-1.60 (2H, m, ring CH); 1.60-1.84 (1H, m, 7-CH); 2.14 (2H, s, 4-CH₂) and 5.40 ppm (1H, br s, NH).

d) 1,5,7-Trimethyl-2-azabicyclo[3.3.1]nonane hydrochloride (1-9).

1 M Borane solution in tetrahydrofuran (2 ml, 2 mmol) was added to a solution of lactam 18 (0.07 g, 0.385 mmol) in tetrahydrofuran (2 ml) and refluxed for 15 h. The mixture was cooled to room temperature and made acidic by addition of conc. aqueous HCl. Solvents were evaporated under reduced pressure and hexane (10 ml) and 20% aqueous NaOH (10 ml) were added to the residue. The organic phase was separated and the aqueous phase was extracted with hexane (2x 5 ml). The combined organic phases were washed with saturated aqueous NaCl (10 ml) and dried over NaOH. The extract was filtered and dry HCl solution in diethyl ether was added. The solvent was evaporated and the residue was treated with diethyl ether (5 ml). The precipitate was collected on a filter to give amine hydrochloride 1-9

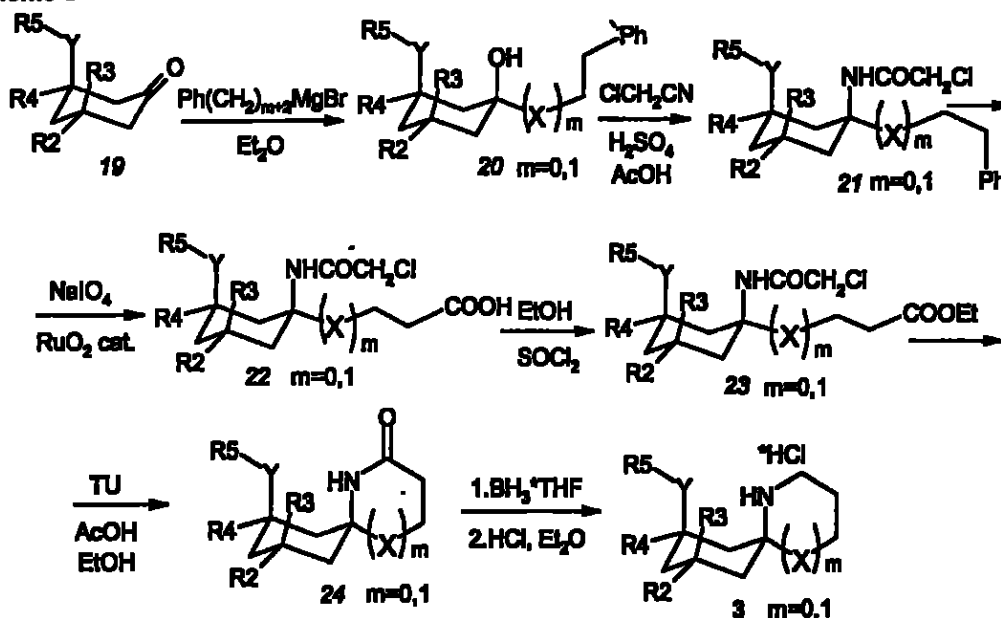
50

(0.02 g, 25%) as a colorless solid.

^1H NMR (CDCl_3 , TMS) δ : 0.80-1.85 (7H, m, ring CH); 0.88 (3H, d, 6.5 Hz, 7- CH_3); 0.96 (3H, s, 5- CH_3); 1.50 (3H, s, 1- CH_3); 2.10-2.40 (2H, m, 7-CH and 8-CH); 3.15-3.35 and 3.30-3.55 (both 1H, m, 3- CH_2); 9.15 and 9.55 ppm (both 1H, br s, NH_2^+).

Overall synthetic scheme and table for 1-Azaspiro compounds (belonging to the structure of formula 3 of the Summary).

Scheme 3



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Table 3

MRZ number	number in synthetic description	R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n
2/1004	3-1	-(CH ₂) _m , (m=0)		Me	Me	Me	H	CH ₂	-
2/1013	3-2	-(CH ₂) _m , (m=1)		Me	Me	Me	H	CH ₂	-

Example 10.

7,7,9,9-Tetramethyl-1-azaspiro[4.5]decane hydrochloride (3-1).

a) 3,3,5,5-Tetramethyl-1-(2-phenylethyl)cyclohexanol (20-1).

A solution of 3,3,5,5-pentamethylcyclohexanone (19) (1.54 g, 10 mmol) in diethyl ether (10 ml) was added to 0.85 M solution of phenylethylmagnesium bromide in diethyl ether (25 ml, 20 mmol), while cooling with an ice bath. The resulting mixture was stirred for 0.5 h and saturated aqueous NH₄Cl (30 ml) was added thoroughly. The organic phase was separated and the aqueous phase was washed with diethyl ether (2x20 ml). The combined organic phases were washed with saturated aqueous NaCl solution (20 ml) and dried over MgSO₄. Filtration and evaporation of the solution gave a residue what was purified by flash chromatography on silica gel eluting with a mixture of light petroleum ether and ethyl acetate (10: 1) to give cyclohexanol 20-1 (2.1 g, 82%) as an oil.

¹H-NMR (CDCl₃, TMS) δ: 0.91 (6H, s, 3,5-CH₃); 1.23 (6H, s, 3,5-CH₃); 1.0-1.6 (7H, m, ring protons and OH); 1.6-1.8 (2H, m, PhCH₂CH₂); 2.6-2.8 (2H, m, PhCH₂CH₂) and 7.0-7.4 ppm. (5H, m, Ph).

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b) 2-Chloro-N-[3,3,5,5-tetramethyl-1-(2-phenylethyl)cyclohexyl]acetamide (21-1).

Prepared in 96% yield from cyclohexanol 20-1 according to the procedure described in Example 8c. A colorless oil.

¹H-NMR (CDCl₃, TMS) δ: 0.93 (6H, s, 3,5-CH₃); 1.17 (6H, s, 3,5-CH₃); 1.0-1.5 (4H, m, 4-CH₂, 2,6-CH); 2.0-2.2 (2H, m, PhCH₂CH₂); 2.24 (2H, d, 14 Hz, 2,6-CH); 2.5-2.6 (2H, m, PhCH₂CH₂); 3.90 (2H, s, CH₂Cl); 6.60 (1H, br s, NH) and 7.1-7.3 ppm (5H, m, Ph).

c) 3-{1-[(2-Chloroacetyl)amino]-3,3,5,5-tetramethylcyclohexyl}propanoic acid (22-1).

Prepared 53% yield from amide 21-1 in according to the procedure described in Example 9a. A colorless crystals with mp 130-131 °C.

¹H-NMR (CDCl₃, TMS) δ: 0.92 (6H, s, 3,5-CH₃); 1.17 (6H, s, 3,5-CH₃); 1.0-1.5 (4H, m, 4-CH₂, 2,6-CH); 2.0-2.4 (6H, m, OCCH₂CH₂, 2,6-CH); 3.97 (2H, s, CH₂Cl) and 6.6 ppm (1H, br s, NH);

d) Ethyl 3-{1-[(2-chloroacetyl)amino]-3,3,5,5-tetramethylcyclohexyl}propanoate (23-1).

Prepared in 82% yield from acid 22-1 according to the procedure described in Example 9b. An oil.

¹H-NMR (CDCl₃, TMS) δ: 0.91 (6H, s, 3,5-CH₃); 1.14 (6H, s, 3,5-CH₃); 1.25 (3H, t, 7 Hz, CH₃CH₂O); 0.8-1.6 (4H, m, 4-CH₂, 2,6-CH); 2.0-2.4 (6H, m, OCCH₂CH₂, 2,6-CH); 3.95 (2H, s, CH₂Cl); 4.11 (2H, q, 7 Hz, CH₃CH₂O) and 6.50 ppm (1H, br s, NH).

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e) 7,7,9,9-Tetramethyl-1-azaspiro[4.5]decan-2-one (24-1).

Prepared in 54% yield from ester 23-1 according to the procedure described in Example 9c. A colorless solid with mp 158-160 °C.

¹H-NMR (CDCl₃, TMS) δ: 1.01 (12H, s, 7,9-CH₃); 1.19 (1H, d, 14 Hz, 8-CH); 1.27 (1H, d, 14 Hz, 8-CH); 1.45 (4H, s, 6,10-CH₂); 2.02 (2H, t, 7.5 Hz, 4-CH₂); 2.36 (2H, t, 7.5 Hz, 3-CH₂) and 5.8 ppm (1H, br s, NH).

f) 7,7,9,9-Tetramethyl-1-azaspiro[4.5]decane hydrochloride (3-1).

Prepared in 76% yield from spiro lactam 24-1 according to the procedure described in Example 9d. Colorless solid.

¹H-NMR (CDCl₃, TMS) δ: 1.01 (6H, s, 7,9-CH₃); 1.08 (6H, s, 7,9-CH₃); 1.23 (1H, d, 14 Hz, 8-CH); 1.35 (1H, d, 14 Hz, 8-CH); 1.8 (4H, br s, 6,10-CH₂); 2.0-2.2 (4H, m, 3,4-CH₂); 3.3 (2H, br s, 2-CH₂) and 9.4 ppm (2H, br s, NH₂⁺).

Example 11.**8,8,10,10-Tetramethyl-1-azaspiro[5.5]undecane hydrochloride (3-2).****a) 3,3,5,5-Tetramethyl-1-(3-phenylpropyl)cyclohexanol (20-2).**

Prepared in 90% yield from ketone 19 according to the procedure described in Example 10a. A colorless oil.

¹H-NMR (CDCl₃, TMS) δ: 0.86 (6H, s, 3,5-CH₃); 1.19 (6H, s, 3,5-CH₃); 1.0-1.8 (11H, m, ring protons, OH and PhCH₂CH₂CH₂); 2.60 (2H, t, 7.5 Hz, PhCH₂CH₂CH₂) and 7.1-7.4 ppm (5H, m, Ph).

b) 2-Chloro-N-[3,3,5,5-tetramethyl-1-(3-phenylpropyl)cyclohexyl]acetamide (21-2).

Prepared in 37% yield from cyclohexanol 20-2 according to the procedure

SH

described in Example 8c. Colorless solid with mp 83-85 °C.

¹H-NMR (CDCl₃, TMS) δ: 0.89 (6H, s, 3,5-CH₃); 1.13 (6H, s, 3,5-CH₃); 0.9-1.9 (8H, m, 4-CH₂, 2,6-CH and PhCH₂CH₂CH₂); 2.15 (2H, d, 14.5 Hz, 2,6-CH); 2.56 (2H, t, 8 Hz, PhCH₂CH₂CH₂); 3.93 (2H, s, CH₂Cl); 6.5 (1H, br s, NH) and 7.1-7.4 ppm. (5H, m, Ph).

c) 4-{1-[(2-Chloroacetyl)amino]-3,3,5,5-tetramethylcyclohexyl}butanoic acid (22-2).

Prepared in 74% yield from amide 21-2 according to the procedure described in Example 9a. Colorless solid with mp 140-141 °C.

¹H-NMR (CDCl₃, TMS) δ: 0.91 (6H, s, 3,5-CH₃); 1.15 (6H, s, 3,5-CH₃); 0.9-1.8 (8H, m, 4-CH₂, 2,6-CH, OCCH₂CH₂CH₂); 2.17 (2H, d, 14.2 Hz, 2,6-CH); 2.33 (2H, t, 7.2 Hz, OCCH₂CH₂CH₂); 3.97 (2H, s, CH₂Cl) and 6.6 ppm. (1H, br s, NH).

d) Ethyl 4-{1-[(2-chloroacetyl)amino]-3,3,5,5-tetramethylcyclohexyl}butanoate (23-2).

Prepared in 98% yield from acid 22-2 according to the procedure described in Example 9b. A colorless oil.

¹H-NMR (CDCl₃, TMS) δ: 0.91 (6H, s, 3,5-CH₃); 1.14 (6H, s, 3,5-CH₃); 1.25 (3H, t, 7 Hz, CH₃CH₂O); 0.9-1.8 (4H, m, 4-CH₂, 2,6-CH, OCCH₂CH₂CH₂); 2.18 (2H, d, 15 Hz, 2,6-CH); 2.26 (2H, t, 8.4 Hz, OCCH₂CH₂CH₂); 3.95 (2H, s, CH₂Cl); 4.13 (2H, q, 7 Hz, CH₃CH₂O) and 6.52 ppm. (1H, br s, NH).

e) 8,8,10,10-Tetramethyl-1-azaspiro[5.5]undecan-2-one (24-2).

Prepared in 76% yield from ester 23-2 according to the procedure described in Example 9c. Colorless solid with mp 126-128° C.

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¹H-NMR (CDCl₃, TMS) δ: 1.01 (6H, s, 8,10-CH₃); 1.09 (6H, s, 8,10-CH₃); 1.19 and 1.30 (both 1H, d, 14 Hz, 9-CH₂); 1.39 and 1.46 (both 2H, d, 14 Hz, 7,11-CH₂); 1.63-1.90 (4H, m, 4,5-CH₂); 2.33 (2H, t, 6 Hz, 3-CH₂) and 5.8 ppm. (1H, br s, NH).

f) **8,8,10,10-Tetramethyl-1-azaspiro[5.5]undecane hydrochloride (3-2).**

Prepared in 46% yield from spirolactam 24-2 according to the procedure described in Example 9d. A colorless solid.

¹H-NMR (CDCl₃, TMS) δ: 1.01 (6H, s, 8,10-CH₃); 1.09 (6H, s, 8,10-CH₃); 1.0-2.1 (12H, m, 3,4,5,7,9,11-CH₂); 3.1 (2H, br s, 2-CH₂) and 9.1 ppm. (2H, br s, NH₂⁺).

Overall synthetic scheme and table for 6-azatricyclo[6.3.1.0^{1,6}] dodecanes (belonging to the structure of formula 2 of the Summary).

5b

Scheme 4

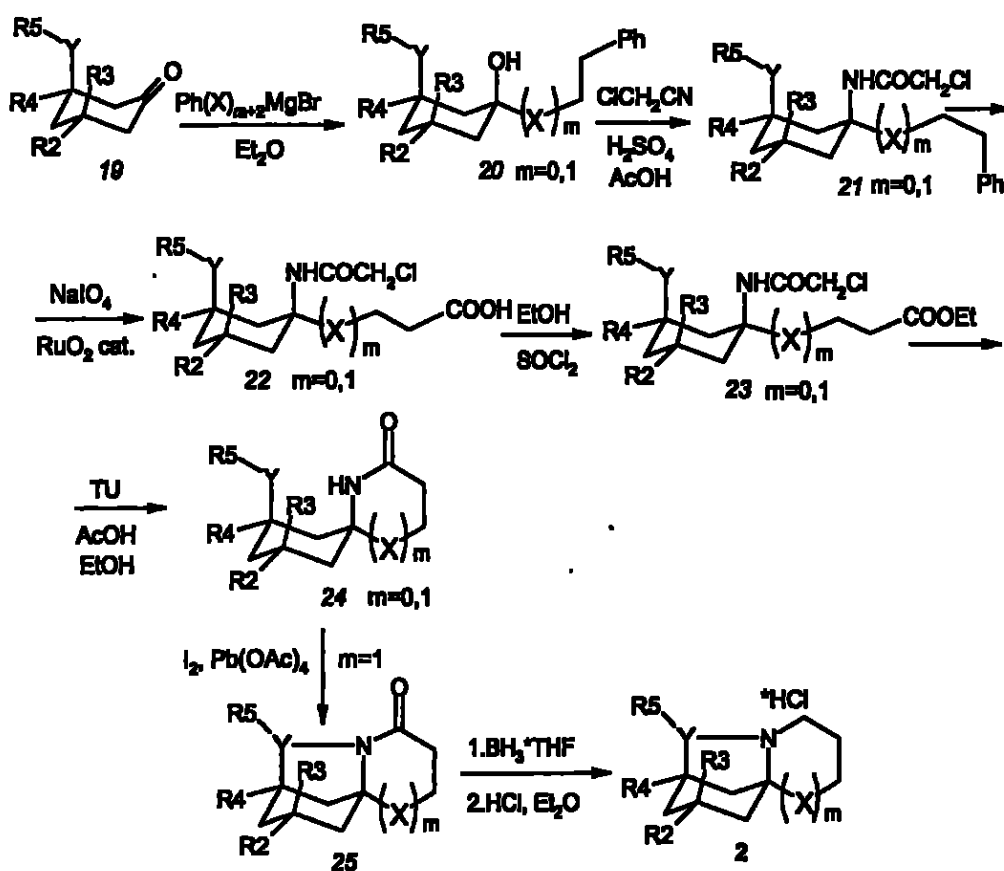


Table 4

MRZ number	number									
	in synthetic	R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n	
	description									
2047	2	-(CH ₂) _m -, (m=1)	Me	Me	Me	H	CH	O		

Example 12.

8,10,10-Trimethyl-8-azatricyclo[6.3.1.0^{1,9}]dodecane hydrochloride (2).

a) 8,10,10-Trimethyl-8-azatricyclo[6.3.1.0^{1,9}]dodecan-5-one (25).

Prepared in 20% yield from spirolactam 24-2 according to the procedure described in Example 3b. An oil.

¹H-NMR (CDCl₃, TMS) δ: 0.95 (3H, s, 10-CH₃); 1.00 (3H, s, 10-CH₃); 1.08 (3H, s, 8-CH₃); 1.20 (1H, d, 12 Hz) and 1.25-1.70 (5H, m, 9,11,12 CH₂); 1.75-1.90 (4H, m, 2,3-CH₂); 2.25-2.40 (2H, m, 4-CH₂); 3.14 and 3.43 ppm (both 1H, d, 12.0 Hz, 7-CH₂).

b) 8,10,10-Trimethyl-8-azatricyclo[6.3.1.0^{1,9}]dodecane hydrochloride (2).

Prepared in 36% yield from lactam 25 according to the procedure given in Example 9d. A colorless solid.

¹H-NMR (CDCl₃, TMS) δ: 0.85-2.45 (12H, m, 2,3,4,9,11,12-CH₂); 0.99 (3H, s, 10-CH₃); 1.05 (3H, s, 10-CH₃); 1.19 (3H, s, 8-CH₃); 3.12 (2H, m, 5-CH₂); 3.20-3.75 (2H, m, 7-CH₂) and 9.05 ppm. (1H, br s, NH⁺).

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.

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.

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 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.

(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 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.

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.

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EXAMPLE 1**Tablet Formulation**

A suitable formulation for a tablet containing 10 milligrams of active ingredient is as follows:

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

EXAMPLE 2**Tablet Formulation**

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

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

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EXAMPLE 3**Capsule Formulation**

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

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

filled in a gelatin capsule.

EXAMPLE 4**Solution for Injection**

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

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

EXAMPLE 5

Liquid oral formulation

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

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

6x

EXAMPLE 6**Liquid oral formulation**

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

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

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EXAMPLE 7**Liquid oral formulation**

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

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

EXAMPLE 8**Aerosol formulation**

180 g aerosol solution contain:

G.	
Active Ingredient	10
Oleic acid	5
Ethanol	81
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.

EXAMPLE 9**TDS formulation**

100 g solution contain:

	G.
Active Ingredient	10.0
Ethanol	57.5
Propyleneglycol	7.5
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.

EXAMPLE 10**Nanoparticle formulation**

10 g of polybutylcyanoacrylate nanoparticles contain:

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

Polybutylcyanoacrylate nanoparticles are prepared by emulsion polymerization in a water/0.1 N HCl/ethanol mixture as polymerization

medium. The nanoparticles in the suspension are finally lyophilized under vacuum.

PHARMACOLOGY - SUMMARY

The active principles of the present invention, and pharmaceutical 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 properties and characteristics:

They are systemically-active, uncompetitive NMDA receptor antagonists with rapid blocking/unblocking kinetics and strong voltage 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 5HT₂ 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 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). 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 125-250µg 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 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 placed into scintillation liquid (5 ml; Ultima Gold) and radioactivity retained on the filters was determined

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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 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

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 Ca^{2+} -free oocyte Ringer solution (82.5 mM NaCl, 2 mM KCl, 2 mM $MgCl_2$, 5 mM HEPES, pH 7.5) for 30 min. at room temperature and washed thoroughly with OR-2 (100 mM NaCl, 2 mM KCl, 1 mM $MgCl_2$, 2 mM $CaCl_2$, 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 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.

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The electrophysiological responses were obtained using the standard two-electrode voltage-clamp method (GeneClamp 500 amplifier), 2-8 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 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 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 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 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

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μM) 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 μM) 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 substrated 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 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 NaHCO_3 /HEPES-buffered minimum essential medium supplemented with 5% fetal calf serum and 5% horse serum (Gibco) and incubated at 37C with 5% CO_2 at 95% humidity. The

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medium was exchanged completely following inhibition of further glial mitosis with cytosine-D-arabinofuranoside (20M 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 (1M) was present in all solutions: a concentration sufficient to cause around 80-85% activation of glycine 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.

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.

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Patch clamp recordings at -70 mV were made from lifted cells, 2-3 days following seeding with polished glass electrodes ($2-8\text{M}\Omega$) in the whole cell mode at room temperature ($20-22^\circ\text{C}$) with an EPC-7 amplifier (List). The contents of the intracellular solution were as follows (mM): CaCl_2 (130), HEPES (10), EGTA (10), MgCl_2 (2), CaCl_2 (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 ($10\mu\text{M}$), 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 ($20 \pm 0.5^\circ\text{C}$). 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 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 ED_{50} s for all parameters scored (anticonvulsive activity and motor side effects) with use of the Litchfield Wilcoxon test for quantal dose responses. Division of the ED_{50} for side effects (ataxia or myorelaxation) by the ED_{50} for antagonism of electroshock convulsions was used as a therapeutic index (TI).

Statistical analysis

IC_{50} s 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

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according to Cheng and Prusoff. Binding values presented are means $\pm$ SEM of 3-5 determinations (each performed in duplicate).

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 used to compare in vitro potencies and in vivo anticonvulsant activity.

RESULTS

MRZ Numbers

MRZ numbers are used to represent chemical names. The MRZ numbers and their respective chemical names are shown in "MRZ LIST", and are cross-referenced in the Examples

MRZ LIST

MRZ	Chemical Name
2/1013	8,8,10,10-Tetramethyl-1-azaspiro[5.5]undecane hydrochloride
2/1004	7,7,9,9-Tetramethyl-1-azaspiro[4.5]decane hydrochloride
2/1003	1,3,3,5,6-Pentamethyl-8-azabicyclo[3.2.1]octane hydrochloride
2/1010	1,3,3,5-Tetramethyl-8-azabicyclo[3.2.1]octane hydrochloride
2007	exo-3-Ethyl-1,5-dimethyl-8-azabicyclo[3.2.1]octane hydrochloride
2011	1,exo-3,5-Trimethyl-8-azabicyclo[3.2.1]octane hydrochloride
2022	5-Ethyl-1,3,3-trimethyl-8-azabicyclo[3.2.1]octane hydrochloride
2023	5-Ethyl-1,exo-3-dimethyl-8-azabicyclo[3.2.1]octane hydrochloride
2028	1, exo-3,5-Trimethyl- <i>exo,endo</i> -7-phenyl-8-azabicyclo[3.2.1]octane hydrochloride
2029	1, exo-3,5, <i>exo,endo</i> -7-Tetramethyl-8-azabicyclo[3.2.1]octane hydrochloride
2046	1,5,exo-7-Trimethyl-2-azabicyclo[3.3.1]nonane hydrochloride
2047	8,10,10-Trimethyl-8-azabicyclo[6.3.1.0 ^{1,4}]dodecane hydrochloride

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Binding MK-801

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

Table 1

MRZ	Group	[3H]MK-801 Ki	SEM	n	NMDA IC50 (µM)	SEM	N
2/1004	Bicyclic	10.48	1.05	3			
2/1013	Bicyclic	3.84	0.22	3	4.72	0.05	8
2/1003	Bridged 579	7.40	0.82	3			
2/1010	Bridged 579	2.59	0.17	3	0.78	0.12	8
2007	Bridged 579	5.48	0.22	3	8.77	0.38	8
2011	Bridged 579	15.82	0.94	3			
2022	Bridged 579	14.42	1.94	3	13.87	2.30	8
2023	Bridged 579	23.32	2.52	3	18.11	3.29	8
2028	Bridged 579	3.21	0.08	3	10.33	0.42	8
2029	Bridged 579	13.22	1.28	3	38.11	1.81	8
2046							
2047							

The results for representative compounds are reported in Figure 1.

