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SUPERINTENDENCIA DE INDUSTRIA ’’ COMERCIO.

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RINIENDENCA

PETITORIO FORMULARIO UNICO DE SOLICITUD
PATENTE PCT
ENTRADA EN FASE NACIONAL P2007/000166

0Patente

___ SOLICITUDDE:I

1 de Invención. I I Patente de Modelo de

L I CapItulo I. X CapItulo II.

0 Nombre: PFIZER PRODUCTS INC IDENTIFICACIÔN

SOLICITANTE Dirección: Eastern Point Road, Groton, C.C. 1 1 NIT F1
(71) Connecticut 06340 E.U.A.
Nacionalidad o Domicilio:ESTADOUNIDENSE C.E. Otro
Lugar de Constitución: Delaware, Estados
Unidos de America. Cual
TelØfono: Fax:

E-mail: Nümero

IDENTIFICACIÔN
Nombre: CARLOS R. OLARTE
C.C.[X NIT

C.E. i i El REPRESENTANTE Dirección: World Trade Center Torre A,
Calle 100 No. 8A-37 Piso 10 0 APODERADO TelØfono: 601-7700 Fax: 601-7799 Cual_______ E-mail: office@olarteraisbeck.com Nümero79782747Bta

TP 74.295

INVENTOR (ES) Dirección:_Eastern Point Road, Groton, Connecticut 06340 E.U.A
(72)
Nacionalidad o Domicilio: ESTADOUNIDENSE PCT (86)

Solicitud Internacional No. PCT/1B2006/000947 Fecha Marzo 27, 2006

Publicación Internacional No. WO 2006/106425 Fecha Octubre 12, 2006

G6TItulo (54) HETEROARILAMIDASr3.1.O1BICICLICAS COMO INHIBIDORES DEL TRANSPORTE DE GLICINA DE TIPO I

Clasificación Internacional (5 1) C07D 403/12, A61 31/4178, A61 31/427, A61 31/4439, A61
25/00, C07D 401/12, C07D 413/12, C07D 417/12

Prioridad

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US Abril 8, 2005 60/669.472

0 Comprobante de pago No. 07-77.743 Fecha 25 Septiembre 2007

ANEXOS

Comprobante de pago de la tasa de presentaciÆnde la solicitud.
Documento que acredita la existencia y representación legal cuando el solicitante sea persona juridica. Poderes, Si fuere el caso. Ver expediente No. 06-051.744. Adjunto copia simple
Documento de cesión del interventor al solicitante 0 a su causante.
Declaraciones.

LIICopia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos).
Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos).

Copia del examen preliminar internacional efectuado por la Autoridad Internacional de Examen Preliminar

(IPEA).
Traducción del examen preliminar internacional 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 indIgenas.
De ser el caso, certificado de depósito del material biológico.
Arte final 12 x 12.

De ser el caso, información sobre otras solicitudes de patente o tItulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con Ia invención de esta solicitud.
De ser el caso, modificaciones efectuadas a la solicitud internacional.
Otros. Bisqueda Internacional

0 FIGURA CARACTERISTICA:

Solicito la concesión de la patente,
NOMBRE:CARLOS R. OLARTE FIRM
C.C. T.P.74.295

SUPERINTENDENCIA DE INDUSTRIA V COMERCIC

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CANT. RENTISTICO CONCEPTO TOTAL CONCEPTO

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TOTAL $ 4S2000.00

50N: CUATROCIENTOS OCHENTA V DOS NIL PESOS

RESPONSABLE

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TRADUCCION OFICIAL No. 05-223

Efectuada el dla 9 de diciembre de 2005, de un documento escrito en Ingles, al cual para su identificación se le estampa el sello de Sergio AndrØs Rueda Iglesias, Traductor e IntØrprete Oficial por Resolución No. 0138 expedida por el Ministerio de Justicia y del Derecho el 11 de febrero de 2002.

Traducción de las Autenticaciones Notariales y subsiguientes correspondientes a un Poder otorgado por PFIZER PRODUCTS,
INC., a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria
Frieri y/o Juan Guillermo Moure y/o Natalia Castro, documento este que viene en espanol, se explica por si solo y fue firmado por Grover F. Fuller, Jr. el 17 de noviembre de 2005 en Nueva York, Estados Unidos de America.

TambiØn en inglØs y en espanol viene CertificaciÆn Notarial mediante la cual se confirma el nombre y cargo de Grover F. Fuller, Jr, asi como la existencia legal de la companla. Dicha certificación notarial estÆ firmada por Susan Z. Killian, Notario Püblico de Nueva York, cuyo cargo expira el 4 de octubre de 2008, segün consta en su correspondiente sello notarial.

Suscrito y jurado ante ml el 17 de noviembre de 2005.

(Fdo.) Susan Z. Killian -IlL
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TRADUCTO F
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ESTADO DE NUEVA YORK - CONDADO DE NUEVA YORK No. 467518

El suscrito, Norman Goodman, Escribano del Condado y del Tribunal Supremo del Estado de Nueva York, tribunal Øste provisto de sello por ley, por medio de este documento certifico conforme a la ley ejecutiva del Estado de Nueva York que Susan Z. Killian, cuyo nombre aparece suscrito en la declaraciôn jurada o certificado de reconocimiento anexo, desempeæaba en el momento de tomar el mismo, las funciones de Notario Püblico, en y para el Estado de Nueva York, estando debidamente comisionado bajo juramento y habilitado como tal; que conforme a la ley en mi despacho obra un certificado de su nombramiento con su firma autógrafa; que conozco bien la letra manuscrita de dicho Notario Püblico o he comparado la firma que aparece en el instrumento anexo con la que reposa en los archivos de mi oficina, y creo en conciencia que la misma es autØntica.

EN FE DE LO CUAL, firmo de mi puno y letra y estampo mi sello oficial., el dia 22 de noviembre de 2005.

(Fdo.) Norman Goodman, Escribano del Condado y del Tribunal Supremo del Estado de Nueva York.

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APOSTILLA

(Convención de La Haya del 5 de octubre de 1961)
1. Pals: Estados tinidos de America
El presente documento pCblico
2. Fue firmado por: Norman Goodman
3. Que actuó en su calidad de: Escribano del Condado
Lieva el sello del Condado de Nueva York
Se certificó:
S. En Nueva York, Nueva York
6. El 22 de noviembre de 2005
7. Por parte del Secretarlo de Estado, (Encargado) del
Estado de Nueva York
8. Bajo el NCmero NYC-10404952A
9. Aparece Sello del Estado de Nueva York
10. Firmado por: James Bizzarri, Secretario de Estado
Especial Encargado

Es traducción fiel y completa efectuada por:
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Sergio An res Rued Iglesias iGLE; i -

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(Convention de La Haye du 5 Octobre 1961)

1. Country: United States of America
This public document
2. has been signed by Norman Goodman
3. acting in the capacity of County Clerk
4. bears the seal/stamp of the county of New York

QCerttfteb

5. At New York, New York 6. the 22nd day of November 2005
7. by Special Deputy Secretary of State, State of New York
8. No. NYC-10404952A
9. Seal/Stamp 10. Signature

04135595.RSL (REV: 2/6/96)

James Bizzarri
Special Deputy Secretary of State

COLOMBIA i!i OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Power of Attorney Poder

The undersigned, El suscrito,
PFIZER PRODUCTS INC.,
domiciled in domiciliado en

Eastern Point Road, Groton, State of Connecticut 06340, United States of America

by means of these presents hereby grants to Carlos
R. Olarte and/or J. Ian Raisbeck and/or
Ana Maria Frieri and/or Juan Guillermo
Moure and/or Natalia Castro full and
sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company’s Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer’s Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Signature/Firma:

Date/Fecha:

Carlos R. Olarte
J. Ian Raisbeck
Ana Maria Frieri

KJ

uan Guillermo Moure
Natalia Castro

Zayde Chahin
Zaava Ravid

Jacqueline Chaparro
Jose Lois Londoæo
Camilo Alvarez
Felipe Mendoza
Camilo Rodriguez
Santiago Pardo

por medio del presente otorga a Carlos R.

OJarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure yb Natalia Castro poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de]as Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseflos Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseæas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de Ia compafila en la Repüblica de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquIa para cumplir con lo encomendado, elevar solicitudes, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compaflIa, otorgar poderes a quienes vayan a representar a la compaæIajudicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dÆndoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

PFIZE RODUCTS INC.,

Grover F. Fuller, Jr.

Vice President, Attorney-In- Fact

City,Country/Ciudad,PaIs: IW?u) q0MI IN 1J54

World Trade Center - Torre A, Calle 100 No. SA - 37, Piso 10, Bogota D.C., Colombia
Tel + 57 1601-7700, Fax + 57 1601-7799, officeiolarteraisbeck.com. www.olarteraisbeck.com

Of Counsel

Guillermo ChahIn
Graciela Melo

OLARTERAISBECK
OLARTE RAISBECK & FRIERI LTDA.

Notarial Certification

On this date,

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

Certificación Notarial

En esta fecha,

el Notario Püblico suscrito certifica:

1. Que
Grover F. Fuller, Jr.
mayor de edad y domiciiiado

Street 150 East 42nd Street
City New York
State New York 10017-5612 USA_

2. That the grantor has executed the foregoing document as Vice President, Attorney-In-Fact
of PFIZER PRODUCTS INC.

3. That PFIZER PRODUCTS INC,
having its principal place of business located in Groton, State of Connecticut 06340, United States of America
is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

suscribió el documento que antecede.

2. Que el otorgante ha suscrito ci referido documento en su carÆcterde
de

4. Que
con sede principal ubicada en

estÆ legaimente constituida, que tiene existencia
legal vigente y que los propósitos para los cuales
se otorga el poder se encuentra dentro de los que
comprenden su objeto social.

4. That the grantor has the authority to execute the 4. Que ci otorgante tiene la representación para Power of Attorney and that his/her representation is suscribir ci poder, y que Østa es legitima.
legal.

NOTARY PUBLIC (Sire):

A. y1zbIfc State of New York
: NoOIKI6116S21

Oua1ed1n New York Cow,i3y,,
*oUission Expires October 4,_

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(71) Applicant (for all designated States except US): PFIZER PRODUCTS INC. [US/US]; Eastern Point Road, Groton,
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Road, Morris Plains, NJ 07950 (US).

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States (unless otherwise indicate4’for every
fn ional protection available): AB, AG, AL, AM,

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ance Notes on Codes andAbbreviations" appearing at the begin-
fling of each regular issue ofthe PCT Gazette,

(54) Title: BICYCLIC [3.1.0] HETEROARYL AMIDES AS TYPE I GLYCINE TRANSPORT INHIBITORS

rI (57) Abstract: The present invention relates to a series of substituted bicyclic[3.1.0] heteroaryl amides of the Formula I, wherein A, Q, X, Y, Z and R1 -R5 groups are defined as in the specification, that exhibit activity as glycine transport inhibitors, their phar-maceutically acceptable salts, pharmaceutical compositions containing them, and their use for the enhancement of cognition and the treatment of the positive and negative symptoms of schizophrenia and other psychoses in mammals, including humans.

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BICYCLIC 13.1.01 HETEROARYL AMIDES AS TYPE I GLYCINE TRANSPORT
INHIBITORS
Backctround

The present invention relates to bicyclic[3. 1.0] heteroaryl amides and to
5 pharmaceutical compositions containing them and to their use in the treatment of central
nervous system disorders, cognitive disorders, schizophrenia, dementia and other disorders
in mammals, including humans. These compounds exhibit activity as inhibitors of the glycine type-1 transporter.
Schizophrenia, a progressive neurological disease, is manifested in its early stages
10 as thought disorders such as hallucinations, paranoid delusions, and bizarre thought patterns,
collectively known as positive symptoms. These easily recognizable symptoms gave the disease the historical name "madness". As the disease progresses, negative symptoms, such as social withdrawal and anhedonia, and cognitive symptoms such as dementia become more apparent. Only about one-third of schizophrenic patients can be treated successfully
15 and returned to society, while the remainder is generally.institutionalized. The burden on
society of this devastating illness and the toll it takes on family members of affected patients make it one of the most costly of all CNS diseases.
Pharmacological treatment for schizophrenia has traditionally involved blockade of
the dopamine system, yhich is thought to be responsible for its positive symptoms. Such
20 treatment, however, ignores the negative and cognitive aspects of the disease. Another
neurotransmitter system believed to play a role in schizophrenia is the glutamate system, the major excitatory transmitter system in the brain. This hypothesis is based on the observation
that blockade of the glutamate system by compounds such as PCP ("angel dust") can replicate many of the symptoms of schizophrenia, including its positive, negative, and
25 cognitive aspects. If schizophrenia involves a deficit of glutamatergic transmission,
augmentation of the glutamate system, and specifically the NMDA receptor, may be beneficial. While glutamate is the principle agonist at NMDA receptors, glycine is required as
a co-agonist to set the "tone" of the receptor for its response to glutamate. Enhancing this "tone" by increasing the effect of glycine would augment NMDA neurotransmission, and
30 provide potential benefit in the treatment of schizophrenia.
A specific mechanism for augmenting the glycinergic "tone" of the NMDA receptor
was disclosed recently by Bergeron, et a). (Proc. Natl. Acad. Sd. USA, 95, 15730, (1998)), which is hereby incorporated by reference. This group showed that a specific and potent inhibitor of the glycine type-1 transporter (GlyTi) responsible for removing glycine from the
35 synapse at the NMDA receptor, termed NFPS (WO 97/45115), could enhance NMDA
receptor function. For example, NFPS increased the postsynaptic current driven by the NMDA receptor, an effect blocked by both a specific NMDA-site antagonist and a glycine-site

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antagonist. Even though glycine levels in the brain are high relative to the amount required to act as an NMDA receptor co-agonist, this work shows that GIyTI removes glycine efficiently
at the synapse, and that inhibition of GIyT1 can augment NMDA receptor function. The present invention provides GIyTI inhibitors as a treatment for disorders or conditions such as
5 schizophrenia through its augmentation of glutamatergic neurotransmission.
Summary of the Invention
The present invention relates to compounds of Formula I, wherein

[1

R11,O
R4

0 R5

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Formula I

10 wherein R1 represents a heteroaryl selected from the group consisting of: imidazolyl, thiazolyl,
pyridyl, oxazolyl, pyrazolyl, triazolyl, oxadiazolyl, quinolinyl, isoxazolyl, pyrroloimidazoyl and thiadiazole, wherein said heteroaryl is optionally substituted by one or more substituents selected from -OH, -NR7R, halogen, (C1-C8)alkyl, (C3-C10)cycloalkyl, (C1-C8)alkoxy, (C1-C12)alkoxyalkyl, (C1-C8)hydroxyalkyl, (C6-C14)aryl and benzyl;
15 R2, R3 and A independently represent H or (C1-C8)alkyl wherein said alkyl Is optionally substituted by one or more -OH, (C1-C8)alkoxy, -NR7R8 or halogen;
Q represents (C1-f2)6-, where n = 1, 2, 3 or 4 or (CH2)mO, where m =2, 3 or 4;
Z represents (C8-C14)aryl, (C1-C8)alkyl or (C3-C3)cycloalkyl;
R4 and R5 each independently represent H, halogen, (C1-C8)alkyl, (C6-C14)aryl, (C6-
20 C14)aryloxy, (C,-C8)alkoxy, (3-10 membered)heterocycloalkyl or (C3-C8)cycloalkoxy; wherein
R4 and R5 are optionally substituted by one or more -OH, (C1-C8)atkoxy, -NR7R8 or halogen;
Y represents -R6, -(CH2)0-R6, -C(R6)3 or -CH(R6)2, wherein o = 1, 2 or 3;
R6 represents I-I, (C6-C14)aryl, (C1-C10)alkyl, (C3-Cjo)cycloalkyl, (C5-C18)bicycloalkyl, (C5-C16)tricycloalkyl, (3-10 membered)heterocycloalkyl, (5-10 membered)heteroaryl, -
25 C(0)NR7R8, or -C(=O)0R7, wherein said R6 groups can optionally be substituted with one or
more groups;

