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Industria y Comercio

SUPERINTENDENCIA

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
INVENTARIO

PCT

DELEGATURA DE PROPIEDAD INDUSTRIAL

DIVISIÓN DE NUEVAS CREACIONES

08-54219

SOLICITUD DE PATENTE DE
INVENCION

TITULO: USO FARMACEUTICO DE AMIDAS SUSTITUIDAS

SOLICITANTE: TRANSTECH PHARMA INC.

DIRECCIÓN: 4170 Mendenhall Oaks Parkway High Point, NC 27265 E.U.A.

APODERADO: CARLOS R. OLARTE

BOGOTÁ 28 de Mayo de 2008

OlarteRaisbeck



SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 08-054219-00000-0000

Fecha: 2008-05-28 16:17:08
Tra. 11 PATENTE IYH
Act. 411 PRESENTACION

Dep. 2020 NUECREACION
Eve: 378 FASE NACIONAL I
Folios: 309

PETITORIO - FORMULARIO ÚNICO DE SOLICITUD PATENTE PCT

ENTRADA EN FASE NACIONAL

P2008/000085

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

**SOLICITANTE
(71)**

Nombre: TRANSTECH PHARMA INC.

Dirección: 4170 Mendenhall Oaks Parkway
High Point, NC 27265 E.U.A.

Nacionalidad o Domicilio: Estadounidense

Lugar de Constitución: Estados Unidos

Teléfono: _____ Fax: _____

E-mail: _____

IDENTIFICACIÓN

C.C. ☐ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número _____

**REPRESENTANTE
O APODERADO**

Nombre: CARLOS R. OLARTE

Dirección: World Trade Center, Torre A, Calle
100 No. 8A-37 Piso 10.

Teléfono: 601-7700 Fax: 601-7799

E-mail: office@olarteraisbeck.com

IDENTIFICACIÓN

C.C. ☒ NIT ☐

C.E. ☐ Otro ☐

Cual _____

Número 79.782.747 Btá
TP 74.295

**INVENTOR (ES)
(72)**

Nombre: VER PAGINA ADJUNTA

Dirección: VER PAGINA ADJUNTA

Nacionalidad o Domicilio: VER PAGINA ADJUNTA

5

PCT (86)

Solicitud Internacional No. PCT/EP2006/068017

Fecha Noviembre 1, 2006

Publicación Internacional No. WO 2007/051811

Fecha Mayo 10, 2007

6

Título (54) USO FARMACEUTICO DE AMIDAS SUSTITUIDAS

Clasificación Internacional (51) A61K 31/4184, A61K 31/404, A61P 3/10

Prioridad

SI ☒ NO ☐

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EP

(32) Fecha

Noviembre 1, 2005

(31) Número de Solicitud

05110226.7

9

Comprobante de pag No. 08-41,432

Fecha Marzo 23 de 2008

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. Adjunto copia simple ver expediente No. 07-021.338

☐

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.

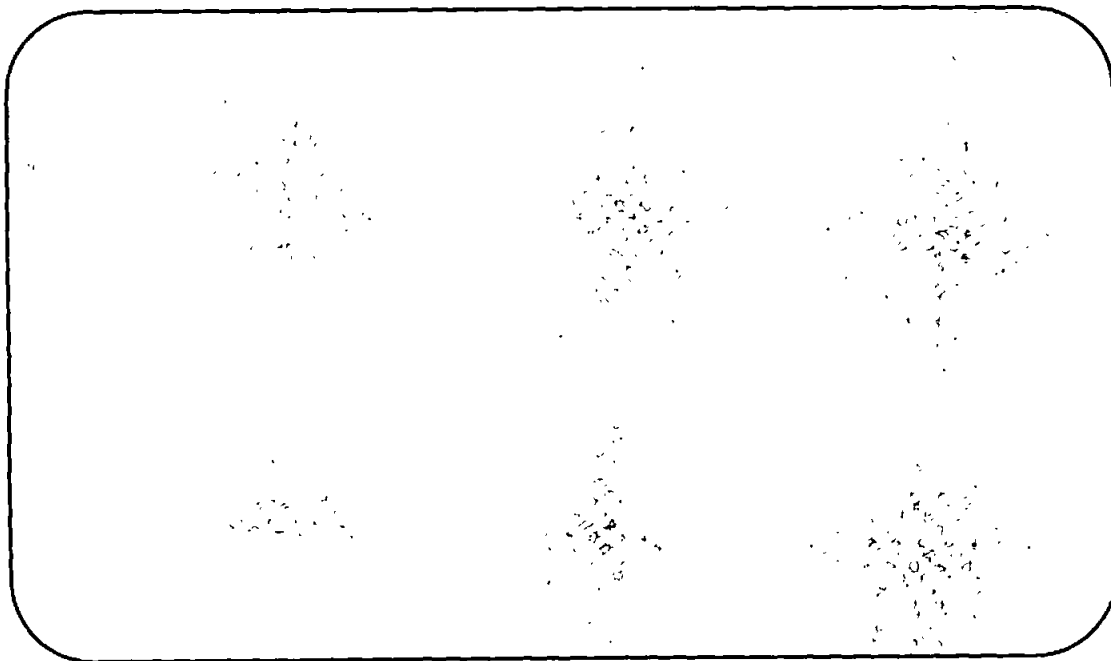
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De ser el caso, modificaciones efectuadas a la solicitud internacional.