NMDA RECEPTOR SUBTYPE EXPRESSION IN XENOPUS OOCYTES.

NMDA receptor blockade by MRZ 2/1010 was determined by applying various concentrations (0.3 to 30 µM in a log 3 dosing regime) for 10 seconds in the continuous presence of glutamate (100 µM) and glycine 10 µM) at -70 mV for 100 seconds in *Xenopus* oocytes expressing NR1α/2A receptors (Figure

2, left). The potency of MRZ 2/1010 ($IC_{50} = 0.76 \mu M$, Hill 0.63) was determined by plotting percent blockade against antagonist concentration and then fitting the curve according to the logistic equation (Figure 2, right).

In vivo

Anti-Convulsive Activity

MES and Myorelaxant action results are presented in Table 2.

Table 2

NRZ	MES ED80	MES CL	Myorelaxation ED80	Myorelaxation CI	Alaxia ED80	Alaxia CI	T1 Myorelaxation	T1 Alaxia
2/1003	16.25	9 - 29,4	16.77	11 - 25,5	20.60	14,8 - 28,1	1.03	1.27
2/1004	24.07	7,3 - 78	27.52	24,5 - 30,9	24.03	16,5 - 34,9	1.14	1.00
2/1010	5.81	3,4 - 10,3	10.82	8,1 - 13,9	24.88	15,5 - 36,8	1.80	4.21
2/1013	9.39	2,6 - 33,8	34.48	21,9 - 54,2	37.24	30,5 - 45,5	3.67	3.67
2007	> 50		> 50		50.00			
2011								
2022								
2023	> 30		> 30		> 30			
2026								
2029	> 50		> 50		> 50			
2049								
2047								

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* * * * *

In conclusion, from the foregoing, it is apparent that the present invention provides novel, valuable, and unpredictable 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 azabicyclic, azatricyclic and azaspirocyclic derivatives of aminocyclohexanes 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, 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 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, 5HT₂ antagonist, or a compound exhibiting 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 medicament.

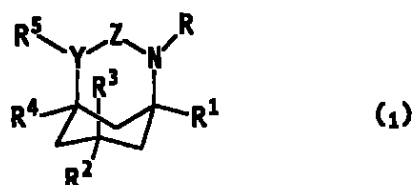
Representative pharmaceutical compositions prepared by admixing the active ingredient with a suitable pharmaceutically-acceptable excipient, diluent, or carrier, include tablets, capsules, solutions for injection, liquid oral formulations, aerosol formulations, TDS formulations, and nanoparticle formulations, thus to produce medicaments for oral, injectable, or dermal use, also in accord with the foregoing.

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Claims**1. Compounds of formula (1)**

wherein R and R¹ - R⁵ are each independently selected from C₁₋₈ alkyl groups, C₂₋₈ alkenyl groups, C₂₋₈ alkynyl groups, C₆₋₁₂ aryl-C₁₋₄ alkyl groups, optionally substituted C₆₋₁₂ aryl groups and, in the case of R and R² - R⁵, hydrogen atoms, with the proviso that at least one of R² and R³ and at least one of R⁴ and R⁵ are other than hydrogen, or R and R¹ together represent a C₃₋₆ alkylene or alkenylene group, R² - R⁵ being as defined above;

Y is CH; and

Z represents a valence bond or a methylene group or, in the case where R and R¹ together represent said alkylene or alkenylene group, Z may additionally represent hydrogen atoms attached to Y and N respectively;

and optical isomers and pharmaceutically acceptable acid and base addition salts thereof.

2. The compounds of claim 1 being:

1,exo -3,5-trimethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

5-ethyl-1,exo-3-dimethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

exo-3-ethyl-1,5-dimethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

1,3,3,5-tetramethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

1,3,3,5,6-pentamethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

5-ethyl-1,3,3-trimethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

1,exo-3,5,exo,endo-7-tetramethyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

1,exo-3,5-trimethyl-exo,endo-7-phenyl-6-azabicyclo[3.2.1]octane and its hydrochloride;

1,5,exo-7-trimethyl-2-azabicyclo[3.3.1]nonane and its hydrochloride;

7,7,9,9-tetramethyl-1-azaspiro[4.5]decane and its hydrochloride;

8,8,10,10-tetramethyl-1-azaspiro[5.5]undecane and its hydrochloride;

and

8,10,10-trimethyl-6-azatricyclo[6.3.1.0^{1,6}]dodecane and its hydrochloride.

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 or carriers.

4. Use of a compound as defined in claim 1 but not subject to the proviso that at least one of R² and R³ and at least one of R⁴ and R⁶ are other than hydrogen as or in the manufacture of an immunomodulatory, anti-malarial, anti-Borna virus, anti-Hepatitis C, anti-trypanosomal or anti-HSV medicament or a medicament for alleviation of a condition treatable by an NMDA, 5HT₃ or neuronal nicotinic receptor antagonist.

5. Use as claimed in claim 4 wherein said condition treatable by an NMDA receptor antagonist is an excitotoxicity selected from ischaemia during stroke, trauma, hypoxia, hypoglycemia, glaucoma and hepatic encephalopathy; a chronic neurodegenerative disease selected from Alzheimer's disease, vascular dementia, Parkinson's disease, Huntington's disease, multiple sclerosis, amyotrophic lateral sclerosis, AIDS-

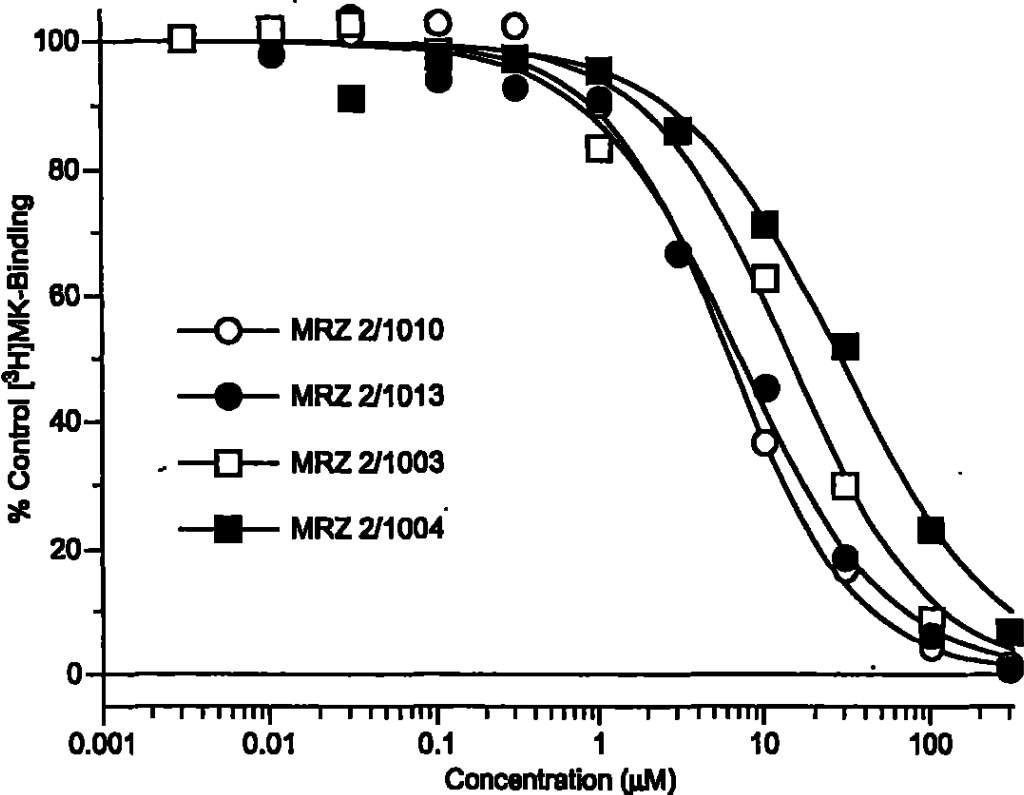
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neurodegeneration, olivopontocerebellar atrophy, Tourette's syndrome, motor neurone disease, mitochondrial dysfunction, Korsakoff syndrome and Creutzfeldt-Jakob disease; a disorder related to long term plastic changes in the central nervous system selected from chronic pain, drug tolerance, drug dependence and drug addiction; epilepsy; tardive dyskinesia; L-DOPA-induced dyskinesia; schizophrenia; anxiety; depression; acute pain; spasticity or tinnitus.

6. Use as claimed in claim 4 wherein said condition treatable by a 5HT₃ receptor antagonist is selected from 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 and emesis.

7. Use as claimed in claim 4 wherein said condition treatable by a neuronal nicotinic receptor antagonist is selected from Tourette's syndrome, anxiety disorders, Schizophrenia, drug abuse, nicotine abuse, cocaine abuse, Morbus Huntington dyskinesia, L-DOPA-induced dyskinesia, attention deficit hyperactivity disorder, Alzheimer's disease, Parkinson's disease and pain.

8. A method of treating a living human or non-human animal subject for Immunomodulatory, anti-malarial, anti-Borna virus, anti-Hepatitis C, anti-trypanosomal or anti-HSV purposes or for alleviation of a condition treatable by an NMDA, 5HT₃ or neuronal nicotinic receptor antagonist, comprising the step of administering to said subject an effective amount of a compound as defined in claim 1 but not subject to the proviso that at least one of R² and R³ and at least one of R⁴ and R⁵ are other than hydrogen.



MRZ 2/1010

Parameter	Value	Std.Error
IC 50	6.1308	0.4393
Slope factor	1.1338	0.0783

MRZ 2/1013

Parameter	Value	Std.Error
IC 50	7.0540	0.6228
Slope factor	0.9762	0.0731

MRZ 2/1003

Parameter	Value	Std.Error
IC 50	13.9825	1.6508
Slope factor	1.0367	0.1136

MRZ 2/1013

Parameter	Value	Std.Error
IC 50	27.5514	3.0482
Slope factor	0.9117	0.0835

FIG. 1

SUBSTITUTE SHEET (RULE 20)

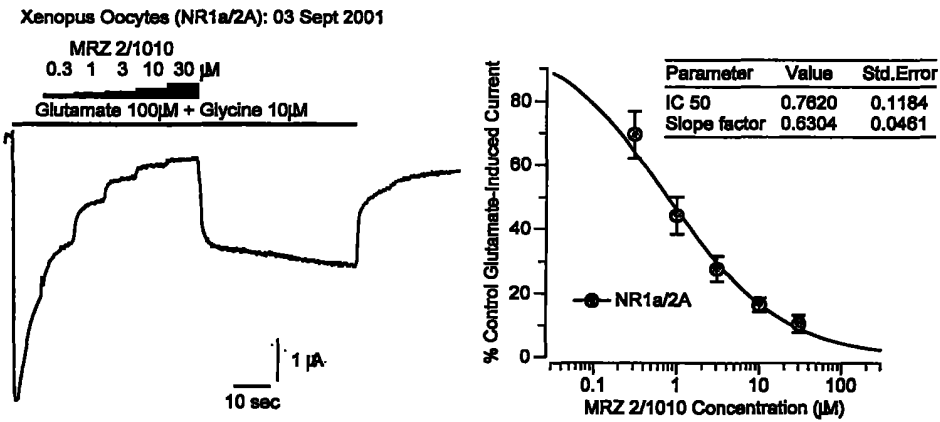


FIG. 2

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INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/01236

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 C07D209/02 C07D221/20 C07D209/54 C07D221/22
C07D487/08 A61P25/16 A61P25/18

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 C07D

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

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

EPO-Internal, BEILSTEIN Data, PAJ, 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.
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 192 (P-712), 4 June 1988 (1988-06-04) & JP 62 297848 A (KONISHIROKU PHOTO IND CO LTD), 25 December 1987 (1987-12-25) abstract; claims	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5577766(brn); 5586551(brn); 5615067(brn) XP002247394 abstract & BULL. SOC. CHIM. FR., vol. 2, 1987, pages 261-264, -/-	1



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

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 E earlier document but published on or after the International filing date
 L document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
 O document relating 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
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 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.
 Z document member of the same patent family

Date of the actual completion of the International search

21 July 2003

Date of mailing of the International search report

05/08/2003

Name and mailing address of the ISA

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Authorized officer

Gavrillu, D

DERIVADOS AZABICÍCLICOS, AZATRICÍCLICOS Y AZAESPIROCÍCLICOS DE AMINCICLOHEXANO COMO ANTAGONISTAS DE LOS RECEPTORES DE NMDA, 5HT₃ Y NICOTÍNICOS NEURONALES

1. Campo de la Invención

Derivados azabíciclicos, azatricíclicos y azaespirocíclicos de aminciclohexanos que son activos sistémicamente como antagonistas de los receptores de NMDA, 5HT₃ y nicotínicos, composiciones farmacéuticas que comprenden a los mismos, método de preparación de los mismos y método de tratamiento de trastornos del CNS que comprenden alteraciones de la transmisión glutaminérgica, serotoninérgica y nicotínica con los mismos, para el tratamiento de trastornos inmunomoduladores y para el tratamiento de enfermedades infecciosas.

2. Arte anterior

Antagonistas de NMDA

El antagonismo de los receptores de glutamato de tipo N-metil-D-aspartato (NMDA) tiene potencialmente un amplio rango de aplicaciones terapéuticas[19]. La inhibición funcional de los receptores de NMDA se puede lograr a través de efectos en diferentes sitios de reconocimiento, tal como el sitio transmisor primario, el sitio de glicina insensible a estricnina (glicinas), el sitio de poliamina y el sitio de fenciclidina localizado dentro del canal de cationes. Los bloqueantes del canal del receptor de NMDA actúan de una manera no competitiva "dependiente del uso", lo cual significa que en general solamente bloquean el canal en su estado abierto. Esta dependencia del uso ha sido interpretada por muchos en el sentido que una activación más fuerte del receptor debería conducir a un mayor grado de antagonismo. Se ha

considerado además que dicho modo de acción implica que esta clase de antagonista puede ser de particular utilidad cuando cabe esperar una sobreactivación de los receptores de NMDA, tal como en la epilepsia, isquemia y traumatismo. Sin embargo, la experiencia clínica inicial con el antagonista del receptor de NMDA selectivo, de gran afinidad, no competitivo fuertemente dependiente del uso, maleato de (+)-5-metil-10,11-dihidro-5H-dibenzociclohepten-5,10-imina ((+)-MK-801), ha sido decepcionante. Es decir, la eficacia terapéutica en la epilepsia era pobre, con evidencia de algunos efectos secundarios psicotrópicos a dosis terapéuticas. Estas observaciones, junto con el hecho que aquellos que abusan de la fenciclidina experimentan síntomas psicotrópicos similares, han llevado a la conclusión que el antagonismo no competitivo de los receptores de NMDA no sea un enfoque terapéutico prometedor.

Sin embargo, el uso de métodos electrofisiológicos más elaborados indica que no hay equivalencia entre los diferentes antagonistas no competitivos dado que factores, tales como la velocidad de bloqueo del receptor (cinética de SI-NO) y la dependencia del voltaje de este efecto, pueden determinar las características farmacodinámicas *in vivo*, es decir, también la seguridad terapéutica. Paradójicamente, sería deseable contar con agentes de una afinidad baja a moderada, en lugar de una gran afinidad. Dichos hallazgos desencadenaron una reconsideración del concepto de antagonismo no competitivo de los receptores de NMDA en el desarrollo de drogas [19, 22]. Se han utilizado clínicamente antagonistas no competitivos del receptor de NMDA, tal como amantadina y memantina que cumplen con los criterios mencionados, por varios años en el tratamiento del mal de Parkinson y

la demencia, respectivamente, y raramente producen efectos secundarios a las dosis terapéuticas usadas en las respectivas indicaciones.

En vista de la evidencia mencionada, los autores han desarrollado una serie de nuevos antagonistas no competitivos del receptor de NMDA basado en la estructura de aminociclohexano azabíclico, azatricíclico y azaespirocíclico.

Antagonistas del receptor de 5-HT₃

Los receptores de 5-HT₃ son receptores ionotrópicos dependientes del ligando, permeable a cationes. En el hombre, la mayor densidad de los receptores de 5-HT₃ se observa sobre las células enterocromafines en la mucosa gastrointestinal, que está inervada por aferencias del vago y el área postrema del tallo encefálico, que constituye la zona desencadenante de quimiorreceptores.

Dado que los receptores de 5-HT₃ no sólo se encuentran a una gran densidad en el área postrema sino también en la región del hipocampo y de la amígdala del sistema límbico, se ha sugerido que los antagonistas selectivos de 5-HT₃ pueden tener efectos psicotrópicos (Greenshaw & Silverstone, 1997).

Aún más, los primeros estudios en animales sugieren que los antagonistas del receptor de 5-HT₃, además de su uso bien reconocido como anti-emético, pueden muy bien ser de utilidad clínica en numerosas áreas. Dichas áreas incluyen trastornos de ansiedad, esquizofrenia, trastornos de abuso de drogas y alcohol, trastornos depresivos, trastornos cognitivos, mal de Alzheimer, temblor cerebeloso, psicosis relacionada con el tratamiento del mal de Parkinson, dolor (migraña y síndrome de intestino irritable) y trastornos de la alimentación.

Antagonistas del receptor nicotínico neuronal

En la actualidad, se conocen diez subunidades alfa (alfa 1-10) y cuatro subunidades beta (beta 1-4) de los receptores nicotínicos. Los receptores $\alpha 4\beta 2$ son probablemente los más comunes en el CNS, en especial en el hipocampo y el cuerpo estriado. Forman canales catiónicos no selectivos con corrientes desensibilizantes lentas, incompletas (tipo II). Los receptores homoméricos $\alpha 7$ son tanto pre como post-sinápticos y se encuentran en el hipocampo, la corteza motora y el sistema límbico, así como en el sistema nervioso autónomo periférico. Estos receptores se caracterizan por su gran permeabilidad al Ca^{2+} y las respuestas rápidas fuertemente desensibilizantes (tipo IA). Los cambios en los receptores nicotínicos se han relacionado con numerosas enfermedades. Entre ellas, el mal de Alzheimer, el mal de Parkinson, el síndrome de Tourette, esquizofrenia, abuso de drogas, abuso de nicotina y el dolor.

Basado en la observación que el propio agonista nicotínico, nicotina, parece tener efectos benéficos, el desarrollo de drogas hasta el momento está enfocado en el descubrimiento de agonistas nicotínicos selectivos.

Por otro lado, no está claro si los efectos de los agonistas nicotínicos en, por ejemplo, el síndrome de Tourette y la esquizofrenia, se deben a una activación o inactivación/desensibilización de los receptores nicotínicos neuronales.

Los efectos de los agonistas sobre los receptores nicotínicos neuronales son fuertemente dependientes del período de exposición. Se produce en milisegundos una rápida subsensibilización reversible, en segundos una desensibilización prolongada, en horas se produce una inactivación irreversible de los receptores que contienen $\alpha 4\beta 2$ y $\alpha 7$ y en días una sensibilización.

En otras palabras, los efectos de los "agonistas" nicotínicos pueden de

hecho deberse a un agonismo parcial, inactivación y/o desensibilización de los receptores nicotínicos neuronales. A su vez, las concentraciones moderadas de los bloqueantes del canal del receptor nicotínico neuronal podría producir los mismos efectos que los informados para los agonistas nicotínicos en las indicaciones mencionadas precedentemente.

LA PRESENTE INVENCION

Se ha encontrado ahora que determinados derivados azabíclicos, azatricíclicos y azaespirocíclicos de aminociclohexanos presentan una pronunciada e inesperada actividad antagonista de los receptores de NMDA, 5HT₃ y nicotínicos. Debidos a la propiedad mencionada, las sustancias son adecuadas para el tratamiento de un amplio rango de trastornos del CNS que comprenden alteraciones de la transmisión glutaminérgica, serotoninérgica y nicotínica, efecto inmunomodulador y propiedades para enfermedades anti-infecciosas. Estos compuestos se encuentran preferentemente en la forma de una composición farmacéutica de los mismos junto con uno o más diluyentes, vehículos o excipientes aceptables para uso farmacéutico.

OBJETOS DE LA INVENCION

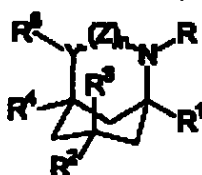
Uno de los objetos de la presente invención comprende la provisión de nuevos compuestos farmacéuticos que son aminociclohexanos azabíclicos, azatricíclicos y azaespirocíclicos antagonistas de los receptores de NMDA, 5HT₃ y nicotínicos y composiciones farmacéuticas con los mismos. Otro objeto de la invención comprende la provisión de un nuevo método para tratar, eliminar, aliviar, paliar o mejorar trastornos indeseables del CNS que comprenden alteraciones de la transmisión glutaminérgica, serotoninérgica, nicotínica, para tratar trastornos inmunomoduladores y para tratar

enfermedades infecciosas empleando un compuesto de la invención o una composición farmacéutica que contiene a los mismos. Un objeto adicional de la invención comprende la provisión de un proceso para producir los principios activos de aminociclohexanos azabíclicos, azatricíclicos y azaespirocíclicos. Aún otros objetos adicionales serán evidentes de aquí en adelante y otros objetos serán evidentes para los especialistas en el arte.