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wherein X = -OH, (C1-C8)alkoxy, -NR11R12, -S02R10, -C(=O)R10, halogen, cyano, (C1-
C8)alkyl, (C1-C10)alkoxyalkyl, (5-10 membered)heteroaryl, (C6-C14)aryl, (C6-C14)aryloxy, benzyl, or (C1-C8)hydroxyalkyl;
wherein R7 and R8 independently represent H, (CI-C8)alkyl, (C3-C8)cycloalkyl, (5-10
5 membered)heterocycloalkyl, (C1-C8)hydroxyalky, (5-10 membered)heteroaryl or (Cj-
C10)alkoxyalkyl; wherein R7 and R8 may optionally be substituted by one or more X groups;
or R7 and R8 together with the nitrogen in which they may be attached may form a (3-
10 membered)heterocycloalkyl group optionally substituted by one or more X groups;
wherein R10 represents (C1-C8)alkyl, (C3-C8)cycloalkyl, (3-10
10 membered)heterocycloalkyl, (C1-C8)hydroxyalkyl, (5-10 membered)heteroaryl or (C1-
C10)alkoxyalkyl;
wherein R11 and R12 independently represent H, (C,-C8)alkyt, (C3-C8)cycloalkyl, (5-10 membered)heterocycloalkyl, (C1-C8)hydroxyalky, (5-10 membered)heteroaryl or (C1-C10)alkoxyalkyl;
W 15 or pharmaceutically acceptable salts, solvates or prodrugs thereof. Detailed Description of the Invention
Unless otherwise indicated, as used herein, the terms "halogen’ and ’halo" include F,
Cl, Br, and I.
Unless otherwise indicated, as used herein, the term "alkyl" includes saturated
20 monovalent hydrocarbon radicals having straight or branched moieties. Examples of alkyl
groups include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, cyclopropylmethylene (-CH2-cyclopropyl) and t-butyl.
Unless otherwise indicated, as used herein, the term "alkenyl" includes alkyl moieties
- having at least one carbon-carbon double bond wherein alkyl is as defined above. Examples
25 of alkenyl include, but are not limited to, ethenyl and propenyl.
Unless otherwise indicated, as used herein, the term "alkynyl" includes alkyl moieties
having at least one carbon-carbon triple bond wherein alkyl is as defined above. Examples of alkynyl groups include, but are not limited to, ethynyl and 2-propynyl.
Unless otherwise- indicated, as used herein, the term "alkoxy", means "alkyl-O-",
30 wherein "alkyl" is as defined above. Examples of "alkoxy" groups include, but are not limited
to, methoxy, ethoxy, propoxy, butoxy, pentoxy and allyloxy.
Unless otherwise indicated, as used herein, the term "alkoxyalkyl" means alkyl-0-
alkyl-, wherein alkyl is defined above.
Unless otherwise indicated, as used herein, the term "hydroxyalkyl" means -alkyl-OH,
35 wherein alkyl is defined above.
Unless otherwise indicated, as used herein, the term "alkenoxy", means "alkenyl-O-", wherein "alkenyl" is as defined above.

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Unless otherwise indicated, as used herein, the term Kalkynoxyi, means "alkynyl-O-,
wherein "alkynyl’ is as defined above.
Unless otherwise indicated, as used herein, the term cycloalkyl includes non-
aromatic saturated cyclic alkyl moieties wherein alkyl is as defined above. Examples of
5 cycloalkyl include, but are not limited to, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and
cycloheptyl. "Bicycloalkyl’ and tricycloalkyl" groups include non-aromatic saturated cyclic alkyl moieties consisting of two or three rings respectively, wherein said rings share at least
one carbon atom. "Bicycloalkyl" and "tricycloalkyl groups also include cyclic moieties consisting of two or three rings respectively, wherein one ring is aryl or heteroaryl and
10 wherein said rings share two carbon atoms. For purposes of the present invention, and unless
otherwise indicated, bicycloalkyl groups include spiro groups and fused ring groups. Examples of bicycloalkyl groups include, but are not limited to, bicyclo-[3.1.0]-hexyl, bicyclo-2.2.1 }-hept-1 -yl, norbornyl, spiro[4.5]decyl, spiro4.4]nonyl, spiro[4.3]octyl, spiro[4.2]heptyl,

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teralene (1,2,3,4-tetrahydronaphiene) and 6, 7, 8, 9-tetrahydro-SH-benzocycloheptene.
15 An example of a tricycloalkyl group is adamantanyl. Other cycloalkyl, bicycloalkyl, and
tricycloalkyl groups are known in the art, and such groups are encompassed by the definitions "cycloalkyl", "bicycloalkyl" and "tricycloalkyl" herein. "Cycloalkenyl", ’bicycloalkenyl’, and "tricycloalkenyl" refer to non-aromatic each cycloalkyl, bicycloalkyl, and tricycloalkyl moieties
as defined above, except that they each include one or more carbon-carbon double bonds
20 connecting carbon ring members (an "endocyclic" double bond) and/or one or more carbon-
carbon double bonds connecting a carbon ring member and an adjacent non-ring carbon (an ’exocyclic" double bond). Examples of cycloalkenyl groups include, but are not limited to, cyclopentenyl, cyctobutenyl, and cyclohexenyl. A non-limiting example of a bicycloalkenyl group is norbornenyl. Cycloalkyl, cycloalkenyl, bicycloalkyl, and bicycloalkenyl groups also
25 include groups that are substituted with one or more oxo moieties. Examples of such groups
with oxo moieties are oxocyclopentyl, oxocyclobutyl, oxocyclopentenyl and norcamphoryl. Other cycloalkenyl, bicycloalkenyl, and tricycloalkenyl groups are known in the art, and such groups are included within the definitions "cycloalkenyl", "bicycloalkenyl" and tricycloalkenyl" herein.

30 Unless otherwise indicated, as used herein, the term "aryl" includes an organic radical derived from an aromatic hydrocarbon by removal of one hydrogen, such as phenyl (Ph), naphthyl, indenyl, indanyl and ftuorenyl. "Aryl" encompasses fused ring groups wherein at least one ring is aromatic.
Unless otherwise indicated, as used herein, the terms "heterocyclic" and
35 "heterocycloalkyl" refer to non-aromatic cyclic groups containing one or more heteroatoms,
preferably from one to four heteroatoms, each selected from 0, S and N. ’Heterobicycloalkyl" groups include non-aromatic two-ringed cyclic groups, wherein said rings share one or two

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atoms, and wherein at least one of the rings contains a heteroatom (0, S. or N). uHeterobicycIoalkyI groups also include two-ringed cyclic groups, wherein said one ring is aryl or heteroaryl ring and wherein said rings share one or two atoms, and wherein at least one of the rings contains a heteroatom (0, S, or N). Unless otherwise indicated, for
5 purposes of the present invention, heterobicycloalkyl groups include spire groups and fused
ring groups. In one embodiment, each ring in the heterobicycloalkyl. contains up to four heteroatoms (i.e. from zero to four heteroatoms, provided that at least one ring contains at least one heteroatom). The heterocyclic groups of this invention can also include ring
systems substituted with one or more oxo moieties. Examples of non-aromatic heterocyclic
10 groups are aziridinyl, azetidinyl, pyrrolldinyl, piperidinyl, azepinyl, piperazinyl, 1,2,3,6-
tetrahydropyridinyl, oxiranyl, oxetany), tetrahydrofuranyl, tetrahydrothienyl, tetrahydropyranyl, tetrahydrothiopyranyl, morpholino, thiomorpho)ino, thioanyl, pyrrolinyl, indolinyl, 2H-pyranyl,
4H-pyranyl, dioxanyl, I,3-dioxo)anyl, pyrazoliny), dihydropyranyl, dihydrothienyl,
. dihydrofuranyl, pyrazolidinyl, imidazolinyl, imidazolidinyl, 3-azabicyclo[3.1.O]hexanyl, 3-
15 azabicyclo[4.1.O]heptanyl, quinolizinyl, quinuclidinyl, I,4-dioxaspiro[4.5]decyl, 1,4-dioxaspiro[4.4]nonyl, I,4-dioxaspiro[4.3]octyl, and I,4-dioxaspiro4.2]heptyl.
Unless otherwise indicated, as used herein, "heteroaryl" refers to aromatic groups
containing one or more heteroatoms, preferably from one to four heteroatoms, selected from 0,
S and N. A multicyclic group containing one or more heteroatoms wherein at least one ring of
20 the group is aromatic is a "heteroaryl" group: The heteroaryl groups of this invention can also
include ring systems substituted with one or more oxo moieties. Examples of heteroaryl groups
are pyridinyl, pyridazinyl, imidazolyl, pyrimidinyl, pyrazolyl, triazolyl, pyrazinyl, quinolyl, isoquinolyl, I,2,3,4-tetrahydroguinolyl, tetrazolyl, furyl, thienyl, isoxazolyl, thiazolyl, oxazolyl, isothiazolyl, pyrrolyl, indolyl, benzimidazolyl, benzofuranyl, cinnolinyl, indazolyl, indolizinyl,
25 phthalazinyl, triazinyl, 1,2,4-trizainyl, 1,3,5-triazinyl, isoindolyl, I -oxoisoindolyl, purinyl,
oxadiazolyl, thiadiazolyl, furazanyl, benzofurazanyl, benzothiophenyl, benzotriazolyl, benzothiazolyl, benzoxazolyl, quinazolinyl, quinoxalinyl, naphthyridinyl, dihydroquinolyl, tetrahydroquinolyl, dihydroisoquinoly), tetrahydroisoquinolyl, benzofuryl, furopyridinyl, pyrolopyrimidinyl, and azaindolyl.
30 Unless otherwise indicated, as used herein, the term "cycloalkoxy", means "cycloalkyl-0-", wherein "cycloalkyl" is as defined above.
Unless otherwise indicated, as used herein, the term "aryloxy", means "aryl-02’
wherein "aryl" is as defined above.
Unless otherwise indicated, as used herein, the term "heterocycloalkoxy", means
35 "heterocycloalky)-0-", wherein ’heterocycloalkyl" is as defined above.
Unless otherwise indicated, as used herein, the term uheteroaryloxy means "heteroaryl-0-", wherein ’heteroary)’ is as defined above.

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Unless otherwise indicated, all the foregoing groups derived from hydrocarbons may
be optionally substituted by one or more halogen atoms (e.g., -CH2F, -CHF2 CF3, -PhCI, etc.).
Unless otherwise indicated, the term "one or more" substituents, or "at least one"
5 substituent as used herein, refers to from one to the maximum number of substituents
possible based on the number of available bonding sites. (Examples of one or more or at least one substituent include, but are not limited to, Ito 10 substituents, or Ito 6 substituents
or I to 3 substituents).
Unless otherwise indicated, all the foregoing groups derived from hydrocarbons may
10 have up to about I to about 20 carbon atoms (e.g. C1-C20 alkyl, CZ-C20 alkenyl, C3-C20
cycloalkyl, (3-20 membered)heterocycloalkyl, Ce-C20 aryl, (5-20 membered)heteroaryl, etc.) or
I to about 15 carbon atoms (e.g., C1-05 alkyl, C2-05 alkenyl, C3-C15 cycloalky), (3-15 membered)heterocycloalkyl, C6-C15 aryl, (5-15 membered)heteroaryl, etc.), or I to about 12 carbon atoms, or I to about 8 carbon atoms, or I to about 6 carbon atoms.
15 The foregoing groups, as derived from the compounds listed above, may be C-attached or N-attached where such is possible. For instance, a group derived from pyrrole may be pyrrol-I -yl (N-attached) or pyrrol-3-yl (C-attached). The terms referring to the groups also encompass all possible tautomers.
In one aspect of the invention, the stereochemistry is defined as in Formula II or
20 Formula lii:

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R2J NZ
R5

Formula 11

N

Y
Formula lii

R4

R5

In one aspect of this invention, R1 is imidazolyl optionally substituted by methyl.
In another aspect, Z is (C5-C14)aryl, and R4 or R5 are each independently H, halogen, 25 -CF3, -OCF3, (C6-C14)aryl or (C6-C14)aryloxy. In yet another aspect of the invention, R2, R3 and A are hydrogen.

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In another aspect, Y is a (C1-C6)alkyl, a (C3-C6)cycloalkyl, a (3-6 membered)heterocycloalkyl or -CH2-(C3-C6)cycloalkyt; wherein V is optionally substituted by halogen, OH, -S02R10, -C(0)R10, or CH2CH2CF3.
In another aspect of this invention, the compound of Formula I has the following
5 structure:

wherein R2-R5, Q, Z, V and A are as defined above,.
Specific embodiments of the present invention are shown in the Examples below.
Compounds of the Formula I may have optical centers and therefore may occur in
10 different enantiomeric and diastereomeric configurations. The present invention includes all
enantiomers, diastereomers, and other stereoisomers of such compounds of the Formula I,
as well as racemic compounds and racemic mixtures and other mixtures of stereolsomers thereof.
- Pharmaceutically acceptable salts of the compounds of Formula I include the acid
15 addition and base salts thereof.
Suitable acid addition salts are formed from acids which form non-toxic salts.
Examples include, but are not limited to, the acetate, adipate, aspartate, benzoate, besylate, bicarbonate/carbonate, bisulphate/sulphate, borate, camsylate, citrate, cyclamate, edisylate, esylate, formate, fumarate, gluceptate, gluconate, glucuronate, hexafluorophosphate,
20 hibenzate, hydrochloride/chloride, hydrobromide/bromide, hydrolodide/lodide, isethionate,
lactate, malate, maleate, malonate, mandelates mesylate, methylsuiphate, naphthylate, 2-napsylate, nicotinate, nitrate, orotate, oxalate, palmitate, pamoate, phosphate/hydrogen phosphate/dihydrogen phosphate, pyroglutamate, salicylate, saccharate, stearate, succinate, sulfonate, stannate, tartrate, tosylate, trifluoroacetate and xinofoate salts.
25 Suitable base salts are formed from bases which form non-toxic salts. Examples include, but are not limited to, the aluminium, arginine, benzathine, calcium, choline, diethylamine, diolamine, glycine, lysine, magnesium, meglumine, olamine, potassium, sodium, tromethamine and zinc salts.