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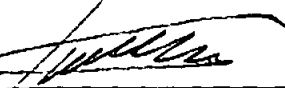
Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:

12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTEFIRMA: C.C. 79.782.747 Btá T.P. 74.295

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 08 - 41,432
FECHA : MAYO 23 DE 2008

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



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Tra. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 309

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
GLARTE RAISREK	CONSIGNACION	BANCO DE BOGOTA	062754387	330805	22/05/2008	4,537,000.00

***** CONCEPTO *****

CANT. RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	501,000.00
	TOTAL :	\$. 501,000.00

SON: QUINIENTOS UN MIL PESOS

RESPONSABLE :

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

TRADUCCIÓN OFICIAL DE UN DOCUMENTO QUE ESTÁ ORIGINALMENTE EN INGLÉS

El documento de Poder adjunto de Transtech Pharma Inc. a Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana Maria Frieri y/o Juan Guillermo Moure y/o Natalia Castro lleva una certificación notarial con el siguiente sello en inglés:

(Firmado) Vanessa McDade

Sello: "Notario Público de Carolina del Norte - Condado de Guilford.
Vanessa McDade. Mi comisión vence el 7/25/2007".

Apostilla adjunta:

Estado de Carolina de Norte	
Departamento del Secretario de Estado	
APOSTILLA:	
(Convention de La Haye du 5 octobre 1961)	
Estados Unidos de América	
1. País:	<u>El presente documento público</u>
2. Ha sido firmado por:	Vanessa McDade
3. Actuando en calidad de:	Notario Público. Comisión vence el 7/25/2007
4. Lleva el sello/estampilla de:	Condado de Guilford, Carolina del Norte
	<u>Certificado</u>
5. En:	Raleigh, Carolina de Norte
6. El:	31 de Enero de 2007
7. Por:	El Subsecretario de Estado. Estado de Carolina del Norte
8. Bajo el No.:	1906
9. Sello / estampilla:	El Estado de Carolina del Norte. Departamento de Estado
10. Firma:	Haley Haynes. Subsecretario de Estado Elaine Marshall. Secretario de Estado

Traductor Oficial

JORGE E. SIERRA RIVERA

Notario 376 - 1993 Notario


Certificación:

Certifico que la presente es una traducción verdadera y completa del documento adjunto: "Transtech P. - Apost."

Fecha: 15 de Febrero de 2007.

Traductor: Jorge Enrique Sierra Reyes.

Licencia No. 376 de 1993, del Ministerio de Justicia.

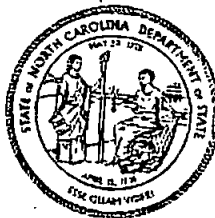
Dirección: Carrera 15 No. 99-13 Oficina 411. Bogotá, Colombia.

Teléfono: (57-1) 2182308, (57-1) 6232925.