RESUMEN DE LA INVENCION

Por ello, los autores consideran que el contenido de la invención se puede resumir, entre otros, en términos de:

Un compuesto seleccionado entre los que son de la fórmula 1,



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donde

R y R¹-R⁵ se seleccionan independientemente entre grupos alquilo C₁₋₆ de cadena lineal o ramificada (por ejemplo, grupos metilo, etilo, propilo o butilo), grupos alquenilo C₂₋₆ de cadena lineal o ramificada (por ejemplo, grupos etenilo o propenilo), grupos alquinilo C₂₋₆ de cadena lineal o ramificada (por ejemplo, grupos etinilo o propinilo), grupos arilo C₆₋₁₂ (por ejemplo, grupos fenilo o naftilo), grupos arilo C₆₋₁₂ sustituidos (por ejemplo, que contienen uno o más sustituyentes seleccionados entre alquilo C₁₋₆, tal como metilo o etilo, alcoxi C₁₋₆, tal como metoxi o etoxi, hidroxí y halo, tal como cloro o bromo), grupos aril-C₁₋₄ alquilo C₆₋₁₂ (por ejemplo, grupos bencilo o fenetilo) y, en el caso de R² y R⁵, átomos de hidrógeno;

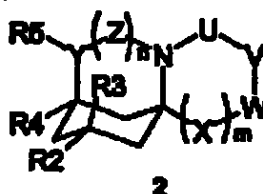
Z es CH₂;

N = 0 ó 1;

Y = CH;

y siempre que al menos uno de R² y R³ no son hidrógeno y al menos uno de R⁴ y R⁵ no son hidrógeno;

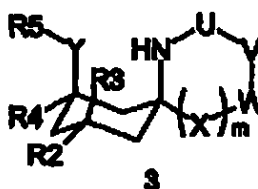
o los compuestos donde R y R¹ se combinan para formar un puente de alquileo o alquenileo C₃-C₆ U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde X = CH₂;

m = 0, 1, 2;

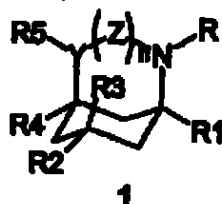
o los compuestos donde R y R¹ se combinan para formar un puente de alquileo o alquenileo C₃-C₆ U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3



donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁵ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

un método de tratamiento de un animal vivo para aliviar una afección donde el compuesto es seleccionado por su eficacia inmunomoduladora, anti-malaria, anti-virus Borna o anti-hepatitis C, anti-tripanosómico y anti-HSV, que comprende el paso de administrar a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde R se selecciona del grupo formado por hidrógeno, alquilo (C_1-C_6) de cadena lineal o ramificada, alqueno (C_2-C_6) de cadena lineal o ramificada, alquino (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^1 se selecciona del grupo formado por alquilo (C_1-C_6) de cadena lineal o ramificada, alqueno (C_2-C_6) de cadena lineal o ramificada, alquino (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

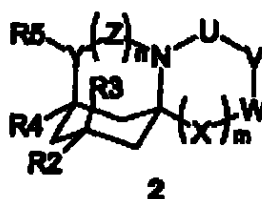
R^2 a R^6 se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C_1-C_6) de cadena lineal o ramificada, alqueno (C_2-C_6) de cadena lineal o ramificada, alquino (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

Z es CH_2 ;

N = 0 ó 1;

Y = CH;

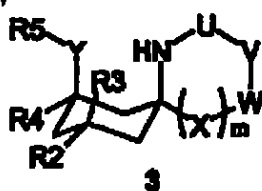
o los compuestos donde R y R^1 se combinan para formar un puente de alqueno o alqueno C_3-C_5 U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde $X = CH_2$;

$m = 0, 1, 2$;

o los compuestos donde R y R¹ se combinan para formar un puente de alquileo o alquenileo C₃-C₅ U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,



donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁵ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección;

un método de tratamiento de un animal vivo para aliviar una afección tratable con un antagonista de NMDA seleccionado del grupo formado por excitotoxicidad seleccionada entre isquemia durante un accidente cerebrovascular, traumatismo, hipoxia, hipoglucemia, glaucoma y encefalopatía hepática,

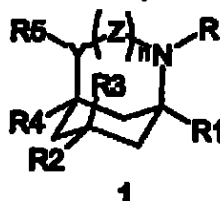
enfermedades neurodegenerativas crónicas seleccionadas entre el mal de Alzheimer, demencia vascular, mal de Parkinson, enfermedad de

Huntington, esclerosis múltiple, esclerosis amiotrófica lateral, neurodegeneración por SIDA, atrofia olivopontocerebelosa, síndrome de Tourette, enfermedad de neuronas motoras, 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 a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C_1-C_6) de cadena lineal o ramificada, alquenilo (C_2-C_6) de cadena lineal o ramificada, alquinilo (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^1 se selecciona del grupo formado por alquilo (C_1-C_6) de cadena lineal o ramificada, alquenilo (C_2-C_6) de cadena lineal o ramificada, alquinilo (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^2 a R^5 se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C_1-C_6) de cadena lineal o ramificada, alquenilo (C_2-C_6) de cadena lineal o ramificada, alquinilo (C_2-C_6) de cadena lineal o ramificada, arilo,

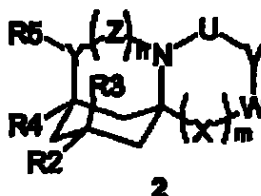
anillo sustituido y arilalquilo;

Z es CH₂;

N = 0 ó 1;

Y = CH;

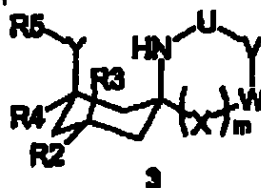
o los compuestos donde R y R¹ se combinan para formar un puente de alquileno o alquenileno C₃-C₅ U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde X = CH₂;

m = 0, 1, 2;

o los compuestos donde R y R¹ se combinan para formar un puente de alquileno o alquenileno C₃-C₅ U-V-W-X y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,

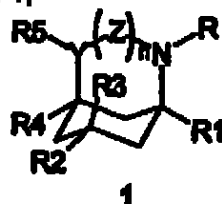


donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁵ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección;

un método de tratamiento de un animal vivo para aliviar una afección tratable con un antagonista del receptor de 5HT₃, que comprende el paso de administrar a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C₁-C₆) de cadena lineal o ramificada, alquenilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R¹ se selecciona del grupo formado por alquilo (C₁-C₆) de cadena lineal o ramificada, alquenilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R² a R⁵ se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C₁-C₆) de cadena lineal o ramificada, alquenilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

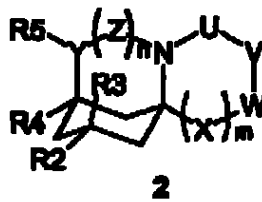
Z es CH₂;

N = 0 ó 1;

Y = CH;

o los compuestos donde R y R¹ se combinan para formar un puente de alquilenilo o alquenilenilo C₃-C₆ U-V-W-X, dando como resultado la estructura representada por la fórmula 2,

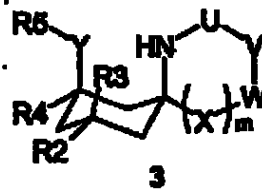
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donde $X = \text{CH}_2$;

$$m = 0, 1, 2;$$

o los compuestos donde R y R¹ se combinan para formar un puente de alquileno o alquencileno C₃-C₅ U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,

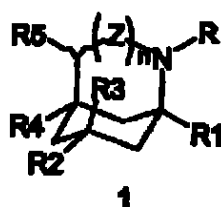


donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁶ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección;

un método de tratamiento de un animal vivo para aliviar una afección tratable con un antagonista del receptor nicotínico neuronal, que comprende el paso de administrar a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C_1-C_9) de cadena lineal o ramificada, alquenilo (C_2-C_9) de cadena lineal o ramificada, alquinilo (C_2-C_9) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R¹ se selecciona del grupo formado por alquilo (C₁-C₆) de cadena lineal o ramificada, alqueniilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

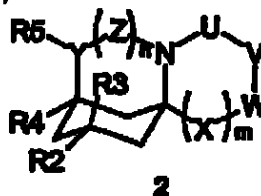
R² a R⁵ se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C₁-C₆) de cadena lineal o ramificada, alquenilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

Z es CH₂:

N = 0 ó 1;

$$Y = CH_3$$

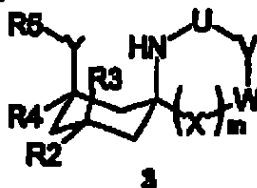
o los compuestos donde R y R¹ se combinan para formar un puente de alquileo o alquenileno C₃-C₆ U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde $X = CH_2$;

 $m = 0, 1, 2;$

o los compuestos donde R y R¹ se combinan para formar un puente de alquileo o alquenileo C₃-C₈ U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,

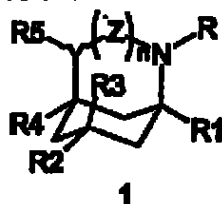


donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁵ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección;

un método de tratamiento de un animal vivo para aliviar una afección tratable con un antagonista de 5HT₂ seleccionado del grupo formado por trastornos de ansiedad, trastornos depresivos, esquizofrenia y psicosis relacionada con el tratamiento, trastornos de abuso de drogas y alcohol, trastornos cognitivos, mal de Alzheimer, mal de Parkinson, temblor cerebeloso, migraña, trastornos de la alimentación, síndrome de intestino inflamatorio (IBS), y emesis, que comprende el paso de administrar a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^1 se selecciona del grupo formado por alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

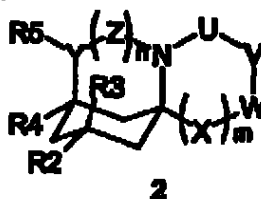
R^2 a R^5 se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

Z es CH_2 ;

N = 0 ó 1;

Y = CH;

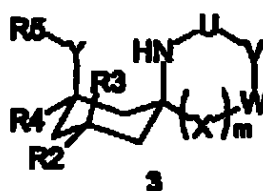
o los compuestos donde R y R^1 se combinan para formar un puente de alquileno o alquenileno C_3-C_8 U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde X = CH_2 ;

m = 0, 1, 2;

o los compuestos donde R y R^1 se combinan para formar un puente de alquileno o alquenileno C_3-C_8 U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,

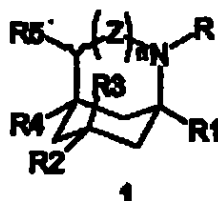


donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R⁵ para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección;

un método de tratamiento de un animal vivo para aliviar una afección tratable con un antagonista del receptor nicotínico neuronal seleccionado del grupo formado por síndrome de Tourette, trastornos de ansiedad, esquizofrenia, abuso de drogas, abuso de nicotina, abuso de cocaína, disquinesia (enfermedad de Huntington, inducido por L-DOPA), trastorno de hiperactividad con déficit atencional (ADHD), mal de Alzheimer, mal de Parkinson y dolor, que comprende el paso de administrar a dicho animal vivo una cantidad de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C₁-C₆) de cadena lineal o ramificada, alquenoilo (C₂-C₆) de cadena lineal o ramificada, alquinilo (C₂-C₆) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R¹ se selecciona del grupo formado por alquilo (C₁-C₆) de cadena lineal

o ramificada, alqueno (C_2-C_6) de cadena lineal o ramificada, alquino (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

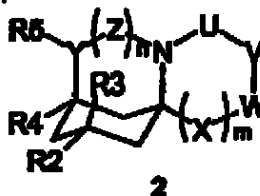
R^2 a R^5 se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C_1-C_6) de cadena lineal o ramificada, alqueno (C_2-C_6) de cadena lineal o ramificada, alquino (C_2-C_6) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

Z es CH_2 ;

$N = 0$ ó 1 ;

$Y = CH$;

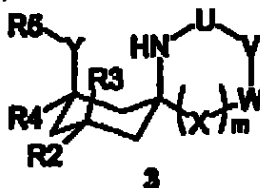
o los compuestos donde R y R^1 se combinan para formar un puente de alqueno o alqueno C_3-C_5 U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde $X = CH_2$;

$m = 0, 1, 2$;

o los compuestos donde R y R^1 se combinan para formar un puente de alqueno o alqueno C_3-C_5 U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,



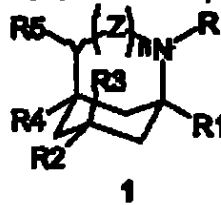
donde el miembro de anillo N está saturado y el miembro de anillo Y está

saturado o se puede combinar junto con R^5 para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

que es eficaz para aliviar dicha afección; y

una composición farmacéutica que consiste de un compuesto seleccionado entre los que son de la fórmula 1,



donde

R se selecciona del grupo formado por hidrógeno, alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^1 se selecciona del grupo formado por alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

R^2 a R^5 se seleccionan independientemente del grupo formado por hidrógeno, alquilo (C_1-C_8) de cadena lineal o ramificada, alquenilo (C_2-C_8) de cadena lineal o ramificada, alquinilo (C_2-C_8) de cadena lineal o ramificada, arilo, arilo sustituido y arilalquilo;

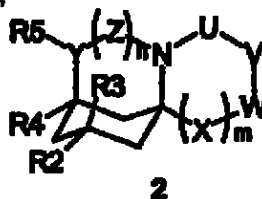
Z es CH_2 ;

N = 0 ó 1;

Y = CH;

o los compuestos donde R y R^1 se combinan para formar un puente de

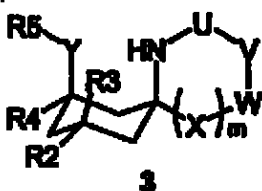
alquileo o alquileo C_3-C_6 U-V-W-X, dando como resultado la estructura representada por la fórmula 2,



donde $X = CH_2$;

$m = 0, 1, 2$;

o los compuestos donde R y R^1 se combinan para formar un puente de alquileo o alquileo C_3-C_6 U-V-W-X, y los miembros del anillo N e Y no se unen para formar un puente, dando como resultado la estructura básica representada por la fórmula 3,



donde el miembro de anillo N está saturado y el miembro de anillo Y está saturado o se puede combinar junto con R^6 para formar un enlace de carbono-hidrógeno con el carbono del anillo al cual está unido;

sus isómeros ópticos y las sales de adición ácida o básica aceptables para uso farmacéutico de los mismos;

en combinación con uno o más diluyentes, excipientes o vehículos aceptables para uso farmacéutico.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Los siguientes detalles y los ejemplos detallados solamente se ofrecen a efectos ilustrativos y no deben considerarse en un sentido limitante.

Esquema y tabla de síntesis general de 6-azabicyclo[3.2.1]octanos (que

pertenecen a la estructura de la fórmula 1 del Resumen):

Esquema 1

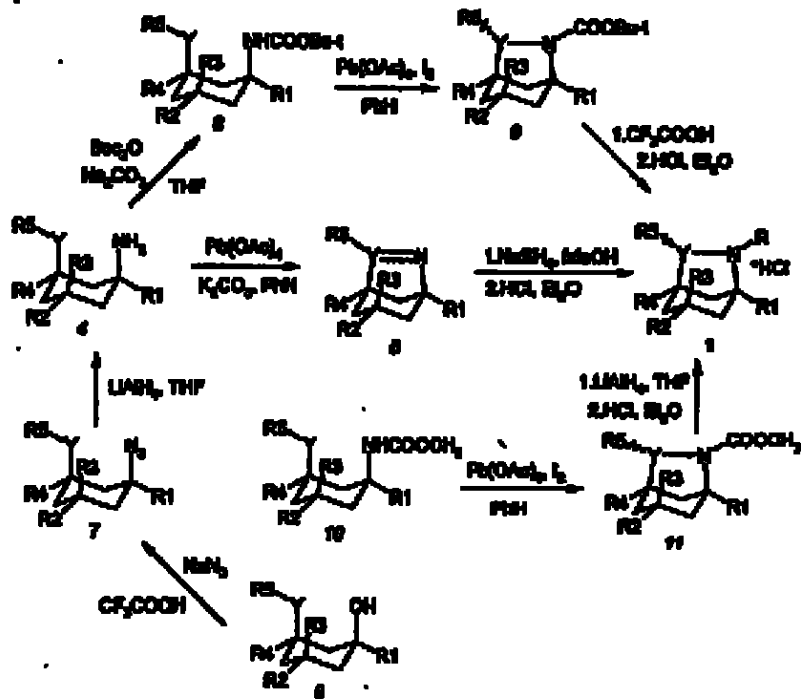


TABLA 1: 6-azabicyclo[3.2.1]octanos 1-1 a 1-8

Nº MRZ	Nº en la descripción de síntesis	R	R¹	R²	R³	R⁴	R⁵	Y	n
2011	1-1	H	Me	Me	H	Me	H	CH	0
2023	1-2	H	Et	Me	H	Me	H	CH	0
2007	1-3	H	Me	Et	H	Me	H	CH	0
2/1010	1-4	H	Me	Me	Me	Me	H	CH	0
2/1003	1-5	Me	Me	Me	Me	Me	H	CH	0
2022	1-6	H	Et	Me	Me	Me	H	CH	0
2029	1-7	H	Me	Me	H	Me	Me	CH	0
2028	1-8	H	Me	Me	H	Me	Ph	CH	0

Ejemplo 1.

Clorhidrato de 1,exo-3,5-trimetil-6-azabicyclo[3.2.1]octano (1-1).

a) 1,exo-3,5-trimetil-6-azabicyclo[3.2.1]oct-6-eno (5-1).

Se agitó una mezcla de 1,3,3-trans-5-tetrametilciclohexanamina (4-1) (3,88 g, 25 mmol), K_2CO_3 (28 g, 0.2 mol) y tetraacetato de plomo (22,2 g, 50 mmol) en benceno seco (125 ml) durante 3 hs bajo ebullición a reflujo. Después se enfrió con agua helada y se filtró. El precipitado se lavó con éter dietílico y el filtrado se evaporó bajo presión reducida. El residuo oleoso se separó por cromatografía en columna sobre gel de sílice (diclorometano-alcohol isopropílico, 20:1, 10:1). Se recolectó una fracción con R_f 0,7 (EtOAc) para obtener, después de concentración bajo presión reducida 1,0 g (26%) de la imina 5-1 como un aceite de color ámbar.

^1H NMR ($CDCl_3$, TMS) δ : 0,86 (3H, d, 6 Hz, 3- CH_3), 0,90-1,80 (7H, m, CH-anillo); 1,12 (3H, s, 1- CH_3); 1,34 (3H, s, 5- CH_3) y 7,36 ppm (1H, s, HC=).

b) Clorhidrato de 1,exo-3,5-trimetil-6-azabicyclo[3.2.1]octano (1-1).

Se agregó por gotas una solución de la imina 5-1 (0,8 g, 5,3 mmol) en MeOH (2 ml) a una suspensión de borohidruro de sodio (0,4 g, 10,6 mmol) en MeOH (6 ml). La mezcla se agitó a temperatura ambiente durante 24 hs, luego se agregaron 10 ml de NaOH acuoso 5%. La mezcla se extrajo con éter dietílico. La fase orgánica se lavó con NaCl acuoso saturado y se secó sobre palets de NaOH. La solución filtrada se trató con una solución de HCl seco en éter dietílico, se evaporó bajo presión reducida y el residuo se recristalizó a partir de CH_3CN seco para obtener el compuesto 1-1 como un sólido incoloro (0,33 g, 35%).

^1H NMR ($CDCl_3$, TMS) δ : 0,96 (3H, d, 6 Hz, 3- CH_3), 0,95-1,15 (1H, m, 2-CH); 1,11 (3H, s, 1- CH_3); 1,41 (1H, d, 12,4 Hz, 8-CH); 1,55-1,70 (1H, m, 2-CH); 1,57 (3H, s, 5- CH_3); 1,70-1,90 (2H, m, 4-CH y 8-CH); 2,00-2,30 (2H, m, 3-CH y 4-CH); 3,00-3,25 (2H, m, 7- CH_2) y 9,30-9,85 ppm (2H, br s, NH_2^+).

Ejemplo 2.**Clorhidrato de 5-etil-1,exo-3-dimetil-6-azabicyclo[3.2.1]octano (1-2).****a) 1-azido-1-etil-3,3-trans-5-trimetilciclohexano (7).**

Se agitó una mezcla enfriada ($\sim 0^{\circ}\text{C}$) de 1-etil-3,3-trans-5-trimetilciclohexanol (6) (3,3 g, 18,1 mmol), azida sódica (2,36 g, 36,3 mmol) y ácido trifluoroacético (10,7 ml) en cloroformo (50 ml) durante 24 hs. Después se alcalinizó por adición de amoníaco acuoso diluido. La fase orgánica se separó, se lavó con agua y se secó sobre K_2CO_3 . La filtración y evaporación del solvente bajo presión reducida permitió obtener un residuo oleoso que se separó por cromatografía instantánea sobre gel de sílice, eluyendo con éter de petróleo ligero, para obtener la azida 7 (2,0 g, 56%) como un aceite incoloro liviano.

^1H NMR (CDCl_3 , TMS) δ : 0,64 (1H, d, 14 Hz, CH-anillo); 0,85-2,15 (8H, m, CH-anillo y ET- CH_2); 0,90 (3H, d, 7 Hz, 5- CH_3); 0,92 (3H, s, 3- CH_3); 0,97 (3H, t, 7,5 Hz, Et- CH_3) y 1,10 ppm (3H, s, 3- CH_3).

b) 1-etil-3,3-trans-5-trimetilciclohexanamina (4-2).

Se agregó una solución de la azida 7 (1,97 g, 10 mmol) en éter dietílico (10 ml) por gotas a una suspensión de hidruro de aluminio y litio (1,13 g, 30 mmol) en éter dietílico (30 ml). La mezcla se agitó durante 20 hs a temperatura ambiente. Después se neutralizó cuidadosamente con NaOH acuoso 10%. La fase orgánica se separó y la fase acuosa se extrajo con éter dietílico. Las fases orgánicas combinadas se lavaron con NaCl acuoso saturado y se secaron sobre NaOH. La filtración y evaporación del solvente bajo presión reducida permitió obtener la amina 4-2 (1,36 g, 80%) como un aceite.

^1H NMR (CDCl_3 , TMS) δ : 0,55-2,15 (9H, m, CH-anillo y ET- CH_2); 0,88

(3H, s, 3-CH_{3eq}); 0,89 (3H, d, 6,5 Hz, 5-CH₃); 0,89 (3H, t, 7 Hz, ET-CH₃) y 1,12 ppm (3H, s, 3-CH_{3ax}).

c) Clorhidrato de 5-etil-1,exo-3-dimetil-6-azabicyclo[3.2.1]octano (1-2).

Se preparó con un rendimiento del 30% a partir de la imina 5-2 de acuerdo con el procedimiento descrito en el Ejemplo 1b. Sólido incoloro.

¹H NMR (CDCl₃, TMS) δ: 0,95-1,15 (7H, m, CH-anillo, 3-CH₃ y CH₃-Et); 1,12 (3H, s, 1-CH₃); 1,48 (1H, d, 13,6 Hz, 8-CH); 1,55-1,76 (3H, m, CH-anillo y CH₂-Et); 1,84-2,04 (2H, m, CH-anillo) y 2,04-2,28 (2H, m, 4,8-CH); 3,14 (2H, m, 7-CH₂) y 9,40 ppm (2H, br s, NH₂⁺).

d) 5-etil-1,exo-3-dimetil-6-azabicyclo[3.2.1]oct-6-eno (5-2).

Se preparó con un rendimiento del 32% a partir de la amina 4-2 de acuerdo con el procedimiento descrito en el Ejemplo 1a. Un aceite.

¹H NMR (CDCl₃, TMS) δ: 0,82-0,95 (1H, m, CH-anillo); 0,91 (3H, d, 6 Hz, 3-CH₃), 0,94 (3H, t, 7,5 Hz, Et-CH₃); 1,15-1,75 (6H, m, CH-anillo); 1,15 (3H, s, 1-CH₃); 1,71 (2H, q, 7,5 Hz, Et-CH₂) y 7,38 ppm (1H, s, HC =).

Ejemplo 3.

Clorhidrato de exo-3-etil-1,5-dimetil-6-azabicyclo[3.2.1]octano (1-3).

a) trans-5-etil-1,3,3-trimetilciclohexilcarbamato de ter-butilo (8-1).

A una solución de clorhidrato de 1,3,3-trimetil-trans-5-etilciclohexanamina (4-3) (1,54 g, 7,5 mmol) en THF (20 ml) se agregó Na₂CO₃ (3,18 g, 30 mmol) y la mezcla se agitó durante 30 min. Después se enfrió con agua helada, se agregó bicarbonato de di-ter-butilo (1,7 g, 7,65 mmol) y se continuó agitando durante 20 hs. Se agregó agua y la mezcla se extrajo dos veces con éter dietílico. Los extractos combinados se lavaron con NaCl acuoso

saturado, se secaron sobre MgSO_4 y se evaporaron. El residuo sólido se trató con hexano, se filtró y se lavó con hexano para obtener el carbamato 8-1. Se aisló una cantidad adicional de 8-1, después el filtrado se evaporó y trató con acetonitrilo. Se obtuvo el carbamato 8-1 (1,18 g, 57%) como un sólido incoloro con un p.f. de 70-71 °C.

^1H NMR (CDCl_3 , TMS) δ : 0,65-1,65 (7H, m, $\text{CH}_2\text{-Et}$ y CH-anillo); 0,88 (3H, t, 6,5 Hz, $\text{CH}_3\text{-Et}$); 0,88 y 0,99 (ambos 3H, s, 3, 3- CH_3); 1,42 (9H, s, t-Bu); 1,85 (1 H, dq, 13,5 y 2,5 Hz, 6- CH_{eq}); 2,24 (1 H, d, 14 Hz, 2- CH_{eq}) y 4,30 ppm (1 H, br s, NH).

b) *exo*-3-etil-1,5-dimetil-6-azabicyclo[3.2.1]octan-6-carboxilato de *tert*-butilo (9-1).

A una mezcla del carbamato 8-1 (1,05 g, 3,85 mmol) y iodo (1,95 g, 7,7 mmol) en benceno seco (35 ml) se agregó tetraacetato de plomo (3,92 g, 8,85 mmol) en una porción. La mezcla se agitó bajo ebullición a reflujo durante 4 hs, luego se enfrió con agua helada y se filtró. El precipitado se lavó con éter dietílico y el filtrado se lavó cuidadosamente con metabisulfito de potasio acuoso saturado seguido de NaHCO_3 acuoso saturado. La fase orgánica se lavó con NaCl acuoso saturado, se secó sobre MgSO_4 y se evaporó. El residuo se purificó por cromatografía instantánea sobre gel de sílice (éter de petróleo ligero-acetato de etilo, 20: 1) para obtener el compuesto 9-1 (0,76 g, 73%) como un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,86 (3H, t, 6,5 Hz, $\text{CH}_3\text{-Et}$); 1,00 (3H, s, 1- CH_3); 1,00-1,80 (7H, m, $\text{CH}_2\text{-Et}$ y CH-anillo); 1,46 (12H, s, t-Bu y 5- CH_3); 1,95-2,45 (2H, m, anillo-CH); 3,06 y 3,36 ppm (ambos 1H, d, 11 Hz, 7- CH_2).

c) Clorhidrato de *exo*-3-etil-1,5-dimetil-6-azabicyclo[3.2.1]octano (1-

3).

