



Libertad y Orden

REPÚBLICA DE COLOMBIA
DIVISIÓN DE PROPIEDAD INDUSTRIAL

PCT
PATE NTE DE INVENC IÓN

Industria y Comercio
SUPERINTENDENCIA

06-33251

TITULO: ANTAGONISTAS DE RECEPTORES DE ACETILCOLINA
MUSCARINICOS

CIP: A61K31/46, C07D451/02, A61P11/00, 11/06

SOLICITANTE: GLAXO GROUP LIMITED.

DIRECCIÓN: Glaxo Wellcome House, Berkeley Avenue, Greenford,
Middlesex UB8 3NN, Inglaterra

APODERADO: CARLOS R. OLARTE

BOGOTÁ, Abril 5 de 2006

60

OLARTE RAISBECK



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Rad: 08-033251- -00000-0000 Fece: 2008-04-05 16:05:14
Dep. 2020 NUECREACIONES
Tra: 11 PATENTEYII Eje 378 FASENACIONALI
Act 411 PRESENTACION Folios: 76

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

14-05-2006

1 SOLICITUD DE:		
☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.		
☒ Capítulo I. ☐ Capítulo II.		
2 SOLICITANTE (71)	Nombre: <u>GLAXO GROUP LIMITED</u> Dirección: <u>Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN</u> Nacionalidad o Domicilio: <u>BRITANICA</u> Lugar de Constitución: <u>INGLATERRA</u> Teléfono: _____ Fax: _____ E-mail: _____	IDENTIFICACIÓN C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número _____
3 REPRESENTANTE APODERADO	Nombre: <u>CARLOS R. OLARTE</u> Dirección: <u>World Trade Center Torre A, Calle 100 No. 8A-37 Piso 10</u> Teléfono: <u>601-7700</u> Fax: <u>601-7799</u> E-mail: <u>office@olarteraisbeck.com</u>	IDENTIFICACIÓN C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual _____ Número <u>79.782.747 Btá</u> TP <u>74.295</u>
4 INVENTOR (ES) (72)	Nombre: <u>1. Michael R. Palovich, 2. Jakob Busch-Petersen, 3. Zehong Wan, 4. Hongxing Yan, 5. Chongjie Zhu.</u> Dirección: <u>709 Swedeland Road, King of Prussia, PA 19406, Estados Unidos de América.</u> Nacionalidad o Domicilio: <u>1. ESTADOUNIDENSE, 2. DANES, 3. 4. 5. CHINA</u>	
5 PCT (86) Solicitud Internacional No. <u>PCT/US2004/033638</u> Fecha <u>Octubre 12, 2004</u> Publicación Internacional No. <u>WO 2005/037280</u> Fecha <u>Abril 28, 2005</u>		
6 Título (54) <u>ANTAGONISTAS DE RECEPTORES DE ACETILCOLINA MUSCARINICOS</u>		
7 Clasificación Internacional (51) <u>A61K 31/46, C07D 451/02, A61P 11/00, 11/06</u>		
8 Prioridad SI ☒ N ☐	(33) País de Origen <u>US</u>	(32) Fecha <u>Octubre 14, 2003</u>
	(31) Número de Solicitud <u>60/511.009</u>	
9 Comprobante de pago No. <u>06-26.002</u> Fecha <u>Abril 4, 2006</u>		

10

ANEXOS

☒

Comprobante de pago de la tasa de presentación de la solicitud.

☐

Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.

☒

Poderes, si fuere el caso.

☐

Documento de cesión del inventor al solicitante o a su causante.

☐

Declaraciones.

☒

Copia 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 indígenas.

☐

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 títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

☐

De ser el caso, modificaciones efectuadas a la solicitud Internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: [Signature]
C.C. 79.782.747 Btá T.P. 74.295

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

3 3

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Rad: 08-033251- -00000-0000 Fax: 2008-04-06 16:05:14
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Tra: 11 PATENTEYII Eva 378 FASENACIONALJ
Act 411 PRESENTACION Folios: 76

RECIBO OFICIAL DE CAJA : 06 - 26,002
FECHA : ABRIL 4 DE 2006

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
OLARTE RAISBEER	CONSIGNACION	BANCO POPULAR	050-00110-6	51156209	04/04/2006	7,609,000.

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01	SOLICITUDES	
1		TRANITES DE SOL. DE PATENTE DE IN	463,000.00
		TOTAL :	\$ 463,000.00

SON: CUATROCIENTOS SESENTA Y TRES MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

4
A

Traducción oficial del Inglés por Marlén Neira Castro, resolución 2117 del
Ministerio de Justicia de Colombia

**APOSTILLA EN PODER DE REPRESENTACIÓN DE
GLAXO GROUP LIMITED**

PODER DE REPRESENTACION

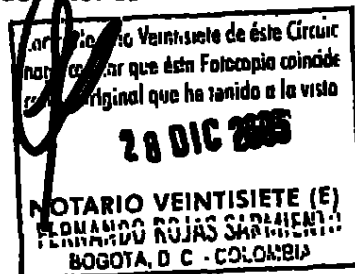
Bilingüe inglés- español otorgado en Brentford, Middlesex, Inglaterra el 13 de
agosto de 2003 y firmado por Peter John Giddings, Apoderado y Funcionario
autorizado.

Certificado de Notario De Pinna en español firmado por James Kerr Milligan

APOSTILLA

(Convención de la Haya del 5 de octubre de 1961)

1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
 2. ha sido firmado por James Kerr Milligan
 3. Quien ejerce funciones de Notario público
 4. Lleva el sello del Notario público
- CERTIFICADO**
5. En Londres
 6. El 14 agosto 2003
 7. Por el Secretario de Estado Principal de su Majestad para Asuntos
exteriores y de la Mancomunidad
 8. No. G229474
 9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
 10. Firma legible de J. Garbrah- Por el Secretario de Estado



Si el documento se usa en un país que no pertenece a la Convención de la Haya del
-5 de octubre de 1961 debe pasar por la sección consular de la Misión que
representa el país.

Es traducción fiel del inglés, con copia archivo para confrontación. Bogotá 21 agosto-03.

Marlen Neira C

Marlen Neira C
MARLEN NEIRA CASTRO
Traductor e Intérprete Ofi.
Inglés - Español - Inglés
Resolución No. 2117 del 7 O.

Yo, el infrascrito **JAMES KERR MILLIGAN**, Notario Público de la Ciudad de Londres, Inglaterra, por la Autoridad Real debidamente admitido y juramentado,

CERTIFICO:

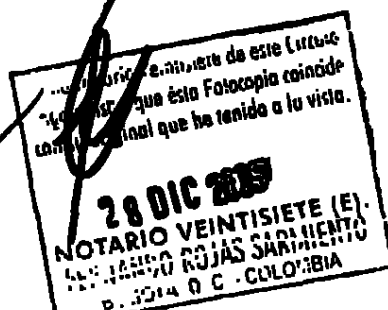
QUE es auténtica la firma suscrita al pie del adjunto Poder, por ser del puño y letra del Señor Don **PETER JOHN GIDDINGS**, cuya identidad me consta, Apoderado de la Sociedad inglesa denominada "**GLAXO GROUP LIMITED**", Sociedad legalmente constituida y existente de acuerdo con las leyes de Inglaterra, e inscrita en la Oficina de Registro de Sociedades bajo el número **305979**, con domicilio social en **Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 ONN, Inglaterra;**

QUE el citado Señor Don **PETER JOHN GIDDINGS** está debidamente autorizado para firmar documentos de esta clase en nombre y representación de dicha Sociedad en virtud de un Poder otorgado por la referida Sociedad fechado 3 de julio de 2002.

Y QUE los objetos para los cuales se otorgó dicho Poder se encuentran dentro de los objetos o actividades de la citada Sociedad, de acuerdo con la Escritura Constitutiva y los Estatutos Sociales, los cuales he tenido a la vista.

Y PARA QUE CONSTE donde y como convenga y fuere necesario expido el presente Certificado que firmo y sello en dicha Ciudad de Londres, el día de hoy vece de agosto del año dos mil tres.

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



APOSTILLE
(Hague Convention of 5 October 1961 / Convention de La Haye du 5 octobre 1961)

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

1. Country: United Kingdom of Great Britain and Northern Ireland
Pays: Royaume-Uni de Grande-Bretagne et d'Irlande du Nord

This public document / Le présent acte public

2. Has been signed by James Kerr Milligan
a été signé par
3. Acting in the capacity of Notary Public
agissant en qualité de
4. Bears the seal/stamp of The Said Notary Public
est revêtu du sceau/timbre de

5. at London/à Londres
6. the/le 14 August 2003
7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

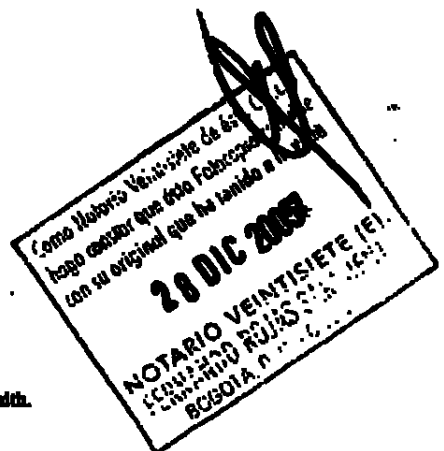
8. Number/num No **G229474**

9. Stamp:
timbre:
10. Signature: J. Garbrah



For the Secretary of State / Pour le Secrétaire d'Etat

If this document is to be used in a country which is not party to the Hague Convention of 5 October 1961,
it should be presented to the consular section of the mission representing that country.



OLARTE RAISBECK

OLARTE RAISBECK & FRIERI, LTDA.
LEGAL & PROFESSIONAL SERVICES

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Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB
by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs 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, appeals, 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.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

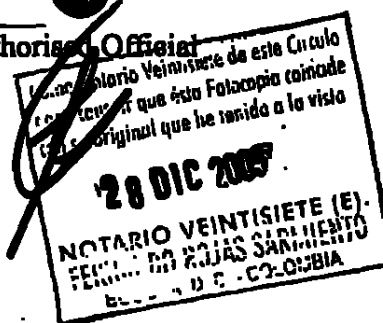
por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier jerarquía para cumplir con lo encomendado, elevar solicitudes, apelaciones, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistirse y percibir. Se concede poder bastante para recibir notificaciones a nombre de la compañía, otorgar poderes a quienes vayan a representar a la compañía judicial y extrajudicialmente, responder en juicio a todas las reclamaciones o demandas que por motivo de lo encomendado se presentaren, dándoles asimismo facultad para sustituir el presente y revocar dichas sustituciones.

Signature/Firma:


Peter John GIDDINGS as Attorney and Authorized Official

Date/Fecha: 13 August 2003

City/Country/Ciudad, País: Brentford, Middlesex, England



(19) World Intellectual Property
Organization
International Bureau



(43) International Publication Date
28 April 2005 (28.04.2005)

PCT

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C07D 451/02

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(30) Priority Date: 60/511,009 14 October 2003 (14.10.2003) US

(71) Applicant (for all designated States except US): GLAXO
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(72) Inventors; and

(73) Inventors/Applicants (for US only): BUSCH-PE-
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[US/US]; 709 Swedeland Road, King of Prussia, PA
19406 (US). WAN, Zehong [CN/US]; 709 Swedeland
Road, King of Prussia, PA 19406 (US). YAN, Hongxing
[CN/US]; 709 Swedeland Road, King of Prussia, PA
19406 (US). ZHU, Chongjie [CN/US]; 709 Swedeland
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(74) Agents: SOMA, Simon, G. et al.; Glaxosmithkline,
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Road, P.O. Box 1539, King of Prussia, PA 19406-0939
(US).

(81) Designated States (unless otherwise indicated, for every
kind of national protection available): AE, AG, AL, AM,
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,
GB, GD, GH, GM, GR, HT, HU, ID, IL, IN, IS, JP, KE,
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,
MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM, PG,
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,
ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, CH,

GM, KI, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,
FR, GB, GR, HU, IL, IT, LU, MC, NL, PL, PT, RO, SI, SK,
TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NI, SN, TD, TG).

Declarations under Rule 4.17:

— as to applicant's entitlement to apply for and be granted
a patent (Rule 4.17(ii)) for the following designations AE,
AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ,
CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE,
EG, ES, FI, GB, GD, GE, GH, GM, HT, HU, ID, IL, IN, IS,
JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA,
MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ, OM,
PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ,
TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA,
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HT, IE,
IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG)

— as to the applicant's entitlement to claim the priority of the
earlier application (Rule 4.17(iii)) for the following desig-
nations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW,
BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ,
EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HT, HU, ID,
IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU,
LV, MA, MD, MG, MK, MN, MW, MX, MY, NA, NI, NO, NZ,
OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY,
TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM,
ZW, ARIPO patent (BW, GH, GM, KE, LS, MW, MZ, NA,
SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ,
BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE,
BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HT, IE,
IT, LU, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI patent
(BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE,
SN, TD, TG)

— of inventorship (Rule 4.17(iv)) for US only

Published:

— with international search report

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

(54) Title: MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS

(57) Abstract: Muscarinic Acetylcholine Receptor Antagonists and methods of using them are provided.

WO 2005/037280 A1

8 8

MUSCARINIC ACETYLCHOLINE RECEPTOR ANTAGONISTS**FIELD OF THE INVENTION**

This invention relates to novel derivatives of 8-azoniabicyclo[3,2,1]octanes, pharmaceutical compositions, processes for their preparation, and use thereof in
5 treating M₃ muscarinic acetylcholine receptor mediated diseases.

BACKGROUND OF THE INVENTION

Acetylcholine released from cholinergic neurons in the peripheral and central nervous systems affects many different biological processes through interaction with two major classes of acetylcholine receptors – the nicotinic and the muscarinic
10 acetylcholine receptors. Muscarinic acetylcholine receptors (mAChRs) belong to the superfamily of G-protein coupled receptors that have seven transmembrane domains. There are five subtypes of mAChRs, termed M₁-M₅, and each is the product of a distinct gene. Each of these five subtypes displays unique pharmacological properties. Muscarinic acetylcholine receptors are widely distributed in vertebrate organs, and
15 these receptors can mediate both inhibitory and excitatory actions. For example, in smooth muscle found in the airways, bladder and gastrointestinal tract, M₃ mAChRs mediate contractile responses. For review, please see {Brown 1989 247 /id}.

Muscarinic acetylcholine receptor dysfunction has been noted in a variety of different pathophysiological states. For instance, in asthma and chronic obstructive
20 pulmonary disease (COPD), inflammatory conditions lead to loss of inhibitory M₂ muscarinic acetylcholine autoreceptor function on parasympathetic nerves supplying the pulmonary smooth muscle, causing increased acetylcholine release following vagal nerve stimulation. This mAChR dysfunction results in airway hyperreactivity mediated by increased stimulation of M₃ mAChRs {Costello, Evans, et al. 1999 72 /id} {Minette,
25 Lammers, et al. 1989 248 /id}. Similarly, inflammation of the gastrointestinal tract in inflammatory bowel disease (IBD) results in M₃ mAChR-mediated hypermotility {Oprins, Meijer, et al. 2000 245 /id}. Incontinence due to bladder hypercontractility has also been demonstrated to be mediated through increased stimulation of M₃ mAChRs {Hegde & Eglen 1999 251 /id}. Thus the identification of subtype-selective
30 mAChR antagonists may be useful as therapeutics in these mAChR-mediated diseases.

Despite the large body of evidence supporting the use of anti-muscarinic receptor therapy for treatment of a variety of disease states, relatively few anti-

a

muscarinic compounds are in use in the clinic. Thus, there remains a need for novel compounds that are capable of causing blockade at M₃ mAChRs. Conditions associated with an increase in stimulation of M₃ mAChRs, such as asthma, COPD, IBD and urinary incontinence would benefit by compounds that are inhibitors of mAChR binding.

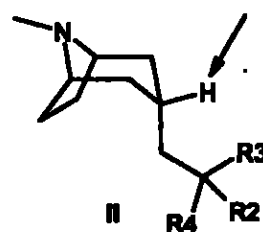
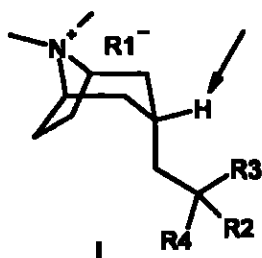
SUMMARY OF THE INVENTION

This invention provides for a method of treating a muscarinic acetylcholine receptor (mAChR) mediated disease, wherein acetylcholine binds to an M₃ mAChR and which method comprises administering an effective amount of a compound of Formula (I) or Formula (II) [except the compound of Formula (II) with R₂ and R₃ as 2-thiophene and R₄ as -OC(O)CH₃] or a pharmaceutically acceptable salt thereof.

This invention also relates to a method of inhibiting the binding of acetylcholine to its receptors in a mammal in need thereof which comprises administering to aforementioned mammal an effective amount of a compound of Formula (I) or Formula (II).

The present invention also provides for the novel compounds of Formula (I) or Formula (II), and pharmaceutical compositions comprising a compound of Formula (I) or Formula (II), and a pharmaceutical carrier or diluent.