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Hemisalts of acids and bases may also be formed, for example, hemisulphate and hemicalcium salts.
For a review on suitable salts, see Handbook of Pharmaceutical Salts: Properties,
Selection, and Use by Stahl and Wermuth (Wiley-VOH, 2002).
5 Pharmaceutically acceptable salts of compounds of Formula I may be prepared by one or more of three methods:
(i) by reacting the compound of Formula I with the desired acid or base;
(ii) by removing an acid- or base-labile protecting group from a suitable
precursor of the compound of Formula I or by ring-opening a suitable cyclic precursor, for
10 example, a lactone or lactam, using the desired acid or base; or
(iii) by converting one salt of the compound of Formula I to another by reaction
with an appropriate acid or base or by means of a suitable ion exchange column.
All three reactions are typically carried out in solution. The resulting salt may
. precipitate out and be collected by filtration or may be recovered by evaporation of the
15 solvent. The degree of ionization in the resulting salt may vary from completely ionised to
almost non-ionised.

The compounds of the invention may exist in a continuum of solid states ranging from
fully amorphous to fully crystalline. The term ’amorphous’ refers to a state in which the
material lacks long range order at the molecular level and, depending upon temperature, may
20 exhibit the physical properties of a solid or a liquid. Typically such materials do not give
distinctive X-ray diffraction patterns and, wlile exhibiting the properties of a solid, are more formally described as a liquid. Upon heating, a change from solid to liquid properties occurs which is characterised by a change of state, typically second order (’glass transition’). The term ’crystalline’ refers to a solid phase in which the material has a regular ordered internal
25 structure at the molecular level and gives a distinctive X-ray diffraction pattern with defined
peaks. Such materials when heated sufficiently will also exhibit the properties of a liquid, but
the change from solid to liquid is characterised by a phase change, typically first order (’melting point’).
The compounds of the invention may also exist in unsolvated and solvated forms.
30 The term ’solvate’ is used herein to describe a molecular complex comprising the compound
of the invention and one or more pharmaceutically acceptable solvent molecules, for example, ethanol. The term ’hydrate’ is employed when said solvent is water.
A currently accepted classification system for organic hydrates is one that defines
isolated site, channel, or metal-ion coordinated hydrates - see Polymorphism in
35 Pharmaceutical Solids by K. R. Morris (Ed. H. C. Brittain, Marcel Dekker, 1995). Isolated site
hydrates are ones in which the water molecules are isolated from direct contact with each other by intervening organic molecules. In channel hydrates, the water molecules lie in lattice

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channels where they are next to other water molecules. In metal-ion coordinated hydrates, the water molecules are bonded to the metal ion.
When the solvent or water is tightly bound, the complex will have a well-defined stoichiometry independent of humidity. When, however, the solvent or water is weakly bound,
5 as in channel solvates and hygroscopic compounds, the water/solvent content will be
dependent on humidity and drying conditions. In such cases, non-stoichiometry will be the

norm.

The compounds of the invention may also exist in a mesomorphic state (mesophase
or liquid crystal) when subjected to suitable conditions. The mesomorphic state is
10 intermediate between the true crystalline state and the true liquid state (either melt or
solution). Mesomorphism arising as the result of a change in temperature is described as ’thermotropic’ and that resulting from the addition of a second component, such as water or another solvent, is described as ’lyotropic’. Compounds that have the potential to form lyotropic mesophases are described as ’amphiphilic’ and consist of molecules which possess
15 an ionic (such as -COONa, -COOK, or -S03Na) or non-ionic (such as -NN(CH3)3) polar
head group. For more information, see Crystals and the Polarizing Microscope by N. H. Hartshorne and A. Stuart, 0’ Edition (Edward Arnold, 1970).
Hereinafter all references to compounds of Formula I include references to salts,
solvates, multi-component complexes and liquid crystals thereof and to solvates, multi-
20 component complexes and liquid crystals of salts thereof.
The compounds of the invention include compounds of Formula I as hereinbefore
defined, including all polymorphs and crystal habits thereof, prodrugs and isomers thereof (including optical, geometric and tautomeric isomers) as hereinafter defined and isotopically-

25 As indicated, so-called ’prodrugs’ of the compounds of Formula I are also within the scope of the invention. Thus certain derivatives of compounds of Formula I which may have
little or no pharmacological activity themselves can, when administered into or onto the body,
be converted into compounds of Formula I having the desired activity, for example, by
 hydrolytic cleavage. Such derivatives are referred to as ’prodrugs’. Further information on the
30 use of prodrugs may be found in Pro-drugs as Novel Delivery Systems, Vol. 14, ACS
Symposium Series (T. Higuchi and W. Stella) and Bioreversible Carriers in Drug Design, Pergamon Press, 1987 (Ed. E. B. Roche, American Pharmaceutical Association).
Prodrugs in accordance with the invention can, for example, be produced by
replacing appropriate functionalities present in the compounds of Formula I with certain
35 moieties known to those skilled in the art as ’pro-moieties’ as described, for example, in
Design of Prodrugs by H. Bundgaard (Elsevier, 1985).

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Some examples of prodrugs in accordance with the invention include, but are not
limited to,

(i) where the compound of Formula I contains a carboxylic acid functionality
(-COOH), an ester thereof, for example, a compound wherein the hydrogen of the
5 carboxylic acid functionality of the compound of Formula (I) is replaced by (C1-C8)alkyl;
(ii) where the compound of Formula I contains an alcohol functionality (-OH), an
ether thereof, for example, a compound wherein the hydrogen of the alcohol functionality of
the compound of Formula I is replaced by (C1-C6)alkanoyloxymethyl; and
(iii) where the compound of Formula I contains a primary or secondary amino
10 functionality (-NH2 or -NHR where R 0 H), an amide thereof, for example, a compound
wherein, as the case may be, one or both hydrogens of the amino functionality of the
compound of Formula I is/are replaced by (C1-C10)alkanoyl.
Further examples of replacement groups in accordance with the foregoing examples
. and examples of other prodrug types may be found in the aforementioned references.
15 Moreover, certain compounds of Formula (may themselves act as prodrugs of, other
compounds of Formula I.
Also included within the scope of the invention are metabolites of compounds of
Formula I, that is, compounds formed in vivo upon administration of the drug. Some examples
of metabolites in accordance with the invention include, but are not limited to,
20 (i) where the compound of Formula I contains a methyl group, an hydroxyrnethyl
derivative thereof (-CH3 -> -CH20H):
(ii) where the compound of Formula I contains an alkoxy group, an hydroxy

derivative thereof (-OR -> -OH); - (iii) where the compound of Formula I contains a tertiary amind group, a
25 secondary amino derivative thereof (-NR1R2 -> -NHR1 or -NHR2);
(iv) where the compound of Formula I contains a secondary amino group, a
primary derivative thereof (-NHR1 -> -NH2);
(v) where the compound of Formula I contains a phenyl moiety, a phenol
derivative thereof (-Ph -> -PhOH); and
30 (vi) where the compound of Formula I contains an amide group, a carboxylic acid
derivative thereof (-CONH2 -> COOH).
Compounds of Formula I containing one or more asymmetric carbon atoms can exist
as two or more stereoisomers. Where a compound of Formula I contains an alkenyl or alkenylene group, geometric cisltrans (or ZIE) isomers are possible. Where structural isomers
35 are interconvertible via a low energy barrier, tautomeric isomerism (’tautomerism’) can occur.
This can take the form of proton tautomerism in compounds of Formula I containing, for example, an imino, keto, or oxime group, or so-called valence tautomerism in compounds

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which contain an aromatic moiety. It follows that a single compound may exhibit more than one type of isomerism.
Included within the scope of the present invention are all stereolsomers, geometric
isomers and tautomeric forms of the compounds of Formula I, including compounds exhibiting
5 more than one type of isomerism, and mixtures of one or more thereof. Also included are
acid addition or base salts wherein the counterion is optically active, for example, d-lactate or !-lysine, or racemic, for example, d/-tartrate or d!-arginine.
Cisitrans isomers may be separated by conventional techniques well known to those
skilled in the art, for example, chromatography and fractional crystallisation.
10 Conventional techniques for the preparation/isolation of individual enantiorners include chiral synthesis from a suitable optically pure precursor or resolution of the racemate
(or the racemate of a salt or derivative) using, for example, chiral high pressure liquid chromatography (HPLC). -
Alternatively, the racemate or racemic mixture (or a racemic precursor) may be
15 reacted with a suitable optically active compound, for example, an alcohol, or, in the case
where the compound of Formula I contains an acidic or basic moiety, a base or acid such as
I -phenylethylamine or tartaric acid. The resulting diastereomeric mixture may be separated
by chromatography and/or fractional crystallization and one or both of the diastereoisomers converted to the corresponding pure enantiomer(s) by means well known to a skilled person.
20 Chiral compounds of the invention (and chiral precursors thereof) may be obtained in enantiomerically-enriched form using chromatography, typically HPLC, on an asymmetric resin with a mobile phase consisting of a hydrocarbon, typically heptane or hexane, containing from 0 to 50% by volume of isopropanol, typically from 2% to 20%, and from 0 to
5% by volume of an alkylamine, typically 0.1% diethylamine. Concentration of the euate
25 affords the enriched mixture.
When any racemate crystallises, crystals of two different types are possible. The first
type is the racemic compound (true racemate) referred to above wherein one homogeneous form of crystal is produced containing both enantiomers in equimolar amounts. The second

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type is the--racemic -mixture-or conglomerate wherein two forms of crystal are produced in
30 equlmolar amounts each comprising a single enantiomer.
While both of the crystal forms present in a racemic mixture have identical physical properties, they may have different physical properties compared to the true racemate. Racemic mixtures may be separated by conventional techniques known to those skilled in the
art - see, for example, Stereochemistry of Organic Compounds by E. L. Eliel and S. H. Wilen
35 (Wiley, 1994).
The present invention includes all pharmaceutically acceptable isotopically-labelled compounds of Formula I wherein one or more atoms are replaced by atoms having the same

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atomic number, but an atomic mass or mass number different from the atomic mass or mass number which predominates in nature.
Examples of isotopes suitable for inclusion in the compounds of the invention include,
but are not limited to, isotopes of hydrogen, such as 2H and 3H, carbon, such as 1’C, ’3C and
5 4C, chlorine, such as 36C1, fluorine, such as 18F, iodine, such as 1231 and 11, nitrogen, such as
13N and 15N, oxygen, such as O, O and 180, phosphorus, such as 32P, and sulphur, such
as 35S.
Certain isotopically-labelled compounds of Formula I, for example, those incorporating a radioactive isotope, are useful in drug and/or substrate tissue distribution
10 studies. The radioactive isotopes tritium, i.e. 3H, and carbon-14, i.e. 14C, are particularly useful
for this purpose in view of their ease of incorporation and ready means of detection.
Substitution with heavier isotopes such as deuterium, i.e. 2H, may afford certain
therapeutic advantages resulting from greater metabolic stability, for example, increased in vivo half-life or reduced dosage requirements, and hence may be preferred in some
15 circumstances.

Substitution with positron emitting isotopes, such as 11C, 18F, 150 and 13N, can be
useful in Positron Emission Topography (PET) studies for examining substrate receptor occupancy.

Isotopically-labeled compounds of Formula I can generally be prepared by
20 conventional techniques known to those skilled in the art or by processes analogous to those
described in the accompanying Examples and Preparations using an appropriate isotopically-labeled reagent in place of the non-labeled reagent previously employed.
Pharmaceutically acceptable solvates in accordance with the invention include those
wherein the solvent of crystallization may be isotopically substituted, e.g. D20, d6-acetone, d6-
25 DMSO.

When preparing compounds of Formula I in accordance with the invention, it is open
to a person skilled in the art to routinely select the form of compound of Formula II which provides the best combination of features for this purpose. Such features include, but are not limited to, the melting point, solubility, processability and yield of the intermediate form and
30 the resulting ease with which the product may be purified on isolation.
This invention also relates to a method of treating a disorder or condition selected
from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with
35 psychotic disorders such as acute mania or depression associated with bipolar disorder and
mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder and autistic disorder, movement disorders such as Tourette’s

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syndrome, akinetic-rigid syndrome, movement disorders associated with Parkinson’s disease, tardive dyskinesia and other drug induced and neurodegeneration based dyskinesias; attention deficit hyperactivity disorder; cognitive disorders such as dementias (including age related dementia, and senile dementia of the Alzheimer’s type) and memory disorders in a
5 mammal, including a human, comprising administering to a mammal in need of such
treatment an amount of a compound of the formula I, or a pharmaceutically acceptable salt thereof, that is effective in treating such condition or disorder.
This invention also relates to a pharmaceutical composition for treating a disorder or
condition selected from psychosis, schizophrenia, conduct disorder, disruptive behavior
10 disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis,
psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders such as acute mania or depression associated with bipolar disorder and mood disorders associated with schizophrenia, behavioral manifestations
of mental retardation, conduct disorder and autistic disorder; movement disorders such as
15 Tourette’s syndrome, akinetic-rigid syndrome, movement disorders associated with
Parkinson’s disease, tardive dyskinesia and other drug induced and neurodegeneration based dyskinesias; attention deficit hyperactivity disorder; cognitive disorders such as dementias (including age related dementia and senile dementia of the Alzheimer’s type) and memory disorders in a mammal, including a human, comprising a compound of the formula I,
20 or a pharmaceutically acceptable salt thereof, in an amount that is effective for treating such
disorder or condition.
This invention also relates to a method of treating a disorder or condition selected
-from psychosis, schizophrenia, conduct disorder, disruptive behavior disorder, bipolar disorder, -psychotic anxiety, anxiety associated with psychosis, psychotic mood
25 -disorders such as severe major depressive disorder; mood disorders associated with
psychotic disorders such as acute mania or depression associated with bipolar disorder and mood disorders associated with schizophrenia, behavioral manifestations of mental retardation, conduct disorder and autistic disorder; movement disorders such as Tourette’s syndrome, akinetic-rigid syndrome,- movement-disorders-associated with Parkinson’s disease,
30 tardive dyskinesia and other drug induced and neurodegeneration based dyskinesias;
attention deficit hyperactivity disorder; cognitive disorders such as dementias (including age related dementia and senile dementia of the Alzheimer’s type) and memory disorders in a mammal, including a human, comprising administering to a mammal in need of such treatment a glycine transport-inhibiting amount of a compound of the formula I, or a
35 pharmaceutically acceptable salt thereof.
This invention also relates to a pharmaceutical composition for treating a disorder or condition selected from psychosis, schizophrenia, conduct disorder, disruptive behavior