Se agregó carbamato 9-1 (0,73 g, 2,7 mmol) a una solución de ácido trifluoroacético (3 ml) en diclorometano (15 ml) y la mezcla se agitó a temperatura ambiente durante 10 h. La solución se evaporó bajo presión reducida y el residuo se trató con NaOH acuoso 10% (5 ml) y se extrajo con éter dietílico. El extracto se lavó con NaCl acuoso saturado y se secó sobre NaOH. La solución filtrada se trató con solución de HCl seco en éter dietílico. El solvente se evaporó bajo presión reducida y el residuo se trató con acetonitrilo seco para obtener el clorhidrato de amina 1-3 como un sólido incoloro (0,34 g, 62%).

^1H NMR (CDCl_3 , TMS) δ : 0,85-2,45 (9H, m, 2,4,8- CH_2 , 3-CH y $\text{CH}_2\text{-Et}$); 0,90 (3H, t, 7 Hz, $\text{CH}_3\text{-Et}$); 1,12 (3H, s, 1- CH_3); 1,59 (3H, s, 5- CH_3); 3,13 (2H, t, 6 Hz, 7- CH_2) y 9,55 ppm (2H, br s, NH_2^+).

Ejemplo 4.

Clorhidrato de 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octano (1-4).

a) 1,3,3,5, 5-pentametilciclohexilcarbamato de ter-butilo (8-2).

Se preparó con un rendimiento del 70% a partir de clorhidrato de 1,3,3,5,5-pentametilciclohexanamina (4-4) de acuerdo con el procedimiento descrito en el Ejemplo 3a. Se purificó por cromatografía instantánea sobre gel de sílice (éter de petróleo ligero-acetato de etilo, 20: 1). Un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,87 (6H, s, 3,5- CH_3); 0,90-1,45 (4H, m, 4- CH_2 y 2,6- CH_2); 1,12 (6H, s, 3,5- CH_3); 1,27 (3H, s, 1- CH_3); 1,42 (9H, s, t-Bu); 2,24 (2H, d, 15 Hz, 2,6- CH_2) y 4,30 ppm (1H, br s, NH).

b) 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octan-6-carboxilato de ter-butilo (9-2).

Se preparó con un rendimiento del 48% a partir del carbamato 8-2 de acuerdo con el procedimiento descrito en el Ejemplo 3b. Un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,91, 0,94 y 0,99 (total 9H, todos s, 1,3,3- CH_3); 0,80-1,75 (5H, m, CH-anillo); 1,34 y 1,52 (total 3H, ambos s, 5- CH_3); 1,41 y 1,44 (total 9H, ambos s, t-Bu); 1,91 y 2,09 (total 1H, ambos d, 14,5 Hz, 6-CH); 3,00 y 3,28 (un rotámero); y 3,03 y 3,33 (otro rotámero; total 2H, todos dd, 11 y 2 Hz, 7- CH_2).

c) Clorhidrato 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octano (1-4).

Se preparó con un rendimiento del 68% a partir del carbamato 9-2 de acuerdo con el procedimiento descrito en el Ejemplo 3c. Sólido incoloro.

^1H NMR (CDCl_3 , TMS) δ : 1,00, 1,13 y 1,29 (total 9H, s, 1,3,3- CH_3); 1,25-1,65 (4H, m, 2- CH_2 y 4,8-CH); 1,64 (3H, s, 5- CH_3); 1,81 (1H, dt, 12,4 y 2,3 Hz, 4-CH); 2,21 (1H, d, 14,5 Hz, 8-CH); 3,10-3,40 (2H, m, 7- CH_2); 9,10 y 9,90 ppm (total 2H, ambos br s, NH_2^+).

Ejemplo 5.

Clorhidrato de 1,3,3,5, 6-pentametil-6-azabicyclo[3.2.1]octano (1-5).

a) 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octan-6-carboxilato de metilo (11).

Se preparó con un rendimiento del 50% a partir de 1,3,3,5,5-pentametilciclohexilcarbamato de metilo (10) de acuerdo con el procedimiento descrito en el Ejemplo 3b. Un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,87 y 0,96 (total 9H, ambos s, 1,3,3- CH_3); 1,00-1,70 (4H, m, 2- CH_2 y 4,8-CH); 1,33 y 1,46 (total 3H, ambos s, 1- CH_3); 1,70-1,20 (2H, m, 4, 8-CH); 3,04 y 3,34 (rotámero mayor) y 3,10 y 3,39 (rotámero menor; total 2H, todos dd, 11,5 y 1,5 Hz, 7- CH_2); 3,59 (mayor) y 3,64

(total 3H, ambos s, OCH₃).

b) Clorhidrato de 1,3,3,5,6-pentametil-6-azabicyclo[3.2.1]octano (1-5).

Se agregó una solución del carbamato 11 (1,0 g, 4,44 mmol) en éter dietílico (10 ml) a una suspensión de hidruro de aluminio y litio (0,34 g, 9 mmol) en éter dietílico (25 ml). La mezcla se agitó durante 20 hs a temperatura ambiente. Después se enfrió con agua helada y se neutralizó cuidadosamente con NaOH acuoso 10%. La fase orgánica se separó y la fase acuosa se extrajo con éter dietílico. Las fases orgánicas combinadas se lavaron con NaCl acuoso saturado y se secaron sobre NaOH.

La solución filtrada se trató con un exceso de solución de HCl seco en éter dietílico. El solvente se evaporó bajo presión reducida y el residuo se trató con acetonitrilo seco y éter dietílico (2: 1), y se enfrió en refrigerador durante 24 hs. El precipitado se filtró y se lavó con éter dietílico para obtener el clorhidrato de amina 1-5 (0,25 g, 26%) como un sólido incoloro.

¹H NMR (CDCl₃, TMS) δ: 1,03, 1,09, 1,16 y 1,22 (total 9H, todo s, 1,3,3-CH₃); 1,44 (3H, s, 5-CH₃); 1,50-2,50 (6H, m, 2,4, 8-CH₂); 2,73 (d, 5 Hz) y 2,80 (total 3H, d, 5,5 Hz, N-CH₃); 2,55 (m) y 2,94 (total 1 H, dd, 12 y 6 Hz, 7-CH); 3,73 (dd, 12 y 8,5 Hz) y 4,07 (total 1H, dd, 13 y 7 Hz, 7-CH); 9,50 y 10,80 ppm (total 1 H, br s, NH⁺).

Ejemplo 6.

Clorhidrato de 5-etil-1,3,3-trimetil-6-azabicyclo[3.2.1]octano (1-6).

a) 5-etil-1,3,3-trimetil-6-azabicyclo[3.2.1]oct-6-eno (5-3).

Se preparó con un rendimiento del 28% a partir de 1-etil-3,3,5,5-tetrametilciclohexanamina (4-5) de acuerdo con el procedimiento descrito en el Ejemplo 1a. Un aceite.

^1H NMR (CDCl_3 , TMS) δ : 0,93 (3H, s, 3- CH_3); 0,94 (3H, t, 7,4 Hz, Et-CH_3); 0,98 (3H, s, 3- CH_3); 1,15 (3H, s, 1- CH_3); 1,20-1,50 (5H, m, CH-anillo); 1,57 (1H, dt, 12,4 y 2 Hz, CH-anillo); 1,69 (2H, dq, 7,5 y 2,8 Hz, Et-CH_2) y 7,47 ppm (1 H, s, HC =).

b) Clorhidrato de 5-etil-1,3,3-trimetil-6-azabicyclo[3.2.1]octano (1-6).

Se preparó con un rendimiento del 33% a partir de la imina 5-3 de acuerdo con el procedimiento descrito en el Ejemplo 1B. Sólido incoloro.

^1H NMR (CDCl_3 , TMS) δ : 1,01 (3H, s, 3- CH_3); 1,03 (3H, t, 7,5 Hz, $\text{CH}_3\text{-Et}$); 1,13 y 1,31 (ambos 3H, s, 1,3- CH_3); 1,25-1,35 (1H, m, CH-anillo); 1,35-1,65 (4H, M, $\text{CH}_2\text{-Et}$ y CH-anillo); 1,69 (1 H, d, 12 Hz, 2-CH); 1,92-2,12 (2H, m, 4,8-CH); 3,05-3,45 (2H, m, 7- CH_2); 9,05 y 9,65 ppm (ambos 1 H, br s, NH_2^+).

Ejemplo 7.

Clorhidrato de 1,exo-3,5,exo,endo-7-tetrametil-6-azabicyclo[3.2.1]octano (1-7).

a) cis-3-etil-1,3,trans-5-trimetilciclohexilcarbamato de ter-butilo (8-3).

Se preparó con un rendimiento del 81% a partir de clorhidrato de 1,3,5-trimetil-cis-3-etilciclohexanamina (4-6) de acuerdo con el procedimiento descrito en el Ejemplo 3a. Se purificó por cromatografía instantánea sobre gel de sílice (éter de petróleo ligero-acetato de etilo, 20: 1). Un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,63 (1H, d, 12,5 Hz, CH-anillo); 0,70-0,90 (1H, m, CH-anillo); 0,79 (3H, t, 7,5 Hz, $\text{CH}_3\text{-Et}$); 0,86 (3H, d, 6,4 Hz, 5- CH_3); 1,28 (3H, s, 3- CH_3); 1,25-1,85 (6H, m, CH-anillo y $\text{CH}_2\text{-ET}$); 1,41 (9H, s, t-Bu); 1,52 (3H, s, 1- CH_3); 2,35 (1 H, d, 12,5 Hz, 2-CH) y 4,31 ppm (1 H, br s, NH).

1,exo-3,5,exo,endo-7-tetrametil-6-azabicyclo[3.2.1]octan-6-

carboxilato de ter-butilo (9-3).

Se preparó con un rendimiento del 57% a partir del carbamato 8-3 de acuerdo con el procedimiento descrito en el Ejemplo 3b. Un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,60-1,85 (6H, m, CH-anillo); 0,85-1,15 (6H, m, 1,3- CH_3); 1,35-1,55 (6H, m, 5, 7- CH_3); 1,45 (9H, s, t-Bu); 2,06 y 2,27 (total 1 H, m, CH-anillo); 3,36 y 3,51 ppm (total 1H, m, 7-CH).

Clorhidrato de 1,exo-3,5,exoendo-7-tetrametil-6-azabicyclo[3.2.1]octano (1-7).

Se preparó con un rendimiento del 70% a partir del carbamato 9-3 de acuerdo con el procedimiento descrito en el Ejemplo 3c. Un sólido incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,96 (3H, d, 5,8 Hz, 3- CH_3); 1,00 (3H, s, 1- CH_3); 1,00-1,15 (1 H, m, 2-CH); 1,36 (1 H, d, 12 Hz, 8-CH); 1,43 (3H, d, 7,4 HZ, 7- CH_3); 1,55-1,75 (2H, m, 2-CH y 4-CH); 1,62 (3H, s, 5- CH_3); 1,90 (1 H, d, 12,6 Hz, 8-CH); 2,15-2,35 (2H, m, 3-CH y 4-CH); 3,65 (1 H, M, 7-CH); 9,00 y 9,95 ppm (total 2H, ambos br s, NH_2^+).

Ejemplo 8.**Clorhidrato de 1,exo-3,5-trimetil-exo,endo-7-fenil-6-azabicyclo[3.2.1]octano (1-8).****a) 3-bencil-3,5-dimetilciclohexanona (13).**

A una solución enfriada ($\sim 20^\circ\text{C}$) de bromuro de bencilmagnesio 1 M en éter dietílico (50 ml) bajo argón se agregó CuCl (0,52 g, 5,3 mmol) y la mezcla se agitó durante 5 min. Después se agregó por gotas una solución de 3,5-dimetil-2-ciclohexen-1-ona (12) (4,4 g, 35,1 mmol) en éter dietílico (15 ml) manteniendo la temperatura debajo de -10°C . La mezcla se agitó durante 2 hs y se neutralizó con ácido acético acuoso 10% (40 ml). La capa orgánica se

separó, se lavó con agua, NaHCO_3 acuoso saturado y NaCl acuoso saturado, y se secó sobre MgSO_4 . La filtración y concentración bajo vacío permitió obtener un residuo oleoso que se separó por cromatografía instantánea sobre gel de sílice (éter de petróleo ligero-acetato de etilo, 10: 1). La ciclohexanona **13** (4,0 g, 53%) se obtuvo como un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,92 (3H, s, 3- CH_3); 1,06 (3H, d, 6 Hz, 5- CH_3), 1,10-2,45 (7H, m, CH-anillo); 2,42 y 2,56 (total 2H, ambos d, 13 Hz, CH_2Ph) y 7,05-7,35 ppm (5H, m, Ph).

b) cis-3-bencil-1,3,trans-5-trimetilciclohexanol (14).

Se agregó por gotas una solución de la cetona **13** (3,9 g, 18,1 mmol) en éter dietílico (10 ml) a MeMgI 1 M en éter dietílico (40 ml). La mezcla se agitó durante 1 h a temperatura ambiente. El extracto etéreo obtenido después de aislamiento y purificación tradicionales para reacciones de Grignard se secó sobre Na_2SO_4 , se filtró y se evaporó para obtener un residuo oleoso que se purificó por cromatografía instantánea sobre gel de sílice (éter de petróleo ligero- acetato de etilo). El ciclohexanol **14** (3,2 g, 76%) se obtuvo como un aceite incoloro.

^1H NMR (CDCl_3 , TMS) δ : 0,75 (3H, s, 3- CH_3); 0,95-1,25 (3H, m, CH-anillo); 0,92 (3H, d, 6,6 Hz, 5- CH_3), 1,23 (3H, s, 1- CH_3); 1,45-1,75 (3H, m, CH-anillo); 2,05-2,25 (1 H, m, 5-CH); 2,77 y 3,04 (ambos 1 H, d, 13 Hz, CH_2Ph) y 7,05-7,35 ppm (5H, m, CH anilo).

c) N-(cis-3-bencil-1,3,trans-5-trimetilciclohexil)-2-cloroacetamida (15).

Se agregó por gotas ácido sulfúrico (2,1 ml, 3,83 g, 39 mmol) a una solución agitada del ciclohexanol **14** (3,0 g, 13 mmol) y cloroacetoniitrilo (4,0 g,

52 mmol) en ácido acético (2,1 ml) bajo enfriamiento con agua helada. La mezcla se agitó durante 24 hs a temperatura ambiente, luego se vertió en agua helada (10 ml). La mezcla se neutralizó con NaOH acuoso 20% y se extrajo con éter dietílico (3X15 ml). Las fases orgánicas combinadas se lavaron con NaCl acuoso saturado y se secaron sobre MgSO₄. El extracto se filtró y el solvente se evaporó. El residuo se purificó por cromatografía instantánea sobre gel de sílice, eluyendo con una mezcla de éter de petróleo ligero y acetato de etilo (10: 1) para obtener la amida 15 (1,32 g, 33%) como un aceite incoloro.

¹H NMR (CDCl₃, TMS) δ: 0,73 (3H, s, 3-CH₃); 0,90-1,40 (3H, m, CH-anillo); 0,98 (3H, d, 6,6 Hz, 5-CH₃), 1,42 (3H, s, 1-CH₃); 1,63 (1 H, m, CH-anillo); 1,80-2,05 (1H, m, 5-CH); 2,12 (1 H, dq, 13,8 y 3 Hz, 6-CH); 2,33 (1 H, d, 12,7 Hz, CH₂Ph); 2,51 (1H, dt, 15 y 2,2 Hz, 2-CH); 3,17 (1H, d, 12,7 Hz, CH₂Ph); 3,95 y 3,96 (total 2H, ambos s, CH₂CO); 6,52 (1H, br s, NH) y 7,00-7,35 ppm (5H, m, CH arilo).

d) Clorhidrato de cis-3-bencil-1,3,trans-5-trimetilciclohexanamina (4-7).

Una solución de la amida 15 (0,62 g, 2 mmol) y tiourea (0,18 g, 2,4 mmol) en una mezcla de etanol (5 ml) y ácido acético (1 ml) fue sometida a reflujo durante 10 hs. La mezcla de reacción se enfrió hasta temperatura ambiente y se agregaron 20 ml de NaOH acuoso 10% bajo agitación. La mezcla resultante se extrajo con éter dietílico (3x 10 ml). Los extractos combinados se lavaron con NaCl acuoso saturado, se secaron sobre NaOH, se filtraron y se trataron con solución de HCl seco en éter dietílico. El solvente se evaporó bajo presión reducida y el residuo se trató con éter dietílico seco para obtener el clorhidrato de amina 4-7 (0,33 g, 35%) como un sólido incoloro.

^1H NMR (CDCl₃, TMS) δ : 0,68 (3H, d, 6,5 Hz, 5-CH₃); 0,70-1,30 (3H, m, CH-anillo); 0,73 (3H, s, 3-CH₃); 1,28 (3H, s, 1-CH₃); 1,50 (1H, d, 15,4 Hz, CH-anillo); 1,60-1,85 (1H, m, CH-anillo); 2,05 (1H, d, 16 Hz, CH-anillo); 2,15-2,50 (1H, m, 5-CH); 2,47 y 3,33 (ambos 1 H, d, 12,8 Hz, CH₂Ph); 7,00-7,35 (5H, m, CH anillo) y 8,42 ppm (3H, br s, NH₃⁺).

e) 1,exo-3,5-trimetil-7-fenil-6-azabicyclo[3.2.1]oct-6-eno (5-4).

Se preparó con un rendimiento del 40% a partir de la amina libre 4-7 de acuerdo con el procedimiento descrito en el Ejemplo 1 A. Un aceite.

^1H NMR (CDCl₃, TMS) δ : 0,94 (3H, d, 6,6 Hz, 3-CH₃); 0,90-1,15 (2H, m, CH-anillo); 1,26 (3H, s, 1-CH₃); 1,30-1,90 (5H, m, CH-anillo); 1,43 (3H, s, 5-CH₃) y 7,30-7,65 ppm (5H, m, CH anillo).

f) Clorhidrato de 1,exo-3,5-trimetil-exo,endo-7-fenil-6-azabicyclo[3.2.1]octano (1-8).

Se preparó con un rendimiento del 33% a partir de la imina 5-4 de acuerdo con el procedimiento descrito en el Ejemplo 1b. Sólido incoloro.

^1H NMR (CDCl₃, TMS) δ : 0,75-1,95 (4H, m, CH-anillo); 0,86 (3H, d, 5,8 Hz, 3-CH₃); 1,20 (3H, s, 1-CH₃); 1,56 (3H, s, 5-CH₃); 1,99 (1H, d, 14,4 Hz, 8-CH); 2,05-2,15 (1 H, m, CH-anillo); 2,20-2,30 (1 H, m, CH-anillo); 4,57 (1 H, m, 7-CH); 7,24 y 7,65 (total 5H, ambos br s, Ph); 9,15 y 10,40 ppm (total 2H, ambos br s, NH₂⁺).

Esquema y tabla de síntesis general para los 6-azabicyclo[3.2.1]nonanos (que pertenecen a la estructura de la fórmula 1 del Resumen).

Esquema 2

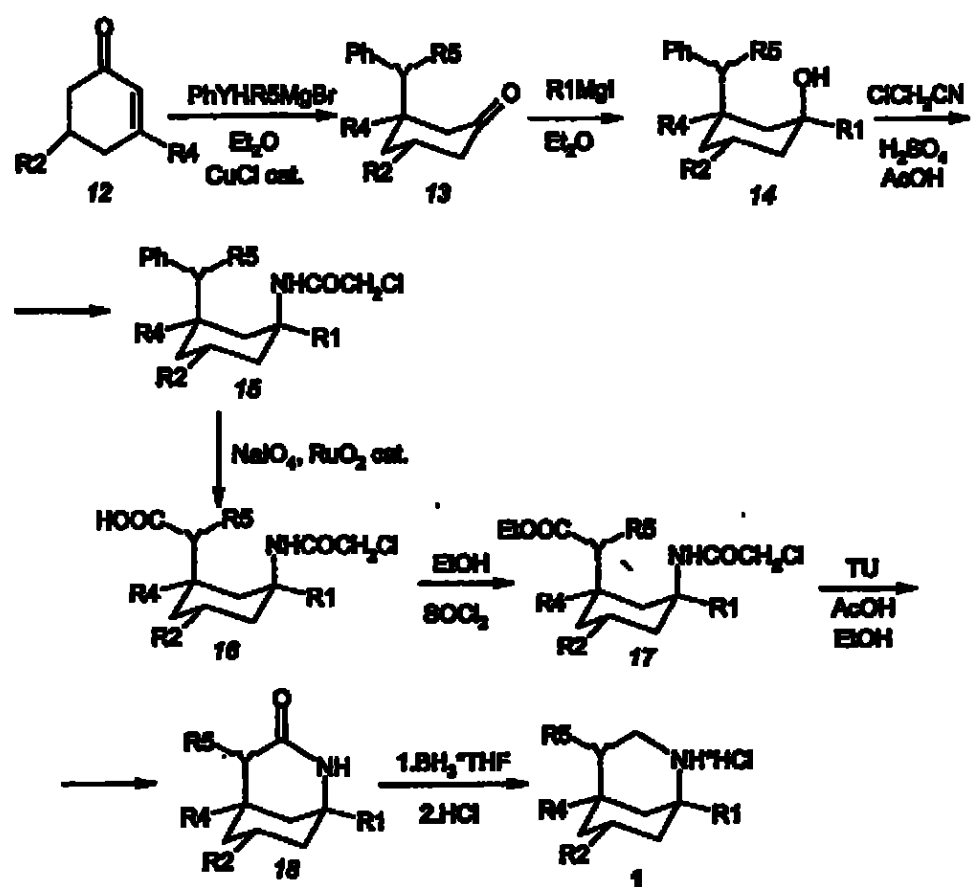


Tabla 2: 6-azabicyclo[3.2.1]nonano 1-9

Nº	Nº en la descripción	R	R¹	R²	R³	R⁴	R⁵	Y	n
MRZ	de síntesis								
2046	1-9	H	Me	Me	H	Me	H	CH	1

Ejemplo 9.

Clorhidrato de 1,5,exo-7-trimetil-2-azabicyclo[3,3,1]nonano (1-9).

a) Ácido 2-{cis-3-[(2-cloroacetil)amino]-1,3,trans-5-trimetilciclohexil}acético (16).

A una solución de 1,5 g (4,9 mmol) de N-(cis-3-bencil-1,3,trans-5-trimetilciclohexil)-2-cloroacetamida (obtenida de una fracción con Rf 0,7-0,8

(Hexanos-EtOAc, 2: 1) separada después de la síntesis del compuesto 15, Ejemplo 8c) en una mezcla de acetonitrilo (16 ml), tetraclorometano (16 ml) y agua (23 ml) se agregó periodato de sodio (10,5 g, 49 mmol) y dióxido de rutenio (7 mg, 0,06 mmol). La mezcla se agitó a temperatura ambiente durante 72 hs, luego se filtró y la torta de filtrado se lavó con diclorometano. La fase orgánica del filtrado se separó y la fase acuosa se extrajo con diclorometano.

Las fases orgánicas combinadas se secaron sobre CaCl_2 , se filtraron y se evaporaron. El residuo se purificó por cromatografía instantánea sobre gel de sílice, eluyendo con cloroformo, para obtener el ácido 16 (0,55 g, 41%) como un aceite.

^1H NMR (DMSO- D_6 , TMS) δ : 0,8-2,6 (7H, m, CH-anillo); 0,84 y 0,85 (total 3H, d, 6 Hz, 5- CH_3); 0,92 y 1,01 (total 3H, s, 1- CH_3); 1,21 y 1,22 (total 3H, s, 3- CH_3); 2,19 y 2,39 (total 2H, ambos d, 13,5 Hz, CH_2CO); 3,97 ppm (2H, s, CH_2Cl); 7,57 y 7,70 (total 1 H, ambos br s, NH) y 12,05 ppm (1 H, br s, COOH).

b) 2-{*cis*-3-[(2-cloroacetil)amino]-1,3,trans-5-trimetilciclohexil} acetato de etilo (17).