Compounds of Formula (I) or Formula (II) useful in the present invention are represented by the structure:



wherein:
the H atom indicated is in the exo position;

10 10

R1⁻ represents an anion associated with the positive charge of the N atom. R1⁻ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate;

- 5 R2 and R3 are independently selected from the group consisting of straight or branched chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups (having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms), heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom, heterocycloalkyl-alkyl (having 6 to 10 carbon atoms) and N or O as the heteroatom, 10 aryl, optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

- R4 is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl, -OR₅, 15 -CH₂OR₅, -CH₂OH, -CN, -CF₃, -CH₂O(CO)R₆, -CO₂R₇, -CH₂NH₂, -CH₂N(R₇)SO₂R₅, -SO₂N(R₇)(R₈), -CON(R₇)(R₈), -CH₂N(R₈)CO(R₆), -CH₂N(R₈)SO₂(R₆), -CH₂N(R₈)CO₂(R₅), -CH₂N(R₈)CONH(R₇);

- R5 is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl; 20

- R6 is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl; 25

- R7 and R8 are, independently, selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, and (C₁-C₆)alkyl-heteroaryl. 30

Suitable pharmaceutically acceptable salts are well known to those skilled in the art and include basic salts of inorganic and organic acids, such as hydrochloric acid, hydrobromic acid, sulphuric acid, phosphoric acid, methane sulphonc acid, ethane sulphonc acid, acetic acid, malic acid, tartaric acid, citric acid, lactic acid, oxalic acid, succinic acid, fumaric acid, maleic acid, benzoic acid, salicylic acid, phenylacetic acid and mandelic acid. In addition, pharmaceutically acceptable salts of compounds of Formula (I) or Formula (II) may also be formed with a pharmaceutically acceptable cation. Suitable pharmaceutically acceptable cations are well known to those skilled in the art and include alkaline, alkaline earth, ammonium and quaternary ammonium cations.

The following terms, as used herein, refer to:

- "halo" - all halogens, that is chloro, fluoro, bromo and iodo.
- "C₁₋₁₀alkyl" or "alkyl" - both straight and branched chain moieties of 1 to 10 carbon atoms, unless the chain length is otherwise limited, including, but not limited to, methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *sec*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl and the like.
- "cycloalkyl" is used herein to mean cyclic moiety, preferably of 3 to 8 carbons, including but not limited to cyclopropyl, cyclopentyl, cyclohexyl, and the like.
- "alkenyl" is used herein at all occurrences to mean straight or branched chain moiety of 2-10 carbon atoms, unless the chain length is limited thereto, including, but not limited to ethenyl, 1-propenyl, 2-propenyl, 2-methyl-1-propenyl, 1-butenyl, 2-butenyl and the like.
- "aryl" - phenyl and naphthyl;
- "heteroaryl" (on its own or in any combination, such as "heteroaryloxy", or "heteroaryl alkyl") - a 5-10 membered aromatic ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O or S, such as, but not limited, to pyrrole, pyrazole, furan, thiophene, quinoline, isoquinoline, quinazolinyl, pyridine, pyrimidine, oxazole, tetrazole, thiazole, thiadiazole, triazole, imidazole, or benzimidazole.
- "heterocyclic" (on its own or in any combination, such as "heterocyclicalkyl") - a saturated or partially unsaturated 4-10 membered ring system in which one or more rings contain one or more heteroatoms selected from the group consisting of N, O, or S; such as, but not limited to, pyrrolidine, piperidine, piperazine, morpholine,

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tetrahydropyran, thiomorpholine, or imidazolidine. Furthermore, sulfur may be optionally oxidized to the sulfone or the sulfoxide.

• "arylalkyl" or "heteroarylalkyl" or "heterocyclicalkyl" is used herein to mean C₁₋₁₀ alkyl, as defined above, attached to an aryl, heteroaryl or heterocyclic moiety, as
5 also defined herein, unless otherwise indicated.

• "sulfinyl" - the oxide S (O) of the corresponding sulfide, the term "thio" refers to the sulfide, and the term "sulfonyl" refers to the fully oxidized S(O)₂ moiety.

• "wherein two R₁ moieties (or two Y moieties) may together form a 5 or 6 membered saturated or unsaturated ring" is used herein to mean the formation of an
10 aromatic ring system, such as naphthalene, or is a phenyl moiety having attached a 6 membered partially saturated or unsaturated ring such as a C₆ cycloalkenyl, i.e. hexene, or a C₅ cycloalkenyl moiety, such as cyclopentene.

Preferred compounds useful in the present invention include:

(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-
15 bicyclo[3.2.1]octane iodide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;
(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;
20 (Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
bromide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;
25 N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-
propionamide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
iodide;
1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-
30 urea;
1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;

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- N*-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 5 *N*-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;
[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and
- 10 (Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.
- More preferred compounds useful in the present invention include:
(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 15 (Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
- 20 iodide;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and
(Endo)-3-(2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

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Methods of Preparation.

Preparation

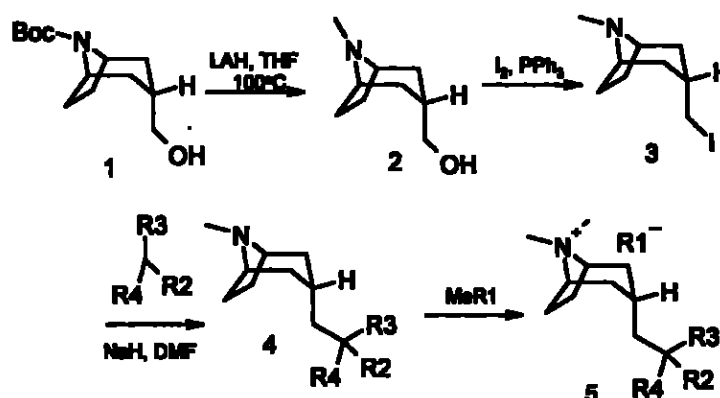
- The compounds of Formula (I) and Formula (II) may be obtained by applying synthetic procedures, some of which are illustrated in the Schemes below. The
- 30 synthesis provided for these Schemes is applicable for producing compounds of Formula (I) and Formula (II) having a variety of different R1, R2, R3 and R4 which are

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reacted, employing substituents which are suitable protected, to achieve compatibility with the reactions outlined herein. Subsequent deprotection, in those cases, then affords compounds of the nature generally disclosed. While some schemes are shown with compounds only of Formula (II), this is merely for illustration purpose only.

- 5 The general preparation method is shown in Scheme I. The synthesis started with compound 1. Reduction with lithium aluminium hydride (LAH) afforded alcohol 2. Displacement with iodine provided 3. Coupling reaction with the anion derived from $\text{HCR}_2(\text{R}_3)(\text{R}_4)$ then furnished compound 4, which was easily converted to ammonium salt 5.

10 **Scheme I.**



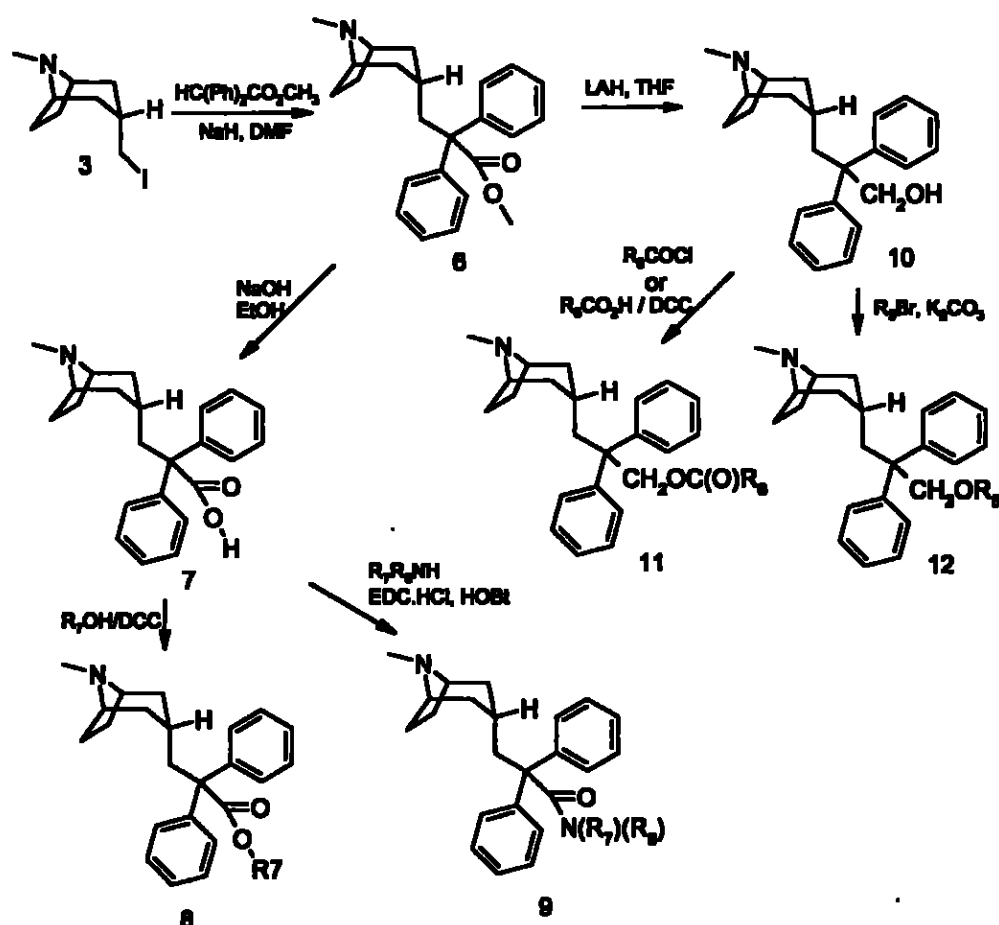
- A more specific preparation method leading to compounds with Formula (II) is outlined in Scheme II. Alkylation of ester $\text{HC}(\text{Ph})_2\text{CO}_2\text{CH}_3$ with 3 afforded compound 6. Hydrolysis of 6 generated acid 7. 1,3-Dicyclohexylcarbodiimide (DCC) mediated condensation of the acid with alcohol (R7)OH then furnished ester 8. Condensation of acid 7 with amine (R7)(R8)NH under suitable amide coupling conditions well known to those skilled in the art such as 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC.HCl) and 1-hydroxybenzotriazole hydrate (HOBt) provided amide 9. Reduction of 6 generated alcohol 10. Reaction of 10 with acid chloride (R6)COCl or acid (R6)CO₂H afforded ester 11. Alkylation of 10 with appropriate reagents such as (R5)Br then furnished 12.

Compounds with structures similar to 6, 7, 8, 9, 10, 11 and 12 were converted to corresponding ammonium salts by reacting with appropriate reaction reagents such as

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MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

Scheme II.

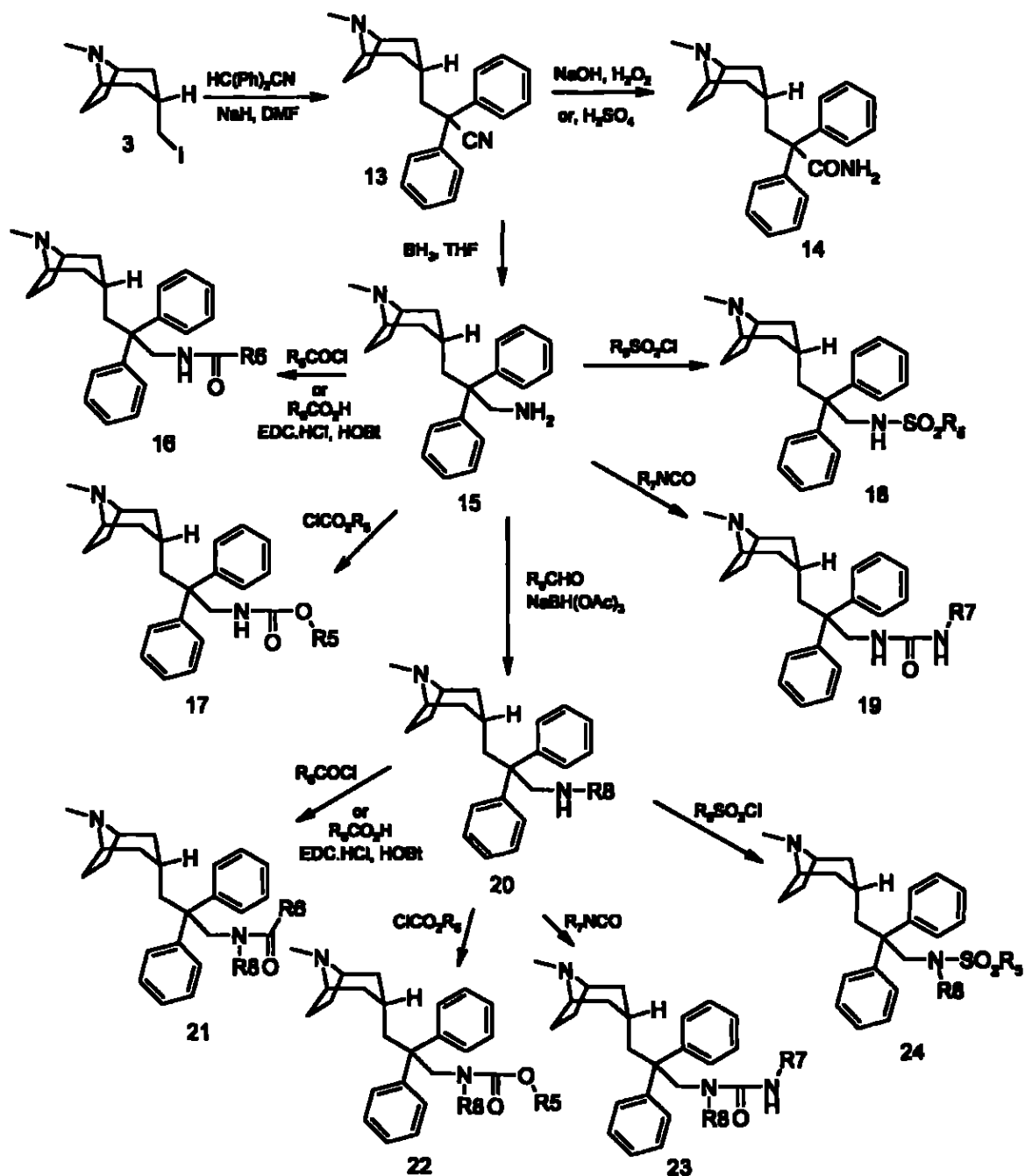


- 5 A more specific preparation method leading to compounds with Formula (II) is outlined in Scheme III. Alkylation of $\text{HC(Ph)}_2\text{CN}$ with **3** provided nitrile **13**. Hydrolysis of **13** under either basic conditions (e.g., NaOH and H_2O_2) or acidic conditions (e.g., H_2SO_4) afforded amide **14**. Reduction of **13** led to amine **15** that was conveniently transformed to amide **16**, carbamide **17**, sulfonamide **18** and urea **19**.
- 10 Condensation of **15** with aldehyde $(\text{R}_8)\text{CH(O)}$ followed by reduction with NaBH(OAc)_3 furnished amine **20** that was easily converted to amide **21**, carbamide **22**, urea **23** and sulfonamide **24**.

Compounds with structures similar to **13**, **14**, **15**, **16**, **17**, **18**, **19**, **20**, **21**, **22**, **23** and **24** were converted to corresponding ammonium salts by reacting with appropriate

reaction reagents such as MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

Scheme III.

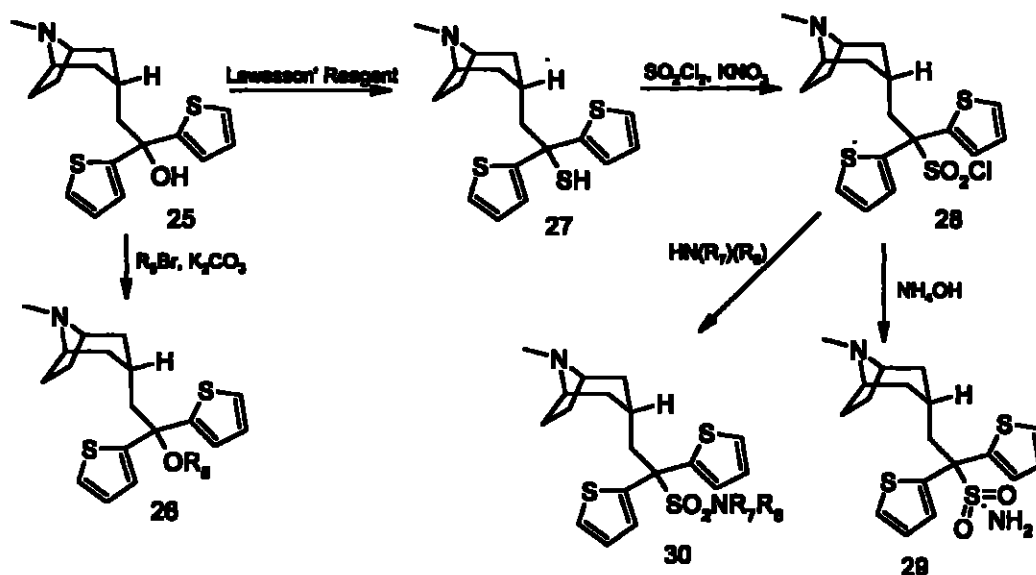


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A more specific preparation method leading to compounds with Formula (II) is outlined in Scheme IV. Alkylation of 25 with (R₅)Br provided 26. Reaction of 25 with Lawesson's reagent afforded 27. Oxidation of 27 with SO₂Cl₂ and KNO₃ furnished 28 that was converted to either 29 or sulfonamide 30.

- 5 Compounds with structures similar to 26, 27, 29 and 30 were easily converted to the corresponding ammonium salts by reacting with appropriate reaction reagents such as MeBr and MeI (not shown in the scheme). Appropriate protection and deprotection methods were utilized in some preparation procedures.