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disorder, bipolar disorder, psychotic episodes of anxiety, anxiety associated with psychosis, psychotic mood disorders such as severe major depressive disorder; mood disorders associated with psychotic disorders such as acute mania or depression associated with bipolar disorder and mood disorders associated with schizophrenia, behavioral manifestations
5 of mental retardation, conduct disorder and autistic disorder; movement disorders such as
Tourette’s syndrome, akinetic-rigid syndrome, movement disorders associated With Parkinson’s disease, tardive dyskinesia and other drug induced and neurodegeneration based dyskinesias; attention deficit hyperactivity disorder; cognitive disorders such as dementias (including age related dementia and senile dementia of the Alzheimer’s type) and
10 memory disorders in a mammal, including a human, comprising a compound of the formula 1,
or a pharmaceutically acceptable salt thereof, in a glycine transport-inhibiting amount.
As used herein, the term "treating" refers to reversing, alleviating or inhibiting the
progress of a disease, disorder or condition, or one or more symptoms of such disease, disorder or condition, to which such term applies. As used herein, "treating" may also refer to
15 decreasing the probability or incidence of the occurrence of a disease, disorder or condition in
a mammal as compared to an untreated control population, or as compared to the same mammal prior to treatment. For example, as used herein, "treating" may refer to preventing a disease, disorder or condition, and may include delaying or preventing the onset of a disease, disorder or condition, or delaying or preventing the symptoms associated with a disease,
20 disorder or condition. As used herein, "treating" may also refer to reducing the severity of a
disease, disorder or condition or symptoms associated with such disease, disorder or condition prior to a mammal’s affliction with the disease, disorder or condition. Such prevention or reduction of the severity of a disease, disorder or condition prior to affliction relates to the administration of the composition of the present invention, as described herein,
25 to a subject that is not at the time of administration afflicted with the disease, disorder or
condition. As used herein "treating" may also refer to preventing the recurrence of a disease, disorder or condition or of one or more symptoms associated with such disease, disorder or condition. The terms "treatment" and "therapeutically," as used herein, refer to the act of ireating, as "treating" is defined above.
30 The compounds of the present invention exhibit glycine transport inhibiting activity and therefore are of value in the treatment of a wide variety of clinical conditions that are characterized by the deficit of glutamateric neurotransmission in mammalian subjects, especially humans. Such conditions include the positive and negative symptoms of schizophrenia and other psychoses, and cognitive deficits.
35 The compounds of this invention can be administered via either the oral, parenteral (such as subcutaneous, intraveneous, intramuscular, intrasternal and infusion techniques), rectal, iritrariasal or topical routes to mammals. In general, these compounds are most desirably

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administered to humans in doses ranging from about 1mg to about 2000 mg per day, although variations will necessarily occur depending upon the weight and condition of the subject being treated and the particular route of administration chosen. However, a dosage level that is in the range of from about 0.1 mg to about 20 mg per kg of body weight per day is most desirably
5 employed. Nevertheless, variations may still occur depending upon the species of animal being
treated and its individual response to said medicament, as well as on the type of pharmaceutical formulation chosen and the time period and interval at which such administration is carried out. In some instances, dosage levels below the lower limit of the aforesaid range may be more than adequate, while in other cases still larger doses may be employed without causing any harmful
10 side effects provided that such higher dose levels are first divided into several small doses for
administration throughout the day.
In one embodiment, the compounds of this invention are administered as adjunctive
therapy with known anti-psychotics such as Ziprasidone (Geodon), Clozapine, Molindone, Loxapine, Pimozide, Risperidone, Olanzapine, Remoxipride, Sertindole, Amisulpride, Quetiapine,
15 Prochlorperazine, Fluphenazine, Trifluoroperazine, Thioridazine, 1-laloperidol, Chloropromazine,
Flupentixol and Pipotiazine.
In another embodiment, the compounds of the present invention may also be used in
combination with CNS agents such as antidepressants (such as sertraline), anti-Parkinsonian drugs (such as deprenyl, L-dopa, Requip, Mirapex, MAOB inhibitors such as selegine and
20 rasagiline, comP inhibitors such as Tasmar, A-2 inhibitors, dopamine reuptake inhibitors,
NMDA antagonists, Nicotine agonists, Dopamine agonists and inhibitors of neuronal nitric oxide synthase), anti-Alzheimer’s drugs such as donepezil, tacrine, a26 inhibitors, COX-2 inhibitors, gaba pentenoids, propentofytline or metryfonate, and antipyschotics such as pbE1 0 inhibitors, 5HT2C agonists, alpha 7 nicotinic receptor agonists, CBI antagonists and
25 -compounds having activity antagonizing dopamine D2 receptors.
The compounds of the present invention may be administered alone or in
combination with pharmaceutically acceptable carriers or diluents by either of the above routes previously indicated, and such administration can be carried out in single or multiple -doses.- -More particularly, the novel therapeutic-agents of the invention can be administered in
30 a wide variety of different dosage forms, i.e., they may be combined with various
pharmaceutically acceptable inert carriers in the form of tablets, capsules, lozenges, troches,
hard candies, powders, sprays, creams, salves, suppositories, jellies, gels, pastes, lotions, ointments, aqueous suspensions, injectable solutions, elixirs, syrups, and the like. Such carriers include solid diluents or fillers, sterile aqueous media and various non-toxic organic
35 solvents, etc. Moreover, oral pharmaceutical compositions can be suitably sweetened and/or
flavored. In general, the therapeutically effective compounds of this invention are present in such dosage forms at concentration levels ranging about 5.0% to about 70% by weight.

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For oral administration, tablets containing various excipients such as microcrystalline
cellulose, sodium citrate, calcium carbonate, dicalcium phosphate and glycine may be employed along with various disintegrants such as starch and preferably corn, potato or tapioca starch, alginic acid and certain complex silicates, together with granulation binders
5 like polyvinylpyrrolidone, sucrose, gelatin and acacia. Additionally, lubricating agents such as
magnesium stearate, sodium lauryl sulfate and talc are often very useful for tabletting purposes. Solid compositions of a similar type may also be employed as fillers in gelatine capsules; preferred materials in this connection also include lactose or milk sugar as well as high molecular weight polyethylene glycols. When aqueous suspensions and/or elixirs are
10 desired for oral administration, the active ingredient may be combined with various
sweetening or flavoring agents, coloring matter or dyes, and, if so desired, emulsifying and/or suspending agents as well, together with such diluents as water, ethanol, propylene glycol, glycerin and various like combinations thereof.
For parenteral administration, solutions of a compound of the present invention in
15 either sesame or peanut oil or in aqueous propylene glycol may be employed. The aqueous
solutions should be suitably buffered (preferably pH>8) if necessary and the liquid diluent first rendered isotonic. These aqueous solutions are suitable for intravenous injection purposes.
The oily solutions are suitable for intra-articular, intra-muscular and subcutaneous injection purposes. The preparation of all these solutions under sterile conditions is readily
20 accomplished by standard pharmaceutical techniques well-known to those skilled in the art.
Additionally, it is also possible to administer the compounds of the present invention topically when treating inflammatory conditions of the skin and this may preferably be done by way of creams, jellies, gels, pastes, ointments and the like, in accordance with standard pharmaceutical practice.
25 The compounds of the present invention were assayed utilizing the GlyTi radioligand
binding assay described below:
Test compound preparation: Compounds are dissolved in DMSO, sonicated if
necessary, diluted to a concentration of 0.2 mM in DMSO and then diluted with de-ionized water to a concentration of 10 uM.

30 Tissue preparation: The GlyTic transporter is expressed in HEK-293 cells and the
frozen cell pellet weighed and polytroned, with I gram cell pellet in 30 mL assay buffer (50
mM Tris base, 120 mM NaCl, and 5 mM KCI, pH’d to 7.4 with 6N HCI). The mixture is centrifuged at 40000 G for 10 mm., the supernatant decanted, and the pellet resuspended at
I mg wet weight per 25 uL assay buffer.
35 Assay: The assay incubation is carried out for 60 mm. at room temperature in 96 well
plates (Beckman 2 mL polypropylene), which are vortexed upon addition of the tissue preparation. To each well is added 25 uL test drug solution or control, 200 uL of 0.7 nM {3H]-

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NPTS (Lowe, John A.; Drozda, Susan E.; Fisher, Katherine; Strick, Christine; Lebe), Lorraine; Schmidt, Christopher; Hiller, Donna; Zandi, Kathleen S. [3H].(R)-NPTS,a radioligand for the type I glycine transporter. Bioorganic Medicinal Chemistry Letters (2003), 13(7), 1291-1292.), and 25 uL tissue. The plates are filtered using a Brandel cell harvester with OF/B
5 filters, the filters are washed with 3 X 1.5 mL assay buffer, air-dried overnight, and counted on
a LKB beta plate counter the next day.
Compounds of the invention analyzed by this assay have been found to have
significant activity in inhibiting glycine reuptake in synaptosornes, having greater than 20%

inhibition at I 1iM.

10 The compounds of the Formula I may be prepared by the methods described below,
together with synthetic methods known in the art of organic chemistry, or modifications and derivatisations that are familiar to those of ordinary skill in the art. Preferred methods include,
but are not limited to, those described below.
During any of the following synthetic sequences it may be necessary and/or desirable
15 to protect sensitive or reactive groups on any of the molecules concerned. This can be
achieved by means of conventional protecting groups, such as those described in T. W. Greene, Protective Groups in Organic Chemistry, John Wiley Sons, 1981; and T. W. Greene and P. G. M. Wuts, Protective Groups in Organic Chemistry, John Wiley Sons, 1991, which are hereby incorporated by reference.
20 Compounds of formula I or their pharmaceutically acceptable salts, can be prepared
according to the following reaction Schemes I through V as discussed herein below. Unless otherwise indicated A, Q, Y, Z and R1 through R5 are defined as above. Isolation and purification of the products is accomplished by standard procedures, which are known to a chemist of ordinary skill.
25 The following schemes are exemplary of the processes for making compounds of

formula I.

Scheme I illustrates a method for the preparation of compounds having the basic
structure of formula I, where A is hydrogen, V is hydrogen and Q, Z and R1 through R8 are defined-as above

30 Referring to Scheme I, a compound of formula (I) [SynLett, 1996, 1097] can be
treated with (BOC)20 in the presence of a suitable base such as triethylamine, in solvents such as CH2Cl2, to produce the desired carbamate of formula (II). Oxidation of the primary alcohol under Swern conditions with DM80 and oxayl chloride, in the presence of a suitable base such as triethyl amine (TEA) or dilsopropylethylamirie (DIEA), in solvents such as
35 CH2Cl2 or I,2-dichloroethane (DCE), at temperatures ranging from 78 °C to room
temperature, preferably at about room temperature, to produce the corresponding aldehyde

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(not depicted). Other suitable oxidation reagents for this transformation include TPAP/NMO

orPCC.

Treatment of the aldehyde with an appropriately substituted amine reagent of
lorumu)a (Ill) and a suitable reducing agent such as NaBH4, in a solvent such as MeOH, at
5 temperatures ranging from 5 °C to room temperature, preferably at about room temperature,
produced the desired amine of formula (IV). Other suitable reducing agents for this reaction include NaCNBH3 or NaHB(OAc)3, in solvents such as MeOH, CH2Cl2 or DCE. Other suitable conditions for this transformation include treatment of the corresponding aldehyde with the amine reagent (Ill) in CH2Cl2 or DCE in the presence of 4 A molecular sieves and a base such
10 as TEA at room temperature, followed by treatment with NaBH4 or NaHB(OAc)3.
Scheme I

OH
OH

(BOC)20, Et3N H H
H

(I) (II)

R1 Cl

DIEA, Pyridine, or DCE

or

(VI)
R1’OH,HBTU

1. (COd)2, DM80

TEA, CH2Cl2
2. NaBH4, MeOH
R4

R5

(lit)

TFA, CH2Cl2

Compounds of formula (VII) can be prepared by treatment of an amine of formula (IV)
with an appropriately substituted acid chloride reagent of formula (V) in the presence of a
15 suitable base such as DIEA, pyridine or TEA, in solvents such as DCE or Cl-1202, at
temperatures ranging from room temperature to about the reflux temperature, preferably at about room temperature, to produce the corresponding amide compounds of formula (VII). Alternatively, compounds of formula (VII) can be prepared by treating amines of formula (IV) with carboxylic acids of formula (VI) and a suitable coupling reagent such as HOBT, HBTU,
20 DCC, EDCI, etc. to produce the corresponding amides of formula (VII). Finally, compounds of
formula (VIII) can be prepared by treatment of a carbamate of formula (VII) with TFA or HCI,
in solvents such as EtOAc, Dioxane, CH2Cl2 or DCE, at temperatures ranging from 0 °C to

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about room temperature, preferably at about room temperature, to produce the corresponding amine of formula (Viii).
Scheme II illustrates a method for the preparation of compounds having the basic
structure of formula I, where A is hydrogen and Y, Q, Z and R1-R6 are described as above.
5 Referring to scheme U below, compounds of formula (IX) can be prepared by treatment of an amine of formula (VIII) with an appropriately substituted aldehyde or ketone
and a reducing agent such as NaHB(OAc)3, in solvents such as CH2Cl2 or DCE, at temperatures ranging from 0 °C to about room temperature, preferably at about room temperature, to produce the corresponding amine of formula (IX). Other suitable conditions
10 for this process include treatment of the amine of formula (VIII) with an aldehyde in toluene, at about the reflux temperature; followed by treatment with NaBH4, in solvents such as MeOH, produce the corresponding amine of formula (IX). Also, treatment of an amine of formula (VIII) with an aldehyde and NaCNBH3 in a solvent such as MeOH, produce the corresponding

15

amine of formula (IX).
Scheme ii

RlyO)4 R1 r4
Q R5NaHB(OAc)3 Q R5
H H X-R6-(CH2)0-CHq1 H
or

(VIII) (IX)
R6 R6

Scheme Ill illustrates an alternative method for the preparation of compounds having
the basic structure of formula I, where A is hydrogen and Y, Q, Z and R1-R5 are described as above. R9 is a cycloa1kyl,-(CH2)0-R6 -CH(R6) or -C(R6)2.
20 Referring to scheme III below, a compound of formula (VIII) can be treated with an epoxide reagent of formula (X) in the presence of a suitable base such as triethyl amine, in solvents such as methanol or ethanol, at temperatures ranging from room temperature to about the reflux temperature, preferably at about the reflux temperature, to produce compounds of formula (IX).

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Scheme HI

R1)4

EtOH, Et3NQ R5

R9’

H,,5tH

(X) (IX) Y
Scheme IV below illustrates an alternative method for the preparation of compounds having the basic structure of formula I, where A is hydrogen and Y, Q, Z and R1-R5 are
5 described as above.

Referring to scheme IV below, compounds of formula (XIII) can be treated with a suitable base such as NaH or KH, and an appropriately substituted alkylating agent of formula (XI), where L is a suitable leaving group such as Cl, Br, I, OMs, OTs, in solvents such as THF
or ether, at temperatures ranging from 0 °C to about room temperature, preferably at about
10 room temperature, to produce the compounds of formula
Scheme IV

YL (Xl)

NaH, THF
(L = leaving group)

Scheme V below illustrates an alternative method for the preparation of compounds having the basic structure of formula I, where A is hydrogen and Y, Q, Z and R1-R8 are
15 described as above.