Se agregó por gotas cloruro de tionilo (0,73 ml, 10 mmol) a una solución del ácido 16 (0,55 g, 1,99 mmol) en etanol seco (5 ml), bajo enfriamiento con agua helada. La solución resultante se agitó durante 15 hs a temperatura ambiente, luego se evaporó bajo presión reducida. El residuo se purificó por cromatografía instantánea sobre gel de sílice, eluyendo con una mezcla de éter de petróleo ligero y acetato de etilo (6: 1) para obtener el éster etílico 17 (0,32 g, 54%) como un aceite.

^1H NMR (CDCl_3 , TMS) δ : 0,7-1,6 (4H, m, CH-anillo); 0,88-0,94 (3H, m, 5- CH_3); 1,04 y 1,14 (total 3H, s, 1- CH_3); 1,25 (2H, t, 7 Hz, CH_3 -etilo); 1,35 y 1,36

(total 3H, s, 3-CH₃); 1,6-1,8 (1H, m, 5-CH); 2,05-2,35 (2H, m, CH-anillo); 2,16 y 2,79 (total 2H, d, 13 Hz, CH₂CO); 3,92 y 3,95 (total 2H, s, CH₂Cl); 4,12 (2H, q, 7 Hz, CH₂O); 6,42 y 7,28 ppm (total 1 H, br s, NH).

c) 1,5,exo-7-trimetil-2-azabicyclo[3,3,1]nonan-3-ona (18).

Una solución del éster etílico 17 (0,32 g, 1,07 mmol) y tiourea (0,098 g, 1,3 mmol) en una mezcla de etanol (5 ml) y ácido acético (1,2 ml) fue sometida a reflujo durante 20 hs. La mezcla de reacción se enfrió hasta temperatura ambiente y los solventes se evaporaron. Se agregó NaOH acuoso 10% y la mezcla se extrajo con cloroformo (3x 10 ml). Los extractos orgánicos combinados se secaron sobre CaCl₂, se filtraron y se evaporaron. El residuo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con una mezcla de éter de petróleo ligero y acetato de etilo (6: 1,3: 1). Se recolectó una fracción con un valor de R_f de 0,4 (Hexano-EtOAc, 2: 1) para obtener la lactama 18 (0,12 g, 39%) como un sólido incoloro con p.f. 176-177 °C.

¹H NMR (CDCl₃, TMS) δ: 0,89 (3H, d, 5,8 Hz, 7-CH₃); 0,75-1,05 (3H, m, CH-anillo); 0,99 (3H, s, 5-CH₃); 1,20 (3H, s, 1-CH₃); 1,24-1,36 (1H, m, CH-anillo); 1,45-1,60 (2H, m, CH-anillo); 1,60-1,84 (1H, m, 7-CH); 2,14 (2H, s, 4-CH₂) y 5,40 ppm (1H, br s, NH).

d) Clorhidrato de 1,5,7-trimetil-2-azabicyclo[3,3,1]nonano (1-9).

Se agregó una solución de borano 1 M en tetrahidrofurano (2 ml, 2 mmol) a una solución de la lactama 18 (0,07 g, 0,385 mmol) en tetrahidrofurano (2 ml) y fue sometida a reflujo durante 15 hs. La mezcla se enfrió hasta temperatura ambiente y se acidificó por adición de HCl acuoso concentrado. Los solventes se evaporaron bajo presión reducida y se agregó hexano (10 ml) y NaOH acuoso 20% (10 ml) al residuo. La fase orgánica se separó y la fase

acuosa se extrajo con hexano (2x 5 ml). Las fases orgánicas combinadas se lavaron con NaCl acuoso saturado (10 ml) y se secaron sobre NaOH. El extracto se filtró y se agregó solución de HCl seco en éter dietílico. El solvente se evaporó y el residuo se trató con éter dietílico (5 ml). El precipitado se recolectó sobre un filtro para obtener el clorhidrato de amina 1-9 (0,02 g, 25%) como un sólido incoloro.

¹H NMR (CDCl₃, TMS) δ: 0,80-1,85 (7H, m, CH-anillo); 0,88 (3H, d, 6,5 Hz, 7-CH₃); 0,96 (3H, s, 5-CH₃); 1,50 (3H, s, 1-CH₃); 2,10-2,40 (2H, m, 7-CH y 8-CH); 3,15-3,35 y 3,30-3,55 (ambos 1H, m, 3-CH₂); 9,15 y 9,55 ppm (ambos 1H, br s, NH₂⁺).

Esquema y tabla de síntesis general para los compuestos 1-azaspiro (que pertenecen a la estructura de la fórmula 3 del Resumen).

Esquema 3

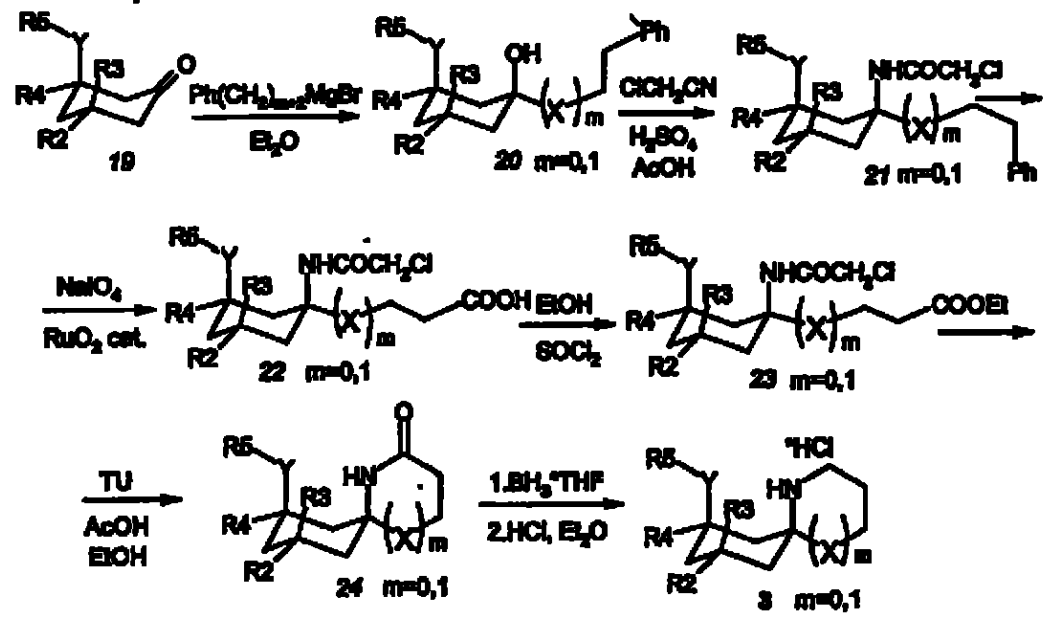


Tabla 3:

N°	N° en la	R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n
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MRZ	descripción								
	de síntesis								
2/1004	3-1	$-(CH_2)_3$, (m = 0)	Me	Me	Me	H	CH ₂	-	
2/1013	3-2	$-(CH_2)_4$, (m = 1)	Me	Me	Me	H	CH ₂		

Ejemplo 10.

Clorhidrato de 7,7,9,9-tetrametil-1-azaspiro [4,5]decano (3-1).

a) 3,3,5,5-tetrametil-L-(2-feniletil)ciclohexanol (20-1).

Se agregó una solución de 3,3,5,5-pentametilciclohexanona (19) (1,54 g, 10 mmol) en éter dietílico (10 ml) a una solución 0,85 M de bromuro de feniletilmagnesio en éter dietílico (25 ml, 20 mmol), bajo enfriamiento sobre baño de hielo. La mezcla resultante se agitó durante 0,5 hs y se agregó exhaustivamente NH₄Cl acuoso saturado (30 ml). La fase orgánica se separó y la fase acuosa se lavó con éter dietílico (2X20 ml). Las fases orgánicas combinadas se lavaron con una solución de NaCl acuoso saturado (20 ml) y se secaron sobre MgSO₄. La filtración y evaporación de la solución permitió obtener un residuo que se purificó por cromatografía Instantánea sobre gel de sílice eluyendo con una mezcla de éter de petróleo ligero y acetato de etilo (10: 1) para obtener el ciclohexanol 20-1 (2,1 g, 82%) como un aceite.

¹H-NMR (CDCl₃, TMS) δ: 0,91 (6H, s, 3,5-CH₃); 1,23 (6H, s, 3,5-CH₃); 1,0-1,6 (7H, m, protones y OH del anillo); 1,6-1,8 (2H, m, PhCH₂CH₂); 2,6-2,8 (2H, m, PhCH₂CH₂) y 7,0-7,4 ppm (5H, m, Ph).

b) 2-cloro-N-[3,3,5,5-tetrametil-1-(2-feniletil)ciclohexil]acetamida (21-1).

Se preparó con un rendimiento del 96% a partir del ciclohexanol 20-1 de acuerdo con el procedimiento descrito en el Ejemplo 8c. Un aceite incoloro.

$^1\text{H-NMR}$ (CDCl_3 , TMS) δ : 0,93 (6H, s, 3,5- CH_3); 1,17 (6H, s, 3,5- CH_3); 1,0-1,5 (4H, m, 4- CH_2 , 2,6-CH); 2,0-2,2 (2H, m, PhCH_2CH_2); 2,24 (2H, d, 14 Hz, 2,6-CH); 2,5-2,6 (2H, m, PhCH_2CH_2); 3,90 (2H, s, CH_2Cl); 6,60 (1 H, br s, NH) y 7,1-7,3 ppm (5H, m, Ph).

c) Ácido 3-{1-[(2-cloroacetil)amino]-3,3,5,5-tetrametilciclohexil}propanoico (22-1).

Se preparó con un rendimiento del 53% a partir de la amida 21-1 de acuerdo con el procedimiento descrito en el Ejemplo 9a. Cristales incoloros con p.f. 130-131 °C.

$^1\text{H-NMR}$ (CDCl_3 , TMS) δ : 0,92 (6H, s, 3,5- CH_3); 1,17 (6H, s, 3,5- CH_3); 1,0-1,5 (4H, m, 4- CH_2 , 2,6-CH,); 2,0-2,4 (6H, m, OCCH_2CH_2 , 2,6-CH); 3,97 (2H, s, CH_2Cl) y 6,6 ppm (1H, br s, NH);

d) 3-{1-[(2-cloroacetil)amino]-3,3,5,5-tetrametilciclohexil}propanoato de etilo (23-1).

Se preparó con un rendimiento del 82% a partir del ácido 22-1 de acuerdo con el procedimiento descrito en el Ejemplo 9b. Un aceite.

$^1\text{H-NMR}$ (CDCl_3 , TMS) δ : 0,91 (6H, s, 3,5- CH_3); 1,14 (6H, s, 3,5- CH_3); 1,25 (3H, t, 7 Hz, $\text{CH}_3\text{CH}_2\text{O}$); 0,8-1,6 (4H, m, 4- CH_2 , 2,6-CH); 2,0-2,4 (6H, m, OCCH_2CH_2 , 2,6-CH); 3,95 (2H, s, CH_2Cl); 4,11 (2H, q, 7 Hz, $\text{CH}_3\text{CH}_2\text{O}$) y 6,50 ppm (1H, br s, NH).

e) 7,7,9,9-tetrametil-1-azaspiro[4,5]decan-2-ona (24-1).

Se preparó con un rendimiento del 54% a partir del éster 23-1 de acuerdo con el procedimiento descrito en el Ejemplo 9c. Un sólido incoloro con p.f. 158-160 °C.

$^1\text{H-NMR}$ (CDCl_3 , TMS) δ : 1,01 (12H, s, 7,9-CH₃); 1,19 (1H, d, 14 Hz, 8-

CH); 1,27 (1H, d, 14 Hz, 8-CH); 1,45 (4H, s, 6,10-CH₂); 2,02 (2H, t, 7,5 Hz, 4-CH₂); 2,36 (2H, t, 7,5 Hz, 3-CH₂) y 5,8 ppm (1H, br s, NH).

f) 7,7,9,9-tetrametil-1-azaspiro [4,5] decano clorhidrato (3-1).

Se preparó con un rendimiento del 76% a partir de la espirolactama 24-1 de acuerdo con el procedimiento descrito en el Ejemplo 9d. Sólido incoloro.

¹H-NMR (CDCl₃, TMS) δ: 1,01 (6H, s, 7,9-CH₃); 1,08 (6H, s, 7,9-CH₃); 1,23 (1 H, d, 14 Hz, 8-CH); 1,35 (1H, d, 14 Hz, 8-CH); 1,8 (4H, br s, 6, 10-CH₂); 2,0-2,2 (4H, m, 3,4-CH₂); 3,3 (2H, br s, 2-CH₂) y 9,4 ppm (2H, br s, NH₂⁺).

Ejemplo 11.

Clorhidrato de 8,8,10,10-tetrametil-1-azaspiro[5,5]undecano (3-2).

a) 3,3,5,5-tetrametil-1-(3-fenilpropil)ciclohexanol (20-2).

Se preparó con un rendimiento del 90% a partir de la cetona 19 de acuerdo con el procedimiento descrito en el Ejemplo 10a. Un aceite incoloro.

¹H-NMR (CDCl₃, TMS) δ: 0,86 (6H, s, 3,5-CH₃); 1,19 (6H, s, 3,5-CH₃); 1,0-1,8 (11 H, m, protones, OH y PhCH₂CH₂CH₂ del anillo); 2,60 (2H, t, 7,5 Hz, PhCH₂CH₂CH₂) y 7,1-7,4 ppm (5H, m, Ph).

b) 2-cloro-N-[3,3,5,5-tetrametil-1-(3-fenilpropil)ciclohexil]acetamida (21-2).

Se preparó con un rendimiento del 37% a partir del ciclohexanol 20-2 de acuerdo con el procedimiento descrito en el Ejemplo 8c. Sólido incoloro con p.f. 83-85 °C.

¹H-NMR (CDCl₃, TMS) δ: 0,89 (6H, s, 3,5-CH₃); 1,13 (6H, s, 3,5-CH₃); 0,9-1,9 (8H, m, 4-CH₂, 2, 6-CH y PhCH₂CH₂CH₂); 2,15 (2H, d, 14,5 Hz, 2,6-CH); 2,56 (2H, t, 8 Hz, PhCH₂CH₂CH₂); 3,93 (2H, s, CH₂Cl); 6,5 (1 H, br s, NH) y 7,1-7,4 ppm. (5H, m, Ph).

c) Ácido 4-{1-[(2-cloroacetil)amino]-3,3,5,5-tetrametilciclohexil} butanoico (22-2).

Se preparó con un rendimiento del 74% a partir de la amida 21-2 de acuerdo con el procedimiento descrito en el Ejemplo 9a. Sólido incoloro con p.f. 140-141 °C.

¹H-NMR (CDCl₃, TMS) δ: 0,91 (6H, s, 3,5-CH₃); 1,15 (6H, s, 3,5-CH₃); 0,9-1,8 (8H, m, 4-CH₂, 2, 6-CH, OCCH₂CH₂CH₂); 2,17 (2H, d, 14,2 Hz, 2,6-CH); 2,33 (2H, t, 7,2 Hz, OCCH₂CH₂CH₂); 3,97 (2H, s, CH₂Cl) y 6,6 ppm. (1H, br s, NH).

d) 4-{1-[(2-cloroacetil)amino]-3,3,5,5-tetrametilciclohexil} butanoato de etilo (23-2).

Se preparó con un rendimiento del 98% a partir del ácido 22-2 de acuerdo con el procedimiento descrito en el Ejemplo 9b. Un aceite incoloro.

¹H-NMR (CDCl₃, TMS) δ: 0,91 (6H, s, 3,5-CH₃); 1,14 (6H, s, 3,5-CH₃); 1,25 (3H, t, 7 Hz, CH₃CH₂O); 0,9-1,8 (4H, m, 4-CH₂, 2, 6-CH, OCCH₂CH₂CH₂); 2,18 (2H, d, 15 Hz, 2,6-CH); 2,26 (2H, t, 8,4 Hz, OCCH₂CH₂CH₂); 3,95 (2H, s, CH₂Cl); 4,13 (2H, q, 7 Hz, CH₃CH₂O) y 6,52 ppm. (1H, br s, NH).

e) 8,8,10,10-tetrametil-1-azaspiro[5,5]undecan-2-ona (24-2).

Se preparó con un rendimiento del 76% a partir del éster 23-2 de acuerdo con el procedimiento descrito en el Ejemplo 9c. Sólido incoloro con p.f. 126-128° C.

¹H-NMR (CDCl₃, TMS) δ: 1,01 (6H, s, 8, 10-CH₃); 1,09 (6H, s, 8, 10-CH₃); 1,19 y 1,30 (ambos 1 H, d, 14 Hz, 9-CH₂); 1,39 y 1,46 (ambos 2H, d, 14 Hz, 7,11-CH₂); 1,63-1,90 (4H, m, 4,5-CH₂); 2,33 (2H, t, 6 Hz, 3-CH₂) y 5,8 ppm. (1H, br s, NH).

f) Clorhidrato de 8, 8, 10, 10-tetrametil-1-azaspiro[5,5]undecano (3-2).

Se preparó con un rendimiento del 45% a partir de la espirolactama 24-2 de acuerdo con el procedimiento descrito en el Ejemplo 9d. Un sólido incoloro.

$^1\text{H-NMR}$ (CDCl_3 , TMS) δ : 1,01 (6H, s, 8, 10- CH_3); 1,09 (6H, s, 8, 10- CH_3); 1,0-2,1 (12H, m, 3,4, 5,7,9,11- CH_2); 3,1 (2H, br s, 2- CH_2) y 9,1 ppm (2H, br s, NH_2^+).

Esquema y tabla de síntesis general para 6-azatriciclo[6,3,1,0^{1,6}]dodecanos (que pertenecen a la estructura de la fórmula 2 del Resumen).

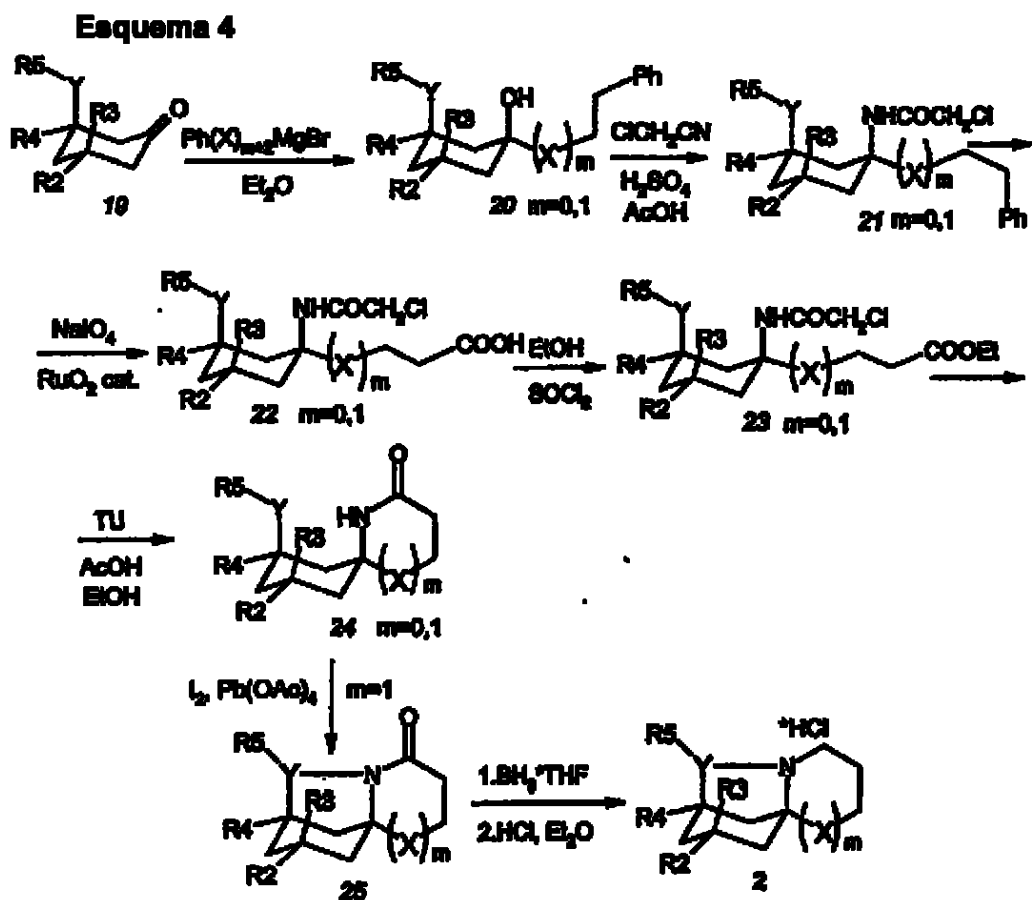


Tabla 4:

N°	N° en la R	R ¹	R ²	R ³	R ⁴	R ⁵	Y	n
MRZ	descripción	de síntesis						
2047	2	-(CH ₂) ₄ , (m = 1)	Me	Me	Me	H	CH	0

Ejemplo 12.

Clorhidrato de 8,10,10-trimetil-6-azatriciclo[6,3,1,0^{1,8}]dodecano (2).

a) 8,10,10-trimetil-6-azatriciclo[6,3,1,0^{1,8}]dodecan-5-ona (25).

Se preparó con un rendimiento del 20% a partir de la espirolactama 24-2 de acuerdo con el procedimiento descrito en el Ejemplo 3b. Un aceite.

¹H-NMR (CDCl₃, TMS) δ: 0,95 (3H, s, 10-CH₃); 1,00 (3H, s, 10-CH₃); 1,08 (3H, s, 8-CH₃); 1,20 (1H, d, 12 Hz) y 1,25-1,70 (5H, m, 9,11,12-CH₂); 1,75-1,90 (4H, m, 2, 3-CH₂); 2,25-2,40 (2H, m, 4-CH₂); 3,14 y 3,43 ppm (ambos 1H, d, 12,0 Hz, 7-CH₂).

b) Clorhidrato de 8,10,10-trimetil-6-azatriciclo [6,3,1,0^{1,8}]dodecano (2).

Se preparó con un rendimiento del 36% a partir de la lactama 25 de acuerdo con el procedimiento descrito en el Ejemplo 9d. Un sólido incoloro.

¹H-NMR (CDCl₃, TMS) δ: 0,85-2,45 (12H, m, 2,3,4,9,11,12-CH₂); 0,99 (3H, s, 10-CH₃); 1,05 (3H, s, 10-CH₃); 1,19 (3H, s, 8-CH₃); 3,12 (2H, m, 5-CH₂); 3,20-3,75 (2H, m, 7-CH₂) y 9,05 ppm (1H, br s, NH⁺).

COMPOSICIONES FARMACÉUTICAS

Los ingredientes activos de la invención, junto con uno o más adyuvantes, vehículos o diluyentes convencionales, se pueden conformar en la forma de composiciones farmacéuticas y dosificaciones unitarias de las mismas, y en dichas formas se pueden emplear como sólidos, tal como

tabletas recubiertas o no recubiertas o cápsulas rellenas, o como líquidos, tal como soluciones, suspensiones, emulsiones, elixires o cápsulas rellenas con las mismas, todos para uso oral; en la forma de supositorios o cápsulas para una administración rectal o en la forma de soluciones inyectables estériles para uso parenteral (incluyendo la vía intravenosa o subcutánea). Dichas composiciones farmacéuticas y formas de dosificación unitaria de las mismas pueden comprender ingredientes convencionales o nuevos en proporciones convencionales o especiales, con o sin compuestos o principios activos adicionales, y dichas formas de dosificación unitaria pueden contener cualquier cantidad eficaz adecuada de ingrediente activo compatible con el rango de dosificación diario pretendido que se usará. Las tabletas que contienen entre veinte (20) y cien (100) miligramos de ingrediente activo o, más generalmente, entre diez (10) y doscientos cincuenta (250) miligramos por tableta, son entonces formas de dosificación unitaria representativas adecuadas.