Scheme IV



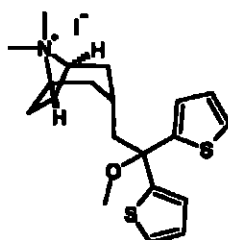
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SYNTHETIC EXAMPLES

The following examples are provided as illustrative of the present invention but not limiting in any way:

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Example 1



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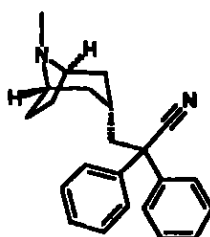
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(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

To a solution of 2-(8-methyl-8-azabicyclo[3.2.1]oct-3-yl)-1,1-dithiophen-2-yl-ethanol (prepared according to US2800482) (212mg, 0.64mmol) in 5 mL
5 methylenechloride and iodomethane (0.40mL, 6.4 mmol), 50% aqueous potassium hydroxide (0.25mL, 3.2 mmol) and tetrabutylammonium chloride (5mg, 3 mol%) was added. The reaction mixture was heated to reflux for 5 d. Each day, an additional 0.2mL iodomethane and 0.1mL potassium hydroxide was added. Upon completion, the
10 reaction mixture was cooled to room temperature, diluted with methylenechloride and washed with water. The aqueous layer was extracted with methylenechloride and the combined organic layers were washed with brine, dried over MgSO₄ and concentrated *in vacuo*. The crude product was recrystallized from methylenechloride/ethyl acetate to give 109mg of the title compound: LCMS (ES) *m/z* 362 (M)⁺.

15

Example 2



3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile

2a) Preparation of ((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanol

A mixture of 1,1-dimethylethyl (endo)-3-(hydroxymethyl)-8-azabicyclo[3.2.1]
20 octane-8-carboxylate (0.50 g, 2.05 mmol) and LiAlH₄ (6.16 mL, 1.0 M in THF, 6.16 mmol) was heated at 80°C with a microwave reactor for 60 min. The solution was then mixed with saturated Na₂SO₄ solution, filtered through celite and concentrated to afford the title compound (0.31 g, 97 %): LCMS (ES) *m/z* 156 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.28 (s, 1H), 1.59 (m, 4H), 1.90 (m, 1H), 2.13 (m, 4H), 2.32 (s, 3H),
25 3.17 (s, 2H), 3.59 (d, 2H).

2b) Preparation of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane

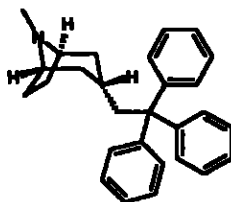
19 19

A solution of iodine (6.67 g, 25.8 mmol) and ((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-methanol (2.0 g, 12.9 mmol) in CH_2Cl_2 (120 mL) was mixed with PPh_3 (on resin, 8.6 g, 3 mmol/g, 25.8 mmol). The resultant mixture was stirred for 17 hours, filtered and concentrated to afford the title compound (2.63 g, 77 %): LCMS (ES) m/z 266 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{CDCl}_3)$ δ 2.05 (m, 4H), 2.39 (m, 3H), 2.79 (d, 3H), 2.98 (m, 2H), 3.45 (d, 2H), 3.81 (s, 2H).

2c) Preparation of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile

A solution of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane (1.06 g, 4.0 mmol) and Ph_2CHCN (2.32 g, 12.0 mmol) in DMF (20 mL) was mixed with NaH (0.288 g, 12.0 mmol). The resultant mixture was stirred at room temperature for 60 minutes. Filtration and purification via a reverse phase HPLC (Gilson) then afforded the title compound (1.16 g, 93 %): LCMS (ES) m/z 331 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.64 (m, 2H), 2.14 (m, 1H), 2.26 (m, 2H), 2.34 (m, 2H), 2.52 (m, 2H), 2.75 (m, 5H), 3.83 (s, 2H), 7.39 (d, 10H).

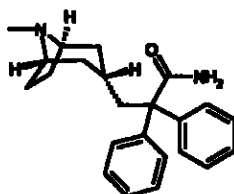
Example 3



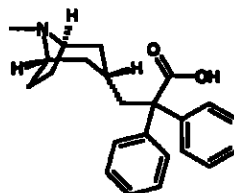
(Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane

A solution of triphenylmethane (0.276 g, 1.13 mmol) in THF (0.5 mL) was mixed with $n\text{-BuLi}$ (0.706 mL, 1.6 M in Hexane, 1.13 mmol). The solution was stirred for 10 minutes and added by a solution of (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane (100 mg, 0.377 mmol) in DMF (1.0 mL). The mixture was stirred at room temperature for 60 minutes, mixed with H_2O (0.1 mL), concentrated and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (23.8 mg, 17 %): LCMS (ES) m/z 382 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{CDCl}_3)$ δ 1.07 (d, 2H), 2.12 (m, 1H), 2.22 (m, 4H), 2.31 (m, 2H), 2.65 (d, 3H), 2.97 (d, 2H), 3.63 (s, 2H), 7.21 (m, 3H), 7.30 (d, 12H).

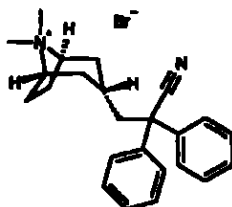
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Example 4**3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide**

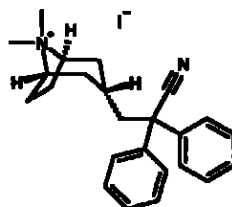
A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (53 mg, 0.16 mmol) in CH_2Cl_2 (0.25 mL) was mixed with H_2SO_4 (0.28 mL, 96 %) and stirred at 40°C for 30 hours. The mixture was then poured into ice, neutralized with $\text{NH}_3\cdot\text{H}_2\text{O}$, extracted with EtOAc and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) provided the title compound (17.2 mg, 30 %): MS (ES) m/z 347 ($\text{M}+\text{H}^+$); ^1H -NMR(CDCl_3) δ 1.31 (d, 2H), 1.98 (m, 1H), 2.28 (m, 4H), 2.39 (m, 2H), 2.67 (d, 3H), 2.79 (d, 2H), 3.66 (s, 2H), 5.82 (s, br, 1H), 6.88 (s, br, 1H), 7.37 (m, 10H).

Example 5**3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid**

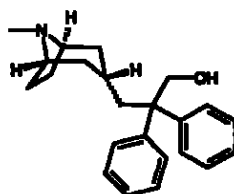
A solution of 2-[(3-endo)-8-methyl-8-azabicyclo[3.2.1]oct-3-yl]-1,1-diphenylethanol (100 mg, 1.56 mmol) in HCOOH (0.25 mL) was quickly added by H_2SO_4 (2.73 mL, 90 %) at 0°C . The reaction vial was capped immediately and stored in a refrigerator at -20°C for 7 days. The solution was poured into ice, neutralized with $\text{NH}_3\cdot\text{H}_2\text{O}$, extracted with EtOAc and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (52 mg, 48 %): LCMS (ES) m/z 350 ($\text{M}+\text{H}^+$); ^1H -NMR(MeOD) δ 1.39 (d, 2H), 1.86 (m, 1H), 1.97 (m, 2H), 2.30 (m, 4H), 2.69 (s, 3H), 2.84 (d, 2H), 3.69 (s, 2H), 7.28 (m, 2H), 7.36 (m, 8H).

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2**Example 6****(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide**

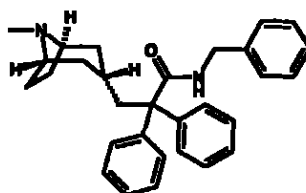
- 5 A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (310 mg, 0.938 mmol) in acetone (6.0 mL) was mixed with MeBr (4.69 mL, 2.0 M in *t*-BuOMe, 9.38 mmol). The resultant mixture was stirred at room temperature for 60 minutes and filtered. The solid was washed with acetone (2 x 3 mL) to afford the title compound (333 mg, 83 %): LCMS (ES) m/z 345 (M)⁺; ¹H-NMR(MeOD) δ 1.82 (d, 2H), 2.17 (m, 1H), 2.35 (m, 2H), 2.49 (m, 4H), 3.01 (d, 2H), 3.07 (s, 3H), 3.10 (s, 3H), 3.79 (s, 2H), 7.36 (m, 2H), 7.43 (m, 4H), 7.49 (m, 4H).
- 10

Example 7**(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide**

- 15 A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (26.5 mg, 0.080 mmol) in CH₂Cl₂ (0.5 mL) and MeCN (0.5 mL) was mixed with MeI (0.125 mL, 2.00 mmol). The resultant mixture was stirred at room temperature for 3 hours, diluted with DMSO (0.3 mL) and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (22.9 mg, 60 %): LCMS (ES) m/z 345 (M)⁺; ¹H-NMR(CDCl₃) δ 1.83 (d, 2H), 2.17 (m, 1H), 2.35 (m, 2H), 2.49 (m, 4H), 3.01 (d, 2H), 3.07 (s, 3H), 3.10 (s, 3H), 3.79 (s, 2H), 7.36 (m, 2H), 7.43 (m, 4H), 7.49 (m, 4H).
- 20

Example 8**3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol**

A mixture of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid (42.5 mg, 0.122 mmol) and LiAlH₄ (0.488 mL, 1.0 M in THF, 0.488 mmol) was heated with a microwave reactor at 100°C for 1 hour. It was diluted with saturated Na₂SO₄ solution, filtered through celite and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (29.1 mg, 71 %): LCMS (ES) *m/z* 336(M+H)⁺; ¹H-NMR(CDCl₃) δ 1.40 (d, 2H), 1.92 (m, 1H), 2.29 (m, 6H), 2.59 (m, 2H), 2.68 (d, 3H), 3.72 (s, 2H), 4.16 (s, 2H), 7.13 (m, 3H), 7.30 (m, 7H).

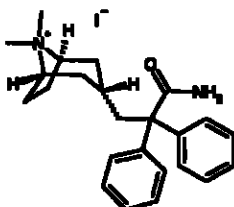
Example 9

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N-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid (82.0 mg, 0.235 mmol) in CH₂Cl₂ (3.0 mL) was mixed with PhCH₂NH₂ (28.2 μL, 0.258 mmol), EDC (49.5 mg, 0.258 mmol), HOBt (3.2 mg, 0.024 mmol) and (CH₃CH₂)₃N (0.232 mL, 1.65 mmol). The mixture was stirred at room temperature for 60 hours and concentrated. The resultant residue was dissolved in DMSO and filtered. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (29.8 mg, 30 %): LCMS (ES) *m/z* 439(M+H)⁺; ¹H-NMR(CDCl₃) δ 1.34 (d, 2H), 1.96 (m,

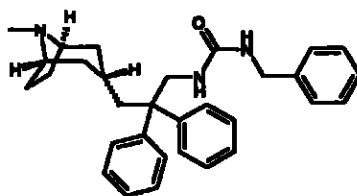
1H), 2.23 (m, 2H), 2.38 (m, 4H), 2.63 (d, 3H), 2.83 (d, 2H), 3.66 (s, 2H), 4.41 (d, 2H), 6.93 (m, 2H), 7.22 (m, 3H), 7.38 (m, 10H).

Example 10

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(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide by following the procedure of Example 7 (33 %
 10 yield): LCMS (ES) m/z 363 (M^+); ^1H -NMR($CDCl_3$) δ 1.49 (d, 2H), 1.95 (m, 1H), 2.25 (m, 2H), 2.42 (m, 4H), 2.84 (d, 2H), 3.17 (s, 3H), 3.23 (s, 3H), 3.93 (s, 2H), 5.65 (s, 1H), 5.91 (s, 1H), 7.39 (m, 10H).

Example 11

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1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

11a) 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile (250 mg, 0.758 mmol) in THF (2.5 mL) was mixed with BH_3 (2.53 mL, 1.5 M in THF, 3.79 mmol) at 0°C. The mixture was stirred at room temperature for 20
 20 hours and diluted with H_2O (1.0 mL). The solution was then mixed with K_2CO_3 (0.1 g) and stirred at room temperature for 1 hour. Organic layers were separated and the aqueous part was extracted with EtOAc (2 x 3 mL). The organic layers were

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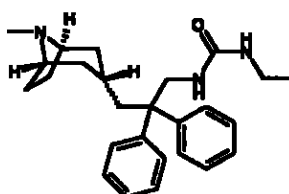
combined, dried over Na_2SO_4 and concentrated. Purification via a reverse phase HPLC (Gilson) afforded the titled compound (159mg, 63%): LCMS (ES) m/z 335 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{MeOD})$ δ 1.35 (d, 2H), 2.01 (m, 3H), 2.34 (s, 4H), 2.55 (s, 2H), 2.68 (s, 3H), 3.73 (m, 5H), 7.26 (m, 4H), 7.33 (m, 2H), 7.43 (m, 4H).

5 11(b) 1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (50.0 mg, 0.149 mmol) in CH_2Cl_2 (2.0 mL) was mixed with PhCH_2NCO (20.4 μL , 0.164 mmol) and $(\text{CH}_3\text{CH}_2)_3\text{N}$ (62.8 μL , 0.447 mmol). The result mixture
10 was stirred at room temperature for 1 hours and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the titled compound (13.0mg, 19%): LCMS (ES) m/z 468 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{MeOD})$ δ 1.24 (d, 2H), 1.94 (m, 3H), 2.25 (m, 4H), 2.49 (d, 2H), 2.67 (s, 3H), 3.62 (s, 2H), 3.97 (s, 2H), 4.23 (s, 2H), 7.22 (m, 6H), 7.33 (m, 4H).

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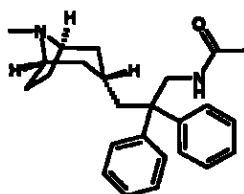
Example 12



1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and $\text{CH}_3\text{CH}_2\text{NCO}$ by following the
20 procedure in Example 11 (45% yield): LCMS (ES) m/z 406 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{MeOD})$ δ 1.03 (t, 3H), 1.33 (d, 2H), 1.94 (m, 3H), 2.25 (m, 4H), 2.55 (d, 2H), 2.67 (s, 3H), 3.07 (q, 2H), 3.68 (s, 2H), 3.94 (s, 2H), 7.24 (m, 6H), 7.34 (m, 4H).

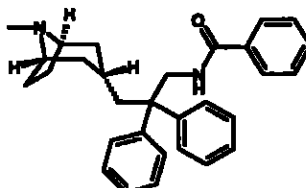
Example 13



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25**N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide**

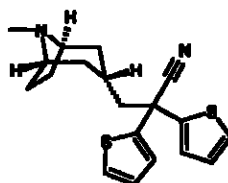
A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (33.4 mg, 0.10 mmol) in CH_2Cl_2 (0.5 mL) was mixed with Ac_2O (18.9 μL , 0.20 mmol) and pyridine (16.2 μL , 0.20 mmol). The mixture was stirred at room temperature for 1 hour and concentrated. Purification *via* a reverse phase HPLC (Gilson) then afforded the title compound (10.7mg, 29%): LCMS (ES) m/z 377 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{MeOD})$ δ 1.26 (d, 2H), 1.82 (s, 3H), 1.96 (m, 3H), 2.26 (s, 4H), 2.53 (d, 2H), 2.67 (s, 3H), 3.66 (s, 2H), 4.00 (s, 2H), 7.24 (m, 6H), 7.33 (m, 4H).

10

Example 14**N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide**

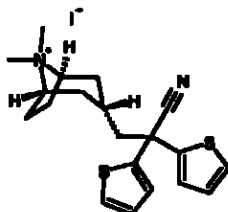
The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and $(\text{PhCO})_2\text{O}$ by following the procedure in Example 13 (8% yield): LCMS (ES) m/z 439 ($\text{M}+\text{H}^+$); $^1\text{H-NMR}(\text{MeOD})$ δ 1.28 (d, 2H), 2.00 (m, 3H), 2.24 (s, 4H), 2.59 (d, 2H), 2.67 (s, 3H), 3.65 (s, 2H), 4.21 (s, 2H), 7.31 (m, 6H), 7.39 (m, 6H), 7.50 (m, 3H).

20

Example 15**3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile**

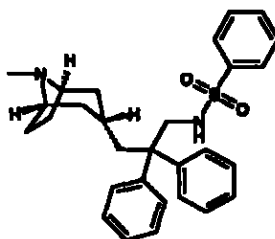
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The title compound was prepared from (endo)-3-iodomethyl-8-methyl-8-aza-bicyclo[3.2.1]octane and 2,2-di-thiophen-2-yl-acetonitrile by following the procedure in Example 2C (34 % yield): LCMS (ES) m/z 343 (M+H)⁺; ¹H-NMR(CDCl₃) δ 1.79 (m, 2H), 2.21 (m, 2H), 2.33 (m, 2H), 2.62 (m, 2H), 2.73 (m, 4H), 3.80 (m, 2H), 4.35 (s, 2H), 7.02 (m, 2H), 7.23 (m, 2H), 7.37 (m, 2H).

Example 16

(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile by following the procedure in Example 7 (43 %): LCMS (ES) m/z 345 (M)⁺; ¹H-NMR(CDCl₃) δ 1.82 (d, 2H), 2.35 (m, 2H), 2.23 (m, 3H), 2.58 (m, 4H), 2.82 (m, 2H), 3.37 (s, 6H), 4.25 (s, 2H), 7.02 (m, 2H), 7.24 (m, 2H), 7.36 (m, 2H).

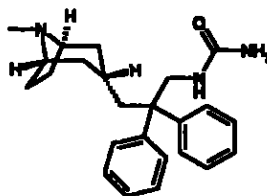
Example 17

N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide

A solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (67.0 mg, 0.20 mmol) in CH₂Cl₂ (2.0 mL) was mixed with PhSO₂Cl (28.2 μ L, 0.22 mmol) and (CH₂CH₂)₃N (84.3 μ L, 0.60 mmol). The result mixture was stirred at room temperature for 1 hours and concentrated. Purification *via* a reverse phase HPLC (Gilson) then afforded the title compound (51.5mg, 54%): LCMS (ES) m/z 475

27
2X

(M+H)⁺; ¹H-NMR(MeOD) δ 1.39 (d, 2H), 2.01 (m, 3H), 2.30 (s, 4H), 2.69 (s, 5H), 3.60 (s, 2H), 3.68 (s, 2H), 7.12 (m, 4H), 7.27 (m, 6H), 7.55 (m, 2H), 7.63(m, 1H), 7.78 (m, 2H).