E-mail: treseser1@yahoo.com. No. 9509


Traductor Oficial
JORGE E. SIERRA REYES
Licencia 376 de 1993

STATE OF NORTH CAROLINA



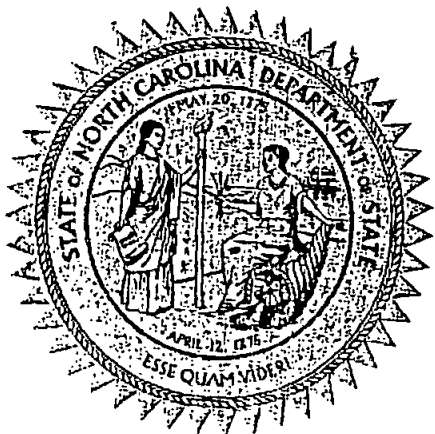
Department of The
Secretary of State

APOSTILLE (Convention de La Haye 5 octobre 1961)

1. COUNTRY: UNITED STATES OF AMERICA
2. This Public Document
has been signed by VANESSA MCDADE
3. acting in the capacity of NOTARY PUBLIC
COMMISSION EXPIRES 7/25/2007
4. bears the seal/stamp of COUNTY OF GUILFORD, NORTH CAROLINA

CERTIFIED

5. at Raleigh, North Carolina
6. the 31ST DAY OF JANUARY, 2007
7. by Secretary of State or Deputy Secretary of State, State of North Carolina
8. No. 1906
9. Seal/Stamp
10. Signature



By:

Haley Haynes
Haley Haynes
Deputy Secretary of State

Claine J. Marshall

Secretary of State

J. Ian Raisbeck
Ana María Frieri
Juan Guillermo Moure
Natalia Castro
Zayde Chah
Jose Luis London
Felipe Mendo
Sivron Salin
Alexander Agude
Carmela A. Rodríguez
Of. Contable
Guillermo Chah
Graciela Méi
Jacqueline Chaparr
Cruz E. de M. nodran

Power of Attorney

Poder

The undersigned,

El suscrito,

TRANSTECH PHARMA, INC.

domiciled in

domiciliado en

4170 Mendenhall Oaks Parkways, Suite 110, High Point,
North Carolina 27265, United States of América.

by means of these presents hereby grants to **Carlos R. Olarte and/or J. Ian Raisbeck and/or Ana María Frieri and/or Juan Guillermo Moure and/or Natalia Castro** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents for Inventions, Utility Models, Layout-Designs (topographies) of Integrated Circuits, Industrial Designs, Trademarks, Advertising Slogans, Trade Names, Commercial Emblems, Geographical Indications, Protection of Trade Secrets, Obtainer's Certificates, Copyrights, Registration of Domain Names, Health Registrations, or any other intellectual property right in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, recourses, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications, collect refunds, desist, settle, conciliate or negotiate. 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.

por medio del presente otorga a **Carlos R. Olarte y/o J. Ian Raisbeck y/o Ana María Frieri y/o Juan Guillermo Moure y/o Natalia Castro** poder especial, amplio y suficiente para presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de las Patentes de Invención, Modelos de Utilidad, Esquemas de Trazados de Circuitos Integrados, Diseños Industriales, Marcas, Lemas Comerciales, Nombres Comerciales, Enseñas Comerciales, Denominaciones de Origen, Protección de Secretos Empresariales, Certificados de Obtentor, Derechos de Autor, Registro de Nombres de Dominio, Registros Sanitarios, o cualquier otro bien de propiedad intelectual de 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, recursos, respuestas y oposiciones, pagar impuestos y anualidades, solicitar testimonios, recibir documentos y valores, desistir, transigir, 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: William V. Buccella



Date/Fecha: January 9, 2007

City/Country/Ciudad,País: High Point, North Carolina, USA

MODEL OF NOTARIAL CERTIFICATION

Notarial Certification

On this date,
January 9, 2007

The undersigned Notary Public certifies:

1. That

of legal age and domiciled in

signed the foregoing document.

2. That the grantor has executed the foregoing document as

of TRANSTECH PHARMA, INC..

3. That TRANSTECH PHARMA, INC., having its principal place of business located in High Point, North Carolina is duly incorporated, is currently in existence, and that the purposes for which the Power of Attorney is granted are within the scope of its corporate purposes.

4. That the grantor has the authority to execute the Power of Attorney and that his/her representation is legal.

5. The foundation for my certifications contained in points 2, 3 and 4 was the exhibition of the following authentic document(s):

Minutes of the Meeting of the Board of Directors held December 1, 1998, Amended Bylaws, executed August 27, 1999 and the Minutes of the Meeting of the Board of Directors held January 23, 2003 where William V. Buccella was elected Senior Vice President of Legal Affairs and Secretary, executed January 23, 2003

Certificación Notarial

En esta fecha,

el Notario Público suscrito certifica:

1. Que

William V. Buccella

mayor de edad y domiciliado

4170 Mendenhall Oaks Pkwy, High Point, NC 27265

suscribió el documento que antecede.