Referring to scheme V below, compounds of formula (VIII) can be treated with a
suitably protected alpha-bromo ester derivative of formula (X), such as alpha-bromo benzyl acetate, in the presence of a base such as potassium carbonate, a suitable ammonium salt such as tetraethyl ammonium chloride and a suitable solvent such as dirnethyl formamide, at
20 room temperature to yield the desired compound of formula (Xl). Compound of formula (XI)
can be treated with a suitable palladium catalyst, such as palladium hydroxide, in solvents such as methanol or ethanol, to produce compounds of formula (XII). Finally, compounds of formula (XIV) can be prepared by treating the acid of formula (XII) with primary and

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secondary amines of general formula (XIII) in the presence of suitable coupling agents such as O-Benzotriazol-1-yI-N, NN’ N’-tetramethyluronitim hexafluorophosphate (HBTU) and triethyl amine, to produce the desired compounds of formula (XIV).
Scheme V
R1O

j4 (X) RlyO RI
r4 0,0"(Br j R5 R5 Pd(OH)2/C (Q gs
A H H A H K2CO3, DMF H2, CH3OH H H
N

Et4NCI N
ii (VIII) LJL.....0) tXI) Ho) (XII)

RIyO j4
H N .

I (XIII) Q R5

R7 R8 I-I H
HBTU,Et3N RB N
(X1V)

5 0

The following examples and preparations illustrate the present invention. It is to be understood, however, that the invention, as fully described herein and as recited in the claims,
is not intended to be limited by the details of the following examples.
10 EXAMPLES
PREPARATION I

6HydroxyrnethyJ3..aza-bicycloF3.I.Olhexane-3-carboxylic acid tert-butyLester
To a solution of (3-Aza-bicyclo[3. I.Ojhex-6-yl)-methanol-1-ICI (11.8gm, 78.7 mmol) in
350 mL of anhydrous CH2Cl2 at room temperature was added Et3N (32.9 mL, 236 mmol),
15 followed by (BOC)20 (18.9 gm, 86.6 mmol) in portions. The reaction was stirred at room temperature for 18 hours. The mixture was washed with saturated NaHCO3, water, brine and dried over anhydrous MQS04. The mixture was filtered and concentrated under reduced pressure to yield the crude material, which was purified via flash chromatography with 10 % MeOH/CI-12Cl2. The product containing fractions were collected and concentrated to yield 6-
20 Hydroxymethyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester (15.6 gm). 400 MHz 1H NMR (CDCI3) 8 3.4-3.6 (m, 4H), 3.2-3.7 (m, 2H), 1.72 (brs, IH), 1.4-1.4 (m, 10 H), 0.9-0.9 (m, li-I); MS (M+1) 213.2.

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PREPARATION 2

6-Formyl-3-aza-bicyclol3.1.0]hexane-3-carboxylic acid tert-butyl ester
To a stirring solution of oxalyl chloride (7.8 mL, 89.5 mmol) in 370 mL of anhydrous
CH2Cl2 at -78 °C, under Nitrogen, was added DMSO (13.8 mL, 193.9 mmol) dropwise. After
5 10 minutes, 6-Hydroxymethyl-3-aza-bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester
(15.9 gm, 74.5mmol) in 72 mL anhydrous CH2Cl2 was added. After the mixture stirred 30 minutes, triethylamine (52.0 mL, 372.9 mmol) was added and the mixture was allowed to slowly warm to 0 °C over 1 hour. The mixture was concentrated, the resulting solid was taken
up in saturated NaHCO3 and EtOAc, the layers were separated and the aqueous layer was
10 extracted with EtOAc. The combined organic layers were washed with brine, dried, filtered
and concentrated to give a quantitative crude yield of 6-Formyl-3-aza-bicyclo[3.1.O]hexane-3-carboxylic acid tert-butyl ester (15.8 gm), which was used in the next step without purification.
400 MHz 1H NMR (CDC)3) 5 9.4 (d, J = 4.1 Hz, I H), 3.6 (dd, J = 11.2 Hz, 37.8 Hz, 2H), 3.4 (d,
J = 9.95, 2H), 2.1 (m, 2H), 1.8-1.7 (q, J- 3.32 Hz, 1H), 1.4 (s, 9H); GCMS (M+0) 211.0.
15 PREPARATION 3 6-T(3-Trifluoromethoxy-benzylamino)-methyll-3-aza-bicyclof3.1.Olhexane-3-carboxylic
acid tert-butyl ester
To a stirring solution of the aldehyde prepared above (1.0 g, 4.7 mmol) in 9.5 mL of
MeOH was added 3-trifluoromethoxy-benzlyamine (0.7 mL, 4.7 mmol). The reaction mixture
20 was stirred at room temperature for 24 hours. Sodium borohydride (0.4 g, 9.5 mmol) was
then added and the reaction mixture stirred for another 24 hours. The reaction was concentrated under reduced pressure and the resulting material was taken up in I N NaOH
and extracted with CH2Cl2. The combined organic layers were dried over anhydrous MgSO4, filtered and concentrated under reduced pressure to yield 1.8 gm of the desired amine, which
25 was taken on without purification. 6-[(S-Trifluoromethoxy-benzylamino)-methyl]-3-azabfcyclo[3. 1.0]hexane-3-carboxylic acid tert-butyl ester 400 MHz 1H NMR (CDCI3) S 7.3 (t,.1
= 7.8 Hz, IH), 7.2 (m, IH), 7.2 (s, IH), 7.1-7.0 (m, IH), 3.8 (s, 2H), 3.5 (dd, J = 39.4 Hz, 10.8
Hz, 2H), 3.8 (t, J = 10.8 Hz, 2H), 2.5 (dt, J = 6.0 Hz, 25.7 Hz, 2H), 1.4 (s, 9H), 1.3 (m, 2H) 0807 (m, I H); MS (M+1) 387.3.

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The following compounds were made using the procedure described in preparation 3. 6-t(3-Trifluoromethyl-benzylamino)-methyll-3-aza-bicyclol3.1.Olhexane-3-carboxidic
acid tert-butyl ester
400 MHz 1H NMR (CDCI3) 8 7.5 (s, I H), 7.5-7.2 (m, 3H), 3.8 (s, 211), 3.5 (dd, J = 37.7
5 Hz, 10.8 Hz, 21-1), 3.2 (m, 2H), 2.5 (dt, J = 17.0 Hz, 5.4 Hz, 2H), 1.4 (s, 9H), 1.3-1.2 (m, 2H)
0.8-0.7 (m, IH); MS (M+1) 371.3.
6-1(3-Chloro-benzylamino)-methyll-3-aza-bicyc)of3.1.Olhexane-3-carboxylic acid tert-
butyl ester
400 MHz 1H NMR (COd3) 6 7.3 (s, IH), 7.2-7.1 (m, 3H), 3.8 (s, 2H), 3.5 (dci, J = 37.3
10 Hz, 10.8 Hz, 2H), 3.3-3.3 (m, 2H), 2.6-2,5 (m, 2H), 1.4 (m, 91-i), 1.3 (m, 2H) 0.8-0.7 (rn, IN);
MS (M+1) 337.2.
4Flvoro-3-trifJuoromethyI-benzyIamjno)-methvfl-3-aza-bicrcIo13.1.Olhexane-3
carboxylic acid tert-butylester
400 MHz 1H NMR (COd3) 6 7,6-7.5(m, 1H), 7.5-7.4 (m, IN), 7.2 (s, IH), 3.8 (s, IN)
15 3.6-3.5 (m, 4H), 2.5-2.5 (m, 2H), 1.4 (s, 9H), 1.3-1.2 (m, 2H) 0.8-0.7 (m, IH); MS (M+1) 389,3.
6-1(3-Chloro-4-fluoro-benzy,amino)-methyll-3-aza-bicyclor3.I.OThexane-3-
carboxylic acid tert-butyl ester
400 MHz 1H NMR (C1JCI3) 6 7.3-7.4 (m, I H); 7.0-7.2 (m, 2H); 3.7(3,2H); 3.4-3.6 (rn,
211); 3.3-3.4 (m, 2H); 2.4-2.6 (m, 2H); 1.4 (m, 9H); 1.3 (m, 2H); 0.8 (m, IH).
20 PREPARATION 4
641(1 -Methyl-I H-imidazole-4-carbonyfl-(-trifluoromethoxy-benzyfl-amino1-methyfl-3-aza-bicyclof3.1.OThexane-3-carboxyjjc acid tert-butyl ester
To a stirring solution of 6-I(3-Trifluoromethoxy-benzylamino)-methyl]-3-aza-
bicyclo[3. 1.O]hexane-3-carboxylic acid tert-butyl ester prepared above (5.9 gm, 15.4 mmol) in
25 192 mL of CH3CN at room temperature under N2 was added DIEA (8.0 rnL, 46.1 mmol) and
1 -Methyl-1 H-imidazole-4-carbonyl chloride HCL (5.6 gm, 30.7 mmol). After 24 hours, reaction
was quenched with H20, extracted with EtOAc. Organic layer was then washed with a 10% Citric acid solution, H20, NaHCO3, and brine. The combined extracts were dried over anhydrous MgSO4, filtered and concentrated under reduced pressure. to yield 6.7 gm of 6-
30 {[(1 -Methyl-I H-imidazole-4-carbonyl)-(3-trifluoromethoxy-benzyl)-amino]-methyl}-3-aza-
bicyclo[3.1.0]hexane-3-carboxylic acid tert-butyl ester 400 MHz 1H NMR (CDCI3) 6 7.8 (d, J =
1.2 Hz, IH), 7.3-7.1 (m, 51-I), 5.4 (s, Il-i), 4.8-4.7 (m, IN), 4.2 (m, IH), 3.7(s, IN), 3.7 (s, 3H), 3.4-3.2 (m, 3H), 1.4 (s, 9H), 1.3 (m, 211), 0.8 (rn, 1H); MS (M+1) 495.3.
The following compounds were made using the procedure described in preparation 4.

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64(1-Methyl-I H.imidazole-4-carbonyl)-(3-trifluoromethvl-benzVl)-aminOl-methvfl-3-aZa-bicyclof3.I.Olhexarie.3-carboxylic acid tert-butyl ester
400 MHz 1H NMR (CDC13) 6 7.6-7.2 (m, 6H), 5.4(s, 1H), 4.9-4.6 (m, I H), 4.2 (m, I H),
3.7 (s, 3H), 3.4-3.2 (m, 7H), 1.4 (m, 9H), 0.8 (m, 1 H); LCMS (M+0) 479.1.
5 6-1(3-Ch1oro-benzvl)-(I-methyl-I 11-imidazole-4-carbonyl)-aminol-methvl}-3-aza-bicyclor3.1.Olhexane-3-carboxylic acid tert-butyl ester
400 MHz 1H NMR (CDCI3) 5 7.6 (s, IH), 7.4 (s, IH), 7.2-7.1 (m, 4H), 5.4 (d, IH), 4.8-
4.7 (m, IH), 4.2 (m, 111), 3.8 (s, 111), 3.7 (s, 311), 3.5-3.4 (m, 211), 3.3-3.2 (m, 211), 1.4 (s, 91-), 1.4-1.3 (m, 2H), 0.8 (m, IH); MS (M+1) 445.3.
10 64fl4-Fluoro-3-trifluoromethyl-benzyfl-(1 -methyl-I H-imidazole-4-carbonyl)-amtnol-methyl}-3-aza-bicyclol3.1.0lhexane-3-carboxyhc acid tert-butyl ester
400 MHz 1H NMR (CDCI3) 5 7.6 (s, IH), 7.5 (m, 2H), 7.3 (m, 1H), 7.1 (t, J = 9.5 Hz,
IH), 5.4 (5, 111), 4.8-4.7 (m, IH), 4.2 (m, IH), 3.9-3.8 (m, 111), 3.7 (s, 311), 3.5 (m, IH), 3.4-
3.2 (m, 4H), 1.4 (m, 211), 1.4 (s, 9H), 0.8 (m, IH); MS (M+I) 497.3.
15 64r(3-Chioro-4.fluoro-benzyl)-(I -methyl-I H-imidazole-4-carbonyfl-aminol-methyl}-3-aza-bicyclol3.1.Olhexane-3-carboxylic acid tert-butyl ester
400 MHz 1H NMR (CDCI3) 8 7.6 (s, IH); 7.3-7.4 (m, 2H); 7.1-7.2 (m, IH); 7.0-7.1 (t,
J= 8.7 Hz, 1H); 5.3-5.4 (m, IH); 4.6-4.8 (m, lI-I); 4.1-4.2 (m, 111); 3.7 (m, 3H); 3.2-3.5(m, 511); 1.3-1.4 (m, 11 H); 0.8 (m, ’111); MS (M+1) 463.0.
20 Example I
1 -Methyl-I H-imidazole-4-carboxylic acid (3-aza-bicvclol3.1.Olhex-6-ylmethyl)-13-trifIuoroniethoxy.benzyI)-amide Hydrochloride
To 6-{[(1 -Methyl-I H-imidazole-4-carbonyl)-(3-tr}fluoromethoxy-benzy))-amino)- methyl}-3-aza-bicyclo[3.I.0]hexane-3-carboxylic acid tert-butyl ester prepared above (7.74gm,
25 15.65 mmol) was added 5 mL of saturated HCI in EtOAc at room temperature. The reaction stirred at room temperature for 4 hours. The mixture was concentrated under reduced pressure to yield 6.63 gm of 1 -Methyl-I H-imidazole-4-carboxylic acid (3-aza-bicyclo[3. I.0]hex-6-ylmethyl)-(3-trifluoromethoxy-benzyl)-amide Hydrochloride.
400 MHz hI1 NMR (CDaOD) 69.0 (s, IH), 8.2 (brs, IH), 7.5-7.2 (m, 4H), 5.0, brs, 2H),
30 4.0-3.9 (m, 4H), 3.6-3.4 (m, 2H), 3.3 (m, 311), 1.8 (brs, 2H), 1.32 (brs, 111); MS (M+1)395.3. The following compounds were made using the procedure described in example 1.
Example 2
I-Methyl-IFl-fmicfazole-4-carboxylic acid (3-aza-bicycloj3. I.Olhex-6-ylmethyl)-(3-trifluoromethyl-benzyl)-amide Hydrochloride
35 400 MHz 1H NMR (CD300) 5 9.0 (s, IH), 8.2 (brs, IH), 7.6 (m, 414), 5.0 (brs, 211), 4.0-3.9 (m, 4H), 3.6 (m, 2H), 3.3-3.2(m, 3H), 1.8 (brs, 211), 1.2 (bra, I H).