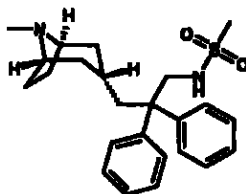
Example 18

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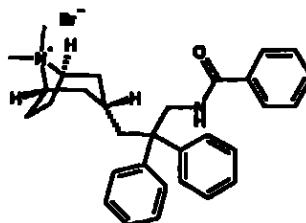
3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl-urea

To a solution of 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine (50.0 mg, 0.149 mmol) in CH₂Cl₂ (4.0 mL), ClSO₂NCO (31.2 μL, 0.358 mmol) was added. The mixture was stirred at room temperature for 2 days and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (21.6mg, 38%): LCMS (ES) *m/z* 378 (M+H)⁺; ¹H-NMR(MeOD) δ 1.33 (d, 2H), 2.01 (m, 3H), 2.29 (s, 4H), 2.57 (m, 2H), 2.68 (s, 3H), 3.69 (s, 2H), 4.01 (s, 2H), 7.25 (m, 6H), 7.34 (m, 4H).

15

Example 19**N-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide**

The title compound was prepared from 3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propylamine and MeSO₂Cl by following the procedure in Example 17 (28% yield): LCMS (ES) *m/z* 413 (M+H)⁺; ¹H-NMR(MeOD) δ 1.39 (d, 2H), 1.97 (m, 3H), 2.30 (s, 4H), 2.68 (s, 3H), 2.76 (s, 3H), 3.68 (s, 2H), 3.84 (s, 2H), 7.23 (s, 6H), 7.33 (s, 4H).

28
28**Example 20**

(Endo)-3-(2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide

- 5 A solution of *N*-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide (29 mg, 0.0683 mmol) in CH₂Cl₂ (0.5 mL) and acetone (0.5 mL) was mixed with MeBr (0.342 mL, 2.0 M in *t*-butyl methyl ether, 0.683 mmol). The resultant mixture was stirred at room temperature for 3 hours and concentrated. Purification via a reverse phase HPLC (Gilson) then afforded the title compound (19.6
- 10 mg, 64 %): LCMS (ES) *m/z* 453 (M)⁺; ¹H-NMR(MeOD) δ 1.20 (d, 2H), 2.32 (m, 7H), 2.65 (d, 2H), 2.98 (s, 3H), 3.02 (s, 3H), 3.60 (s, 2H), 4.22 (s, 2H), 7.30(m, 6H), 7.39(m, 6H), 7.50 (s, 3H).

BIOLOGICAL EXAMPLES

15

The inhibitory effects of compounds at the M₃ mAChR of the present invention are determined by the following *in vitro* and *in vivo* assay:

Analysis of Inhibition of Receptor Activation by Calcium Mobilization:

- 20 Stimulation of mAChRs expressed on CHO cells were analyzed by monitoring receptor-activated calcium mobilization as previously described¹⁰. CHO cells stably expressing M₃ mAChRs were plated in 96 well black wall/clear bottom plates. After 18 to 24 hours, media was aspirated and replaced with 100 µl of load media (EMEM with Earl's salts, 0.1% RIA-grade BSA (Sigma, St. Louis MO), and 4 µM Fluo-3-
- 25 acetoxyethyl ester fluorescent indicator dye (Fluo-3 AM, Molecular Probes, Eugene, OR) and incubated 1 hr at 37° C. The dye-containing media was then aspirated, replaced with fresh media (without Fluo-3 AM), and cells were incubated for 10

29

minutes at 37° C. Cells were then washed 3 times and incubated for 10 minutes at 37° C in 100 µl of assay buffer (0.1% gelatin (Sigma), 120 mM NaCl, 4.6 mM KCl, 1 mM KH₂ PO₄, 25 mM NaH CO₃, 1.0 mM CaCl₂, 1.1 mM MgCl₂, 11 mM glucose, 20mM HEPES (pH 7.4)). 50 µl of compound (1×10^{-11} – 1×10^{-5} M final in the assay) was
5 added and the plates were incubated for 10 min. at 37° C. Plates were then placed into a fluorescent light intensity plate reader (FLIPR, Molecular Probes) where the dye loaded cells were exposed to excitation light (488 nm) from a 6 watt argon laser. Cells were activated by adding 50 µl of acetylcholine (0.1-10 nM final), prepared in buffer containing 0.1% BSA, at a rate of 50 µl/sec. Calcium mobilization, monitored as
10 change in cytosolic calcium concentration, was measured as change in 566 nm emission intensity. The change in emission intensity is directly related to cytosolic calcium levels ¹¹. The emitted fluorescence from all 96 wells is measured simultaneously using a cooled CCD camera. Data points are collected every second. This data was then plotting and analyzed using GraphPad PRISM software.

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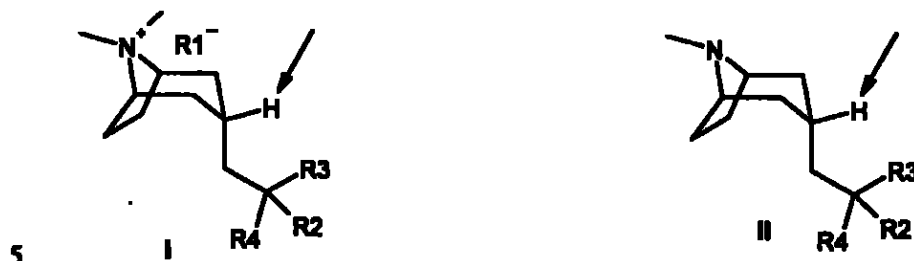
Methacholine-induced bronchoconstriction

Airway responsiveness to methacholine was determined in awake, unrestrained BalbC mice (*n* = 6 each group). Barometric plethysmography was used to measure enhanced pause (Penh), a unitless measure that has been shown to correlate with the changes in
20 airway resistance that occur during bronchial challenge with methacholine¹². Mice were pretreated with 50 µl of compound (0.003-10 µg/mouse) in 50 µl of vehicle (10% DMSO) intranasally, and were then placed in the plethysmography chamber. Once in the chamber, the mice were allowed to equilibrate for 10 min before taking a baseline Penh measurement for 5 minutes. Mice were then challenged with an aerosol of
25 methacholine (10 mg/ml) for 2 minutes. Penh was recorded continuously for 7 min starting at the inception of the methacholine aerosol, and continuing for 5 minutes afterward. Data for each mouse were analyzed and plotted by using GraphPad PRISM software.

30

What is claimed is:

1. A compound having structure I or II as indicated below except the compound of Formula (II) with R2 and R3 as 2-thiophene and R4 as $-\text{OC}(\text{O})\text{CH}_3$:



wherein:

the H atom indicated is in the exo position;

- 10 R1⁻ represents an anion associated with the positive charge of the N atom. R1⁻ may be but is not limited to chloride, bromide, iodide, sulfate, benzene sulfonate and toluene sulfonate;

- 15 R2 and R3 are independently selected from the group consisting of straight or branched chain lower alkyl groups (having preferably from 1 to 6 carbon atoms), cycloalkyl groups (having from 5 to 6 carbon atoms), cycloalkyl-alkyl (having 6 to 10 carbon atoms), heterocycloalkyl (having 5 to 6 carbon atoms) and N or O as the heteroatom, heterocycloalkyl-alkyl (having 6 to 10 carbon atoms) and N or O as the heteroatom, aryl, optionally substituted aryl, heteroaryl, and optionally substituted heteroaryl;

- 20 R4 is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl, -OR₅, -CH₂OR₅, -CH₂OH, -CN, -CF₃, -CH₂O(CO)R₆, -CO₂R₇, -CH₂NH₂, -CH₂N(R₇)SO₂R₅, -SO₂N(R₇)(R₈), -CON(R₇)(R₈), -CH₂N(R₈)CO(R₆), -CH₂N(R₈)SO₂(R₆), -CH₂N(R₈)CO₂(R₅), -CH₂N(R₈)CONH(R₇);

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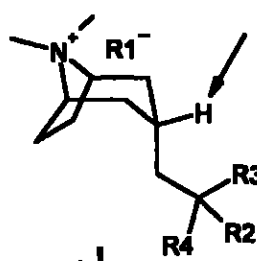
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R5 is selected from the group consisting of (C₁-C₆)alkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

- 5 R6 is selected from the group consisting of (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, aryl, heteroaryl, (C₁-C₆)alkyl-aryl, (C₁-C₆)alkyl-heteroaryl;

- 10 R7 and R8 are, independently, selected from the group consisting of H, (C₁-C₆)alkyl, (C₃-C₁₂)cycloalkyl, (C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl(C₃-C₁₂)cycloalkyl, (C₁-C₆)alkyl(C₃-C₇)heterocycloalkyl, (C₁-C₆)alkyl-aryl, and (C₁-C₆)alkyl-heteroaryl.

2. A compound according to claim 1 having structure I below:



15

3. A compound according to claim 1 selected from the group consisting of:
 (Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionitrile;
 20 (Endo)-8-methyl-3-(2,2,2-triphenyl-ethyl)-8-aza-bicyclo[3.2.1]octane;
 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionic acid;
 (Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
 25 (Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propan-1-ol;

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- N*-Benzyl-3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propionamide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 5 1-Benzyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
1-Ethyl-3-[3-((endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-acetamide;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzamide;
- 10 3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-di-thiophen-2-yl-propionitrile;
(Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-benzenesulfonamide;
- 15 [3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-urea;
N-[3-((Endo)-8-methyl-8-aza-bicyclo[3.2.1]oct-3-yl)-2,2-diphenyl-propyl]-methanesulfonamide; and
(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.
- 20
4. A compound according to claim 3 selected from the group consisting of:
(Endo)-3-(2-methoxy-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane
- 25 iodide;
(Endo)-3-(2-cyano-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide;
(Endo)-3-(2-carbamoyl-2,2-diphenyl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide;
- 30 (Endo)-3-(2-cyano-2,2-di-thiophen-2-yl-ethyl)-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane iodide; and

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(Endo)-3-{2,2-diphenyl-3-[(1-phenyl-methanoyl)-amino]-propyl}-8,8-dimethyl-8-azonia-bicyclo[3.2.1]octane bromide.

5. A pharmaceutical composition for the treatment of muscarinic acetylcholine
5 receptor mediated diseases comprising a compound according to claim 1 and a
pharmaceutically acceptable carrier thereof.
6. A method of inhibiting the binding of acetylcholine to its receptors in a
mammal in need thereof comprising administering a safe and effective amount of a
10 compound according to claim 1.
7. A method of treating a muscarinic acetylcholine receptor mediated disease,
wherein acetylcholine binds to said receptor, comprising administering a safe and
effective amount of a compound according to claim 1.
- 15 8. A method according to claim 7 wherein the disease is selected from the group
consisting of chronic obstructive lung disease, chronic bronchitis, asthma, chronic
respiratory obstruction, pulmonary fibrosis, pulmonary emphysema and allergic
rhinitis.
- 20 9. A method according to claim 7 wherein administration is via inhalation via the
mouth or nose.
10. A method according to claim 7 wherein administration is via a medicament
25 dispenser selected from a reservoir dry powder inhaler, a multi-dose dry powder inhaler
or a metered dose inhaler.
11. A method according to claim 7 wherein the compound is administered to a
human and has a duration of action of 12 hours or more for a 1 mg dose.
- 30 12. A method according to claim 11 wherein the compound has a duration of action
of 24 hours or more.

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13. A method according to claim 12 wherein the compound has a duration of action of 36 hours or more.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US04/33638

A CLASSIFICATION OF SUBJECT MATTER IPC(7) A61K 31/46 , C07D 451/02 US CL 514/304 , 546/124, 125 According to International Patent Classification (IPC) or to both national classification and IPC		
B FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) U S 514/304 , 546/124, 125 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN STRUCTURE SEARCH, FILE CAPLUS		
C DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2,800,481 (ZIRKLE et al) 23 July 1957 (23 07 1957), see examples 1-23 and claims 1-6	1-13
A	US 2,800,478 (ZIRKLE et al) 23 July 1957 (23 07 1957), see examples 2-12 and claims 1-6	1-13
☐ Further documents are listed in the continuation of Box C ☐ See patent family annex.		
* Special categories of cited documents		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance, the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance, the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"A" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 22 December 2004 (22 12 2004)		Date of mailing of the international search report 07 JAN 2005
Name and mailing address of the ISA/US Mail Stop PCT, Attn: ISA/US Commissioner for Patents P O Box 1450 Alexandria, Virginia 22313-1450 Facsimile No (703) 305-3230		Authorized officer <i>Jenuland Shaler for</i> Cecilia Tsang Telephone No (703)308-1235

Form PCT/ISA/210 (second sheet) (January 2004)

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ANTAGONISTAS DE RECEPTORES DE ACETILCOLINA MUSCARÍNICOS

CAMPO DE LA INVENCION

Esta invención se refiere a nuevos derivados de 8-azoniabicyclo[3.2.1]octanos, composiciones farmacéuticas, procedimientos para su preparación y su uso para tratar enfermedades mediadas por receptores de acetilcolina muscarínicos M₃.

ANTECEDENTES DE LA INVENCION

La acetilcolina liberada de neuronas colinérgicas en los sistemas nerviosos periférico y central afecta a muchos procedimientos biológicos diferentes a través de la interacción con dos clases principales de receptores de acetilcolina: los receptores de acetilcolina nicotínicos y los muscarínicos. Los receptores de acetilcolina muscarínicos (mAChRs) pertenecen a la superfamilia de receptores acoplados a proteína G que tienen siete dominios de transmembranas. Hay cinco subtipos de mAChRs, denominados M₁-M₅, y cada uno de ellos es el producto de un gen distinto. Cada uno de los cinco subtipos exhibe propiedades farmacológicas únicas. Los receptores de acetilcolina muscarínicos están ampliamente distribuidos en los órganos de los vertebrados, y estos receptores pueden mediar en acciones tanto inhibitoras como excitadoras. Por ejemplo, en los músculos lisos que se encuentran en las vías respiratorias, la vejiga y el tracto gastrointestinal, los M₃ mAChRs median las respuestas contráctiles. Para una exposición de esto, véase {Brown 1989 247 /id}.

La disfunción de receptores de acetilcolina muscarínicos ha sido apreciada en una diversidad de diferentes estados patofisiológicos. Por ejemplo, en el asma y enfermedad de obstrucción pulmonar crónica (COPD), estados inflamatorios que conducen a pérdida de función inhibitora de autoreceptores de acetilcolina muscarínicos M₂ sobre los nervios parasimpáticos que suministra el músculo liso pulmonar, provocando una liberación aumentada de acetilcolina a

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continuación de una estimulación nerviosa vagal. Esta dis-
función de mAChR da lugar a una hiper-reactividad de las
vías respiratorias mediada por una estimulación aumentada
de M₃ mAChRs {Costello, Evans, et al. 1999 72 /id}{Minette,
5 Lammers, et al. 1989 248 /id}. Análogamente, la inflamación
del tracto gastrointestinal en la enfermedad de inflamación
intestinal (IBD) da lugar a la hipermovilidad mediada por
M₃ mAChRs {Oprins, Meijer, et al. 2000 245 /id}. La incon-
tinencia debida a la hipercontractilidad de la vejiga ha
10 sido demostrada también que está mediada a través de la es-
timulación aumentada de M₃ mAChR {Hegde & Eglen 1999 251
/id}. Por tanto, la identificación de antagonistas de
mAChRs selectivos para subtipos puede ser útil como agentes
terapéuticos en estas enfermedades mediadas por mAChR.

15 A pesar del amplio conjunto de evidencias que apoyan
el uso de una terapia de receptores anti-muscarínicos para
el tratamiento de una diversidad de estados en enfermedad,
se usan relativamente pocos compuestos anti-muscarínicos en
el campo clínico. Por tanto, continúa habiendo una necesi-
20 dad de nuevos compuestos que sean capaces de provocar el
bloqueo de M₃ mAChRs. Los estados asociados con un aumento
de la estimulación de M₃ mAChRs, como el asma, COPD, IBD e
incontinencia urinaria podrían aprovecharse de los compues-
tos que son inhibidores de la unión de mAChR.

25 SUMARIO DE LA INVENCIÓN

Esta invención proporciona un método para tratar una
enfermedad mediada por receptores de acetilcolina muscarí-
nicos (mAChR), en la que la acetilcolina se une a un M₃
mAChR, método que comprende administrar una cantidad eficaz
30 de un compuesto de Fórmula (I) o fórmula (II) [excepto el
compuesto de Fórmula (II) en el que R₂ y R₃ son 2-tiofeno y
R₄ es -OC(O)CH₃] o una sal farmacéuticamente aceptable del
mismo.

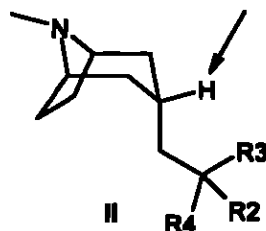
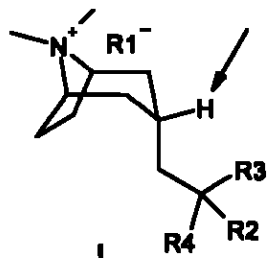
Esta invención se refiere también a un método para in-
35 hibir la unión de acetilcolina a sus receptores en un mamí-

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fero que lo necesita, que comprende administrar al mamífero anteriormente mencionado una cantidad eficaz de un compuesto de Fórmula (I) o Fórmula (II).