MÉTODO DE TRATAMIENTO

Debido a su alto grado de actividad y su baja toxicidad, junto con el hecho de presentar un índice terapéutico muy favorable, los principios activos de la invención pueden ser administrados a un sujeto, por ejemplo, un animal vivo (incluyendo el hombre), que lo necesita, para tratar, aliviar o mejorar, paliar o eliminar una enfermedad o afección que sea susceptible a los mismos o, representativamente, una de las enfermedades o afecciones enumeradas en otra parte de esta solicitud, preferentemente de forma concurrente, simultánea o junto con uno o más excipientes, vehículos o diluyentes aceptables para uso farmacéutico, en especial y preferentemente en la forma de una composición farmacéutica de los mismos, ya sea por vía oral, rectal o parenteral (incluyendo

las vías intravenosa y subcutánea) o, en algunos casos, aún la vía tópica, en una cantidad eficaz. Los rangos de dosificación adecuados comprenden 1-1000 miligramos por día, preferentemente 10-500 miligramos por día y en especial 50-500 miligramos por día, dependiendo como siempre del modo exacto de administración, la forma en que son administrados, la enfermedad a la que están dirigidos, el sujeto a tratar y el peso corporal del sujeto, y la preferencia y experiencia del médico o veterinario de cabecera.

EJEMPLOS DE COMPOSICIONES FARMACÉUTICAS REPRESENTATIVAS

Los productos de reacción pueden ser procesados en tabletas, tabletas recubiertas, cápsulas, soluciones de goteo, supositorios, preparaciones para inyección e infusión y semejantes con la ayuda de los solventes, agentes auxillares y vehículos utilizados comúnmente, y pueden ser aplicados para fines terapéuticos por las rutas oral, rectal, parenteral y otras vías. A continuación se describen las composiciones farmacéuticas representativas.

(a) Las tabletas adecuadas para una administración oral que contienen al ingrediente activo se pueden preparar utilizando las técnicas de conformación de tabletas convencionales.

(b) Para supositorios, se puede emplear cualquiera de las bases comunes para supositorios para incorporar en las mismas utilizando los procedimientos comunes el ingrediente activo, tal como un polietilenglicol, que es un sólido a la temperatura ambiente normal pero que se funde a la temperatura corporal.

(c) Para las soluciones estériles parenterales (incluyendo la intravenosa y la subcutánea), se emplea el ingrediente activo junto con los ingredientes

convencionales en las cantidades habituales tal como, por ejemplo, cloruro de sodio y agua doblemente destilada c.s., de acuerdo con procedimientos convencionales, tal como filtración, rellenado aséptico en ampollas o en botellas para goteo IV y autoclave para la esterilización.

Otras composiciones farmacéuticas adecuadas resultarán evidentes para el especialista en el arte.

Los siguientes ejemplos se ofrecen, otra vez, solamente a efectos ilustrativos y no deben ser considerados como limitaciones de la invención.

EJEMPLO 1

Formulación de tabletas

A continuación se muestra una formulación adecuada para una tableta que contiene 10 miligramos de ingrediente activo:

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

EJEMPLO 2

Formulación de tabletas

A continuación se muestra otra formulación adecuada para una tableta que contiene 100 mg:

	mg
Ingrediente activo	100

Almidón de papa	20
Polivinilpirrolidona	10

Recubiertas con una película y coloreada.

El material de la película de recubrimiento consiste de:

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

EJEMPLO 3

Formulación de cápsulas

A continuación se muestra una formulación adecuada para una cápsula que contiene 50 miligramos de ingrediente activo:

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

rellenado en una cápsula de gelatina.

EJEMPLO 4

Solución para inyecciones

A continuación se muestra una formulación adecuada para una solución inyectable que contiene un por ciento de ingrediente activo:

Ingrediente activo, mg	12
Cloruro de sodio, mg	8
Agua estéril hasta completar en ml	1

EJEMPLO 5

Formulación líquida oral

A continuación se muestra una formulación adecuada para 1 litro de una mezcla líquida que contiene 2 miligramos de ingrediente activo en un mililitro de la mezcla:

	g
Ingrediente activo	2
Sacarosa	250
Glucosa	300
Sorbitol	150
Saborizante de naranja	10
Amarillo Sunset.	
Agua purificada hasta completar un total de 1000 ml	

EJEMPLO 6

Formulación líquida oral

A continuación se muestra otra formulación adecuada para 1 litro de una mezcla líquida que contiene 20 miligramos de ingrediente activo en un mililitro de mezcla:

	g
Ingrediente activo	20,00

Tragacanto	7,00
Glicerol	50,00
Sacarosa	400,00
Metilparabeno	0,50
Propilparabeno	0,05
Saborizante de grosella negra	10,00
Color rojo soluble	0,02
<u>Agua purificada hasta completar un total de 1000 ml</u>	

EJEMPLO 7

Formulación líquida oral

A continuación se muestra otra formulación adecuada para 1 litro de una mezcla líquida que contiene 2 miligramos de ingrediente activo en un mililitro de mezcla:

	<u>g</u>
Ingrediente activo	2
Sacarosa	400
Tintura de piel de naranja amarga	20
Tintura de piel de naranja dulce	15
<u>Agua purificada hasta completar un total de 1000 ml</u>	

EJEMPLO 8

Formulación de aerosol

Una solución de 180 g de aerosol contiene:

	<u>g</u>
Ingrediente activo	10
Ácido oleico	5

Etanol	81
Agua purificada	9
Tetrafluoroetano	75

se introducen 15 ml de la solución en recipientes de aluminio para aerosol, se tapan con una válvula dosificadora, se purgan con 3,0 bar.

EJEMPLO 9

Formulación TDS

Una solución de 100 g contiene:	
	<u>g</u>
Ingrediente activo	10,0
Etanol	57,5
Propilenglicol	7,5
Dimetilsulfóxido	5,0
Hidroxietilcelulosa	0,4
Agua purificada	19,6

se colocan 1,8 ml de la solución sobre una tela recubierta con una película de soporte adhesiva. El sistema se cierra con un protector que será retirado antes de su uso.

EJEMPLO 10

Formulación de nanopartículas

Una composición de 10 g de nanopartículas de polibutirianoacrilato contiene:

	<u>g</u>
Ingrediente activo	1,00
Poloxámero	0,10

Butilcianoacrilato	8,75
Manitol	0,10
Cloruro de sodio	0,05

Las nanopartículas de polibutilcianoacrilato se preparan por polimerización en emulsión en una mezcla de agua/HCl 0,1 N/etanol como medio de polimerización. Finalmente, se liofilizan las nanopartículas en la suspensión bajo vacío.

FARMACOLOGÍA - RESUMEN

Los principios activos de la presente invención, y las composiciones farmacéuticas con los mismos y el método de tratamiento con los mismos, se caracterizan por sus propiedades ventajosas e inesperadas únicas, que vuelve no evidente al "objeto como un todo", reivindicado en la presente. Los compuestos, y las composiciones farmacéuticas con los mismos, han presentado las siguientes propiedades y características valiosas en procedimientos de prueba confiables que son de aceptación general: son sistémicamente activos, son antagonistas no competitivos del receptor de NMDA con una cinética rápida de bloqueo/desbloqueo y una fuerte dependencia del voltaje y son, por consiguiente, de utilidad para tratar, eliminar, paliar, aliviar y mejorar las afecciones que responden a los mismos, por aplicación o administración a dicho animal vivo huésped para el tratamiento de un amplio rango de trastornos del CNS que comprenden alteraciones de la transmisión glutaminérgica.

Estos compuestos también son antagonistas sistémicamente activos, no competitivos de 5HT₃ y del receptor nicotínico neuronal y son, por lo tanto, de utilidad para tratar, eliminar, paliar, aliviar y mejorar de las afecciones que

responden a los mismos, por aplicación o administración a dicho animal vivo huésped para el tratamiento de un amplio rango de trastornos del CNS que comprenden alteraciones de la transmisión serotoninérgica o nicotínica.

Métodos

Estudios de unión al receptor

Se decapitaron ratas Sprague-Dawley macho (200-250 g) y se retiraron rápidamente los cerebros. Se disecó la corteza y se homogeneizó en 20 volúmenes de sacarosa helada 0,32 M usando un homogeneizador de vidrio-Teflon. El homogenato se centrifugó a 1000 xg durante 10 min. Se descartó el pelet y el sobrenadante se centrifugó a 20.000 xg durante 20 min. El pelet resultante se volvió a suspender en 20 volúmenes de agua destilada y se centrifugó durante 20 min a 8000 xg. A continuación, el sobrenadante y la capa leuco-plaquetaria se centrifugaron a 48.000 xg durante 20 min en presencia de Tris-HCl 50 mM, pH 8,0. El pelet se resuspendió y se centrifugó dos a tres veces más a 48.000 xg durante 20 min en presencia de Tris-HCl 50 mM, pH 8,0. Todos los pasos de centrifugación se llevaron a cabo a 4 °C. Después de resuspender en 5 volúmenes de Tris-HCl 50 mM, pH 8,0, la suspensión de membranas se congeló rápidamente a -80 °C.

El día del ensayo, las membranas se descongelaron y se lavaron cuatro veces por resuspensión en Tris-HCl 50 mM, pH 8,0, y centrifugación a 48.000 xg durante 20 min y finalmente se volvieron a suspender en Tris-HCl 50 mM, pH 7,4. La cantidad de proteína en la preparación final de membranas (250-500, µg/ml) se determinó de acuerdo con el método de Lowry et al. (1951). Las incubaciones se iniciaron por adición de [³H]-(+)-MK-801 (23,9 Ci/mmol, 5 nM, Dupont NEN) a viales que contenían glicina (10 µM), glutamato (10 µM) y 125-

250 µg de proteína (volumen total de 0,5 ml) y distintas concentraciones de los agentes evaluados (10 concentraciones por duplicado). Las incubaciones continuaron a temperatura ambiente durante 120 min (se llegó al equilibrio bajo las condiciones usadas). La unión no específica se definió por la adición de (+)-MK-801 (10 µM) no marcado. Las incubaciones se terminaron usando un sistema de filtros Millipore. Las muestras se lavaron dos veces con 4 ml de solución amortiguadora de ensayo helada sobre filtros de fibra de vidrio (Schleicher & Schuell) bajo vacío constante. Después de separar y lavar los filtros, se colocaron en líquido de centelleo (5 ml; Ultima Gold) y se determinó la radioactividad retenida sobre los filtros con un contador de líquido de centelleo convencional (Hewlett Packard, Analizador de Líquido de Centelleo). La Kd de [³H]-(+)-MK-801 de 4,6 nM se determinó mediante análisis Scatchard y se usó de acuerdo con la relación de Cheng Prussoff para calcular la afinidad de los desplazamientos como valores de Kd. La mayoría de los antagonistas fue evaluada en 3 a 7 experimentos separados.

Expresión de subtipos de los receptores de NMDA y nicotínicos neuronales en oocitos de Xenopus

Se anestesiaron hembras maduras de *Xenopus laevis* con Tricaina 0,2% sobre hielo durante 15 min antes de la cirugía. Se retiraron los oocitos y se incubaron en colagenasa (tipo II) 2 mg/ml en solución de Ringer para oocitos libre de Ca²⁺ (NaCl 82,5 mM, KCl 2 mM, MgCl₂ 2 mM, HEPES 5 mM, pH 7,5) durante 30 min a temperatura ambiente y se lavaron cuidadosamente con OR-2 (NaCl 100 mM, KCl 2 mM, MgCl₂ 1 mM, CaCl₂ 2 mM, HEPES 5 mM, pH 7,5). La capa remanente de células foliculares se separó manualmente con pinzas finas y los oocitos se mantuvieron en OR-2. El ARN se disolvió en agua

destilada estéril tratada con DEPC. El ARN de la subunidad NR1a NMDA se mezcló 1: 1 con el ARN de la subunidad NR2a. De manera similar, se mezcló el ARN de la subunidad $\alpha 4$ del receptor nicotínico neuronal 1: 1 con el ARN de la subunidad $\beta 2$. Se inyectaron 50 a 100 nanolitros de cada mezcla de ARN en el citoplasma de los oocitos usando un inyector de nanolitros (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 usando el método estándar de fijación de voltaje de dos electrodos (amplificador GeneClamp 500), 2-6 días después de la inyección. Los electrodos tenían una resistencia entre 0,2 y 0,4 M Ω y se llenaron con KCl 3 M. Los registros se efectuaron en una cámara adaptada con tiempos de intercambio de 2 a 3 segundos. La solución del baño se preparó sin Ca^{2+} , para evitar las corrientes de Cl^- inducidas por Ca^{2+} (NaCl 100 mM, KCl 2 mM, HEPES 5 mM, BaCl_2 2 mM, pH 7,35). Los receptores de NMDA fueron activados por co-aplicación manual de glutamato 1 mM y glicina 10 μM durante 30-40 segundos cada 2 a 3 minutos a los oocitos fijados en -70 mV. Los receptores nicotínicos neuronales fueron activados por aplicación de acetilcolina 100 μM durante 20-30 segundos cada 2 a 3 min a los oocitos fijados en -70mV. Después de obtener respuestas control estables, se obtuvieron curvas completas de concentración-respuesta con los antagonistas preincubando 6-7 concentraciones diferentes a intervalos de log 3.

Solamente se aceptaron los resultados de las células estables para su inclusión en el análisis final, es decir las que muestran al menos un 50% de recuperación de respuestas a NMDA después de eliminar el antagonista

evaluado. A pesar de ello, la recuperación de las acciones de la droga no siempre fue del 100% debido a desensibilizaciones o acumulaciones menores en algunas células. Cuando ese era el caso, esto siempre era compensado basando el % de antagonismo a cada concentración en ambos grupos control y recuperación y suponiendo un transcurso de tiempo lineal para esta desensibilización. Todos los antagonistas fueron evaluados a nivel de bloqueo en el estado estacionario con 6 a 7 concentraciones en al menos 4 células. El bloqueo del equilibrio se alcanzó con 1 a 3 aplicaciones de agonista, dependiendo de la concentración de antagonista.

Los experimentos cinéticos se efectuaron aplicando varias concentraciones de amino-alquilciclohexanos insaturados (habitualmente 5 en un régimen de dosificación de 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 expresan receptores NR1a/2a. El sistema de perfusión usado para estos experimentos fue un sistema carrusel (continuo) de oocitos modificado que permite una rápida incorporación y elución de agonista y antagonista con tiempos de cambio menores que un segundo. Se efectuaron ajustes exponenciales usando el programa TIDA para Windows y la mayoría de las respuestas eran bien ajustadas con un solo exponencial. Este mismo sistema se usó para estudiar la dependencia de voltaje del bloqueo, pero en este caso la solución del baño contenía ácido flufenámico (100 μ M) para bloquear las corrientes endógenas de Cl^- activadas por voltaje y activadas por Ca^{2+} . Además, el Ba^{2+} (2 mM) se sustituyó por concentraciones bajas de Ca^{2+} (0,2 mM). Después del bloqueo del equilibrio por concentraciones mayores de antagonista (normalmente alrededor de 10 veces el valor de la IC_{50}), se

aplicaron cinco rampas de -70 mV a +30 mV sobre un período de dos segundos. Se aplicaron rampas similares en soluciones de baño y de glutamato sin antagonista, ambos antes de la aplicación del antagonista y después de la recuperación de respuestas. Las corrientes de fuga en ausencia de glutamato se sustrajeron de las curvas de glutamato y glutamato más antagonista. Después se determinó la dependencia del voltaje por comparación de las curvas de glutamato y glutamato más antagonista.

Patch Clamp para NMDA y nicotina

Se obtuvieron hipocampos de embriones de rata (E20 a E21) y fueron transferidos luego a solución salina de Hank libre de calcio y magnesio (Gibco) sobre hielo. Las células se disociaron mecánicamente en DNAase 0,05%/ovomucoide 0,3% (Sigma) después de una pre-incubación de 8 minutos con tripsina 0,66%/DNAase 0,1% (Sigma). Las células disociadas se centrifugaron luego a 18 xg durante 10 minutos, se volvieron a suspender en medio mínimo esencial (Gibco) y se plaquearon a una densidad de 150.000 células cm⁻² sobre cajas de Petri de plástico (Falcon) recubiertas previamente con poli-L-lisina (Sigma). Las células se alimentaron con medio mínimo esencial regulado con NaHCO₃/HEPES suplementado con suero fetal bovino 5% y suero de caballo (Gibco) 5% y se incubaron a 37 °C con CO₂ 5% y 95% de humedad. El medio se cambió completamente después de inhibir toda mitosis glial adicional con citosina-D-arabinofuranósido (20 M Sigma) después de 7 días aproximadamente *in vitro*. Posteriormente, el medio se cambió parcialmente dos veces por semana.

Los registros de *patch clamp* se obtuvieron a partir de estas neuronas con electrodos de vidrio pulido (4-6 m) en la modalidad de célula completa a

temperatura ambiente (20-22 °C) con la ayuda de un amplificador EPC-7 (List). Las sustancias de prueba se aplicaron cambiando los canales de un sistema de superfusión rápida adaptado con un flujo de salida común (tiempos de intercambio de 10-20 ms). La solución intracelular tenía el siguiente contenido (mM): CsCl (120), TEACl (20), EGTA (10), MgCl₂ (1), CaCl₂ (0,2), glucosa (10), ATP (2), AMPc (0,25); el pH se ajustó en 7,3 con CsOH o HCl. Las soluciones extracelulares tenían la siguiente composición básica (mM): NaCl (140), KCl (3), CaCl₂ (0,2), glucosa (10), HEPES (10), sacarosa (4,5), tetrodotoxina (TTX 3*10⁻⁴). Todas las soluciones contenían glicina (1 M): una concentración suficiente como para causar alrededor de un 80-85% de activación de los receptores de glicina. Solamente se aceptaron los resultados de las células estables para su inclusión en el análisis final, es decir, después de la recuperación de respuestas a NMDA en al menos un 75% de su depresión por los antagonistas evaluados.

Patch clamp para 5-HT₃

Se adquirieron células N1E-115 de la Colección Europea de Cultivos Celulares (ECACC, Salisbury, Reino Unido) y se guardaron a -80 °C hasta el momento del uso. Las células se plaquearon a una densidad de 100.000 células cm⁻² sobre cajas de Petri de plástico (Falcon) y se alimentaron con medio mínimo esencial (MEM) amortiguador con NaHCO₃/HEPES suplementado con suero fetal bovino (Gibco) 15% y se incubaron a 37 °C con CO₂ 5% con un 95% de humedad. El medio se cambió completamente todos los días. Una vez cada tres días, se volvieron a sembrar células sobre cajas de Petri nuevas después de tratamiento con tripsina-EDTA (1% en PBS), resuspensión en MEM y centrifugación a 1000 rpm durante cuatro minutos.

Los registros del *patch clamp* a -70 mV se efectuaron con células desprendidas, 2-3 días después de la siembra, con electrodos de vidrio pulido (2-6 M Ω) en la modalidad de célula completa a temperatura ambiente (20-22 °C) con un amplificador EPC-7 (List). La solución intracelular tenía el siguiente contenido (mM): CaCl (130), HEPES (10), EGTA (10), MgCl₂ (2), CaCl₂ (2), K-ATP (2), Tris-GTP (0,2), D-glucosa (10); el pH se ajustó en 7,3 con CsOH o HCl. Las soluciones extracelulares tenían la siguiente composición básica (mM): NaCl (124), KCl (2,8), HEPES (10), el pH se ajustó en 7,3 con NaOH o HCl.

Una vez establecida la configuración de célula completa, las células se desprendieron del sustrato de vidrio y se les aplicó serotonina (10 μ M), memantina y derivados de aminoalquilciclohexano insaturado a distintas concentraciones usando un dispositivo de superfusión rápida. Se usó una pipeta de aplicación de cilindro doble impulsado por un transductor piezoeléctrico para exponer la célula desprendida a una solución que contenía serotonina o sin serotonina. Se aplicó un pulso de serotonina de dos segundos cada 60 segundos. Los antagonistas putativos se disolvieron en agua bidestilada y se disolvieron con la solución hasta la concentración deseada. Solamente se aceptaron los resultados de las células estables para su inclusión en el análisis final, es decir, las que presentaban una recuperación de al menos un 50% de respuestas a la serotonina después de eliminar los compuestos. A pesar de ello, la recuperación de las acciones de la droga no siempre era del 100% debido a la desensibilización en algunas células (< = 10% sobre un período de 10 minutos). Cuando sucedía esto, siempre era compensado basando el porcentaje de antagonismo a cada concentración en ambos grupos

control y recuperación y suponiendo un transcurso de tiempo lineal para esta desensibilización. Todos los antagonistas fueron evaluados a nivel de bloqueo en el estado estacionario con 3 a 6 concentraciones en al menos cinco células. El bloqueo del equilibrio se alcanzó con 2 a 5 aplicaciones de agonista, dependiendo de la concentración de antagonista.

Actividad anticonvulsiva in vivo

Se usaron ratones NMR hembra (18-28 g), albergados en grupos de 5 por jaula, para las pruebas de electroshock máximo (MES) y deterioro motor. Todos los animales se mantuvieron con agua y alimentos *ad libitum* con un ciclo de luz-oscuridad de 12 horas (la luz se encendía a las 6 AM) y a temperatura controlada ($20 \pm 0,5$ °C). Todos los experimentos se llevaron a cabo entre las 10 AM y las 5 PM. Los agentes evaluados fueron inyectados por vía i.p. 30 min. Antes de inducir las convulsiones si no se establecía de otra manera (véase más adelante). Todos los compuestos se disolvieron en salina 0,9%.

La prueba de MES se realizó junto con pruebas para la acción miorelajante (reflejo de tracción) y coordinación motora (Rotarod). Para la prueba del reflejo de tracción, los ratones se colocaron con sus patas delanteras sobre una varilla horizontal y se les requería que colocaran las 4 patas sobre el alambre dentro de los 10 segundos. Para evaluar la ataxia (coordinación motora) los ratones se colocaron sobre un sistema de rotación con aceleración Rotarod y se les requería que permanecieran sobre la varilla durante 1 minuto. Se consideraba que solamente los ratones que no cumplieran con los criterios en las tres repeticiones de cada prueba presentaban miorelajación o ataxia, respectivamente. Estas pruebas eran seguidas de MES

(100 Hz, shock de 0,5 segundos de duración, Intensidad de shock de 50 mA, duración del impulso de 0,9 ms, Ugo Basile) aplicado a través de electrodos en la córnea. Se calificó la presencia de convulsiones tónicas (extensión tónica de las patas traseras con un ángulo mínimo con el cuerpo de 90). La meta era obtener valores de ED_{50} para todos los parámetros calificados (actividad anticonvulsiva y efectos secundarios motores) con el uso de la prueba de Litchfield Wilcoxon para respuestas a la dosis cuantitativa. Se usó el cociente entre los valores ED_{50} para efectos secundarios (ataxia o miorelajación) y los valores ED_{50} para antagonismo de convulsiones por electroshock como índice terapéutico (TI).

Análisis estadístico

Los valores de IC_{50} en los estudios con *patch clamp* y de unión se calcularon de acuerdo con la ecuación de cuatro parámetros logísticos usando el programa para computadora Grafit (Erithacus Software, Inglaterra). Después se determinó el valor de la K_i para los estudios de unión de acuerdo con Cheng y Prusoff. Los valores de unión que se muestran son las medias $\pm$ SEM de 3-5 determinaciones (cada una realizada por duplicado).

Se evaluaron 4-7 dosis de antagonistas en cada una de las pruebas *in vivo* (5-8 animales por dosis) para poder calcular los valores graduales de ED_{50} de acuerdo con el análisis probit (Litchfield y Wilcoxon) con corrección para 0% a 100% de efectos.

Los valores de ED_{50} se determinaron con límites de confianza del 95% (CI). Se usó el análisis de correlación del momento o producto de Pearson (Sigma Stat, Jandel Scientific) para comparar las potencias *in vitro* y la actividad anticonvulsiva *in vivo*.