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Example 3
1 -Methyl-I H-imidazole-4-carboxylic acidj3-aza-bicycloE3.I.Olhex-6-ylmethyfl-(3-chloro-benzyl)-amide Hydrochloride
400 MHz hil NMR (CD30D) 69.0 (s, IH), 8.2 (brs, IH), 7.3-7.2 (m, 4H), 5.0, brs, 2H),
5 4.-3.9 (m, 4H), 3.56 (m, 2H), 3.3 (m, 3H), 1.8 (brs, 2H), 1.2 (brs, IH); MS (M+1) 345.I.
Example 4
I-Methyl-I H-imidazole4-carboxylic acid (3-aza-bicycloj3.1.OThex-6-ylmethyfl-(4-fluoro-3-trifluoromethyl-benzyl)-amide Hydrochloride
400 MHz I NMR (CD300) 8 9.0 (s, 11-I), 8.2 (brs, IH), 7.6 (m, 2H), 7.4 (s, IH), 4.9
10 (brs, 2H), 4.0 (m, 4H), 3.6-3.4 (m, 2H), 3.3 (s, 3H), 1.8 (bra, 2H), 1.4 (brs, I H).
Example 5
I-Methyl-IH-imidazole-4-carboxylic acid (3-aza-bicyclof3.1.Olhex-6-ylmethyfl-(3-chlorO-4-fluoro-benzyfl-amide Hydrochloride
400 MHz IHNMR (CDOD) 69.1 (a, IH); 8.3 (brs, 1H); 7.5 m, IH); 7.2-7.4 (m, 2H);
15 4.8-5.2 (m, 4H); 3.9-4.1 (m, 3H); 3.5-3.6 (m, 2H); 3.2-3.3 (m, 2H); 1.8 (m, 3H); 1.4 (m;. I H);
MS (M+1) 363.0
Example 6
I-Methyl-I H-imidazole-4-carboxylic acid (3-aza-bicyclol3.1.Olhex-6-ylmethvfl-(4-fluoro-3-isopropoxy-benzyfl-amide
20 100 MHz 3C NMR (CD30D) 6 19.44, 21.26, 21.78, 35.94, 49.72, 60.37, 72.27, 116.33, 120.59, 124.55, 126.54, 137.30,146.35, 151.91, 154.35, 158.89, 171.74.
Example 7
I -Methyl-I l-1-imidazole-4-carboxylic acid (3-aza-bicyclof3.I.Olhex-6-ylmethyl)-(3-cyclopentyloxy-4-fluoro-benzyfl-amide
25 100 MHz 13C NMR (CD30D) 6 19.45, 21.75, 23.71, 32.55, 33.25, 35.80, 49.64, 51.77, 60.36, 79.18, 81 i06, 112.50, 116.16, 118.73, 120.05, 124.59, 126.51, 132.29, 133.54, 137.25, 146.44, 152.76 (d, J=248),158.77,171.74.
Example 8
1 -Methyl-I I-1-imidazole-4-carboxylic acid (3-aza-bicyclol3.I.01hex-6-ylmethyfl-r3-2,2-
30 dimethyl-propoxy)-4-fluoro-benzyll-amide
100 MHz 13C NMR (CD30D)6 19.41, 21.74, 25.73, 31.79, 35.80, 49.68, 51.74, 79.03, 112.49, 114.60, 115.85, 120.02, 124.53, 126.51, 137.21, 148.05, 152.20 (d, J245), 158.85.

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Example 9
I-Methyl-I H-imjçlazole-4-carboxylic acid (3-aza-bicycloj3.1 Qlhex-6-ylmethylI-(3-cyclohexyloxy-4-fluoro-benzyl)-amide
100 MHz 13C NMR (CD300) 6 19.46, 21.73, 23.31, 25.49, 31.62, 35.79, 41.04, 49.56,
5 51.63, 52.51, 77.23, 116.52, 120.63, 124.59, 126.51, 129.48, 137.21, 151.02, 153.21 (d,
J--245),158.68.
Example 10
I-Methyl-1 H-imidazole-4-carboxylic acid (3-aza-bicyclol3.1.Olhex-6-ylmethyfl-13-(2,2,2-trifluoro-1 -trifluoromethyl-ethyl)-benzylJmide 10 400 MHz 1HNMR (CDCI3) 87.5 (s, IH); 7.2-7.4 (m, 5H); 5.4 (brs, IH); 4.8 (brs, IH); 3.9-4.1 (m, 2H); 3.6 (s, 3M); 3.3 (m, IH); 2.6-3.0 (m, 4H); 1.2-1.3 (m, 2H); 0.8-0.9 (m, IH);
100 MHz 13C NMR (CD300) 8 17.70, 19.01, 21.63, 23.35, 28.55, 33.72, 47.53, 48.24, 49.23, 50.19, 51.74, 54.19 (h, J29), 118.92, 121.71, 124.54, 126.54, 126.78, 127.34, 128.55, 129.40, 136.85, 138.26, 139.96, 164.28; MS (M+1)461.
15 Example II
1 -Methyl-I H-imidazole-4-carboxy(ic acid (3-aza-bicyclor3.1.Olhex-6-vimethvl)-F3-(2,2,2-trifluoro-ethyl)-benzyll-amide
400 MHz 1HNMR (CDCI3) 87.5 (s, IH); 7.1-7.3 (m, 5H); 5.4 (brs, IH); 4.8 (brs, IH);
3.9 (brs, 11-I); 3.6 (m, 3H); 3.2-3.3 (m, 3(1); 2.7-2.8 (m, 3M); 2.1-2.2 (m, 11-1); 1.4 (m, 2H);
20 0.7-0.8 (m, IH); 100 MHz 13C NMR (CD30D) 5 3.13, 17.34, 18.69, 23.82, 33.75, 40.26 (q,
J=30), 47.64, 48.89, 49.54, 51.82, 53.66, 121.81, 124.57, 126.43, 127.33, 128.97, 129.42, 130.08, 130.46,136.85, 138.46, 139.31,164.29; MS (M+1)393.0.
Example 12
I -Methyl-I H-imidazole-4-carboxylic acid (3-cyclopropylmethyl-3-aza-bicyclol3.I.01hex-
25 6-ylmethyl)-(3-trifluoromethoxy-benzyfl-amide
To a stirring solution of 1 -Methyl-I H-imidazole-4-carboxylic acid 3-aza-bicyclo[3.1.0]hex-6-ylmethy()-(3-trifluoromethoxy-benzyl)-amide Hydrochloride prepared above (0.8 gm, 1.9 mmol) in 18.5 ml of DCE at room temperature was added Cyclopropanecarbaldehyde (0.1 mL, 1.6 mmol) and NaHB(OAc)3 (0.8 gm, 3.7 mmol). The
30 reaction stirred at room temperature for 16 hours, was quenched by the addition of saturated
NaHCO3, and extracted with CH2Cl2. The combined organic layers were dried over anhydrous MgSO4, filtered and concentrated under reduced pressure to yield the crude material, which was purified via flash chromatography with 5-30% MeOH/CH2Cl2. The product containing fractions were collected and concentrated to yield 1 -Methyl-I H-imidazole-
35 4-carboxylic acid (3-cyclopropylrnethyl-3-aza-bicyclo[3.1.O]hex-6-ylmethyl)-(3-
trifluoromethoxy-benzyl)-amide 0.5 gm. 400 MHz 1H NMR (CDCI3) 6 7.5 (s, 1H), 7.3 (m, 2H) 7.2-7.0 (m, 3H), 5.5 (brs, IH) 4.8 (brs, 1H), 4.0 (brs, 1H), 3.7 (s,. 3H), 3.3 (brs, 1H), 3.0 (m,

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2H), 2.2 (m, 4H), 1.5 (brs, IH), 1.3 (m, 21-1), 0.8 (m, IH), 0.4(m, 21-1), 0.0 (m, 2H); MS (M+1)

449.3.

General procedure for the reductive alkylation preparation of compounds of Formula IX To a stirring solution of 1.0 equiv. of a compound of formula (VIII) in 1,2-
5 dichloroetharie (0.1 M) at room temperature was added the appropriately substituted
aldehyde or ketone reagent (1.0-1.5 equiv.), and sodium triacetoxyborohydride (2.0 equiv.). The reaction mixtures were stirred at room temperature for up to 24 hours. The mixtures were then quenched by the addition of saturated sodium bicarbonate solution and extracted with methylene chloride. The combined organic layers were dried over anhydrous MgSO4
10 and concentrated under reduced pressure. If needed, the resulting crude material was
purified by flash chromatography with 4% MeOH/CH2Cl2. The product containing fractions were collected and concentrated to yield the desired tertiary amines in 70-95 yield.
The following compounds were made using the above procedure of Example 12,
starting with the appropriate starting amine of formula (VIII) and the appropriate aldehyde or
15 ketone reagent.
Furthermore, pharmaceutically acceptable salts of the compounds listed below can
be prepared as follows. To a stirring solution of compounds of the general formula (IX) (prepared as described above in Example I and Example 12, 1.0 equiv.) in a suitable solvent such as ethyl acetate, dioxane, diethyl ether, methyl ethyl ketone, methylene
20 chloride/methanol (1:1) or methanol (0.1 M) at room temperature was added the appropriate
acid, such as hydrochloric acid, citric acid, trifluoroacetic acid, p-toluenesulfonic acid, methansulfonic acid or benzene sulfonic acid (2-3 equiv) in one portion. The resulting mixture
was stirred at room temperature for up to 18 hours, then concentrated under reduced -----pres-sure-to-affordLthe-desired-salts.--
25 Example 13
1 -Methyl-I H-imidazole-4-carboxylic acid (3-cyclopentvlmethyl-3-aza-bicycloF3.1.Olhex-6-ylmethyfl-(3-trifluoromethoxy-benzyl)-amide 400 MHz 1H NMR (CDCI3) 6 7.5 (m, 111), 7.3-7.0 (m, 51-1), 5.5 (brs, IH) 4.8 (brs, IH),
4.0 (brs, 11-1), 3.7 (s, 31-1), 3.3 (brs, IH), 2.9-2.8 (m, 2H), 2.19 (m, 4H), 1.8 (brs, IH), 1.6-1.1
30 (m, IOH); MS (M+1) 477.3.
Example 14
1 -Methyl-I H-imidazole-4-carboxylic acid (3-trifluoromethoxy-benzyl)-13-(4-trifluoromethoxy-benzyfl-3-aza-bicyclof3.I.Olhex-6-ylmethyll-amide
400 MHz 1H NMR (CDCI3) 8 7.5 (s, IH), 7.5-7.0 (m, 9H), 5.5 (brs, IH) 4.8 (brs, IH),
35 4.0 (brs, IH), 3.7 (s, 3H), 3.5-3.4 (m, 2H), 3.3 (m, IH), 2.8-2.7 (rn, 21-1), 2.2 (brs, 21-1), 1.4 (brs,
IH), 1.2 (brs, 2H); MS (M+1) 569.5.

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Example 15
1 -Methyl-I H-jmkfazole-4-carboxylic acid (3-chloro-benzfl-(3-cyclopropylmethyl-3-aza-bicyclol3.1.Olhex-6-ylmethyfl-amide
400 MHz 1H NMR (CDC13) 6 7.5 IH), 7.3-7.2 (m, 511), 5.4 (brs, IH) 4.8 (brs, IH),
5 4.0 (brs, IH), 3.7 (s, 3H), 3.3 (brs, IH), 3.0 (brs, 111), 2.2 (brs, 411), 1.7 (brs, 2H), 1.4 (brs,
IH), 1.3 (brs, 2H), 0.4 (m, 211), 0.0 (m, 2H); MS (M+1) 399.3.
Example 16
Methyl-I H-imidazole-4-carboxylic acid (3-chloro-benzyfl43-cyclopentylmethyl-3-aza-bicycloT3.1.OThex-6-ylmethyB-amide
10 400 MHz 1H NMR (CDCI3) 6 7.6 111), 7.3-7.2 (m, 5H), 5.4 (brs, IH) 4.8 (brs, IH), 3.9 (brs, IH), 3.7 (brs, 311), 3.3 (m, 111), 2.9 (m, 2H), 2.2 (m, 311), 1.9-1.1 (m, 13H); MS (10+1) 427.4.
Example 17
1 -Methyl-I H-imidazole-4-carboxyhc acid (3-chloro-benzyl)43-(4-trifluorometh2x3c
15 benzyfl-3-aza-bicyclol3.1.OThex-6-ylmethyll-amide
400 MHz 1H NMR(CDCI3) 67.6 (d, IH), 7.5-7.1 (m, 911), 5.4 (brs, IH), 4. 8 (brs, IH),
4.0 (brs, I H), 3.7 (s, 311), 3.5 (brs, 2H), 3.3 (d, I H), 2.8 (m, 2H), 2.2 (m, 211), 1.40 (brs, I H),
1.2 (brs, 211); MS (M+1) 519.4.
Example 18
20 1 -Methyl-I H-imidazole-4-carboxvlic acid (3-cvclopropvlmethvl-3-aza-bicyclo(3.1.Q)flex-6-ylmethyl).(3-trifluoromethyl-benzyl)-amide
400 MHz 1H NMR (COd3) 6 7.6-7.4 (in, 611), 5.4 (brs, 1H) 4.8 (brs, 11-i), 3.9-3.7 (m,
5H), 3.0 (m, 2H), 2.9 (m, 211), 2.4 (brs, 2H), 1.8 (m, 211), 1.4 (rn, 211), 0.7 (m, 2H), 0.4-0.3’(m, 211); MS (M+1) 433.3.
25 Example 19
1 -Methyl-I H-lmidazole-4-carboxylic acid (3-ethyl-3-aza-bicyclor3.1.Olhex-6-ylmethyfl-(4-fluoro.3-trifluoromethyl-benzyl)-amide
400 MHz IHNMR (CDC13) 6 7.5-7.6 (m, 3H), 7.3 (s, IH); 7.1 (t, J = 9.3, 1H), 5.4 (brs,
IH), 4.8 (brs, IH), 4.0 (brs, 11-I), 3.7 (s, 3H), 3.3 (brs, IH), 2.2-3.0 (m, 4H), 1.0-1.7 (m, 8H).
30 Example 20
1 -Methyl-I H-imidazole-4-carboxylic acid (4-fluoro-3-trifluoromethyl-benzyfl-(3-methyl-3-aza-bicyclo13.I.Olhex-6-ylmethyl)-amide
400 MHz IHNMR (COd3) 67.5-7.6 (m, 3H); 7.3 (s, I H); 7.1 (t, J = 9.3, IH); 5.4 (brs,
111); 4.8 (brs, IH); 4.0 (brs, IH); 3.6-3.7 (m, 3H); 3.3 (brs, IH); 2.8-3.1 (brs, 2H); 2.3 (brs, 5H);
35 1.2-1.4 (m, 311).