La presente invención proporciona también nuevos compuestos de Fórmula (I) o Fórmula (II), y composiciones farmacéuticas que comprenden un compuesto de Fórmula (I) o Fórmula (II), y un vehículo o diluyente farmacéutico.

Los compuestos de Fórmula (I) o Fórmula (II) útiles en la presente invención están representados por las estructuras:



en las cuales:

el átomo de H indicado está en la posición exo;

R1⁻ representa un anión asociado con la carga positiva del átomo de N. R1⁻ puede ser, pero sin estar limitado a ello, cloruro, bromuro, yoduro, sulfato, benceno-sulfonato y tolueno-sulfonato;

R2 y R3 se seleccionan independientemente entre el grupo que consiste en grupos alquilo inferior de cadena lineal o ramificada (que tienen preferentemente de 1 a 6 átomos de carbono), grupos cicloalquilo (que tienen de 5 a 6 átomos de carbono), cicloalquil-alquilo (que tienen 6 a 10 átomos de carbono), heterocicloalquilo (que tienen 5 a 6 átomos de carbono) y N u O como el heteroátomo, heterocicloalquil-alquilo (que tiene 6 a 10 átomos de carbono) y N u O como el heteroátomo, arilo, arilo opcionalmente sustituido, heteroarilo, y heteroarilo opcionalmente sustituido;

R4 se selecciona entre el grupo que consiste en alquilo (C₁-C₆), cicloalquilo (C₃-C₁₂), heterocicloalquilo (C₃-C₇),

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alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-heterocicloalquilo (C₃-C₇), arilo, heteroarilo, alquil (C₁-C₆)-arilo, alquil (C₁-C₆)-heteroarilo, -OR₅, -CH₂OR₅, -CH₂OH, -CN, -CF₃, -CH₂O(CO)R₆, -CO₂R₇, -CH₂NH₂,
 5 -CH₂N(R₇)SO₂R₅, -SO₂N(R₇)(R₈), -CON(R₇)(R₈),
 -CH₂N(R₈)CO(R₆), -CH₂N(R₈)SO₂(R₆), -CH₂N(R₈)CO₂(R₅),
 -CH₂N(R₈)CONH(R₇);

R₅ se selecciona entre el grupo que consiste alquilo (C₁-C₆), alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-
 10 heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-arilo o alquil (C₁-C₆)-heteroarilo;

R₆ se selecciona entre el grupo que consiste en alquilo (C₁-C₆), cicloalquilo (C₃-C₁₂), heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-
 15 heterocicloalquilo (C₃-C₇), arilo, heteroarilo, alquil (C₁-C₆)-arilo o alquil (C₁-C₆)-heteroarilo;

R₇ y R₈ se seleccionan, independientemente, entre el grupo que consiste en H, alquilo (C₁-C₆), cicloalquilo (C₃-C₁₂), heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-cicloalquilo
 20 (C₃-C₁₂), alquil (C₁-C₆)-heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-arilo o alquil (C₁-C₆)-heteroarilo.

Las sales farmacéuticamente aceptables adecuadas son bien conocidas por los expertos en la técnica e incluyen sales básicas de ácidos inorgánicos y orgánicos, como ácido
 25 clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido fosfórico, ácido metano-sulfónico, ácido etano-sulfónico, ácido acético, ácido málico, ácido tartárico, ácido cítrico, ácido láctico, ácido oxálico, ácido succínico, ácido fumárico, ácido maleico, ácido benzoico, ácido salicílico,
 30 ácido fenilacético y ácido mandélico. Además, se pueden formar también sales farmacéuticamente aceptables de los compuestos de Fórmula (I) o Fórmula (II) con un catión farmacéuticamente aceptable. Los cationes farmacéuticamente
 35 acetables adecuados son bien conocidos por los expertos en la técnica e incluyen cationes alcalinos, alcalino-térreos,

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de amonio y de amonio cuaternario.

Los siguientes términos, usados en la presente memoria descriptiva, se refieren a:

- "halo" - todos los halógenos, es decir, cloro, flúor,
5 bromo y yodo;
- "alquilo C₁₋₁₀" o "alquilo" - restos tanto de cadena lineal como ramificada de 1 a 10 átomos de carbono, salvo que la longitud de la cadena esté limitada por algún otro motivo, incluidos, pero sin limitación, metilo, etilo, n-
10 propilo, iso-propilo, n-butilo, sec-butilo, iso-butilo, terc-butilo, n-pentilo y similares;
- "cicloalquilo" es usado en la presente memoria descriptiva para indicar un resto cíclico, preferentemente de 3 a 8 átomos de carbono, incluidos, pero sin limitación,
15 ciclopropilo, ciclopentilo, ciclohexilo y similares;
- "alquenilo" es usado en la presente memoria descriptiva en todas sus apariciones para indicar un resto de cadena lineal o ramificada de 2-10 átomos de carbono, salvo que la longitud de la cadena esté limitada para el mismo, que incluyen, pero sin limitación, etenilo, 1-propenilo, 2-
20 propenilo, 2-metil-1-propenilo, 1-butenilo, 2-butenilo y similares;
- "arilo" - fenilo y naftilo;
- "heteroarilo" (como tal o en cualquier combinación,
25 como "heteroariloxi" o "heteroaril-alquilo") - un sistema de anillos aromáticos de 5-10 miembros en el que uno o más anillos contienen uno o más heteroátomos seleccionados entre el grupo que consiste en N, O o S, tal como, pero sin limitación, pirrol, pirazol, furano, tiofeno, quinolina,
30 isoquinolina, quinazolinilo, piridina, pirimidina, oxazol, tetrazol, tiazol, tiadiazol, triazol, imidazol o bencimidazol;
- "heterocíclico" (como tal o en cualquier combinación, como "heterociclilalquilo") - un sistema de anillos de 4-10

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miembros saturado o parcialmente insaturado en el que uno o más anillos contienen uno o más heteroátomos seleccionados entre el grupo que consiste en N, O o S, tal como, pero sin limitación, pirrolidina, piperidina, piperazina, morfolina, 5 tetrahidropirano, tiomorfolina o imidazolina. Además de ello, el azufre puede ser opcionalmente oxidado a la sulfona o el sulfóxido;

• "arilalquilo" o "heteroarilalquilo" o "heterociclilalquilo" son usados en la presente memoria descriptiva para 10 indicar alquilo C_{1-10} , como se definió con anterioridad, unido a un resto arilo, heteroarilo o heterocíclico, como se definieron también con anterioridad, salvo que se indique otra cosa;

• "sulfinilo" - el óxido $S(O)$ del correspondiente sulfuro, en término "tio" se refiere al sulfuro, y el término 15 "sulfonilo" se refiere al resto $S(O)_2$ completamente oxidado;

• "en el que dos restos R_1 (o dos restos Y) pueden formar conjuntamente un anillo saturado o insaturado de 5 ó y 20 miembros" es usado en la presente memoria descriptiva para indicar la formación de un sistema de anillos aromáticos, como naftaleno, o es un resto fenilo que tiene unido un anillo parcialmente saturado o insaturado de 6 miembros como un cicloalquenilo C_6 , es decir, ciclohexeno, o un resto 25 cicloalquenilo C_5 como ciclopenteno.

Los compuestos preferidos útiles en la presente invención incluyen:

Yoduro de (endo)-3-(2-metoxi-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

30 3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo;

(Endo)-8-metil-3-(2,2,2-trifenil-etil)-8-aza-biciclo[3.2.1]octano;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionamida;

Ácido 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propiónico;

5 Yoduro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Bromuro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

10 3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propan-1-ol;

N-Bencil-3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionamida;

Yoduro de (endo)-3-(2-carbamoil-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

15 1-Bencil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea;

1-Etil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea;

20 N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-acetamida;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-benzamida;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-di-tiofen-2-il-propionitrilo;

25 Yoduro de (endo)-3-(2-ciano-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-bencenosulfonamida;

30 [3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-metanosulfonamida; y

Bromuro de (endo)-3-(2,2-difenil-3-[(1-fenil-metanoil)-amino]-propil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano.

Los compuestos más preferidos útiles en la presente invención incluyen:

Yoduro de (endo)-3-(2-metoxi-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Yoduro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Bromuro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Yoduro de (endo)-3-(2-carbamoil-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Yoduro de (endo)-3-(2-ciano-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano; y

Bromuro de (endo)-3-(2,2-difenil-3-[(1-fenil-metanoil)-amino]-propil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano.

Métodos y preparación

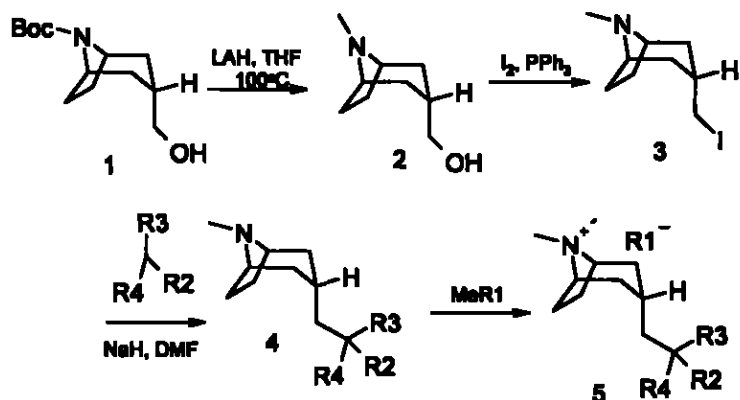
Preparación

Los compuestos de Fórmula (I) y Fórmula (II) pueden ser obtenidos aplicando procedimiento sintéticos, algunos de los cuales están ilustrados en los Esquemas siguientes. La síntesis proporcionada para estos Esquemas es aplicable para producir compuestos de Fórmula (I) y Fórmula (II) que tienen una diversidad de diferentes R1, R2, R3 y R4 que se hacen reaccionar, empleando sustituyentes que estén adecuadamente protegidos, para conseguir una compatibilidad con las reacciones indicadas en la presente memoria descriptiva. La posterior desprotección, en esos casos, suministra seguidamente los compuestos de la naturaleza generalmente descritos. Aunque se muestran algunos esquemas con compuestos solamente de Fórmula (II), esto es meramente para fines de ilustración tan solo.

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El método general de preparación es mostrado en el Esquema I. La síntesis partió del compuesto 1. La reducción con hidruro de litio-aluminio (LAH) suministró el alcohol 2. El desplazamiento con yodo proporcionó 3. Una reacción de acoplamiento con el anión derivado de $\text{HCR}_2(\text{R}_3)(\text{R}_4)$ suministró seguidamente el compuesto 4, que fue fácilmente convertido en la sal de amonio 5.

Esquema I.



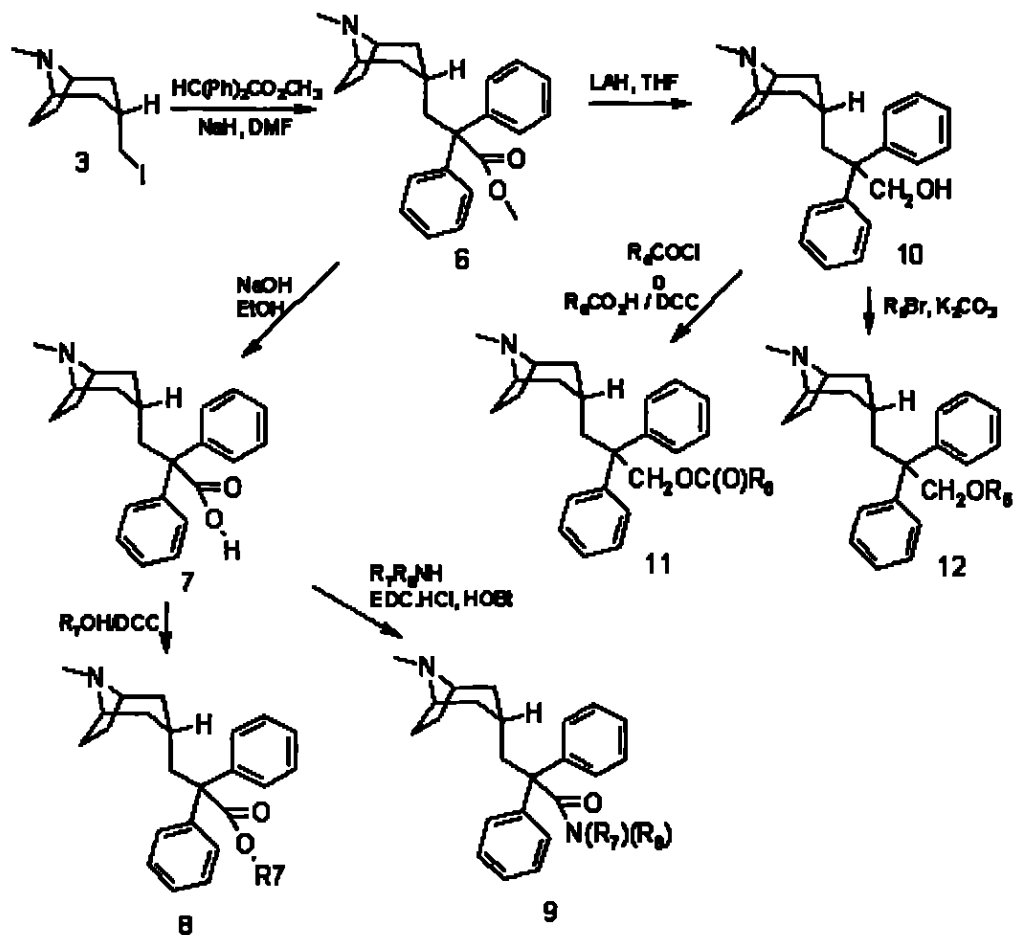
Un método de preparación más específico que conduce a compuestos de Fórmula (II) está indicado en el Esquema II. La alquilación del éster $\text{HC}(\text{Ph})_2\text{CO}_2\text{CH}_3$ con 3 proporcionó el compuesto 6. La hidrólisis de 6 generó el ácido 7. La condensación mediada por 1,3-diciclohexilcarbodiimida (DCC) del ácido con el alcohol $(\text{R}_7)\text{OH}$ suministró seguidamente el éster 8. La condensación del ácido 7 con la amina $(\text{R}_7)(\text{R}_8)\text{NH}$ bajo condiciones adecuadas de acoplamiento de amidas bien conocidas por los expertos en la técnica como hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDC.HCl) e hidrato de 1-hidroxibenzotriazol (HOBt) proporcionó la amina 9. La reducción de 6 generó el alcohol 10. La reacción de 10 con un cloruro de ácido $(\text{R}_6)\text{COCl}$ o un ácido $(\text{R}_6)\text{CO}_2\text{H}$ proporcionó el éster 11. La alquilación de 10 con reactivos apropiados como $(\text{R}_5)\text{Br}$ suministró seguidamente 12.

Los compuestos con estructuras similares a 6, 7, 8, 9,

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10, 11 y 12 fueron convertidos en las correspondientes sales de amonio haciéndolos reaccionar con reactivos apropiados para la reacción como MeBr y MeI (no mostrados en el esquema). Se utilizaron métodos apropiados de protección y desprotección en algunos procedimientos de preparación.

Esquema II



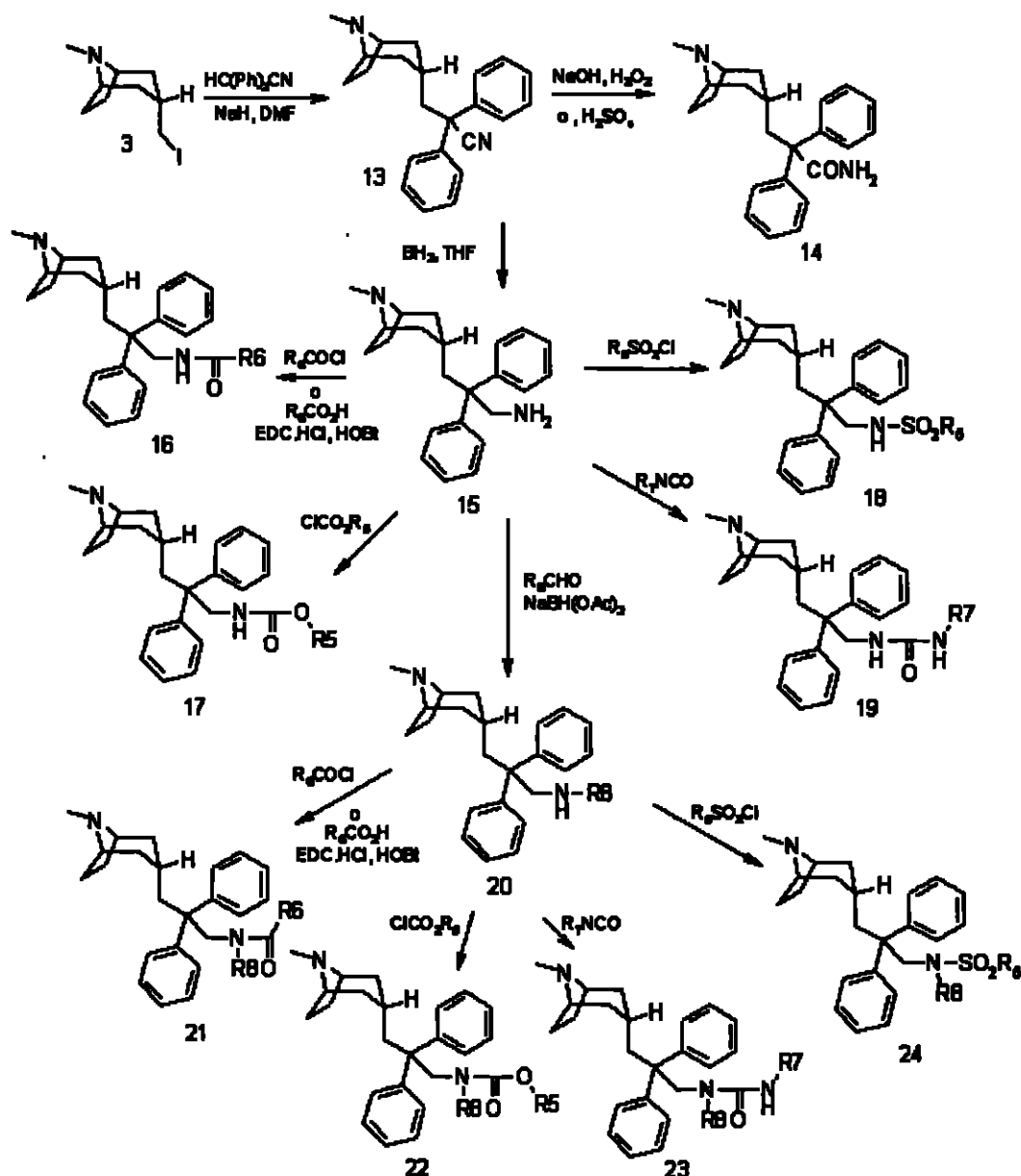
Un método de preparación más específico que conduce a compuestos de Fórmula (II) es indicado en el Esquema III. La alquilación de $\text{HC(Ph)}_2\text{CN}$ con 3 proporcionó el nitrilo 13. La hidrólisis de 13 bajo condiciones básicas (por ej., NaOH y H_2O_2) o bien condiciones ácidas (por ej., H_2SO_4) suministró la amina 14. La reducción de 13 condujo a la amina 15 que fue convenientemente transformada en la amida 16, carbamida 17, sulfonamida 18 y la urea 19. La

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condensación de 15 con el aldehído (R8)CH(O) seguida de reducción con NaBH(OAc), suministró la amina 20 que fue fácilmente convertida en la amida 21, carbamida 22, urea 23 y sulfonamida 24.