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

4. Que

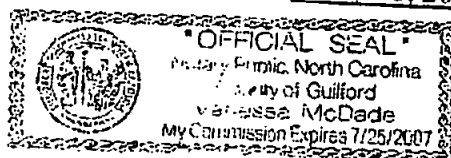
con sede principal ubicada en

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

4. Que el otorgante tiene la representación para suscribir el poder, y que ésta es legítima.

5. El fundamento de mis certificaciones contenidas en los puntos 2, 3 y 4 fue la exhibición de los (del) siguiente(s) documento(s) auténtico(s):

NOTARY PUBLIC (Signature): Vanessa McDade
My Commission Expires: July 25, 2007



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2007 (10.05.2007)

PCT

(10) International Publication Number
WO 2007/051811 A2

- (51) International Patent Classification: **Not classified**
- (21) International Application Number: PCT/EP2006/068017
- (22) International Filing Date: 1 November 2006 (01.11.2006)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data: 05110226.7 1 November 2005 (01.11.2005) EP
- (71) Applicant (for all designated States except US): **NOVO NORDISK A/S** [DK/DK]; Novo Allé, DK-2880 Bagsværd (DK).
- (72) Inventors; and
- (75) Inventors/Applicants (for US only): **KILBURN, John**, Paul [GB/DK]; Hjørtvej 23, DK-4690 Haslev (DK). **ANDERSEN, Henrik**, Sune [DK/DK]; Gustav Adolfs Vej 2, DK-2800 Lyngby (DK). **KAMPEN, Gita**, Camilla, Tejlgaard [DK/DK]; Gårdebuen 18, DK-2850 Nærum (DK). **EBDRUP, Søren** [DK/DK]; Nymarksvej 11, DK-4000 Roskilde (DK).
- (74) Common Representative: **NOVO NORDISK A/S**; Corporate Patents, Novo Allé, DK-2880 Bagsværd (DK).
- (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, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.
- (84) Designated States (unless otherwise indicated, for every kind of regional protection available): ARIPO (BW, GH, GM, KE, 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, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- Published:**
— without international search report and to be republished upon receipt of that report
- For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: **PHARMACEUTICAL USE OF SUBSTITUTED AMIDES**

(57) Abstract: The use of substituted amides for modulating the activity of 11-hydroxysteroid dehydrogenase type 1 (11HSD1) and the use of these compounds as pharmaceutical compositions, are described. Also a novel class of substituted amides, their use in therapy, pharmaceutical compositions comprising the compounds, as well as their use in the manufacture of medicaments are described. The present compounds are modulators and more specifically inhibitors of the activity of 11HSD1 and may be useful in the treatment, prevention and/or prophylaxis of a range of medical disorders where a decreased intracellular concentration of active glucocorticoid is desirable.

WO 2007/051811 A2

PHARMACEUTICAL USE OF SUBSTITUTED AMIDES

FIELD OF INVENTION

[0001] The present invention relates to use of substituted amides and pharmaceutical compositions comprising the same for treating disorders where it is desirable to modulate the activity of 11β -hydroxysteroid dehydrogenase type 1 (11β HSD1). The present invention also relates to novel substituted amides, to their use in therapy, to pharmaceutical compositions comprising the same, to the use of said compounds in the manufacture of medicaments, and to therapeutic methods comprising the administration of the compounds. The present compounds modulate the activity of 11β -hydroxysteroid dehydrogenase type 1 (11β HSD1) and are accordingly useful in the treatment of diseases in which such a modulation is beneficial, such as the metabolic syndrome.

BACKGROUND OF THE INVENTION

[0002] The metabolic syndrome is a major global health problem. In the US, the prevalence in the adult population is currently estimated to be approximately 25%, and it continues to increase both in the US and worldwide. The metabolic syndrome is characterised by a combination of insulin resistance, dyslipidemia, obesity and hypertension leading to increased morbidity and mortality of cardiovascular diseases. People with the metabolic syndrome are at increased risk of developing frank type 2 diabetes, the prevalence of which is equally escalating.