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Example 21
1 -Methyl-I H-imidazole-4-carboxylic acid (3-chloro-benzyfl-(3-ethyl-3-aza-
bicyclof3. I.Olhex-6-vlmethyl)-amide
400 MHz IHNMR (COd3) 8 7.5 (m, IH); 7.1- 7.3 (m, 5H); 5.4 (brs, IH); 4.8 (brs, IH);
5 4.0 (brs, IH); 3.7 (m, 3H); 3.3 (brs, IH); 3.0 (brs, 2H); 2.1-2.4 (m, 4H); 1.2-1.4 (m, 3H); 0.9-
1.0 (m, 3H).
Example 22
I-Methyl-I H-imidazole-4-carboxylic acid (3-ethyl-3-aza-bicyclol3.I.Olhex-6-ytmethyfl-(3-trifluoromethoxy-benzyfl-am,de Hydrochloride
10 400 MHz IHNMR (CD30D) & 7.6 (m, 2H); 7.1-7.4 (m, 4H); 5.3 (brs, IH); 4.8 (brs,
1H); 3.8 (brs, 1H); 3.7 (brs, 3H); 3.3 (brs, I H); 2.8 (brs, 2H); 2.3-2.5 (m, 4H); 1.3 (brs, 3H);
1.0 (m, 3H).
Example 23
. 1 -Methyl-I H-imidazole-4-carboxylic acid (3-methyl-3-aza-bicyclo[3.I.Olhex-6-ylmethyl)-
15 (3-trifkioromethoxy-benzyl)-amide
400 MHz IHNMR (CDCI3) 8 7.5 (m, IH); 7.1-7.3 (m, 5 I-I); 5.5 (brs, IH); 4.8 (brs,
1H); 4.0 (brs, IH); 3.7 (brs, 3H); 3.3 (brs, IH); 2.9 (brs, 2H); 2.2 (brs, 5H); 1.3-1.4 (m, 3H).
Example 24
I-Methyl-I H-imidazole-4-carboxvlic acid (3-ethvl-3-aza-bicvclol3.1.Olhex-6-vlmethvfl-13-
20 trifluoromethyl-benzyfl-amide
400 MHz 1HNMR (CDCI3) 37.6 (m, IH); 7.3-7.5(m, 5 H); 5.5 (brs, IH); 4.9 (brs, IH);
4.0 (brs, 11-1); 3.6-3.7 (m, 3H); 3.3 (bra, IH); 3.0 (brs, 2H); 2.0-2.4 (m, 4H); 1.2-1.5 (m, 3H);
1.0 (brs, 3H).
- Example 25
25 1 -Methyl-I H-imidazole-4-carboxvlic acid (3-methvl-3-aza-bicvcloF3.1.Olhex-6-vlmethvfl-
3-trifluoromethyl-benzyfl-amide
400 MHz 1HNMR (CDC13) 67.3-7.6 (m, 6H); 5.5 (brs, 1H); 4.8 (brs, 1H); 4.0 (brs, IH);
3.6-3.7 (m, 3H); 3.3 (brs, I H); 3.0 (m, 2H); 2.3 (m, 5H); 1.3-1.7 (m, 3H).
Example 26
30 1 -Methyl-I H-imidazole-4-carboxylic acid (3.5-dichloro-benzyfl-(3-methyl-3-aza-bicyclol3.1.Olhex-6-ylmethyl)-amide
400 MHz 1HNMR (CDCI3) 6 7.6 (m, IH); 7.3 (brs,.IH); 7.1-7.2 (m, 3H); 5.4 (brs, IH);
4.7 (brs, IH); 4.0 (brs, IH); 3.7 (brs, 3H); 3.3 (brs, IH); 2.9 (brs, 2H); 2.3 (brs, 5H); 1.2-1.4
(m, 3H).

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Example 27
I-Methyl-I H-imidazole-4-carboxylic acid (3,5-dichloro-benzyl)-(3-ethyl-3-aza-bicyclol3.1.Olhex-6-ylmethyfl-amjde Hydrochloride
400 MHz 1HNMR (CD30D) 69.0 (s, IH); 8.3 (brs, IH) 7.3-7.4 (m, 3H); 4.8 (brs, 2H);
5 4.0-4.1 (m, 4H); 3.5-3.6 (rn, 5H); 3.1-3.2 (m, 2H); 1.8 (m, 3H); 1.2-1.3 (m, 3H).
Example 28
1 -Methyl-I H-imidazole-4-carboxylic acid (3-chloro-4-fluoro-benzyfl-(3-methyl-3-aza-bicyclof3.I.0lhex-6-ylmethyl)-amlde
400 MHz 1HNMR (CDCI3) 37.52 (s, IH), 7.28 (m, 2H), 7.11 (rn, IH), 7.00 #, J=8, IH),
10 4.67 and 5.355 (m, 2H), 3.65 (s, 3H), 3.24 and 3.925 (m, 2H), 2.86 (m, 2H), 2.19 (s, 5H), 1.36 (m, IH), 1.26 (m, 2H); MS (M+1) 377.1. 100 MHz 13C-NMR (CDCI3, 6): 18.375, 19.616, 22.763, 33.791, 41.499, 47.025, 48.355, 49.522, 50.112, 57.133, 116.5785 (d, J=21), 120.929,126.724,127.576,129.789,135.7,136.742,138.432,157.325 fd, J=248),164.039. Example 29
15 I -Methyl-I H-imidazole-4-carboxyljc acid (3-chloro-4-fluoro-benzyl)-3-ethyl-3-aza-bicyclol3.I.Olhex-6-ylmethyl)-amide 400 MHz 1HNMR (CD30D) 69.0 (s, IH); 8.2-8.3 (m, IH) 7.5 (s, IH); 7.3 (m, 2H); 4.8
(brs, 2H); 3.8-4.0 (m, 4H); 3.4-3.6 (m, 4H); 3.1-3.3 (m, 2H); 1.6-1.8 (m, 3H); 1.3 (m, 3H). Example 30
20 I-Methyl-I H-irnidazoje-4-carboxyljc acid (3-chloro-benzyl)-(3-methyl-3-aza-bicyclol3.I.Olhex-6-ylmethyfl-amide
400 MHz 1HNMR (CDCI3) 6 7.6 (s, 11-1); 7.2-7.3 (rn, 51-I); 5.4 (brs, IH); 4.8 (brs, IH);
4.0 (brs, I H); 3.7 (s, 3H); 3.3 (brs, 1 H); 3.0 (brs, 2H); 2.2-2.3 (rn, 5H); 1.3-1.5 (m, 3H).
Example 31
25 I-Methyl-I H-imidazole-4-carboxylic acid (3-azetidin-3-yl-3-aza-blcyclof3.I.Olhex-6-ylmethyl)-(3-trifluoromethoxy-benzyI)amjde 100 MHz C-NMR (CDCI3) 315.45, 19.4, 21.79, 33.88, 42.10, 47.56, 50.31, 50.75,
53.10, 119.33, 119.67, 120.23, 121.89, 126.22, 128.62, 129.09, 130.10, 137.13, 137.75, 141.29, 149.63, 164.38,
30 Example 32
1 -Methyl-I H-imidazole-4-carboxyljc acid (2,4-dichloro-benzyl)-(3-rnethyl-3-aza-bicycloj3.1.0Ihex-6-ylmethyl)-amide 400 MHz 1HNMR (CDCI3)6 7.6 (brs, It-I); 7.2 (m, 3 H); 7.1 (m, IH); 5.5 (brs, IF-I); 4.8
(brs, IH); 4.1 (brs, IH); 3.7 (brs, 3H); 3.3 (brs, IH); 2.9 (brs, 2H); 2.2 (brs, 5H); 1.3-1.4 (m,
35 3H); MS (M+1) 393.0.

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Example 33
1 -Methyl-I H-imidazole-4-carboxylic acid (2,4-dichloro-benzyl)-(3-ethyl-3-aza-bicyclo[3.I.Olhex-6-ylmethyl)-amide
400 MHz 1HNMR (CDCI3) 6 7.6 (brs, IH); 7.2 -7.4 (m, 3 I-I); 7.1 (m, IH); 5.5 (brs,
5 IH); 4.8 (brs, IH); 4.1 (brs, IH); 3.6-3.7 (m, 3H); 3.3 (brs, IH); 2.9- 3.0 (m, 2H); 2.4 (m, 2H); 2.2 (m, 2H); 1.3-1.4 (m, 3M); 0.9-1.0 (m, 3H); MS (M+I) 407.0.
Example 34
1 -Methyl-I H-imidazole-4-carboxylic acid (3,4-dichloro-benzyl)-(3-methyl-3-aza-bicyclol3.I.Olhex-6-ylmethyl)-amide
10 400 MHz 1HNMR (CDCI3) 67.6 (m, IH); 7.3-7.4 3H); 7.1 (brs, IH); 5.4 (brs, IH);
4.7 (brs, IH); 4.0 (brs, IH); 3.6 (brs, 3H); 3.3 (bra, IH); 3.0 (brs, 2H); 2.2-2.3 (m, 5H); 1.2-1.4
(m, 3H).
Example 35
. 1 -Methyl-I H-imidazole-4-carboxylic acid (3,4-d ichloro-benzyl)-(3-ethyl-3-aza-
15 bicyclol3.1.0lhex6-ylmethyl)-amide
400 MHz 1HNMR (CDCI3) 37.6 (s, IH); 7.3-7.4 (m, 3M); 7.1 (brs, IH); 5.4 (brs, IH);
4.7 (bra, 1H); 4.0 (brs, IH); 3.7 (s, 3H); 3.3 (bra, IH); 3.0 (brs, 2H); 2.2-2.4 (m, 4H); 1.2-1.4
(m, 3H); 1.0 (brs, 3H).
Example 36
20 1 -Methyl-I l-1-imidazole-4-carboxvlic acid 13-(1 -methanesulfonvl-azetidin-3-yl)-3-aza-bicyclof3.I.Olhex-6-ylmethyfl-(3-trifluoromethoxy.benzyl)-amide
100 MHz 13C-NMR (CDCI3) 18.42, 19.70, 21.98, 33.84, 35.62, 47.70, 49.72, 50.69,
51.21, 54.75, 112.50, 119.55, 120.30, 125.98, 126.72, 129.95, 136.82, 138.39, 149.61, 164.17.

25 Example 37-
1 -Methyl-I H-imidazole-4-carboxyljc acid (3-azetidin-3-yl-3-aza-bicycloF3.I.Ojhex-6-ylmethyl)-(4-fluoro-3-trifluoromethyl-benzyfl-amide 100 MHz 13C-NMR (CDCI3) 8 18.30, 19.62, 22.02, 22.09, 33.78, 47.55, 48.73, 49.93,
50.67, 51.28, 51.57, 53.06, 53.45, 56.49, 57.66, 117.01 (d, J=21), 121.40, 124.11, 126.28,
30 126.32, 126.74, 133.23, 135.19, 136.85, 138.12, 158.93 (d, J=255), 164.02; MS(M+1)452.2. Example 38
1 -Methyl-I H-imidazole-4-carboxylic acid (3-azetidin-3-yl-3-aza-bicyclol3.1.Olhex-6-ylmethyfl-(3-chloro-4-fluoro-benzyfl-amide 100 MHz 13C-NMR (CDCI3) 6 18.29, 19.56, 21.99, 33.83, 47.44, 48.52, 49.69, 50.31,
35 50.58, 51.29, 51.52, 56.37, 116.59 (d, J=21),126.62,127.44,129.75,135.85,136.90,138.08, 157.29 (d, J245), 164.10; MS (M+1) 418.2.

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Example 39
1 -Methyl-I H-imiciazole-4-carboxylic acid (4-fluoro-34rifluoromethyl-benz)ll)-[3-(1 - methyl-azetidin-3-yl)-3-aza-bicyclo[3.I.Olhex-6-ylmethyll-amide
100 MHz 13C-NMR (CDCI3) 6 18.40, 19.65, 22.15, 33.84, 46.09, 47.66, 48.95, 50.70,
5 51.82, 52.97, 61.05, 116.92, 117.12, 126.33, 126.90, 133.29, 136.79; MS (M+1) 466.2.
Example 40
1 -Methyl-I H-imidazole-4-carboxylic acid (3-chloro-4-fluoro-benzyl)-13-(1 -methyl-azetidin-3-yl)-3-aza-bicyclol3.1.Olhex-6-ylmethyll-amide
100 MHz 13C-NMR (COd3) 8 18.43, 22.11, 33.85, 45.95, 47.55, 49.71, 50.61, 51.84,
10 52.89, 61.00, 74.97, 116.50, 116.71, 126.82, 127.71, 129.93, 136.85; MS (M+1)464.2.
Example 41
I -Methyl-I H-imidazole-4-crboxylic acid (3-azetidin-3-yl-3-aza-bicyclof3.1.Olhex-6-ylmethyfl-(3-trifluoromethyl-benzyl)-amide
100 MHz 13C-NMR (CDCI3) 821.84, 22.02, 25.90, 33.88, 47.17, 50.31, 50.79, 51.53,
15 52.50, 53.19, 57.37, 124.36, 126.69, 129.14, 131.04, 136.84, 161.09, 164.25; MS (M+1)
434.1.

Example 42
I-Methyl-I H-imidazole-4-carboxylic acid 13-(i-methyl-azetidin-3-yl)-3-aza-bicyclol3.1.Ojhex-6-ylmethyll-(3-trifluoromethyl-benzyl)-amide
20 100 MHz 13C-NMR (COd3) 8 18.41, 19.72, 22.14, 33.83, 45.86, 47.75, 49.23, 49.90, 51.33, 51.79, 52.82, 60.96, 124.05, 124.40, 126.74, 129.07, 131.01, 136.82, 164.17; MS (M+1) 448.4.
Example 43
I -Methyl-I H-imidazole-4-carboxylic acid (3-chloro-benzyfl-13-(1 -methyl-azetidin-3-vl)-3-
25 --- -- --------- aza-bicyclol3.1.01hex-6-ylmethvfl-amide
100 MHz 13C-NMR(fOC6) 8 18.43, 19.66, 22.12, 33.82, 46.02, 47.59, 48.97, 51.12,
51.82, 52.89, 61.06,126.03, 126.67, 127.35, 127.67, 129.86, 134.50, 136.81, 138.55, 164.08;
MS MS (M+1) 414.2.
Example 44
30 1 -Methyl-I H-imidazole-4-carboxvlic acid (3-methvl-3-aza-bicvclol3.I.Olhex-6-vlmeth
[(2,2,2-trifluoro-ethyl)-benzyll-amide 400 MHz 1HNMR (CDCI3) 6 7.5 (s, IH); 7.1-7.3 (m, 5H); 5.4 (brs, IH); 4.8 (brs, IH);
3.9 (brs, IH); 3.6 (s, 3H); 3.2-3.3 (m, 3H); 2.9 (brs, 2H); 2.2 (m, 5H); 1.4 (m, IH); 1.2-1.3
(m, 2H); 100 MHz 13C-NMR (CDCI3) 618.47, 19.64, 22.73, 33.74, 40.31 (q, J29), 41.50,
35 46.87, 48.76, 49.22, 50.87, 57.17, 121.87, 124.59, 126.38, 127.34, 128.96, 129.40, 130.45, 136.73,138.60,139.32,164.20; MS (M+1)407.1.