- 5 Los compuestos con estructuras análogas a 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23 y 24 fueron convertidos en las correspondientes sales de amonio haciéndolos reaccionar con reactivos apropiados para la reacción como MeBr o MeI (no mostrados en el esquema). En algunos procedimientos de
10 preparación fueron utilizados métodos apropiados de protección y desprotección.

Esquema III



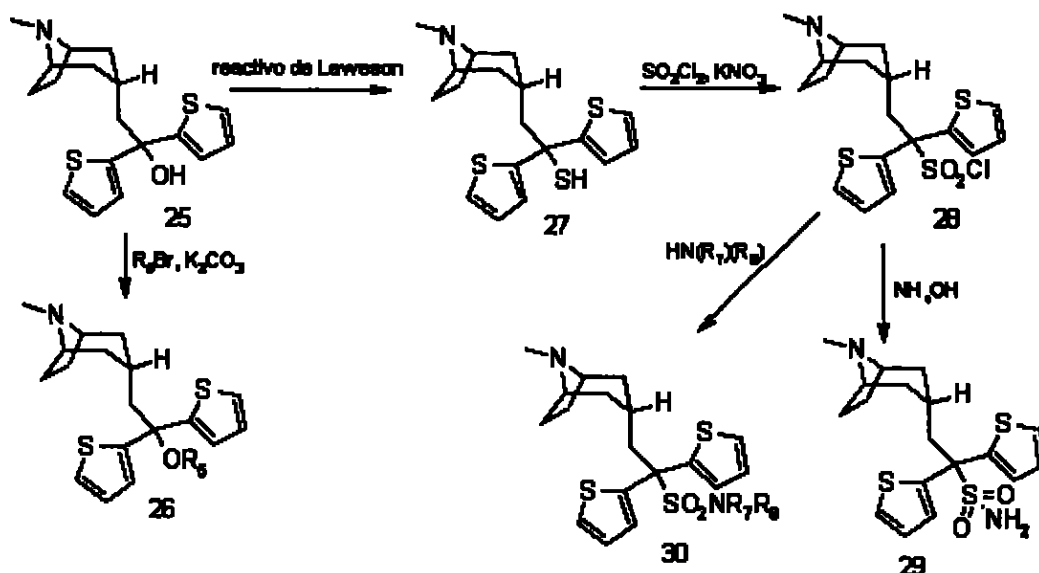
Un método más específico de preparación que conduce a compuestos de Fórmula (II) es indicado en el Esquema IV. La
 5 alquilación de 25 con $(\text{R}_5)\text{Br}$ proporcionó 26. La reacción de 25 con el reactivo de Lawesson suministró 27. La oxidación de 27 con SO_2Cl_2 y KNO_3 suministró 28 que fue convertido en 29 o bien en la sulfonamida 30.

Los compuestos con estructuras análogas a 26, 27, 29 y
 10 30 fueron fácilmente convertidos en las correspondientes

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sales de amonio haciéndolos reaccionar con reactivos apropiados para la reacción como MeBr y MeI (no mostrados en el esquema). Se utilizaron métodos apropiados de protección y desprotección en algunos procedimientos de preparación.

Esquema IV

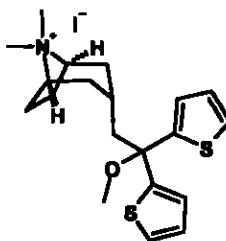


EJEMPLOS SINTÉTICOS

Los siguientes ejemplos se proporcionan como ilustración de la presente invención, pero sin limitarla en modo alguno:

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Ejemplo 1



Yoduro de (Endo)-3-(2-metoxi-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano

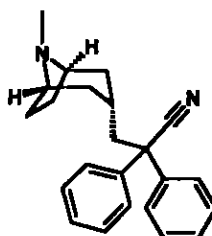
5 A una solución de 2-(8-metil-8-azabicyclo[3.2.1]oct-3-il)-1,1-ditiofen-2-il-etanol (preparada según el documento US 2800482) (212 mg, 0,64 mmol) en 5 ml de cloruro de metileno y yodometano (0,40 ml, 6,4 mmol), se añadieron hidróxido de potasio acuoso al 50% (0,25 ml, 3,2 mmol) y

10 cloruro de tetrabutilamonio (5 mg, 3% en moles). La mezcla de reacción se calentó a reflujo durante 5 días. Cada día, se añadieron 0,2 ml adicionales de yodometano y 0,1 ml de hidróxido de potasio. Tras completarse, la mezcla de reacción se enfrió a temperatura ambiente, se diluyó con cloruro me metileno y se lavó con agua. La capa acuosa se extra-

15 jo con cloruro de metileno y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre MgSO₄ y se concentraron a vacío. El producto en bruto se recrystalizó en cloruro de metileno/acetato de etilo para proporcionar 109

20 mg del compuesto del título. LCMS (ES) m/z 362 (M)⁺.

Ejemplo 2



3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo

25 2a) Preparación de ((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-metanol

Una mezcla de (endo)-3-(hidroximetil)-8-azabicyclo[3.2.1] octane-8-carboxilato de 1,1-dimetiletilo y LiAlH_4 (6,16 ml, 1,0 M en THF, 6,16 mmol) se calentó a 80°C con un reactor microondas durante 60 minutos. La solución se mezcló seguidamente con solución saturada de Na_2SO_4 , se filtró a través de celite y se concentró para proporcionar el compuesto del título (0,31 g, 97%): LCMS (ES) m/z 156 ($\text{M}+\text{H}^+$); ^1H -RMN(CDCl_3) δ 1,28 (s, 1H), 1,59 (m, 4H), 1,90 (m, 1H), 2,13 (m, 4H), 2,32 (s, 3H), 3,17 (s, 2H), 3,59 (d, 2H).

2b) Preparación de (endo)-3-iodometil-8-metil-8-azabicyclo[3.2.1]octano

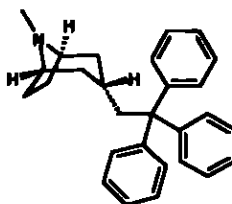
Una solución de yodo (6,67 g, 25,8 mmol) y ((endo)-8-metil-8-aza-bicyclo[3.2.1]oct-3-il)-metanol (2,0 g, 12,9 mmol) en CH_2Cl_2 (120 ml) se mezcló con PPh_3 (sobre resina, 8,6 g, 3 mmol/g, 25,8 mmol). La mezcla resultante se agitó durante 17 horas, se filtró y se concentró para suministrar el compuesto del título (2,63 g, 77%): LCMS (ES) m/z 266 ($\text{M}+\text{H}^+$); ^1H -RMN(CDCl_3) δ 2,05 (m, 4H), 2,39 (m, 3H), 2,79 (d, 3H), 2,98 (m, 2H), 3,45 (d, 2H), 3,81 (s, 2H).

2c) Preparación de 3-((endo)-8-metil-8-azabicyclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo

Una solución de (endo)-3-iodometil-8-metil-8-azabicyclo[3.2.1]octano (1,06 g, 4,0 mmol) y F_2CHCN (2,32 g, 12,0 mmol) en DMF (20 ml) se mezcló con NaH (0,288 g, 12,0 mmol). La mezcla resultante se agitó a temperatura ambiente durante 60 minutos. Una filtración y purificación a través de HPLC de fase invertida (Gilson) proporcionaron seguidamente el compuesto del título (1,16 g, 93 %): LCMS (ES) m/z 331 ($\text{M}+\text{H}^+$); ^1H -RMN(CDCl_3) δ 1,64 (m, 2H), 2,14 (m, 1H), 2,26 (m, 2H), 2,34 (m, 2H), 2,52 (m, 2H), 2,75 (m, 5H), 3,83 (s, 2H), 7,39 (d, 10H).

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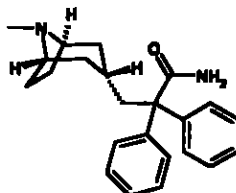
Ejemplo 3



(Endo)-8-metil-3-(2,2,2-trifenil-etil)-8-aza-biciclo[3.2.1]octano

- 5 Una solución de trifenilmetano (0,276 g, 1,13 mmol) en THF (0,5 ml) se mezcló con n-BuLi (0,706 ml, 1,6 M en hexano, 1,13 mmol). La solución se agitó durante 10 minutos y se añadió una solución de endo)-3-iodometil-8-metil-8-aza-biciclo[3.2.1]octano (100 mg, 0,377 mmol) en DMF (1,0 ml).
- 10 La mezcla se agitó a temperatura ambiente durante 60 minutos, se mezcló con H₂O (0,1 ml), se concentró y se filtró. Una purificación mediante HPLC de fase invertida (Gilson) proporcionó seguidamente el compuesto del título (23,8 mg, 17 %): LCMS (ES) m/z 382 (M+H)⁺; ¹H-RMN(CDCl₃) δ 1,07 (d, 2H), 2,12 (m, 1H), 2,22 (m, 4H), 2,31 (m, 2H), 2,65 (d, 3H), 2,97 (d, 2H), 3,63 (s, 2H), 7,21 (m, 3H), 7,30 (d, 12H).
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Ejemplo 4



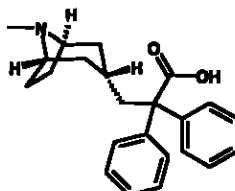
3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionamida

- 20 Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo (53 mg, 0,16 mmol) en CH₂Cl₂ (0, 25 ml) se mezcló con H₂SO₄ (0,28 mol, 96%) y se agitó a 40°C durante 30 horas. La mezcla se vertió seguidamente sobre hielo, se neutralizó con NH₃.H₂O, se extrajo con EtOAc y se concentró. El residuo resultante
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se disolvió en DMSO y se filtró. Una purificación mediante HPLC de fase invertida (Gilson) proporcionó el compuesto del título (17,2 mg, 30 %): MS (ES) m/z 347 (M+H)⁺; ¹H-RMN(CDCl₃) δ 1,31 (d, 2H), 1,98 (m, 1H), 2,28 (m, 4H), 2,39 (m, 2H), 2,67 (d, 3H), 2,79 (d, 2H), 3,66 (s, 2H), 5,82 (s, br, 1H), 6,88 (s, br, 1H), 7,37 (m, 10H).

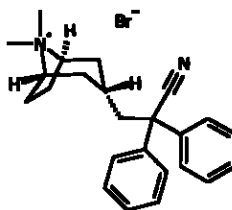
Ejemplo 5



10 Ácido 3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propiónico

A una solución de 2-((3-endo)-8-metil-8-azabicyclo[3.2.1]oct-3-il)-1,1-difeniletanol (100 mg, 1,56 mmol) en HCOOH (0,25 ml) se añadió H₂SO₄ (2,73 ML, 90%) a 0°C. El vial de reacción se tapó inmediatamente y se almacenó en un refrigerador a -20°C durante 7 días. La solución se vertió en hielo, se neutralizó con NH₃.H₂O, se extrajo con EtOAc y se concentró. El residuo resultante se disolvió en DMSO y se filtró. Una purificación mediante una HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (52 mg, 48 %): LCMS (ES) m/z 350 (M+H)⁺; ¹H-RMN(MeOD) δ 1,39 (d, 2H), 1,86 (m, 1H), 1,97 (m, 2H), 2,30 (m, 4H), 2,69 (s, 3H), 2,84 (d, 2H), 3,69 (s, 2H), 7,28 (m, 2H), 7,36 (m, 8H).

Ejemplo 6

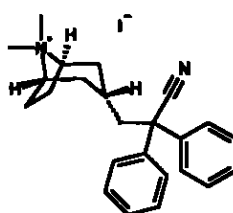


Bromuro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-

dimetil-8-azonia-biciclo[3.2.1]octano

Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo (310 mg, 0,938 mmol) in acetona (6,0 ml) se mezcló con MeBr (4,69 ml, 2,0 M en *t*-BuOMe, 9,38 mmol). La mezcla resultante se agitó a temperatura ambiente durante 60 minutos y se filtró. El sólido se lavó con acetona (2 x 3 ml) para suministrar el compuesto del título (333 mg, 83 %): LCMS (ES) *m/z* 345 (M)⁺; ¹H-RMN(MeOD) δ 1,82 (d, 2H), 2,17 (m, 1H), 2,35 (m, 2H), 2,49 (m, 4H), 3,01 (d, 2H), 3,07 (s, 3H), 3,10 (s, 3H), 3,79 (s, 2H), 7,36 (m, 2H), 7,43 (m, 4H), 7,49 (m, 4H).

Ejemplo 7

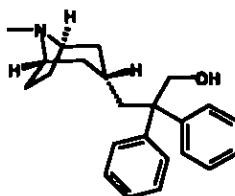


15 Yoduro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano

Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo (26,5 mg, 0,080 mmol) en CH₂Cl₂ (0,5 ml) y MeCN (0,5 ml) se mezcló con MeI (0,125 ml, 2,00 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 horas, se diluyó con DMSO (0,3 ml) y se concentró. Una purificación a través de HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (22,9 mg, 60 %): LCMS (ES) *m/z* 345 (M)⁺; ¹H-RMN(CDCl₃) δ 1,83 (d, 2H), 2,17 (m, 1H), 2,35 (m, 2H), 2,49 (m, 4H), 3,01 (d, 2H), 3,07 (s, 3H), 3,10 (s, 3H), 3,79 (s, 2H), 7,36 (m, 2H), 7,43 (m, 4H), 7,49 (m, 4H).

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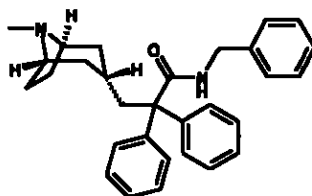
Ejemplo 8



3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propan-1-ol

5 Una mezcla de ácido 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propiónico (42,5 mg, 0,122 mmol) y LiAlH_4 (0,488 ml, 1,0 M en THF, 0,488 mmol) se calentó con un reactor microondas a 100°C durante 1 hora. Se diluyó con solución saturada de Na_2SO_4 , se filtró a través de celite y se concentró. El residuo resultante se disolvió en DMSO y se filtró. Una purificación mediante HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (29,1 mg, 71 %): LCMS (ES) m/z 336($\text{M}+\text{H}$)⁺; ^1H -RMN(CDCl_3) δ 1,40 (d, 2H), 1,92 (m, 1H), 2,29 (m, 6H), 2,59 (m, 2H), 2,68 (d, 3H), 3,72 (s, 2H), 4,16 (s, 2H), 7,13 (m, 3H), 7,30 (m, 7H).

Ejemplo 9



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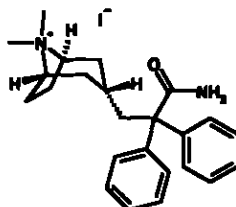
N-Bencil-3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionamida

Una solución de ácido 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propiónico (82,0 mg, 0,235 mmol) en CH_2Cl_2 (3,0 ml) se mezcló con FCH_2NH_2 (28,2 μl , 0,258 mmol), EDC (49,5 mg, 0,258 mmol), HOBT (3,2 mg, 0,024 mmol) y $(\text{CH}_3\text{CH}_2)_3\text{N}$ (0,232 ml, 1,65 mmol). La mezcla se

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agitó a temperatura ambiente durante 60 horas y se concentró. El residuo resultante se disolvió en DMSO y se filtró. Una purificación por HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (29,8 mg, 30 %): LCMS (ES) m/z 439 ($M+H$)⁺; ¹H-RMN(CDCl₃) δ 1,34 (d, 2H), 1,96 (m, 1H), 2,23 (m, 2H), 2,38 (m, 4H), 2,63 (d, 3H), 2,83 (d, 2H), 3,66 (s, 2H), 4,41 (d, 2H), 6,93 (m, 2H), 7,22 (m, 3H), 7,38 (m, 10H).