[0003] In type 2 diabetes, obesity and dyslipidemia are also highly prevalent and around 70% of people with type 2 diabetes additionally have hypertension once again leading to increased mortality of cardiovascular diseases.

[0004] In the clinical setting, it has long been known that glucocorticoids are able to induce all of the cardinal features of the metabolic syndrome and type 2 diabetes.

[0005] 11β -hydroxysteroid dehydrogenase type 1 (11β HSD1) catalyses the local generation of active glucocorticoid in several tissues and organs including predominantly the liver and adipose tissue, but also e.g. skeletal muscle, bone, pancreas, endothelium, ocular tissue and certain parts of the central nervous system. Thus, 11β HSD1 serves as a local regulator of glucocorticoid actions in the tissues and organs where it is expressed (Tannin et al., *J. Biol. Chem.*, 266, 16653 (1991); Bujalska et al., *Endocrinology*, 140, 3188 (1999); Whorwood et al., *J Clin Endocrinol Metab.*, 86, 2296 (2001); Cooper et al., *Bone*, 27, 375 (2000); Davani et al., *J. Biol. Chem.*, 275, 34841 (2000); Brem et al., *Hypertension*, 31, 459

(1998); Rauz et al., *Invest. Ophthalmol. Vis. Sci.*, 42, 2037 (2001); Moisan et al., *Endocrinology*, 127, 1450 (1990)).

[0006] The role of 11 β HSD1 in the metabolic syndrome and type 2 diabetes is supported by several lines of evidence. In humans, treatment with the non-specific 11 β HSD1 inhibitor carbenoxolone improves insulin sensitivity in lean healthy volunteers and people with type 2 diabetes. Likewise, 11 β HSD1 knock-out mice are resistant to insulin resistance induced by obesity and stress. Additionally, the knock-out mice present with an anti-atherogenic lipid profile of decreased VLDL triglycerides and increased HDL-cholesterol. Conversely, mice that overexpress 11 β HSD1 in adipocytes develop insulin resistance, hyperlipidemia and visceral obesity, a phenotype that resembles the human metabolic syndrome (Andrews et al., *J. Clin. Endocrinol. Metab.*, 88, 285 (2003); Walker et al., *J. Clin. Endocrinol. Metab.*, 80, 3155 (1995); Morton et al., *J. Biol. Chem.*, 276, 41293 (2001); Kotelevtsev et al., *Proc. Natl. Acad. Sci. USA*, 94, 14924 (1997); Masuzaki et al., *Science*, 294, 2166 (2001)).

[0007] The more mechanistic aspects of 11 β HSD1 modulation and thereby modulation of intracellular levels of active glucocorticoid have been investigated in several rodent models and different cellular systems. 11 β HSD1 promotes the features of the metabolic syndrome by increasing hepatic expression of the rate-limiting enzymes in gluconeogenesis, namely phosphoenolpyruvate carboxykinase and glucose-6-phosphatase, promoting the differentiation of preadipocytes into adipocytes thus facilitating obesity, directly and indirectly stimulating hepatic VLDL secretion, decreasing hepatic LDL uptake and increasing vessel contractility (Kotelevtsev et al., *Proc. Natl. Acad. Sci. USA*, 94, 14924 (1997); Morton et al., *J. Biol. Chem.* 276, 41293 (2001); Bujalska et al., *Endocrinology*, 140, 3188 (1999); Souness et al., *Steroids*, 67, 195 (2002), Brindley & Salter, *Prog. Lipid Res.*, 30, 349 (1991)).

[0008] WO 01/90090, WO 01/90091, WO 01/90092, WO 01/90093 and WO 01/90094 discloses various thiazol-sulfonamides as inhibitors of the human 11 β -hydroxysteroid dehydrogenase type 1 enzyme, and further states that said compounds may be useful in treating diabetes, obesity, glaucoma, osteoporosis, cognitive disorders, immune disorders and depression.

[0009] We have now found substituted amides that modulate the activity of 11 β HSD1 leading to altered intracellular concentrations of active glucocorticoid. More specifically, the present compounds inhibit the activity of 11 β HSD1 leading to decreased intracellular concentrations of active glucocorticoid. Thus, the present compounds can be used to treat disorders where a decreased level of active intracellular glucocorticoid is desirable, such as e.g. the metabolic syndrome, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting

glucose (IFG), dyslipidemia, obesity, hypertension, diabetic late complications, cardiovascular diseases, arteriosclerosis, atherosclerosis, myopathy, muscle wasting, osteoporosis, neurodegenerative and psychiatric disorders, and adverse effects of treatment or therapy with glucocorticoid receptor agonists.