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Example 45
I-Methyl-1H-imidazole-4-carboxylic acid (3-methvi-3-aza-bicvclor3.1.OThex-6-vlmethvfl-13-(2,2,2-trifluoro-1 -trifluoromethyl-ethy9-benzyfl-amjde
400 MHz 1F-INMR (COd3) 8 7.5 (s, IH); 7.2-7.4 (m, 5H); 5.4 (brs, IH); 4.8 (brs, IH);
5 3.9-4.0 (m, 2H); 3.6 (s, 3H); 3.3 (brs, IH); 2.8 (m, 2H); 2.2 (m, 5H); 1.4 (m, IH); 1.2 (m,
2H); 100 MHz 13C-NMR (CDCI3) 818.44, 19.62, 22.76, 33.72, 41.43, 47.09, 48.85, 49.50, 50.88, 54.37 (h, J=29), 57.09, 118.94, 121.71, 124.51, 126.48, 126.70, 127.33, 128.26, 129-39,136.73,138.51,139.70,164.22; MS (M+1) 475.1.
Example 46
10 1 -Methyl-I H-imidazole-4-carboxylic acid 13-(1 -hydroxy-cyclohexylmethyfl-3-aza-bicyclor3.1.Olhex-6-ylmethyll-(3-trifluoromethoxy-benzyfl-amide
Methylenecyclohexane epoxide was added to a 15 mL round bottomed flask under
nitrogen, followed by ethanol (3.3 mL), triethylamine (0.097 mL, 0.696 mmol), and 1 -Methyl-

40 1 H-imidazole-4-carboxylic acid (3-aza-bicyclof3.1.Ojhex-6-ylmethyl)-(3-trifluoromethoxy-

15 benzyl)-amide hydrochloride (0.100 g, 0.232 mmol). The reaction warmed to 60 °C, then
refluxed for 4.5 hours and then cooled to room temperature. The reaction was then quenched
with saturated sodium bicarbonate solution and extracted twice with methylene chloride. The
combined organic layers were dried (MgSO4), filtered, and concentrated in vacuo to give
0.087 g of 1 -Methyl-I H-imidazole-4-carboxylic acid [3-(I -hydroxy-cyclohexylmethyl)-3-aza-
20 bicyclo[3.1.O]hex-6-ylmethyl]-(3-trifluoromethoxy-benzyl)-amide. 400 MHz 1H NMR (COd3) 8
7.6 (S. IH), 7.0-7.3 (m, 5H), 5.4 (brs, IH), 4.8 (brs, IH), 4.0 (brs, IH), 3.7(s, 3H), 3.3 (brs,
1H), 2.9-3.0 (rn, 2H), 2.4-2.5 (m, 21-1), 2.3 (m, 2H), 1.2-1.8 (m, 13H); MW (M+1) 507.1
Other examples prepared according to the procedure for Example 46 described
above include:

25 Example 47
1 -Methyl-I H-imidazole-4-carboxylic acid {3-12-(2-chloro-phenyfl-2-hydroxy-ethyfl-3-aza-bicyclol3.I.Olhex-6-ylmethyR-(3-trjftuoromethoxy-benzyfl-amjde
400 MHz 1H NMR (CDCI3) 57.6 (d, J = 1.24 Hz, 1H), 7.1-7.4(m, 9H), 5.5 (brs, IH),
4.8 (brs, IH), 4.5 (brs, 11-I), 4.0 (brs, IH), 3.7 (s, 311), 3.3 (brs, 1H), 2.8-3.2 (m, 21-I), 2.1-
2.6 (m, 4H), 1.2-1.6 (m, 3H); MW (M+1) 549.3.
Example 48
I-Methyl-I H-imidazole-4-carboxylic acid 1341 -hydroxy-cyclopentyln,ethyl)-3-aza-bicyclol3.1.Olhex-6-ylmethyll-(3-trjfluoromethoxy-benzyfl-amide
400 MHz 111 NMR (CDCI3) 8 7.6 (d, J = 1.7 Hz, 1H), 7.3 (t, J = 7.9 Hz, 2H), 7.1-7.2
35 (m, 2H), 7.1 (d, J = 8.3 Hz, IH), 5.5 (brs, IH), 4.8 (brs, IH), 4.0 (brs, IH), 3.7 (s, 3H), 3.3
(brs, 21-), 3.0 (m, 2H), 2.4-2.5 (m, 4H), 1.7-1.8 (m, 2H), 1.4-1.6 (m, 6H), 1.3-1.4 (m, 3H); MW (M+1)493;3.

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Preparation 5
Benzyl 2(6-((N.(3-(trifluoromethOxV)benZVfl-1 -methyl-I H-imidazole-4-carboxamido)rnethyfl-3-aza-biCVClOI3.I.0lhexan-3-yflacetate
To a stirring solution of 6-{[(1 -Methyl-I H-imidazole-4-carbonyl)-(3-trifluoromethoXY-
5 benzyl)-aminol-methyl}-3-aza-bicyClO[3.1.O]hexane-3-carboxylic acid tert-butyl ester prepared
above (2.63 gm, 5.63 mmol) in 30 mL DMF was added potassium carbonate (3.89 gm, 28.2 mmol), tetraethylammonium chloride (150 mg), followed by benzyl 2-bromoacetate (0.88 mL, 5.63 mmol). The reaction was stirred at room temperature for 20 hours and quenched with water. The mixture was diluted with ethyl acetate, the layers separated and the aqueous
10 layer extracted three times with ethyl acetate. The combined organic layers were dried over
anhydrous sodium sulfate, filtered and concentrated to yield 2.8 gm of crude material. The crude material was purified by flash chromatography to yield 2.7 gm of benzyl 2-(6-((N-(3-(trifluoromethoxy)benzyl)-I -methyl-I H-imidazcle-4-carboxamido)methyl)-3-aza-bicyclo[3.1.O]hexan-3-yl)acetate; MS (M+1) 543.3.
15 Preparation 6 2-(6-((N-(3-(trifluoromethoxV)beflZVfl-1 -methyl-I H-imidazole-4-carboxamido)methVl)-3-aza-bucyclol3.I.Olhexan-3-yflacetic acid To a par bottle charged with benzyl 2-(6-((N-(3-(trifluoromethoxy)benZYl)-1-methYt-
I H-imfdazole-4-carboxamido)methyl)-3-aZa-biCyClof3. I.Ojhexan-3-yl)acetate (2.7 gm, 5.07
20 mmol) in 80 mL CH30H, was added 300 mg palladium hydroxide on carbon (20%). The
mixture was hydrogenated under 40 psi H2 at room temperature for 1 hour. The mixture was filtered over a celite, the celite pad was washed with CH30H and the resulting solution was concentrated to yield 2.3 gm of 2-(6-((N-(3-(trifluoromethoxy)benzyl)-I -methyl-i H-imidazole-4arboxamido)methyl)-3-aza-bicyclo[3.1.0]hexan-3-yl)acetic acid as a yellow solid; 400 MHz
25 1H NMR (CDCI3) & 7.54 (s, IH),7.23-.733 (m, 3H), 7.15 (s, 111), 7.05 (d, J = 7.9 Hz, IH), 5.4
(brs, 2H), 4.81 (brs, IH), 3.96 (brs, IH), 3.68 (s, 3H), 3.49 (s, 2H), 3.28 (brs, IH), 3.12 (brs, 21-I), 1.76 (brs, IH), 1.66 (brs, 2H); MS (M+i)452.i.
General Procedure for Amide Couplings A solution of 2-(6-((N-(3-(trifluoromethoxy)benzyl)-1 -methyl-I H-imidazole-4-
30 carboxamido)methyl)-3-aza-biCyclo[3. I.0]hexan-3-yl)acetic acid prepared above (1.0 equiv.)
in 1,2-dichloroethane/triethylamine/dimethylfOrmamide solution was added to the amines (1.9 equiv.), followed by HBTU (2.1 equiv). The reactions stirred at room temperature overnight, quenched with IN NaOH and extracted with dichloromethane. The combined organic layers were dried and concentrated to yield the crude amides that were further purified by flash
35 chromatography or HPLC.
Alternatively, amides could be prepared by utilizing a parallel library synthesis procedure as described below.

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Industria y Comercio
REPUBLICA DE COLOMBIA S U P E R I N T E N D E N C I A SUPERINTENDENCIA DE INDIJSTRIA Y COMERCIO

RESOLUCION 10 411
Por la cual se otorga una patente de invenciOn

CERTIFIcADO

Rad. PCT N° 07-104271

EL SUPERINTENDENTE DE INDUSTRIA Y COMERCIO

en ejerciclo de sus facultades legales, en especial de las que se confineron en el articulo 3, numeral 26, del Decreto 4886 de 2011, y

CONSIDERANDO:

PRIMERO: Que mediante escrilo radicado en esta Supenntendencia el dia 04 de Octubre de 2007 con el No 07-104271-00000-0000, el doctor Carlos Reinaldo Olarte Garcia, en su calidad de apoderado de PFIZER PRODUCTS INC, presentô la solicitud de patente de invenciôn titulada "H ETEROARILAMI DAS [3.1.0]BICICL1CAS COMO INHIBIDORES DEL TRANSPORTE DE GLICINA DE TWO I", correspondiente a la solicitud intemacional PCT/113 20061000947 de fecha 27 de marzo de 2006, para que se iniciara (a fase nacional en virtud del Tratado de Cooperación en Materia de Patentes (PCT).

SEGUNDO: Que el extracto de esta solicitud tue publicado en la Gaceta de la Propiedad Industrial NO 597 del 31 de Octubre de 2008, sin que se hubieran presentado oposiciones por parte de terceros.

TERCERO: Que realizado el examen de fondo mediante Oficio No 05897 y notificado pot fijación en lista el 01 de abril de 2011 se requiriô a (a solicitante en los tØrminos del articulo 45 de la DecisiOn 486 de la ComisiOn de la Comunidad Andina, para que presentara respuesta a las observaciones’ de carâcter tØcnico visibles a folios 255 a 255 del cuaderno administrativo, relacionadas con la patentabilidad o cumplimiento de los requisitos establecidos por esta Decision, para la concesiôn de la patente.

CUARTO: Que la solicitante mediante escrito radicado bajo el No 07-104271-00005-0000 del 28 de jun10 de 2011, respondiO oportunamente el requerimiento formulado, y presentO nuevas reivindicaciones I y 2 (Fl.259) que reemplazan las originalmente presentadas, atendiendo de esta manera las observaciones efectuadas en el examen de fondo. Se aceptO el nuevo capitulo reivindicatorio presentado, como quiera que se ajusta a las prescripciones contenidas en el articulo 34 de la Decision 486.

QUINTO: Que en virtud de lo dispuesto en el articulo 14 de la DecisiOn 486 expedida por la ComisiOn de la Comunidad Andina ’7lJos paises miçmbros otorgarÆnpatentes para las invenciones, sean do producto Q do pmcedimiento, ei todos los campos de la tecnologIa, siempre quo sean nuevas, ten’gan nWoI inventivo y sean susceptibles do aplicaciOn
industrial." -

PSgina 1 do 3 Sedo Centro: Carrera 13 No. 27-00 Pisos 3,4, 5 y 10. Sede CAN: Av. Carrera 50 No. 27-55, mt. 2.
Conmutadores: 5870000 y 5880234
Fax: 5870284. Linea 0160000-910165
Web: www.slc.aov.co e-mail: lnfosIc.aov.co
Bogota D.C. - Colombia

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Industria y Comercio
REPLJBLICA DE COLOMBIA S U P E R I N T E N 0 E N C I A
SUPERINTENDENCIA DE INDUSTRIA V COMERCIO

RESOLUCION 0 43j1J
Per la cual so otorga una patente de invericiOn

CERTIFItADO

Rad. PCT N° 07-104271

SEXTO: Que en el presente caso las reivindicaciones I y 2 contenidas en el folio 259 cumplen los requisitos indicados en el considerando anterior y, en consecuencia, este Despacho encuentra procedente conceder para las mismas la patente solicitada.

SEPTJMO: Que de acuerdo con el objeto concedido se modifica el titulo de la invenciôn, el cual quedarÆde la siguiente manera: "COMPUESTO (-CLORO-4-FLUOROBENClL)-(3-METIL-3-AZA-BICICLQ[3.I.O]HEX-6-ILMETIL) AMIpA DEL AciDo I METIL -IH-IMIDAZOL-4-CARBOXiLICO COMO 1NHIBIDOR DEL TRANSPORTE DE GLICINA DE TIPO I Y COMPOSICIONES FARMACEUTICAS QUE LO CONTIENEN’.

RESUELVE:

ARTCULO PRIMERO: Otorgar patente de invenciÔn a la solicitud que entró en fase nacional on virtud del Tratado de Cooperaciôn en Materia de Patentes (PCT), para la creaciOn titulada:

"COMPUESTO (3.CLOR0.4-FLUOROBENCIL)-(3-MET1L-3-AZA-

BICICLOf3.1.O1HEX-6-ILMETIL) AMIDA DEL ACIDO I MET1L -IH-IMIDAZOL-4-
CARBOXILICO COMO INHIBIDOR DEL TRANSPORTE DE GLICINA DE TWO Y COMPOSICIONES FARMACEUTICAS QUE LO CONTIENEN".

Clasificación IPC: C 07D 403/12, 401/12, 417/12, 4 13/12; A 61 K 31/4178, 31/427, 31/4439, A 61 P 25/00.
Reivindicaciones: I y 2 Folio: 259.

Titular: PFIZER PRODUCTS INC

Domicilio: Eastern Point Road, Groton, Connecticut 0634, Estados Unidos do AmØnca

Inventores: Stanton Furst Mchardy y John Adams Lowe III.

Prioridad N°: 60/669.4 72 Fecha: 08 de Abril cle 2005 Pals: US.

Solicitud Intemacional N’: PCT/IB 2006/00094 7 Fecha: 27 do mario do 2006

Vigente desde: 27 do mario do 2006 Hasta: 27 de mario de 2026.

ARTICULO SEGUNDO: El titular tendrÆlos derechos y las obligaciones establecidos en la

Pgina 2 de 3 Sede Centro: Carrara 13 No. 27-00 P1505 3,4 Sy 10.

Sede CAN: Av. Carrera 50 No, 27-55, ml. 2.
ConmutadoreS: 5870000 y 5880234
Fax: 5870284, Lines 0180000-910165
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Bogota D.C. - Colombia

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Industria y Comercio
REPUBLICADECOLOMBIA SLIPERINTENDENCIA SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

RESOLUCION 0 43J4
Por la cual se otorga una patente de invención

CERTII*ADO

Rad. PCT No 07-104271

Decision 486 de la ComisiOn de’ la Comunidad Andina y en las demÆsdisposiciones legates vigentes sobre propiedad industrial, precisando que para mantener vigente Ia patente se deberÆ cancelar la tasa anual de mantenimiento, conforme to dispone el
articulo 80 de la referida norma comunitaria.

ARTICULO TERCERO: Entregar al titular copia autØntica de esta resoluciOn y el certificado de patente, previas las anotaciones en loslibros de registro.

AR1ICULO CUARTO: Notificar personalmente el contenido de la presente resoluciôn al doctor Carlos Reinaldo Olarte Garcia, en su calidad de apoderado de PFIZER PRODUCTS INC, 0 8 quien haga sus veces, entregÆndole copia de la misma y advirtlØndole que contra ella procede el recurso de reposiciôn, ante el Superintendente de Industria y Comercio, el cual podrÆ serinterpuesto en el momento de la notificaciOn 0 dentro de los cinco 5 dias hàbiles siguientes a ella.

NOTIFIQUESE Y CUMPLASE 31 ENE. 22 Dada en Bogota, D.C., a los
EL SUPERINTENDENTE DE INDJSTRIA Y COMERCIO,

JosE?G

EL LA

ALLE

RESTREPO

Doctor
CARLOS REINALDO OLARTE GARCIA Diagonal 34 No 5-28,
Bogota D.C.

ElaborØ: Maria del Pilar Obando
Revisó: Gloria Jacqueline Atfonso.

AprobO: JosØ Luis Londoo F.

Revisó: Jose Luis Salazar L.

PagIna 3 de 3 Sede Centro: Carrara 13 No. 27-00 Pisos 3,4, 5y 10.
Sede CAN: Av. Carrara 50 No. 27-55 Int. 2.
Conmutadores: 5570000 y 5880234
Fax: 5870284. Linea 0180000-910165
Web: www,sic.poV e-mail: lnfosic.ciov.Q
BogotØ D.C. - Colombia

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