Ejemplo 10



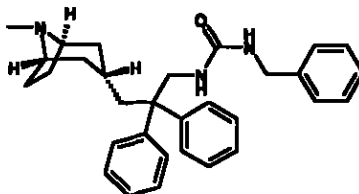
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Yoduro de (endo)-3-(2-carbamoyl-2,2-difenil-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano

El compuesto del título se preparó a partir de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionamida siguiendo el procedimiento del Ejemplo 7 (33 % de rendimiento): LCMS (ES) m/z 363 (M)⁺; ¹H-RMN(CDCl₃) δ 1,49 (d, 2H), 1,95 (m, 1H), 2,25 (m, 2H), 2,42 (m, 4H), 2,84 (d, 2H), 3,17 (s, 3H), 3,23 (s, 3H), 3,93 (s, 2H), 5,65 (s, 1H), 5,91 (s, 1H), 7,39 (m, 10H).

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Ejemplo 11



1-Bencil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea

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11a) 3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina

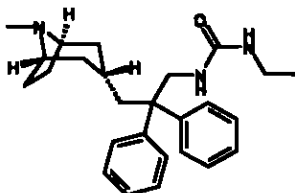
Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propionitrilo (250 mg, 0,758 mmol) en THF (2,5 ml) se mezcló con BH₃ (2,53 ml, 1,5 M en THF, 3,79 mmol) a 0°C. La mezcla se agitó a temperatura ambiente durante 20 horas y se diluyó con H₂O (1,0 ml). La solución se mezcló seguidamente con K₂CO₃ (0,1 g) y se agitó a temperatura ambiente durante 1 hora. Las capas orgánicas se separaron y la parte acuosa se extrajo con EtOAc (2 x 3 ml). Las capas orgánicas se combinaron, se secaron sobre Na₂SO₄ y se concentraron. Una purificación mediante HPLC de fase invertida (Gilson) suministró el compuesto del título (159mg, 63%): LCMS (ES) m/z 335 (M+H)⁺; ¹H-RMN(MeOD) δ 1,35 (d, 2H), 2,01 (m, 3H), 2,34 (s, 4H), 2,55 (s, 2H), 2,68 (s, 3H), 3,73 (m, 5H), 7,26 (m, 4H), 7,33 (m, 2H), 7,43 (m, 4H).

11b) 1-Bencil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea

Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina (50,0 mg, 0,149 mmol) en CH₂Cl₂ (2,0 ml) se mezcló con FCH₂NCO (20,4 μL, 0,164 mmol) y (CH₃CH₂)₃N (62,8 μl, 0,447 mmol). La mezcla resultante se agitó a temperatura ambiente durante 1 hora y se concentró. Una purificación a través de HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (13,0 mg, 19%): LCMS (ES) m/z 468 (M+H)⁺; ¹H-RMN(MeOD) δ 1,24 (d, 2H), 1,94 (m, 3H), 2,25 (m, 4H), 2,49 (d, 2H), 2,67 (s, 3H), 3,62 (s, 2H), 3,97 (s, 2H), 4,23 (s, 2H), 7,22 (m, 6H), 7,33 (m, 4H).

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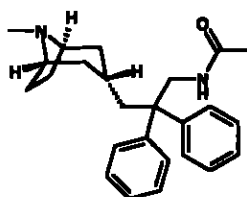
Ejemplo 12



1-Etil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea

- 5 El compuesto del título se preparó a partir de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina y $\text{CH}_3\text{CH}_2\text{NCO}$ siguiendo el procedimiento del Ejemplo 11 (45% de rendimiento): LCMS (ES) m/z 406 $(\text{M}+\text{H})^+$; ^1H -RMN (MeOD) δ 1,03 (t, 3H), 1,33 (d, 2H), 1,94 (m, 3H),
10 2,25 (m, 4H), 2,55 (d, 2H), 2,67 (s, 3H), 3,07 (q, 2H), 3,68 (s, 2H), 3,94 (s, 2H), 7,24 (m, 6H), 7,34 (m, 4H).

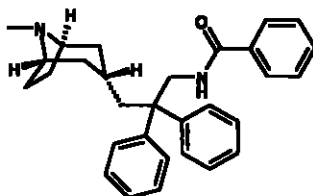
Ejemplo 13



- 15 **N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-acetamida**
Una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina (33,4 mg, 0,10 mmol) en CH_2Cl_2 (0,5 ml) se mezcló con Ac_2O (18,9 μl , 0,20 mmol) y piridina (16,2 μl , 0,20 mmol). La mezcla se
20 agitó a temperatura ambiente durante 1 hora y se concentró. Una purificación a través de HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (10,7 mg, 29%): LCMS (ES) m/z 377 $(\text{M}+\text{H})^+$; ^1H -RMN (MeOD) δ 1,26 (d, 2H), 1,82 (s, 3H), 1,96 (m, 3H), 2,26 (s, 4H), 2,53 (d, 2H),
25 2,67 (s, 3H), 3,66 (s, 2H), 4,00 (s, 2H), 7,24 (m, 6H), 7,33 (m, 4H).

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Ejemplo 14

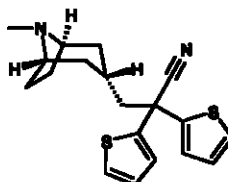


N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-

2,2-difenil-propil]-benzamida

El compuesto del título se preparó a partir de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina y (FCO)₂O siguiendo el procedimiento del Ejemplo 13 (8% de rendimiento): LCMS (ES) *m/z* 439 (M+H)⁺; ¹H-RMN(MeOD) δ 1,28 (d, 2H), 2,00 (m, 3H), 2,24 (s, 4H), 2,59 (d, 2H), 2,67 (s, 3H), 3,65 (s, 2H), 4,21 (s, 2H), 7,31 (m, 6H), 7,39 (m, 6H), 7,50 (m, 3H).

Ejemplo 15



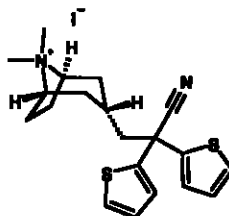
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3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-di-tiofen-2-il-propionitrilo

El compuesto del título se preparó a partir de (endo)-3-iodometil-8-metil-8-aza-biciclo[3.2.1]octano y 2,2-di-tiofen-2-il-acetonitrilo siguiendo el procedimiento del Ejemplo 2C (34% de rendimiento): LCMS (ES) *m/z* 343 (M+H)⁺; ¹H-RMN(CDCl₃) δ 1,79 (m, 2H), 2,21 (m, 2H), 2,33 (m, 2H), 2,62 (m, 2H), 2,73 (m, 4H), 3,80 (m, 2H), 4,35 (s, 2H), 7,02 (m, 2H), 7,23 (m, 2H), 7,37 (m, 2H).

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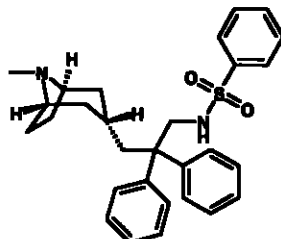
Ejemplo 16



(Endo)-3-(2-ciano-2,2-di-tiofen-2-il-etil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano

El compuesto del título se preparó a partir de 3-
 5 ((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-di-
 tiofen-2-il-propionitrilo siguiendo el procedimiento del
 Ejemplo 7 (43 %): LCMS (ES) m/z 345 (M)⁺; ¹H-RMN(CDCl₃) δ
 1,82 (d, 2H), 2,35 (m, 2H), 2,23 (m, 3H), 2,58 (m, 4H),
 2,82 (m, 2H), 3,37 (s, 6H), 4,25 (s, 2H), 7,02 (m, 2H),
 10 7,24 (m, 2H), 7,36 (m, 2H).

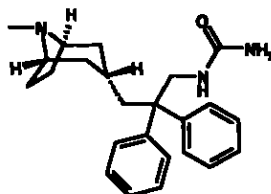
Ejemplo 17



N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-bencenosulfonamida

15 Una solución de 3-((endo)-8-metil-8-aza-
 biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina (67,0 mg,
 0,20 mmol) en CH₂Cl₂ (2,0 ml) se mezcló con FSO₂Cl (28,2 μ l,
 0,22 mmol) y (CH₃CH₂)₃N (84,3 μ l, 0,60 mmol). La mezcla re-
 sultante se agitó a temperatura ambiente durante 1 hora y
 20 se concentró. Una purificación a través de HPLC de fase in-
 vertida (Gilson) suministró seguidamente el compuesto del
 título (51,5mg, 54%): LCMS (ES) m/z 475 ($M+H$)⁺; ¹H-
 RMN(MeOD) δ 1,39 (d, 2H), 2,01 (m, 3H), 2,30 (s, 4H), 2,69
 (s, 5H), 3,60 (s, 2H), 3,68 (s, 2H), 7,12 (m, 4H), 7,27 (m,
 25 6H), 7,55 (m, 2H), 7,63(m, 1H), 7,78 (m, 2H).

Ejemplo 18

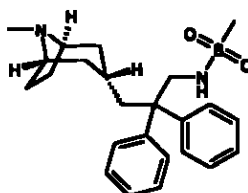


3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-urea

A una solución de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina (50,0 mg, 0,149 mmol) en CH_2Cl_2 (4,0 ml), se añadió ClSO_2NCO (31,2 μl , 0,358 mmol). La mezcla se agitó a temperatura ambiente durante 2 días y se concentró. Una purificación mediante HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (21,6mg, 38%): LCMS (ES) m/z 378 ($\text{M}+\text{H}$)⁺; ^1H -RMN(MeOD) δ 1,33 (d, 2H), 2,01 (m, 3H), 2,29 (s, 4H), 2,57 (m, 2H), 2,68 (s, 3H), 3,69 (s, 2H), 4,01 (s, 2H), 7,25 (m, 6H), 7,34 (m, 4H).

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Ejemplo 19

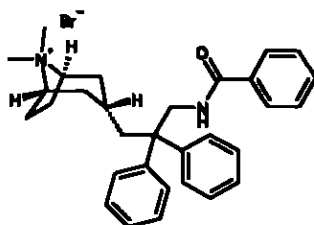


N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propil]-metanosulfonamida

El compuesto del título se preparó a partir de 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-difenil-propilamina y MeSO_2Cl siguiendo el procedimiento del Ejemplo 17 (28% de rendimiento): LCMS (ES) m/z 413 ($\text{M}+\text{H}$)⁺; ^1H -RMN(MeOD) δ 1,39 (d, 2H), 1,97 (m, 3H), 2,30 (s, 4H), 2,68 (s, 3H), 2,76 (s, 3H), 3,68 (s, 2H), 3,84 (s, 2H), 7,23 (s, 6H), 7,33 (s, 4H).

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Ejemplo 20



Bromuro de (endo)-3-(2,2-difenil-3-[(1-fenilmetanoil)-amino]-propil)-8,8-dimetil-8-azonia-biciclo[3.2.1]octano

Una solución de N-[3-((endo)-8-metil-8-azabicyclo[3.2.1]oct-3-il)-2,2-difenil-propil]-benzamida (29 mg, 0,0683 mmol) en CH₂Cl₂ (0,5 ml) y acetona (0,5 ml) se mezcló con MeBr (0,342 ml, 2,0 M en t-butil-metil-éter, 0,683 mmol). La mezcla resultante se agitó a temperatura ambiente durante 3 horas y se concentró. Una purificación a través de HPLC de fase invertida (Gilson) suministró seguidamente el compuesto del título (19,6 mg, 64 %): LCMS (ES) m/z 453 (M)⁺; ¹H-RMN (MeOD) δ 1,20 (d, 2H), 2,32 (m, 7H), 2,65 (d, 2H), 2,98 (s, 3H), 3,02 (s, 3H), 3,60 (s, 2H), 4,22 (s, 2H), 7,30 (m, 6H), 7,39 (m, 6H), 7,50 (s, 3H).

EJEMPLOS BIOLÓGICOS

Los efectos inflamatorios de los compuestos en los M₃ mAChR de la presente invención están determinados por el siguiente ensayo *in vitro* e *in vivo*:

Análisis de la inhibición de la activación de receptores por movilización de calcio:

La estimulación de los mAChRs expresado sobre células de CHO se analizó verificando la movilización de calcio activada por receptores como se describió previamente. Las células de CHO que expresan establemente M₃ mAChRs fueron dispuestas en placas en un conjunto de placas de paredes negras/fondo transparente de 96 pocillos. Después de 18 a 24 horas, los medios fueron aspirados y repuestos con 100 µl de medios de carga (EMEM con sales de Earl, BSA de ca-

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lidad RIA al 0,1% (Sigma, St. Louis MO) y colorante indicador fluorescente de éster Fluo-3-acetoximetílico 4 μ M (Fluo-3 AM, Molecular Probes, Eugene, OR) y se incubaron a 37°C. Los medios que contenían colorante fueron seguidamente aspirados, repuestos con medios de nueva aportación (sin Fluo-3 AM) y las células fueron incubadas durante 10 minutos a 37°C. Las células fueron seguidamente lavadas 3 veces e incubadas durante 10 minutos a 37°C en 100 μ l de tampón del ensayo (0,1% de gelatina (Sigma), NaCl 120 mM, KCl 4,6 mM, KH_2PO_4 1 mM, NaHCO_3 25 mM, CaCl_2 1,0 mM, MgCl_2 1,1 mM, glucosa 11 mM, HEPES 20 mM (pH 7,4)). Se añadieron 50 μ l de compuesto (1×10^{-11} - 1×10^{-5} M final en el ensayo) y las placas fueron incubadas durante 10 minutos a 37°C. Las placas fueron seguidamente colocadas en un lector de placas de intensidad luminosa fluorescente (FLIPR, Molecular Probes) en el que las celdas con contenido de colorante fueron expuestas a una luz de excitación (488 nm) desde un láser de argón de 2 watios. Las celdas fueron activadas añadiendo 50 μ l de acetilcolina (0,1-10 mM final), preparada en tampón que contenía 0,1% de BSA, a una velocidad de 50 μ l/s. La movilización de calcio, verificada como el cambio en la concentración de calcio citosólico, se midió como el cambio en la intensidad de emisión a 566 nm. El cambio en la intensidad de emisión está directamente relacionado con los niveles de calcio citosólico. La fluorescencia emitida desde la totalidad de los 96 pocillos es medida simultáneamente usando una cámara CCD enfriada. Los puestos de datos son recogidos cada segundo. Estos datos fueron seguidamente representados gráficamente y analizados usando el programa de ordenador GrafPad PRISM.

Brococonstricción inducida por metacolina

La respuesta de las vías respiratorias a la metacolina fue determinada en ratones BalbC no enjaulados y despiertos (n=6 en cada grupo). Se usó una pletismografía barométrica para medir la pausa aumentada (Penh), una medida sin unida-

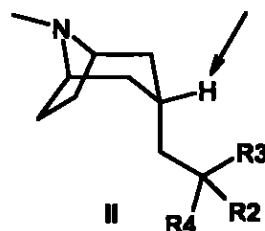
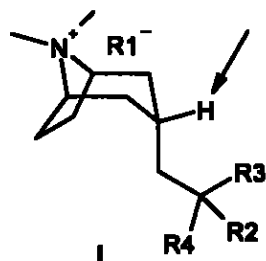
des que se ha mostrado que está correlacionada con los cambios en la resistencia de las vías respiratorias que se produce durante la estimulación bronquial con metacolina. Los ratones fueron previamente tratados con 50 μ l de compuesto (0,003-10 μ g/ratón) en 50 μ l de vehículo (DMSO al 10% por vía intranasal, y seguidamente fueron colocados en la cámara de pletismografía. Una vez en la cámara, se permitió que los ratones se equilibraran durante 10 minutos antes de tomar una medición de la Penh de línea de base durante 5 minutos. Los ratones fueron seguidamente estimulados con un aerosol de metacolina (10 mg/ml) durante 2 minutos. Se registró la Penh continuamente durante 7 minutos partiendo de la percepción del aerosol de metacolina, y continuando durante 5 minutos con posterioridad. Los datos para cada ratón fueron analizados y representados gráficamente usando un programa de ordenador GrafPad PRISM.