- 5 [0010] One object of the present invention is to provide compounds, pharmaceutical compositions and use of compounds that modulate the activity of 11 β HSD1.

DEFINITIONS

10 [0011] In the following structural formulas and throughout the present specification, the following terms have the indicated meaning. The examples provided in the definitions present in this application are non-inclusive unless otherwise stated. They include but are not limited to the recited examples.

[0012] The term "halo" includes fluorine, chlorine, bromine, and iodine.

15 [0013] The term "trihalomethyl" includes trifluoromethyl, trichloromethyl, tribromomethyl, and triiodomethyl.

[0014] The term "trihalomethoxy" includes trifluoromethoxy, trichloromethoxy, tribromomethoxy, and triiodomethoxy.

20 [0015] The term "alkyl" includes C₁-C₈ straight chain saturated and methylene aliphatic hydrocarbon groups and C₃-C₈ branched saturated hydrocarbon groups having the specified number of carbon atoms. For example, this definition includes methyl (Me), ethyl (Et), propyl (Pr), butyl (Bu), pentyl, hexyl, isopropyl (i-Pr), isobutyl (i-Bu), *tert*-butyl (*t*-Bu), *sec*-butyl (*s*-Bu), isopentyl, and neopentyl.

25 [0016] The term "alkenyl" includes C₂-C₆ straight chain unsaturated aliphatic hydrocarbon groups and branched C₃-C₆ unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition includes ethenyl, propenyl, butenyl, pentenyl, hexenyl, methylpropenyl, and methylbutenyl.

30 [0017] The term "alkynyl" includes C₂-C₈ straight chain unsaturated aliphatic hydrocarbon groups and C₄-C₈ branched unsaturated aliphatic hydrocarbon groups having the specified number of carbon atoms. For example, this definition includes ethynyl, propynyl, butynyl, pentynyl, hexynyl, and methylbutynyl.

[0018] The term "saturated or partially saturated monocyclic, bicyclic, or tricyclic ring system" represents but is not limited to aziridinyl, azepanyl, azocanyl, pyrrolinyl, pyrrolidinyl, 2-imidazolinyl, imidazolidinyl, 2-pyrazolinyl, morpholinyl, piperidinyl, thiomorpholinyl, piperazinyl, phthalimide, 1,2,3,4-tetrahydro-quinolinyl, 1,2,3,4-tetrahydro-isoquinolinyl, 1,2,3,4-tetrahydro-quinoxalinyl, indolinyl, 1, 6-aza-bicyclo[3.2.1]octane, 2-aza-bicyclo[4.1.1]octane,

2-aza-bicyclo[3.2.1]octanyl, 7-aza-bicyclo[4.1.1]octanyl, 9-aza-bicyclo[3.3.2]decanyl, 4-aza-tricyclo[4.3.1.1^{3,8}]undecanyl, 9-aza-tricyclo[3.3.2.0^{3,7}]decanyl.

[0019] The term "saturated or partially saturated ring" represents cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, tetrahydrofuranyl, and tetrahydropyranyl.

[0020] The term "saturated or partially saturated aromatic ring" represents cyclopentyl, cyclohexyl, cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, cyclodecenyl, tetrahydrofuranyl, tetrahydropyranyl, phenyl, pyridyl, and pyrimidinyl.

[0021] The term "cycloalkyl" represents a saturated, mono-, bi-, tri- or spirocarbocyclic group having the specified number of carbon atoms (e.g., cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cycloheptyl, cyclooctyl, cyclononyl, cyclodecyl, bicyclo[3.2.1]octyl, spiro[4.5]decyl, norpinyl, norbornyl, norcaryl, and adamantyl).

[0022] The term "cycloalkylalkyl" represents a cycloalkyl group as defined above attached through an alkyl group having the indicated number of carbon atoms or substituted alkyl group as defined above (e.g., cyclopropylmethyl, cyclobutylethyl, and adamantylmethyl).

[0023] The term "cycloalkenyl" represents a partially saturated, mono-, bi-, tri- or spirocarbocyclic group having the specified number of carbon atoms (e.g., cyclobutenyl, cyclopentenyl, cyclohexenyl, cycloheptenyl, cyclooctenyl, cyclononenyl, and cyclodecenyl).