RESULTADOS

Números de MRZ

Se usaron los números de MRZ para representar los nombres químicos. Los números de MRZ y sus respectivos nombres químicos se muestran en la "Lista de MRZ" y se hace referencia a los mismos en los Ejemplos

LISTA DE MRZ

MRZ	Nombre químico
2/1013	Clorhidrato de 8,8,10,10-tetrametil-1-azaspiro[5,5]undecano
2/1004	Clorhidrato de 7,7,9,9-tetrametil-1-azaspiro[4,5]decano
2/1003	Clorhidrato de 1,3,3,5,6-pentametil-6-azabicyclo[3.2.1]octano
2/1010	Clorhidrato de 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octano
2007	Clorhidrato de exo-3-etil-1,5-dimetil-6-azabicyclo[3.2.1]octano
2011	Clorhidrato de 1,exo-3,5-trimetil-6-azabicyclo[3.2.1]octano
2022	Clorhidrato de 5-etil-1,3,3-trimetil-6-azabicyclo[3.2.1]octano
2023	Clorhidrato de 5-etil-1,exo-3-dimetil-6-azabicyclo[3.2.1]octano
2028	Clorhidrato de 1,exo-3,5-trimetil-exo,endo-7-fenil-6-azabicyclo[3.2.1]octano
2029	Cloruro de 1,exo-3,5, exo, endo-7-tetrametil-6-azabicyclo[3.2.1]octano
2046	Clorhidrato de 1,5,exo-7-trimetil-2-azabicyclo[3,3,1]nonano
2047	Clorhidrato de 8,10,10-trimetil-8-azatriciclo[8,3,1,0 ^{1,6}]dodecano

Unión a MK-801

Todos los compuestos desplazaron [³H]-(+)-MK-801 con valores de Ki entre 1 y 83 µM (véase la Tabla 1).

Tabla 1

MRZ	Grupo	[³ H]MK-801 KI	SEM	n	IC ₅₀ NMDA (µM)	SEM	N
2/1004	Bicíclico	10,46	1,05	3			
2/1013	Bicíclico	3,64	0,22	3	4,72	0,05	6
2/1003	Con puente 579	7,40	0,52	3			
2/1010	Con puente 579	2,59	0,17	3	0,76	0,12	6
2007	Con puente 579	5,46	0,22	3	6,77	0,36	6

2011	Con puente 579	15,82	0,84	3			
2022	Con puente 579	14,42	1,84	3	13,87	2,30	6
2023	Con puente 579	23,32	2,52	3	16,11	3,29	6
2028	Con puente 579	3,21	0,08	3	10,33	0,42	6
2029	Con puente 579	13,22	1,28	3	38,11	1,81	6
2046							
2047							

Los resultados para los compuestos representativos se muestran en la Figura 1.

EXPRESIÓN DE SUBTIPOS DEL RECEPTOR DE NMDA EN OOCITOS DE XENOPUS

El bloqueo de los receptores de NMDA por MRZ 2/1010 se determinó aplicando distintas concentraciones (0,3 a 30 µM en régimen de dosificación log 3) durante 10 segundos en presencia continua de glutamato (100 µM) y glicina 10 µM) a -70 mV durante 100 segundos en oocitos de *Xenopus* que expresaban los receptores NR1a/2A (Figura 2, izquierda). La potencia de MRZ 2/1010 (IC₅₀ = 0,76 µM, Hill 0,63) se determinó graficando el porcentaje de bloqueo contra la concentración de antagonista y ajustando posteriormente la curva de acuerdo con la ecuación logística (Figura 2, derecha).

Actividad anticonvulsiva *in vivo*

Los resultados de MES y de la acción miorelajante se muestran en la Tabla 2.

Tabla 2

MRZ	ED ₅₀ MES	CI MES	ED ₅₀ miorelajación	CI miorelajación	ED ₅₀ Ataxia	CI Ataxia	miorelajación TI	Ataxia TI
2/1003	16,25	9-29,4	16,77	11-25,5	20,80	14,8-29,1	1,03	1,27
2/1004	24,07	7,3-79	27,52	24,5-30,9	24,03	16,5-34,9	1,14	1,00
2/1010	5,91	3,4-	10,62	8,1-13,9	24,86	15,5-39,8	1,80	4,21

		10,3						
2/1013	9,39	2,6-33,8	34,49	21,9-54,2	37,24	30,5-45,5	3,87	3,97
2007	>50		>50		50,00			
2011								
2022								
2023	>30		>30		>30			
2028								
2029	>50		>50		>50			
2046								
2047								

En conclusión, a partir de lo anterior, resulta evidente que la presente invención provee aplicaciones y usos novedosos, valiosos e imprevisibles de los compuestos de la presente invención, donde dichos compuestos comprenden el principio activo acorde con la presente invención, así como nuevas composiciones farmacéuticas con los mismos y métodos de preparación de los mismos y de tratamiento con los mismos, siendo que todos poseían las características y ventajas más específicamente enumeradas.

El alto grado de actividad del agente activo de la presente invención y las composiciones con los mismos, evidenciado en las pruebas informadas, es indicativo de la utilidad basado en la actividad valiosa para seres humanos, así como en animales inferiores. Sin embargo, no se ha completado aún la evaluación clínica en seres humanos. Se comprenderá claramente que la distribución y comercialización de cualquier compuesto o composición que se encuentra dentro del alcance de la presente invención para su uso en seres humanos se basará, por supuesto, en la aprobación previa por parte de las agencias gubernamentales, tal como la Administración de Alimentos y Drogas de EE.UU. [*U. S. Federal Food and Drug Administration*], que constituyen las

entidades responsables y autorizadas para emitir juicio en dichos temas.

Conclusiones

Los presentes derivados azabicíclicos, azatricíclicos y azaespirocíclicos de aminociclohexanos representan una nueva clase de antagonistas no competitivos del receptor de NMDA, sistémicamente activos, con una cinética rápida de bloqueo/desbloqueo y una fuerte dependencia del voltaje. En vista de su moderada potencia y la rápida cinética asociada, constituirán sustancias terapéuticas útiles para un amplio rango de trastornos del CNS que comprendan alteraciones de la transmisión glutaminérgica.

Por consiguiente, estos compuestos encuentran aplicación en el tratamiento de los siguientes trastornos de un animal vivo, en especial el hombre. 1. Excitotoxicidad, tal como isquemia durante un accidente cerebrovascular, traumatismos, hipoxia, hipoglucemia, glaucoma y encefalopatía hepática. 2. Enfermedades neurodegenerativas crónicas, tal como mal de Alzheimer, demencia vascular, mal de Parkinson, enfermedad de Huntington, esclerosis múltiple, esclerosis amiotrófica lateral, neurodegeneración por SIDA, atrofia olivopontocerebelosa, síndrome de Tourette, enfermedad de neuronas motoras, disfunción mitocondrial, síndrome de Korsakoff, enfermedad de Creutzfeldt-Jakob. 3. Otros trastornos relacionados con cambios plásticos a largo plazo en el sistema nervioso central se seleccionan entre dolor crónico, tolerancia, dependencia y adicción a drogas (por ejemplo, opioides, cocaína, benzodiazepinas, nicotina y alcohol). 4. Epilepsia, disquinesia tardía, esquizofrenia, ansiedad, depresión, dolor agudo, espasticidad y tinnitus.

Aún más, se encontró que estos compuestos son antagonistas del

receptor nicotínico neuronal y también del receptor de 5HT₃. Los compuestos de la invención se pueden aplicar entonces en el tratamiento de trastornos en un animal vivo, en especial el hombre, en las indicaciones mediadas por los receptores nicotínicos y de 5HT₃, tanto para fines sintomáticos como neuroprotectores (por ejemplo, emesis, abuso de nicotina, esquizofrenia, temblor cerebeloso, IBS, migraña, trastornos depresivos, trastornos cognitivos, psicosis relacionado con el tratamiento del mal de Parkinson y trastornos de la alimentación).

Además, como ya se estableció, debido al menos en parte a su sustituyente amina, los compuestos de la presente invención también son eficaces en las indicaciones no relacionadas con el mecanismo de acción mencionado precedentemente, por lo cual exhibe actividad inmunomoduladora, potencia antimalaria y antitripanosómico, actividad anti-virus Borna, anti-HSV y anti-hepatitis C.

El método de tratamiento de un animal vivo con un compuesto de la invención, para inhibir el avance o aliviar las enfermedades seleccionadas en la misma, es como se estableció previamente utilizando cualquiera de las rutas farmacéuticas normalmente aceptadas, empleando la dosificación seleccionada que es eficaz para aliviar la enfermedad particular que se desea tratar.

El uso de los compuestos de la presente invención en la elaboración de un medicamento para el tratamiento de un animal vivo por inhibición de la progresión o alivio de las enfermedades o condiciones seleccionadas, en particular las enfermedades o condiciones susceptibles a un tratamiento con un antagonista de receptor de NMDA, un antagonista del receptor nicotínico neuronal, un antagonista de 5HT₃ o un compuesto que exhiba actividad

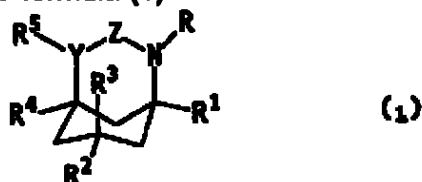
inmunomoduladora, potencia antimalaria y antitripanosómica, actividad anti-virus Borna y anti-HSV y anti-hepatitis C, se efectúa de la manera habitual, que comprende el paso de mezclar una cantidad eficaz de un compuesto de la invención con un diluyente, excipiente o vehículo aceptable para uso farmacéutico, y el método de tratamiento, las composiciones farmacéuticas y el uso de un compuesto de la presente invención en la elaboración de un medicamento.

Las composiciones farmacéuticas representativas preparadas mezclando el ingrediente activo con un excipiente, diluyente o vehículo aceptable para uso farmacéutico adecuado, incluyen tabletas, cápsulas, soluciones inyectables, formulaciones líquidas orales, formulaciones en aerosol, formulaciones para TDS y formulaciones nanoparticuladas, para producir así medicamentos destinados al uso oral, inyectable o dérmico, también de acuerdo con la descripción precedente.

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REIVINDICACIONES:**1. Compuestos de la fórmula (1)**

donde R y R¹-R⁵ se seleccionan independientemente entre grupos alquilo C₁₋₆, grupos alquenilo C₂₋₆, grupos alquinilo C²⁻⁶, grupos aril C₆₋₁₂-alquilo C₁₋₄, grupos arilo C₆₋₁₂ sustituidos opcionalmente y, en el caso de R y R²-R⁵, átomos de hidrógeno, con la condición que al menos uno de R² y R³ y al menos uno de R⁴ y R⁵ son distintos de hidrógeno, o R y R¹ representan juntos un grupo alquileno o alquenileno C₃₋₆, siendo R²-R⁵ como se definieron precedentemente;

Y es CH; y

Z representa un enlace de valencia o un grupo metileno o, en el caso donde R y R¹ representan juntos dicho grupo alquileno o alquenileno, Z puede representar además átomos de hidrógeno unidos a Y y N, respectivamente;

e isómeros ópticos y sales de adición ácida y básica aceptables para uso farmacéutico de los mismos.

2. Los compuestos de la cláusula 1, que comprenden:

- 1, exo-3,5-trimetil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
- 5-etil-1,exo-3-dimetil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
- exo-3-etil-1,5-dimetil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
- 1,3,3,5-tetrametil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
- 1,3,3,5, 6-pentametil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
- 5-etil-1,3,3-trimetil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;

1,exo-3,5,exo,endo-7-tetrametil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
 1,exo-3,5-trimetil-exo,endo-7-fenil-6-azabicyclo[3.2.1]octano y su sal clorhidrato;
 1,5,exo-7-trimetil-2-azabicyclo[3,3,1]nonano y su sal clorhidrato;
 7,7,9,9-tetrametil-1-azaspiro[4,5]decano y su sal clorhidrato;
 8,8,10,10-tetrametil-1-azaspiro[5,5]undecano y su sal clorhidrato;

y

8,10, 10-trimetil-6-azatriciclo[6,3,1,0^{1,6}]dodecano y su sal clorhidrato.

3. Una composición farmacéutica que comprende uno de los compuestos de la cláusula 1 o de la cláusula 2 en combinación con uno o más diluyentes, excipientes o vehículos aceptables para uso farmacéutico.

4. El uso de uno de los compuestos definidos en la cláusula 1, pero no sujetos a la condición de que al menos uno de R² y R³ y al menos uno de R⁴ y R⁵ sean distintos de hidrógeno, en o para la elaboración de un medicamento inmunomodulador, anti-malario, anti-virus Borna, anti-hepatitis C, anti-tripanosómico o anti-HSV o de un medicamento para aliviar una afección tratable con un antagonista del receptor de NMDA, de 5HT₃ o nicotínico neuronal.

5. El uso de la cláusula 4, donde dicha afección tratable con un antagonista del receptor de NMDA es una excitotoxicidad seleccionada entre isquemia durante un accidente cerebrovascular, traumatismo, hipoxia, hipoglucemia, glaucoma y encefalopatía hepática; una enfermedad neurodegenerativa crónica seleccionada entre mal de Alzheimer, demencia vascular, mal de Parkinson, enfermedad de Huntington, esclerosis múltiple, esclerosis amiotrófica lateral, neurodegeneración por SIDA, atrofia olivopontocerebelosa, síndrome de Tourette, enfermedad de neuronas motoras, disfunción mitocondrial, síndrome

de Korsakoff y enfermedad de Creutzfeldt-Jakob; un trastorno relacionado con cambios plásticos a largo plazo en el sistema nervioso central seleccionado entre dolor crónico, tolerancia a drogas, dependencia de drogas y adicción a drogas; epilepsia; disquinesia tardía; disquinesia inducida por L-DOPA; esquizofrenia; ansiedad; depresión; dolor agudo; espasticidad o tinnitus.

6. El uso de la cláusula 4, donde dicha afección tratable con un antagonista del receptor de 5HT₃ se selecciona entre trastornos de la ansiedad, trastornos depresivos, esquizofrenia y psicosis relacionado con el tratamiento, trastornos de abuso de drogas y alcohol, trastornos cognitivos, mal de Alzheimer, mal de Parkinson, temblor cerebeloso, migraña, trastornos de la alimentación, síndrome de intestino inflamatorio y emesis.

7. El uso de la cláusula 4, donde dicha afección tratable con un antagonista del receptor nicotínico neuronal se selecciona entre síndrome de Tourette, trastornos de ansiedad, esquizofrenia, abuso de drogas, abuso de nicotina, abuso de cocaína, disquinesia por enfermedad de Huntington, disquinesia inducida por L-DOPA, trastorno de hiperactividad con déficit atencional, mal de Alzheimer, mal de Parkinson y dolor.

8. Un método de tratamiento de un sujeto humano o no humano vivo para fines inmunomoduladores, anti-malaria, anti-virus Borna, anti-hepatitis C, anti-tripanosómicos o anti-HSV o para aliviar una afección tratable con un antagonista del receptor de NMDA, 5HT₃ o nicotínico neuronal, que comprende el paso de administrar a dicho sujeto una cantidad eficaz de uno de los compuestos definidos en la cláusula 1 pero no sujetos a la condición que al menos uno de R² y R³ y al menos uno de R⁴ y R⁵ sea distinto de hidrógeno.

**DERIVADOS AZABICÍCLICOS, AZATRICÍCLICOS Y AZAESPIROCÍCLICOS
DE AMINCICLOHEXANO AS ANTAGONISTAS DE LOS RECEPTORES DE
NMDA, 5HT₂ Y NICOTÍNICOS NEURONALES**

RESUMEN

Derivados azabicíclicos, azatricíclicos y azaespirocíclicos de aminciclohexanos de la fórmula I (donde n, Y, Z, R, R¹-R⁵ son como se definieron en las reivindicaciones) que son sistémicamente activos como antagonistas de los receptores de NMDA, 5HT₂ y nicotínicos, composiciones farmacéuticas que comprenden a los mismos, métodos de preparación de los mismos y métodos de tratamiento de trastornos del CNS que comprenden alteraciones de la transmisión glutaminérgica, serotoninérgica y nicotínica, el tratamiento de trastornos inmunomoduladores, y actividad antimalaria, antitripanozómico, anti-virus Borna, anti-HSV y anti-virus de la hepatitis C.

TEXTO DE LAS FIGURAS

INGLÉS	ESPAÑOL
FIGURA 1	
% Control [³ H]MK-Binding	% Unión MK[³ H] Control
Concentration	Concentración
Parameter	Parámetro
Value	Valor
Std. Error	Error estándar
Slope factor	Factor de la pendiente
FIGURA 2	
<i>Xenopus</i> Oocytes	Oocitos de <i>Xenopus</i>
Glutamate	Glutamato
Glycine	Glicina
% Control Glutamate-Induced Current	% Corriente inducida por glutamato control
MRZ 2/1010 Concentration (µM)	Concentración de MRZ 2/1010 (µM)
Parameter	Parámetro
Value	Valor
Std. Error	Error estándar
Slope factor	Factor de la pendiente

COPY

European Patent Office
D-80298 München
Germany

date 30 April 2004
your ref
our ref 408.80589.jcm

BY FACSIMILE

Dear Sirs

International Patent Application No. PCT/GB03/01236 -
Merz Pharma GmbH & Co. KGaA *et al*

I refer to the Written Opinion dated 2 January 2004, the response period to which has been extended as confirmed by your letter of 13 April 2004.

It is stated that claims 1 and 3-7 lack novelty over documents D1-D7. It should be noted, however, that the presently claimed compounds carry an obligatory R¹ substituent on the cyclohexyl ring carbon atom which carries the amino group, since as will be seen from the third line following formula (1) of claim 1, R¹ cannot represent a hydrogen atom. There is no explicit disclosure of such a substituent pattern in Citation D1, and it will be seen specific embodiments of compounds of formula II, e.g. the compounds A-1 and A-2 on page 27 of the specification, are not substituted at this position.

Similarly there is no substituent at the 5-position of the compounds shown in D2, D3, D4 and D7 or the 1-position of the compounds of D5 and D6.

It is accordingly requested that the International Preliminary Examination Report should contain a positive finding in respect of novelty for all of claims 1-7.

Form 1037 for acknowledgement purposes follows with the postal confirmation copy of this letter.

Yours faithfully
Frank B. Dehn & Co.

J. C. Marsden

/erd

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PATENT COOPERATION TREATY

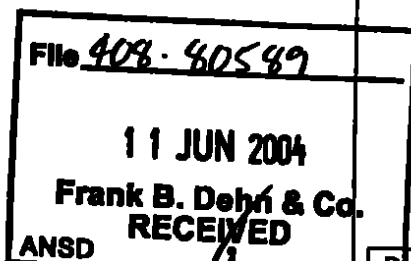
16M

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:

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



NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing
(day/month/year)

09.08.2004

Applicant's or agent's file reference
408.80589

IMPORTANT NOTIFICATION

International application No.
PCT/GB 03/01236

International filing date (day/month/year)
21.03.2003

Priority date (day/month/year)
21.03.2002

Applicant

MERZ PHARMA GMBH & CO. KGAA et al

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 inventions 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-80288 Munich
Tel. +49 89 2399 - 0 Tlx 523856 epmu d
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Authorized Officer

Ambrosia, J.R.

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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 408.80589		FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEAA18)	
International application No. PCT/GB 03/01236		International filing date (day/month/year) 21.03.2003	Priority date (day/month/year) 21.03.2002
International Patent Classification (IPC) or both national classification and IPC A61K31/40, A61K31/40			
Applicant MERZ PHARMA GMBH & CO. KGAA et al			
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 7 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 70.16 and Section 607 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 68.2(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 17.10.2003		Date of completion of this report 09.06.2004	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80299 Munich Tel. +49 89 2399 - 0 Tlx 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Gavrilu, D Telephone No. +49 89 2399-8274 	

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 03/01236

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

1-8 as originally filed

Drawings, Sheets

1/2-2/2 as originally filed

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 03/01236**

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:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☐ claims Nos.

because:

- ☒ the said international application, or the said claims Nos. 8 relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the Standard.

☐ the computer readable form has not been furnished or does not comply with the Standard.

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	1-7
	No: Claims	
Inventive step (IS)	Yes: Claims	
	No: Claims	1-7
Industrial applicability (IA)	Yes: Claims	1-7
	No: Claims	

2. Citations and explanations

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/GB 03/01236**

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Claims 8 relates to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the novelty, inventive step and industrial applicability of the subject-matter of this claims(article 34(4)(a)(I)PCT).

Re Item 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. Reference is made to the following documents:

- D1: JP 62297848
- D2: DATABASE CROSSFIRE BEILSTEIN [ONLINE], Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Mein, De; Database accession no. 5577766 (bm), 5586551(bm); 5615067(bm), XP002247394, abstract & Bull. Soc. Chim. Fr., vol. 2, 1987, pages 261-264
- D3: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DARWISH, Y. M. ET ALL: "Heterocyclic quaternary ammonium salts as plant growth retardants", Database accession no. 97:2169, XP002247359 & Acta Phytologica Academiae Scientiarum Hungaricae (1981), 16(1-2), 249-58.
- D4: DATABASE CHEMCATS [Online], Chemical Abstracts Service, Columbus, Ohio, US; XP002247396; order number st032465/an
- D5: EP 0018077 A
- D6: EP 0072438 A
- D7: WO 9408964 A
- D8: EP 0578560 A
- D9: GB 1153973 A
- D10: GB1472334 A
- D11: WO 9606081 A
- D12: WO9212149 A
- D13: US 5936088 A
- D14: WO0032600

D15: WO0198253 A

2. Novelty (Article 33(1) and (2) PCT)

The subject matter of the present application describes azabicyclic, azatricyclic and azaspirocyclic derivatives of formula (I) (see claim 1), useful as medicaments in treatment of CNS disorders.

The compounds claimed by the present Claim 1 and 2 differ from the prior art compounds(D1-D7) either through the R1 substituent (which cannot be hydrogen) , through R2/R3 substituents(D10), through the substituent from the nitrogen atom (D8-D9) or through the azabicyclo core structure. Therefore, the novelty of the present subject-matter is acknowledged (considering also the arguments brought by the Applicant with the letter of 30.04.2004)

3. Inventive step (Article 33(1) and (3) PCT).

The subject-matter of the present application relates to 6-aza-bicyclo[3.2.1]octane, 2-aza-bicyclo[3.3.1]nonane derivatives or azaspiro or azatricyclo derivatives, useful as medicaments for treating CNS disorders which involve disturbances of glutamatergic, serotonergic and nicotinic transmission.

Document D5, discloses 5-phenylmorphans which differ from the present compounds through the phenyl moiety from the position 5, and through the absence of the alkyl moiety in the position 1 of the bicyclo ring. The compounds claimed by the D5 are also useful in treating CNS diseases.

Document D7 discloses N-phenethylazepine derivatives, which differ from the present claimed compounds (claim 2) through the absence of the alkyl moiety from the position 1 of aza-bicyclo ring. The compounds disclosed by D7 are also useful for treating schizophrenia as claimed for the present compounds in claim 5. . . .

Document D8 discloses a derivate of 6-aza-bicyclo[3.2.1] octane (see compound 26858-page 11), which differ from the present claimed compounds only through the N-substituent. The above-mentioned compound is disclosed by D8 as having antipsychotic, antiparkinson and antidepressive activity. The above-mentioned activity are also claimed for the present compounds in the present claims 5-7.

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Document D9 discloses 1-azaspiro[4.5]decane derivatives, which differ from the present claimed compounds only through the substituent from the nitrogen atom. The compounds described by D9 are useful in the treatment of CNS diseases.

Document D10 discloses 6-aza-bicyclo[3.2.1]octane, which do not have in the position 3 a substituent as in the present case (at least one of R2, R3 should not be hydrogen). The compounds claimed by D10 are useful as analgesic, stronger as codeine. In the present case there are also tests "in vivo" for the anti-convulsive activity (see page 72).

That means that, starting from the closest prior art (which is represented by the compounds disclosed by D5, D7 and D10), the technical problem of providing further compounds useful in treatment of different CNS diseases, has been solved either by introducing an alkyl group in the position 1 (regarding the compounds claimed by claim 2), or a different substituent on the nitrogen atom in the known compounds. Therefore it appears that the skilled person would not be surprised that this minimal modifications of the prior compounds, would allow to obtain further compounds, useful as medicaments for treating CNS diseases. Consequently, an inventive step can be acknowledged only if it is shown by means of comparative tests that the compounds of the present invention have unexpected effect vis-à-vis the compounds of D5, D7-D10.