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REIVINDICACIONES

1. Un compuesto que tiene la estructura I o II que se indican a continuación, excepto el compuesto de Formula (II) en la que R2 y R2 son 2-tiofeno y R4 es -OC(O)CH₃:

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en las cuales:

el átomo de H indicado está en la posición exo;

R1⁻ representa un anión asociado con la carga positiva del átomo de N. R1⁻ puede ser, pero sin estar limitado a ello, cloruro, bromuro, yoduro, sulfato, benceno-sulfonato y tolueno-sulfonato;

R2 y R3 se seleccionan independientemente entre el grupo que consiste en grupos alquilo inferior de cadena lineal o ramificada (que tienen preferentemente de 1 a 6 átomos de carbono), grupos cicloalquilo (que tienen de 5 a 6 átomos de carbono), cicloalquil-alquilo (que tienen 6 a 10 átomos de carbono), heterocicloalquilo (que tienen 5 a 6 átomos de carbono) y N u O como el heteroátomo, heterocicloalquil-alquilo (que tiene 6 a 10 átomos de carbono) y N u O como el heteroátomo, arilo, arilo opcionalmente sustituido, heteroarilo, y heteroarilo opcionalmente sustituido;

R4 se selecciona entre el grupo que consiste en alquilo (C₁-C₆), cicloalquilo (C₃-C₁₂), heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-heterocicloalquilo (C₃-C₇), arilo, heteroarilo, alquil (C₁-C₆)-arilo, alquil (C₁-C₆)-heteroarilo, -OR₅, -CH₂OR₅, -CH₂OH, -CN, -CF₃, -CH₂O(CO)R₆, -CO₂R₇, -CH₂NH₂, -CH₂N(R₇)SO₂R₅, -SO₂N(R₇)(R₈), -CON(R₇)(R₈),

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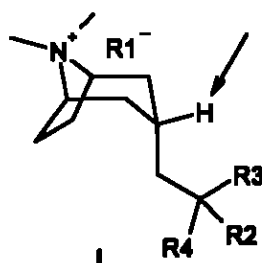
$-\text{CH}_2\text{N}(\text{R8})\text{CO}(\text{R6})$, $-\text{CH}_2\text{N}(\text{R8})\text{SO}_2(\text{R6})$, $-\text{CH}_2\text{N}(\text{R8})\text{CO}_2(\text{R5})$,
 $-\text{CH}_2\text{N}(\text{R8})\text{CONH}(\text{R7})$;

R5 se selecciona entre el grupo que consiste alquilo
 (C₁-C₆), alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-
 5 heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-arilo o alquil
 (C₁-C₆)-heteroarilo;

R6 se selecciona entre el grupo que consiste en
 alquilo (C₁-C₆), cicloalquilo (C₃-C₁₂), heterocicloalquilo
 (C₃-C₇), alquil (C₁-C₆)-cicloalquilo (C₃-C₁₂), alquil (C₁-C₆)-
 10 heterocicloalquilo (C₃-C₇), arilo, heteroarilo, alquil (C₁-
 C₆)-arilo o alquil (C₁-C₆)-heteroarilo;

R7 y R8 se seleccionan, independientemente, entre el
 grupo que consiste en H, alquilo (C₁-C₆), cicloalquilo (C₃-
 C₁₂), heterocicloalquilo (C₃-C₇), alquil (C₁-C₆)-cicloalquilo
 15 (C₃-C₁₂), alquil (C₁-C₆)-heterocicloalquilo (C₃-C₇), alquil
 (C₁-C₆)-arilo o alquil (C₁-C₆)-heteroarilo.

2. Un compuesto según la reivindicación 1, que tiene
 la estructura I siguiente:



20 3. Un compuesto según la reivindicación 1, selecciona-
 do entre el grupo que consiste en:

Yoduro de (endo)-3-(2-metoxi-2,2-di-tiofen-2-il-etil)-
 8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-
 25 difenil-propionitrilo;

(Endo)-8-metil-3-(2,2,2-trifenil-etil)-8-aza-
 biciclo[3.2.1]octano;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-
 difenil-propionamida;

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Ácido 3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-
2,2-difenil-propiónico;

Yoduro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-
dimetil-8-azonia-biciclo[3.2.1]octano;

5 Bromuro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-
dimetil-8-azonia-biciclo[3.2.1]octano;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-
difenil-propan-1-ol;

N-Bencil-3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-
10 il)-2,2-difenil-propionamida;

Yoduro de (endo)-3-(2-carbamoil-2,2-difenil-etil)-8,8-
dimetil-8-azonia-biciclo[3.2.1]octano;

1-Bencil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-
3-il)-2,2-difenil-propil]-urea;

15 1-Etil-3-[3-((endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-
il)-2,2-difenil-propil]-urea;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-
2,2-difenil-propil]-acetamida;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-
20 2,2-difenil-propil]-benzamida;

3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-
di-tiofen-2-il-propionitrilo;

Yoduro de (endo)-3-(2-ciano-2,2-di-tiofen-2-il-etil)-
8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

25 N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-
2,2-difenil-propil]-bencenosulfonamida;

[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-2,2-
difenil-propil]-urea;

N-[3-((Endo)-8-metil-8-aza-biciclo[3.2.1]oct-3-il)-
30 2,2-difenil-propil]-metanosulfonamida; y

Bromuro de (endo)-3-{2,2-difenil-3-[(1-fenil-
metanoil)-amino]-propil}-8,8-dimetil-8-azonia-
biciclo[3.2.1]octano.

4. Un compuesto según la reivindicación 3, selecciona-

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do entre el grupo que consiste en:

Yoduro de (endo)-3-(2-metoxi-2,2-di-tiofen-2-il-etil)-
8,8-dimetil-8-azonia-biciclo[3.2.1]octano;

Yoduro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-
5 dimetil-8-azonia-biciclo[3.2.1]octano;

Bromuro de (endo)-3-(2-ciano-2,2-difenil-etil)-8,8-
dimetil-8-azonia-biciclo[3.2.1]octano;

Yoduro de (endo)-3-(2-carbamoil-2,2-difenil-etil)-8,8-
dimetil-8-azonia-biciclo[3.2.1]octano;

10 Yoduro de (endo)-3-(2-ciano-2,2-di-tiofen-2-il-etil)-
8,8-dimetil-8-azonia-biciclo[3.2.1]octano; y

Bromuro de (endo)-3-(2,2-difenil-3-[(1-fenil-
metanoil)-amino]-propil)-8,8-dimetil-8-azonia-
biciclo[3.2.1]octano.

15 5. Una composición farmacéutica para el tratamiento de
enfermedades mediadas por receptores de acetilcolina musca-
rínicos, que comprende un compuesto según la reivindicación
1 y un vehículo farmacéuticamente aceptable para el mismo.

20 6. Un método para inhibir la unión de acetilcolina a
sus receptores en un mamífero que lo necesita, que compren-
de administrar una cantidad segura y eficaz de un compuesto
según la reivindicación 1.

25 7. Un método para tratar una enfermedad mediada por
receptores de acetilcolina muscarínicos, en el que la ace-
tilcolina se une a dicho receptor, que comprende adminis-
trar una cantidad segura y eficaz de un compuesto según la
reivindicación 1.

30 8. Un método según la reivindicación 7, en el que la
enfermedad es seleccionada entre el grupo que consiste en
enfermedad crónica de obstrucción pulmonar, bronquitis cró-
nica, asma, obstrucción respiratoria crónica, fibrosis pul-
monar, enfisema pulmonar y rinitis alérgica.

9. Un método según la reivindicación 7, en el que la
administración es a través de inhalación por la boca o la

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nariz.

10. Un método según la reivindicación 7, en el que la administración es a través de un dispositivo de suministro de medicamentos seleccionado entre un inhalador de polvos secos de depósito, un inhalador de polvos secos de dosis múltiples o un inhalador de dosis medidas.

11. Un método según la reivindicación 7, en el que el compuesto es administrado a un ser humano y tiene una duración de la acción de 12 horas o más para una dosis de 1 mg.

10 12. Un método según la reivindicación 11, en el que el compuesto tiene una duración de la acción de 24 horas o más.

15 13. Un método según la reivindicación 12, en el que el compuesto tiene una duración de la acción de 36 horas o más.

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RESUMEN DE LA DESCRIPCIÓN

Se proporcionan antagonistas de receptores de acetilcolina muscarínicos y métodos para usarlos.

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference PU60539	FOR FURTHER ACTION	see Form PCT/ISA/220 as well as, where applicable, item 5 below
International application No PCT/US04/33638	International filing date (<i>day/month/year</i>) 12 October 2004 (12 10 2004)	(Earliest) Priority Date (<i>day/month/year</i>) 14 October 2003 (14 10 2003)
Applicant GLAXO GROUP LIMITED		

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

This international search report consists of a total of 2 sheets.



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

I Basis of the Report

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



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

b ☐ With regard to any nucleotide and/or amino acid sequence disclosed in the international application, see Box No. I.

2 ☐ Certain claims were found unsearchable (See Box No. II).

3 ☐ Unity of invention is lacking (See Box No. III).

4 With regard to the title,



the text is approved as submitted by the applicant.



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

5 With regard to the abstract,



the text is approved as submitted by the applicant.



the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box No. IV. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6 With regard to the drawings,

a the figure of the drawings to be published with the abstract is Figure No. _____



as suggested by the applicant.



as selected by this Authority, because the applicant failed to suggest a figure.



as selected by this Authority, because this figure better characterizes the invention.

b ☐ none of the figures is to be published with the abstract.

INTERNATIONAL SEARCH REPORT

International application No

PCT/US04/33638

A. CLASSIFICATION OF SUBJECT MATTER IPC(7) A61K 31/46 , C07D 451/02 US CL 514/304 , 546/124, 125 According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) US 514/304 , 546/124, 125 Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched Electronic data base consulted during the international search (name of data base and, where practicable, search terms used) STN STRUCTURE SEARCH, FILE CAPLUS		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No
A	US 2,800,481 (ZIRKLE et al) 23 July 1957 (23 07 1957), see examples 1-23 and claims 1-6	1-13
A	US 2,800,478 (ZIRKLE et al) 23 July 1957 (23 07 1957), see examples 2-12 and claims 1-6	1-13
☐ Further documents are listed in the continuation of Box C ☐ See patent family annex.		
* Special categories of cited documents		
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention	
"E" earlier application or patent published on or after the international filing date	"X" document of particular relevance the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone	
"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"Y" document of particular relevance the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art	
"O" document referring to an oral disclosure, use, exhibition or other means	"G" document member of the same patent family	
"P" document published prior to the international filing date but later than the priority date claimed		
Date of the actual completion of the international search 22 December 2004 (22 12 2004)	Date of mailing of the international search report 07 JAN 2005	
Name and mailing address of the ISA/US Mail Stop PCT Attn ISA/US Commissioner for Patents P O Box 1450 Alexandria, Virginia 22313-1450 Facsimile No (703) 305-3230	Authorized officer <i>Janelash Shaker Jr</i> Cecilia Tsang Telephone No (703)308-1235	

Form PCT/ISA/210 (second sheet) (January 2004)

PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To
SOMA G SIMON
GLAXOSMITHKLINE
CORPORATE INTELLECTUAL PROPERTY UW2220
709 SWEDLAND ROAD P O BOX 1539
KING OF PRUSSIA, PA 19406-0939

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43bis 1)

Applicant's or agent's file reference PU60539		Date of mailing (day/month/year) 07 JAN 2005 FOR FURTHER ACTION See paragraph 2 below
International application No PCT/US04/33638	International filing date (day/month/year) 12 October 2004 (12 10 2004)	Priority date (day/month/year) 14 October 2003 (14 10 2003)
International Patent Classification (IPC) or both national classification and IPC IPC(7) A61K 31/46 , C07D 451/02 and US Cl 514/304 , 546/124 125		
Applicant GLAXO GROUP LIMITED		

1 This opinion contains indications relating to the following items

- ☒ Box No I Basis of the opinion
- ☐ Box No II Priority
- ☐ Box No III Non-establishment of opinion with regard to novelty inventive step and industrial applicability
- ☐ Box No IV Lack of unity of invention
- ☒ Box No V Reasoned statement under Rule 43bis 1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement
- ☐ Box No VI Certain documents cited
- ☐ Box No VII Certain defects in the international application
- ☐ Box No VIII Certain observations on the international application

2 FURTHER ACTION

If a demand for international preliminary examination is made this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66 1bis(b) that written opinions of this International Searching Authority will not be so considered

If this opinion is, as provided above considered to be a written opinion of the IPEA the applicant is invited to submit to the IPEA a written reply together where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date whichever expires later

For further options see Form PCT/ISA/220

3 For further details see notes to Form PCT/ISA/220

Name and mailing address of the ISA/ US Mail Stop PCT Attn: ISA US Commissioner for Patents P O Box 1450 Alexandria Virginia 22313-1450 Facsimile No (703) 305 3230	Authorized officer CHARANJIT S AWLAKH Telephone No (703)308 1235
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Form PCT/ISA/237 (cover sheet) (January 2004)

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WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No

PCT/US04/33638

7B
x3

Box No 1 Basis of this opinion

1 With regard to the language, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item

☐ This opinion has been established on the basis of a translation from the original language into the following language _____, which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b))

2 With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of

a type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b format of material

☐ in written format

☐ in computer readable form

c time of filing/furnishing

☐ contained in international application as filed

☐ filed together with the international application in computer readable form

☐ furnished subsequently to this Authority for the purposes of search

3 ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished

4 Additional comments

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No
PCT/US04/33638

Box No V Reasoned statement under Rule 43 *bis* 1(a)(i) with regard to novelty, inventive step or industrial applicability, citations and explanations supporting such statement

1 Statement

Novelty (N)	Claims <u>1-13</u>	YES
	Claims <u>NONE</u>	NO
Inventive step (IS)	Claims <u>1-13</u>	YES
	Claims <u>NONE</u>	NO
Industrial applicability (IA)	Claims <u>1-13</u>	YES
	Claims <u>NONE</u>	NO

2 Citations and explanations

Claims 1-13 meet the criteria set out in PCT Article 33(2)-(3) because the prior art does not teach or fairly suggest the instant compounds of formulae I and II, pharmaceutical compositions containing these compounds and a method of using these compounds

Claims 1-13 meet the criteria set out in PCT Article 33(4) and thus have industrial applicability because the subject matter claimed can be made or used in industry

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NOTES TO FORM PCT/ISA/220 (continued)

The letter must indicate the differences between the claims as filed and the claims as amended. It must, in particular, indicate, in connection with each claim appearing in the international application (it being understood that identical indications concerning several claims may be grouped) whether

- (i) the claim is unchanged
- (ii) the claim is cancelled,
- (iii) the claim is new,
- (iv) the claim replaces one or more claims as filed,
- (v) the claim is the result of the division of a claim as filed

The following examples illustrate the manner in which amendments must be explained in the accompanying letter

- 1 [Where originally there were 48 claims and after amendment of some claims there are 51]
'Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers, claims 30, 33 and 36 unchanged, new claims 49 to 51 added'
- 2 [Where originally there were 15 claims and after amendment of all claims there are 11]
'Claims 1 to 15 replaced by amended claims 1 to 11'
- 3 [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]
'Claims 1 to 6 and 14 unchanged, claims 7 to 13 cancelled, new claims 15, 16 and 17 added' or
'Claims 7 to 13 cancelled, new claims 15, 16 and 17 added, all other claims unchanged'
- 4 [Where various kinds of amendments are made]
'Claims 1, 10 unchanged, claims 11 to 13, 18 and 19 cancelled, claims 14, 15 and 16 replaced by amended claim 14, claim 17 subdivided into amended claims 15, 16 and 17, new claims 20 and 21 added'

"Statement under Article 19(1)" (Rule 46.4)

The amendments may be accompanied by a statement explaining the amendments and indicating any impact that such amendments might have on the description and the drawings (which cannot be amended under Article 19(1)).

The statement will be published with the international application and the amended claims.

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

It should not be confused with and does not replace the letter indicating the differences between the claims as filed and as amended. It must be filed on a separate sheet and must be identified as such by a heading, preferably by using the words "Statement under Article 19(1)".

It may not contain any disparaging comments on the international search report or the relevance of citations contained in that report. Reference to citations relevant to a given claim contained in the international search report may be made only in connection with an amendment of that claim.

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments and any accompanying statement under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the time of filing the amendments (and any statement) with the International Bureau, also file with the International Preliminary Examining Authority a copy of such amendments (and of any statement) and, where required, a translation of such amendments for the procedure before that Authority (see Rules 55.3(a) and 62.2, first sentence). For further information, see the Notes to the demand form (PCT/IPEA/401).

Consequence with regard to translation of the international application for entry into the national phase

The applicant's attention is drawn to the fact that, upon entry into the national phase, a translation of the claims as amended under Article 19 may have to be furnished to the designated/elected Offices instead of, or in addition to, the translation of the claims as filed.

For further details on the requirements of each designated/elected Office, see the *PCT Applicant's Guide* Volume II.



Industria y Comercio

SUPERINTENDENCIA

Delegatura de Propiedad Industrial
División de Nuevas Creaciones

REQUISITOS NECESARIOS PARA PRESENTACIÓN Y AGILIZACIÓN DEL TRAMITE

PATENTE DE INVENCION ()	MODELO DE UTILIDAD ()	USUARIO ()	RADICADOR ()
-Indicación de que se solicita la concesión de una patente. ✓	()	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud. ✓	()	()	()
-Descripción de la invención. ✓	()	()	()
-Dibujos de ser estos pertinentes. X	()	()	()
-Comprobante de Pago de las tasas establecidas. ✓	()	()	()
COMPLETA ()	INCOMPLETA ()	()	()

DISEÑO INDUSTRIAL ()			
-Indicación de que se solicita el registro de Diseño Industrial.	()	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()	()
-Representación gráfica y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	()	()	()
-Comprobante de Pago de las tasas establecidas.	()	()	()
COMPLETA ()	INCOMPLETA ()	()	()

ESQUEMA DE TRAZADO ()			
-Indicación de que se solicita el registro de Diseño Industrial.	()	()	()
-Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()	()
-Representación gráfica del Esquema Trazado.	()	()	()
-Comprobante de Pago de las tasas establecidas.	()	()	()
COMPLETA ()	INCOMPLETA ()	()	()

Firma Responsable:

Fecha:

Abril 5 de 2006.

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REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
GLAXO GROUP LIMITED

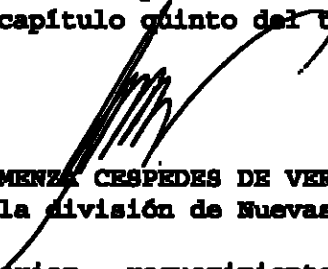
REFERENCIA	Radicación No.	06 33251
	Solicitud internacional	US2004/033638
	Fecha inicio fase nacional	14/05/2006
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8429

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

1. La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486.

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única No.10 de 2001.


ALIX CARMONA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de fecha 04 AGO. 2008
jramos