[0024] The term "cycloalkylcarbonyl" represents a cycloalkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group (e.g., cyclopropylcarbonyl and cyclohexylcarbonyl).

[0025] The term "cycloalkylalkylcarbonyl" represents a cycloalkyl group as defined above attached through an alkyl group having the indicated number of carbon atoms or substituted alkyl group as defined above (e.g., cyclohexylmethylcarbonyl and cycloheptylethylcarbonyl).

[0026] The term "hetcycloalkyl" represents a saturated mono-, bi-, tri-, or spirocarbocyclic group having the specified number of atoms with 1-4 of the specified number being heteroatoms or groups selected from nitrogen, oxygen, sulphur, SO, and SO₂ (e.g., tetrahydrofuranyl, tetrahydropyranyl, tetrahydrothiopyranyl, piperidine, and pyridine).

[0027] The term "hetcycloalkylalkyl" represents a hetcycloalkyl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., tetrahydrofuranylmethyl, tetrahydropyranylethyl, and tetrahydrothiopyranylmethyl).

[0028] The term "hetcycloalkylcarbonyl" represents a hetcycloalkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group (e.g., 1-piperidin-4-yl-carbonyl and 1-(1,2,3,4-tetrahydro-isoquinolin-6-yl)carbonyl).



[0029] The term "alkyloxy" represents an alkyl group having the indicated number of carbon atoms attached through an oxygen bridge (e.g., methoxy, ethoxy, propyloxy, allyloxy, and cyclohexyloxy).

5 [0030] The term "alkyloxyalkyl" represents an alkyloxy group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., methyloxy-methyl).

[0031] The term "aryl" includes a carbocyclic aromatic ring that is monocyclic, bicyclic, or polycyclic, such as phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, fluorenyl, indenyl, pentalenyl, azulenyl, and biphenylenyl. Aryl also includes the partially hydrogenated
10 derivatives of the carbocyclic aromatic enumerated above. Examples of partially hydrogenated derivatives include 1,2,3,4-tetrahydronaphthyl and 1,4-dihydronaphthyl.

[0032] The term "aryl1" includes phenyl, biphenyl, naphthyl, anthracenyl, phenanthrenyl, and fluorenyl.

[0033] The term "aryl2" includes phenyl, biphenyl, and naphthyl.

15 [0034] The term "hetaryl" includes pyrrolyl (2-pyrrolyl), pyrazolyl (3-pyrazolyl), imidazolyl (1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 5-imidazolyl), triazolyl (1,2,3-triazol-1-yl, 1,2,3-triazol-2-yl, 1,2,3-triazol-4-yl, 1,2,4-triazol-3-yl), oxazolyl (2-oxazolyl, 4-oxazolyl, 5-oxazolyl), isoxazolyl (3-isoxazolyl, 4-isoxazolyl, 5-isoxazolyl), thiazolyl (2-thiazolyl, 4-thiazolyl, 5-thiazolyl), thiophenyl (2-thiophenyl, 3-thiophenyl, 4-thiophenyl, 5-thiophenyl), furanyl (2-furanyl, 3-furanyl,
20 4-furanyl, 5-furanyl), pyridyl (2-pyridyl, 3-pyridyl, 4-pyridyl, 5-pyridyl), 5-tetrazolyl, pyrimidinyl (2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 6-pyrimidinyl), pyrazinyl, pyridazinyl (3-pyridazinyl, 4-pyridazinyl, 5-pyridazinyl), quinolyl (2-quinolyl, 3-quinolyl, 4-quinolyl, 5-quinolyl, 6-quinolyl, 7-quinolyl, 8-quinolyl), isoquinolyl (1-isoquinolyl, 3-isoquinolyl, 4-isoquinolyl, 5-isoquinolyl, 6-isoquinolyl, 7-isoquinolyl, 8-isoquinolyl), benzo[b]furanyl (2-
25 benzo[b]furanyl, 3-benzo[b]furanyl, 4-benzo[b]furanyl, 5-benzo[b]furanyl, 6-benzo[b]furanyl, 7-benzo[b]furanyl), 2,3-dihydro-benzo[b]furanyl (2-(2,3-dihydro-benzo[b]furanyl), 3-(2,3-dihydro-benzo[b]furanyl), 4-(2,3-dihydro-benzo[b]furanyl), 5-(2,3-dihydro-benzo[b]furanyl), 6-(2,3-dihydro-benzo[b]furanyl), 7-(2,3-dihydro-benzo[b]furanyl)), 1,4-benzodioxin (2-(1,4-benzodioxin), 3-(1,4-benzodioxin), 5-(1,4-benzodioxin), 6-(1,4-benzodioxin)),
30 benzo[b]thiophenyl (2-benzo[b]thiophenyl, 3-benzo[b]thiophenyl, 4-benzo[b]thiophenyl, 5-benzo[b]thiophenyl, 6-benzo[b]thiophenyl, 7-benzo[b]thiophenyl), 2,3-dihydro-benzo[b]thiophenyl (2-(2,3-dihydro-benzo[b]thiophenyl), 3-(2,3-dihydro-benzo[b]thiophenyl), 4-(2,3-dihydro-benzo[b]thiophenyl), 5-(2,3-dihydro-benzo[b]thiophenyl), 6-(2,3-dihydro-benzo[b]thiophenyl), 7-(2,3-dihydro-benzo[b]thiophenyl)), 4,5,6,7-tetrahydro-benzo[b]thiophenyl (2-
35 (4,5,6,7-tetrahydro-benzo[b]thiophenyl), 3-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 4-