4. Industrial applicability (Article 33(4)PCT).

For the assessment of the present claims 13-54 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

INTERNATIONAL PATENT COOPERATION TREATY

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From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

WRITTEN OPINION
(PCT Rule 66)

To:

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

File 408.80.589

- 5 JAN 2004

Frank B. Dehn & Co.
RECEIVED

ANSD

Date of mailing
(day/month/year)

02.01.2004

Applicant's or agent's file reference
408.80589

REPLY DUE

within 3 month(s)
from the above date of mailing

International application No.
PCT/GB 03/01236

International filing date (day/month/year)
21.03.2003

Priority date (day/month/year)
21.03.2002

International Patent Classification (IPC) or both national classification and IPC
A61K31/40

Applicant

MERZ PHARMA GMBH & CO. KGAA et al

- This written opinion is the first drawn up by this International Preliminary Examining Authority.
- This opinion contains indications relating to the following items:
 - ☒ Basis of the opinion
 - ☐ Priority
 - ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
 - ☐ Lack of unity of invention
 - ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - ☐ Certain documents cited
 - ☐ Certain defects in the international application
 - ☐ Certain observations on the international application
- 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.
- The final date by which the international preliminary examination report must be established according to Rule 66.2 is: 21.07.2004

DUE DATES
NOTED

Name and mailing address of the international
preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tlx 523656 epmu d
Fax: +49 89 2399 - 4485

Authorized Officer

Gavriliu, D

Formalities officer (incl. extension of time limits)

Ambrosia, J.R.

Telephone No. +49 89 2399-8012



WRITTEN OPINIONInternational application No. **PCT/GB 03/01236****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

1-8 as originally filed

Drawings, Sheets

12-22 as originally filed

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:

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)).

6. Additional observations, if necessary:

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WRITTEN OPINION

International application No. **PCT/GB 03/01236**

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:
- ☐ the entire international application,
 - ☒ claims Nos. 8 (with respect to industrial applicability)
because:
 - ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):
 - ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
 - ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
 - ☐ no international search report has been established for the said claims Nos.
2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:
- ☐ the written form has not been furnished or does not comply with the Standard.
 - ☐ the computer readable form has not been furnished or does not comply with the Standard.

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	1(no), 2(yes), 3-7(no)
Inventive step (IS)	Claims	1-7(no)
Industrial applicability (IA)	Claims	1-7(yes)

2. Citations and explanations

see separate sheet

**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/GB03/01236

Re Item I**Basis of the opinion**

Should amendments be filed in response to this written opinion, these will only be taken into account when the applicant identifies clearly all amendments made (e.g. by submitting one set of originally pages with hand-written opinion amendments) and indicate on which pages of the original application these amendments are based (Rule 66.8 PCT)

Re Item III**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

Claims 8 relates to subject-matter considered by this Authority to be covered by the provision of Rule 67.1(iv)PCT. Consequently, no opinion will be formulated with respect to the novelty, inventive step and industrial applicability of the subject-matter of this claims(article 34(4)(a)(i)PCT).

Re Item 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. Reference is made to the following documents:**

- D1:** PATENT ABSTRACTS OF JAPAN vol. 012, no. 192 (P-712), 4 June 1988 (1988-06-04) & JP 62 297848 A (KONISHIROKU PHOTO IND CO LTD), 25 December 1987 (1987-12-25)
- D2:** DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5577766(bm); 5586551(bm); 5615067(bm) XP002247394 & BULL. SOC. CHIM. FR., vol. 2, 1987, pages 261-264,
- D3:** DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DARWISH, Y. M. ET AL: 'Heterocyclic quaternary ammonium salts as plant growth retardants' retrieved from STN Database accession no. 97:2169 XP002247395 & ACTA PHYTOPATHOLOGICA ACADEMIAE SCIENTIARUM HUNGARICAE (1981), 16(1-2), 249-58 ,
- D4:** DATABASE CHEMCATS [Online] Chemical Abstracts Service, Columbus,

- Ohio, US; XP002247396 & 'TimTec Natural compounds' 14 October 2002 (2002-10-14), TIMTEC, INC., NEWARK, DE, 19714-8941, USA
- D5: EP-A-0 018 077 (LILLY CO ELI) 29 October 1980 (1980-10-29)
- D6: EP-A-0 072 438 (BASF AG) 23 February 1983 (1983-02-23)
- D7: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKAHASHI, NOBUYUKI ET AL: 'Preparation of phenethylhexahydroazepine derivatives as agents with affinity for sigma receptor' retrieved from STN Database accession no. 121:205227 XP002248386 -& WO 94 08964 A (ASAHI KASEI KOGYO K. K., JAPAN) 28 April 1994 (1994-04-28)
- D8: EP-A-0 578 560 (CEPBEPE) 12 January 1994 (1994-01-12)
- D9: GB-A-1 153 973 (GILL, JENNINGS & EVERY GB) 4 June 1969 (1969-06-04)
- D10: GB-A-1 472 334 (TANABE SEIYAKU CO) 4 May 1977 (1977-05-04)
- D11: WO 96 06081 A (BUTLER TODD W ;PFIZER (US); CHENARD BERTRAND L (US)) 29 February 1996 (1996-02-29)
- D12: WO 92 12149 A (SMITHKLINE BEECHAM PLC) 23 July 1992 (1992-07-23)
- D13: US-A-5 936 088 (OLESEN PREBEN HOULBERG) 10 August 1999 (1999-08-10)
- D14: WO 00 32600 A (NIELSEN ELSEBET OESTERGAARD ;NEUROSEARCH AS (DK); OLSEN GUNNAR M () 8 June 2000 (2000-06-08)
- D15: WO 01 98253 A (MERZ & CO GMBH & CO) 27 December 2001 (2001-12-27)
- D16: WO-A-9212149
- D17: US-A-5936088
- D18: WO-A-0032600
- D19: WO-A-0198253

2. Novelty (Article 33(1) and (2) PCT)

The subject matter of the present application describes azabicyclic, azatricyclic and azaspirocyclic derivatives of formula (I) (see claim 1), useful as medicaments in treatment of CNS disorders.

Document D1 discloses derivatives of 6-azabicyclo[3.2.1]octane (see formula II of D1) which for R1 being hydrogen, alkyl or aryl group and R4 being halogen, present an overlap with the formula (I) claimed by the present claim 1. Moreover

he means R³ in Konica!

not - but Konica
R⁴ can be alkyl, which

177

the compounds A-2 disclosed by D1 (page 3836) are novelty destroying for the general structure (I) of the present application.

Documents D2-D4 disclose N-derivatives of 1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane, which are novelty destroying compounds for the Markush formula (I) claimed by the present invention.

The general structure disclosed by claim 1 of D5 presents an overlap, when R4 is hydrogen, C1-C10 alkyl, phenyl C1-C3 alkyl or CH2-C2-C6 with the Markush structure (I) claimed by the present claim 1. Moreover examples 7-9, 13-16 disclosed by D5 are novelty destroying compounds for the general structure (I) claimed by the present application.

N-(2-chloro-4-aminophenyl)-6-azabicyclo[3.2.1]octane and the corresponding nitro derivate disclosed by D6 as starting material for the synthesis of the compounds 85-88 (page 14), are embodiments of the general structure (I) claimed by the present invention.

The general structure disclosed (I) by D7, presents an overlap, when B is the compound 24 (see page 4) and A is a saturated C2-C3 alkylene, with the present Markush formula (I). Moreover four of the compounds (with the m: 157943-00-5; 157943-01-6; 157943-02-7 and 157943-03-8) disclosed by D7 are embodiments of the present formula (I) claimed by the present invention.

Consequently, considering the fact that the documents D1-D7 disclose compounds which are 6-aza-bicyclo[3.2.1]octane derivatives with structure falling under the general formula (I) of the present case, the present application does not meet the requirements of Article 33(1) and (2) PCT.

3. Inventive step (Article 33(1) and (3) PCT).

Since, D1-D7 disclose a lot of novelty destroying compounds and overlapping region, the assessment for the inventive step will be related only to the compounds claimed by claim 2 which are novel over D1-D7.

The subject-matter of the present application relates to 6-aza-bicyclo[3.2.1]octane,

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**WRITTEN OPINION
SEPARATE SHEET**

International application No. PCT/GB03/01236

2-aza-bicyclo[3.3.1]nonane derivatives or azaspiro or azatricyclo derivatives, useful as medicaments for treating CNS disorders which involve disturbances of glutamatergic, serotonergic and nicotinic transmission.

Document D5, discloses 5-phenylmorphans which differ from the present compounds through the phenyl moiety from the position 5, and through the absence of the alkyl moiety in the position 1 of the bicyclo ring. The compounds claimed by the D5 are also useful in treating CNS diseases.

Document D7 discloses N-phenethylazepine derivatives, which differ from the present claimed compounds (claim 2) through the absence of the alkyl moiety from the position 1 of aza-bicyclo ring. The compounds disclosed by D7 are also useful for treating schizophrenia as claimed for the present compounds in claim 5.

Document D8 discloses a derivate of 6-aza-bicyclo[3.2.1] octane (see compound 26858-page 11), which differ from the present claimed compounds only through the N-substituent. The above-mentioned compound is disclosed by D8 as having antipsychotic, antiparkinson and antidepressive activity. The above-mentioned activity are also claimed for the present compounds in the present claims 5-7.

Document D9 discloses 1-azaspiro[4.5]decane derivatives, which differ from the present claimed compounds only through the substituent from the nitrogen atom. The compounds described by D9 are useful in the treatment of CNS diseases.

Document D10 discloses 6-aza-bicyclo[3.2.1]octane, which do not have in the position 3 a substituent as in the present case (at least one of R2, R3 should not be hydrogen). The compounds claimed by D10 are useful as analgesic, stronger as codeine. In the present case there are also tests "in vivo" for the anti-convulsive activity (see page 72).

That means that, starting from the closest prior art (which is represented by the compounds disclosed by D5, D7 and D10), the technical problem of providing further compounds useful in treatment of different CNS diseases, has been solved either by introducing an alkyl group in the position 1 (regarding the compounds claimed by claim 2), or a different substituent on the nitrogen atom in the known

compounds. Therefore it appears that the skilled person would not be surprised that this minimal modifications of the prior compounds, would allow to obtain further compounds, useful as medicaments for treating CNS diseases. Consequently, an inventive step can be acknowledged only if it is shown by means of comparative tests that the compounds of the present invention have unexpected effect vis-à-vis the compounds of D5, D7-D10.

4. Industrial applicability (Article 33(4)PCT).

For the assessment of the present Claims 8 on the question whether they are industrial applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may also allow, however, claims to a known compound for the manufacture of a medicament for a new medical treatment.

PATENT CO PERATION TREATY

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From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To:

FRANK B. DEHN & CO.
Attn. Marsden, John C.
179 Queen Victoria Street
London EC4V 4EL
UNITED KINGDOM

File 408-80589

- 4 AUG 2003

Frank B. Dehn & Co.
RECEIVED

ANSD

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL SEARCH REPORT
OR THE DECLARATION

(PCT Rule 44.1)

Date of mailing
(day/month/year)

05/08/2003

Applicant's or agent's file reference

408.80589

FOR FURTHER ACTION

See paragraphs 1 and 4 below

International application No.

PCT/GB 03/01236

International filing date

(day/month/year)

21/03/2003

Applicant

MERZ PHARMA GMBH & CO. KGAA

1. ☒ The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 18:

The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Facsimile No.: (41-22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. ☐ The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. ☐ With regard to the protest against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

☐ the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

☐ no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. Further action(s): The applicant is reminded of the following:

Shortly after 18 months from the priority date, the International application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the International application, or of the priority claim, must reach the International Bureau as provided in Rules 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for International publication.

Within 18 months from the priority date, a demand for International preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 18 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority



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

Authorized officer

Panayota Georgakopoulou

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 408.80589	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, Item 5 below.	
International application No. PCT/GB 03/01236	International filing date (day/month/year) 21/03/2003	(Earliest) Priority Date (day/month/year) 21/03/2002
Applicant MERZ PHARMA GMBH & CO. KGAA		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 8 sheets.

☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the language, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international search 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.

2. ☒ Certain claims were found unsearchable (See Box I).

3. ☐ Unity of invention is lacking (see Box II).

4. With regard to the title,

☐ the text is approved as submitted by the applicant.

☒ the text has been established by this Authority to read as follows:

AZABICYCLIC, AZATRICYCLIC AND AZASPIROCICLYC DERIVATIVES OF AMINOCYCLOHEXANE AS NMDA, 5HT₃, AND NEURONAL NICOTINIC RECEPTOR ANTAGONISTS

5. With regard to the abstract,

☐ the text is approved as submitted by the applicant.

☒ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the drawings to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☒ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

1-2

☐ None of the figures.

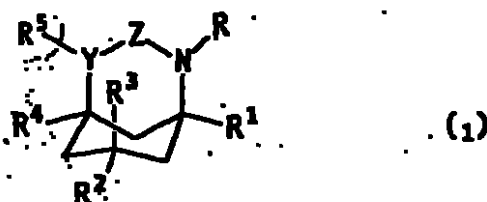
INTERNATIONAL SEARCH REPORT

International application No.

PCT/GB 03/ 01236

Box III TEXT OF THE ABSTRACT (Continuation of Item 5 of the first sheet)

Azabicyclic, azatricyclic and azaspirocyclic derivatives of aminocyclohexanes of formula I (N, Y, Z, R, R₁- R₅ - as defined in the claims) which are systemically-active as NMDA, 5HT₂, and nicotinic receptor antagonists, pharmaceutical compositions comprising the same, method of preparation thereof, and method of treating CNS disorders which involve disturbances of glutamatergic, serotonergic, and nicotinic transmission, treating immunomodulatory disorders, and antimalaria, antitrypanosomal, anti-Borna virus, anti-HSV and anti-Hepatitis C virus activity.



INTERNATIONAL SEARCH REPORT

International Application No.

PCT/GB 03/01236

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/40 C07D209/02 C07D221/20 C07D209/54 C07D221/22
C07D487/08 A61P25/16 A61P25/18

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 C07D

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

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

EPO-Internal, BEILSTEIN Data, PAJ, 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.
X	PATENT ABSTRACTS OF JAPAN vol. 012, no. 192 (P-712), 4 June 1988 (1988-06-04) & JP 62 297848 A (KONISHIROKU PHOTO IND CO LTD), 25 December 1987 (1987-12-25) abstract; claims	1
X	DATABASE CROSSFIRE BEILSTEIN 'Online! Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; Database accession no. 5577766(brn); 5586551(brn); 5615067(brn) XP002247394 abstract & BULL. SOC. CHIM. FR., vol. 2, 1987, pages 261-264, -/-	1

☒ 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 claim(s) 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.

"Z" document member of the same patent family

Date of the actual completion of the international search

21 July 2003

Date of mailing of the international search report

05/08/2003

Name and mailing address of the ISA

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

Authorized officer

Gavriliu, D

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01236

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; DARWISH, Y. M. ET AL: "Heterocyclic quaternary ammonium salts as plant growth retardants" retrieved from STN Database accession no. 97:2169 XP002247395 abstract & ACTA PHYTOPATHOLOGICA ACADEMIAE SCIENTIARUM HUNGARICAE (1981), 16(1-2), 249-58 ,	1
X	DATABASE CHEMCATS 'Online! Chemical Abstracts Service, Columbus, Ohio, US; XP002247396 order number: st032465/an & "TimTec Natural compounds" 14 October 2002 (2002-10-14) , TIMTEC, INC. , NEWARK, DE, 19714-8941, USA	1
X	EP 0 018 077 A (LILLY CO ELI) 29 October 1980 (1980-10-29) page 23, line 19 -page 24, line 30; claims 1,11; examples 7-9,13-16	1-5
X	EP 0 072 438 A (BASF AG) 23 February 1983 (1983-02-23) compounds 85-88 page 3, line 25 -page 6, line 35	1
X	DATABASE CA 'Online! CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; TAKAHASHI, NOBUYUKI ET AL: "Preparation of phenethylhexahydroazepine derivatives as agents with affinity for sigma receptor" retrieved from STN Database accession no. 121:205227 XP002248386 compounds 157943-01-6/rn; 157943-02-7/rn; 157943-03-8/rn and 157943-00-5/rn abstract -& WO 94 08964 A (ASAHI KASEI KOGYO K. K., JAPAN) 28 April 1994 (1994-04-28)	1-5
Y	EP 0 578 560 A (CEPBEPE) 12 January 1994 (1994-01-12) page 4, line 44 -page 10, line 30; claims; table 1	1-5
	-/-	

INTERNATIONAL SEARCH REPORT

International Application No

PCT/GB 03/01236

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	GB 1 153 973 A (GILL, JENNINGS & EVERY GB) 4 June 1969 (1969-06-04) page 3, line 30-39; claims	1-5
Y	GB 1 472 334 A (TANABE SEIYAKU CO) 4 May 1977 (1977-05-04) page 1, line 15 -page 2, line 45; claims; examples	1-5
A	WO 96 06081 A (BUTLER TODD W ;PFIZER (US); CHENARD BERTRAND L (US)) 29 February 1996 (1996-02-29) page 14, line 1 -page 19, line 20; claims	1-5
A	WO 92 12149 A (SMITHKLINE BEECHAM PLC) 23 July 1992 (1992-07-23) page 21, line 1-15; claims	1-5
A	US 5 936 088 A (OLESEN PREBEN HOULBERG) 10 August 1999 (1999-08-10) column 5, line 28 -column 7, line 54; claims	1-15
A	WO 00 32600 A (NIELSEN ELSEBET OESTERGAARD ;NEUROSEARCH AS (DK); OLSEN GUNNAR M () 8 June 2000 (2000-06-08) page 18, line 26 -page 28, line 25; claims	1-5
A	WO 01 98253 A (MERZ & CO GMBH & CO) 27 December 2001 (2001-12-27) page 4, line 31 -page 5, line 5; claims	1-5

INTERNATIONAL SEARCH REPORT

International application No.
PCT/GB 03/01236

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:

Although claim 8 is 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.
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.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/01236

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
JP 62297848	A	25-12-1987	NONE
EP 0018077	A	29-10-1980	BE 882152 A1 10-09-1980 CA 1148150 A1 14-06-1983 EP 0018077 A2 29-10-1980 EP 0059989 A1 15-09-1982 FR 2451368 A1 10-10-1980 GB 2045248 A ,B 29-10-1980 GB 2111976 A ,B 13-07-1983 HU 179836 B 28-12-1982 IT 1129740 B 11-06-1986 JP 55124768 A 26-09-1980 LU 82235 A1 06-06-1980 US 4278797 A 14-07-1981
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WO 9606081	A	29-02-1996	AT 243679 T 15-07-2003 AU 684359 B2 11-12-1997 AU 2351195 A 14-03-1996 BR 9503694 A 28-05-1996 CA 2197451 A1 29-02-1996

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/GB 03/01236

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 9606081	A	CZ 9700474 A3	12-11-1997
		EP 0777652 A1	11-06-1997
		FI 970664 A	17-02-1997
		HU 77520 A2	28-05-1998
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		AU 761055 B2	29-05-2003
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WO 0198253	A	27-12-2001	
		AU 8186101 A	02-01-2002
		CA 2410852 A1	27-12-2001
		WO 0198253 A2	27-12-2001
		EP 1303477 A2	23-04-2003
		NO 20026103 A	19-02-2003

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) 408.80589

Box No. I TITLE OF INVENTION	
Azabicyclic, Azatricyclic and Azaspirocyclic Derivatives of Aminocyclohexane 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 Eckenheimer Landstrasse 100 Frankfurt am 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 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.	

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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> DANYSZ, Wojciech Vor den Garten 16 D-81130 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. Dzirgale 108/2-38 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, Aigars Hospitalu iela 3-103 Rīga 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> GOLD, Markus Kranichstrasse 9 D-64589 Neuheim 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> VANEJEVS, Maksims Mezhothas str. 58 Rīga LV 1002 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	
☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.	

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Supplemental Box

If the Supplemental Box is not used, this sheet should not be included in the request.

1. *If, in any of the Boxes, except Boxes Nos. VIII(1) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No. ..." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*
 - (i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. 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;*
 - (ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*
 - (iii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor-applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*
 - (iv) *If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*
 - (v) *If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*
 - (vi) *If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*
2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

CONTINUATION OF BOX NO. IV

The following, also of Frank B. Dehn & Co., are also appointed as agents:

Woodman, D.; Tomlinson, K.J.; Butler, M.J.; Pett, C.P.; Davies, C.R.; Pléssold, A.J.; Matthews, D.P.; Dzieglewska, H.E.; Calamita, R.; Leckey, D.H.; Hague, A.J.; Towler, P.D.; Hughes, A.M.; Tothill, J.; Cockbain, J.R.M.C.; Jackson, R.P.; Jones, E.L.; Grant, A.R.; Golding, L.A.; Hall, M.B.; Stevens, J.P.; Dixon, P.M.; Gardner, R.K.; Jeffrey, P.M.; Beacham, A.R.; Samuels, A.J.; Campbell, N.B.; Webber, P.M.; Power, P.L.

See Notes to the request form

Box No. IX CHECK LIST; LANGUAGE OF FILING		
This international application contains: (a) In paper form, the following number of sheets: request (including declaration sheets) : 7 description (excluding sequence listings and/or tables related thereto) : 78 claims : 3 abstract : 1 drawings : 2 Sub-total number of sheets : 91 sequence listings : tables related thereto : <i>(for both, actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (c) below)</i> Total number of sheets : 91 (b) ☐ only in computer readable form (Section 801(a)(i)) (i) ☐ sequence listings (ii) ☐ tables related thereto (c) ☐ also in computer readable form (Section 801(a)(ii)) (i) ☐ sequence listings (ii) ☐ tables related thereto Type and number of carriers (diskette, CD-ROM, CD-R or other) on which are contained the ☐ sequence listings: ☐ tables related thereto: <i>(additional copies to be indicated under items 9(ii) and/or 10(ii), in right column)</i>		This international application is accompanied by the following item(s) (mark the applicable check-boxes below and indicate in right column the number of each item): 1. ☒ fee calculation sheet : 1 2. ☐ original separate power of attorney : 3. ☐ original general power of attorney : 4. ☐ copy of general power of attorney; reference number, if any: : 5. ☐ statement explaining lack of signature : 6. ☒ priority document(s) identified in Box No. VI as item(s): US 60/388,388 : 1 7. ☐ translation of international application into (language): : 8. ☐ separate indications concerning deposited microorganism or other biological material : 9. ☐ sequence listings in computer readable form (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Rule 13ter only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(i) or (c)(i) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Rule 13ter : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listings mentioned in left column : 10. ☐ tables in computer readable form related to sequence listings (indicate type and number of carriers) (i) ☐ copy submitted for the purposes of international search under Section 802(b-quater) only (and not as part of the international application) : (ii) ☐ (only where check-box (b)(ii) or (c)(ii) is marked in left column) additional copies including, where applicable, the copy for the purposes of international search under Section 802(b-quater) : (iii) ☐ together with relevant statement as to the identity of the copy or copies with the tables mentioned in left column : 11. ☐ other (specify): :
Figure of the drawings which should accompany the abstract:		Language of filing of the international application: English
Box No. X SIGNATURE OF APPLICANT, AGENT OR COMMON REPRESENTATIVE <i>Next to each signature, indicate the name of the person signing and the capacity in which the person signs (if such capacity is not obvious from reading the request).</i>		
_____ John Christopher Marsden - Agent for the Applicant		

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:	

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION 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:



Fecha: 31 Aso 01.



2020
Bogotá, D.C.,

Doctor:
DILIA MARÍA F. DRÍGUEZ D'ALEMAN
Apoderado
MERZ PHARMA GMBH & CO. KGAA.

Oficio N°
178853

ASUNTO:	Radicación N°	04-85290
	Solicitud internacional	PCT/GB2003/01236
	Fecha inicio fase nacional	21/10/2004
	Trámite	011
	Evento	379
	Actuación	430
	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 la copia del documento en que consta la cesión del derecho a la 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 los 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 ésta fuere persona

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, 24 SET 2004