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(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 5-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 6-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), 7-(4,5,6,7-tetrahydro-benzo[b]thiophenyl), thieno[2,3-b]thiophenyl, 4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl (4-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 5-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 6-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl), 7-(4,5,6,7-tetrahydro-thieno[2,3-c]pyridyl)), indolyl (1-indolyl, 2-indolyl, 3-indolyl, 4-indolyl, 5-indolyl, 6-indolyl, 7-indolyl), isoindolyl (1-isoindolyl, 2-isoindolyl, 3-isoindolyl, 4-isoindolyl, 5-isoindolyl, 6-isoindolyl, 7-isoindolyl), 1,3-dihydro-isoindolyl (1-(1,3-dihydro-isoindolyl), 2-(1,3-dihydro-isoindolyl), 3-(1,3-dihydro-isoindolyl), 4-(1,3-dihydro-isoindolyl), 5-(1,3-dihydro-isoindolyl), 6-(1,3-dihydro-isoindolyl), 7-(1,3-dihydro-isoindolyl)), indazole (1-indazolyl, 3-indazolyl, 4-indazolyl, 5-indazolyl, 6-indazolyl, 7-indazolyl), benzimidazolyl (1-benzimidazolyl, 2-benzimidazolyl, 4-benzimidazolyl, 5-benzimidazolyl, 6-benzimidazolyl, 7-benzimidazolyl, 8-benzimidazolyl), benzoxazolyl (1-benz-oxazolyl, 2-benzoxazolyl), benzothiazolyl (1-benzothiazolyl, 2-benzothiazolyl, 4-benzothiazolyl, 5-benzothiazolyl, 6-benzothiazolyl, 7-benzothiazolyl), benzo-[1,2,5]oxadiazolyl, (4-benzo[1,2,5]oxadiazole, 5-benzo[1,2,5]oxadiazole), carbazolyl (1-carbazolyl, 2-carbazolyl, 3-carbazolyl, 4-carbazolyl), piperidinyl (2-piperidinyl, 3-piperidinyl, 4-piperidinyl), and pyrrolidinyl (1-pyrrolidinyl, 2-pyrrolidinyl, 3-pyrrolidinyl).

[0035] The term "arylalkyl" represents an aryl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., benzyl, phenylethyl, 3-phenylpropyl, 1-naphthylmethyl, and 2-(1-naphthyl)ethyl).

[0036] The term "hetarylalkyl" or "hetaralkyl" represents a hetaryl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., (2-furyl)methyl, (3-furyl)methyl, (2-thienyl)methyl, (3-thienyl)methyl, (2-pyridyl)methyl, and 1-methyl-1-(2-pyrimidyl)ethyl).

[0037] The term "aryloxyhetaryl" represents an aryloxy group as defined above attached through a hetaryl group (e.g., 2-phenoxy-pyridyl).

[0038] The term "aryloxy" represents an aryl group as defined above attached through an oxygen bridge (e.g., phenoxy and naphthyloxy).

[0039] The term "hetaryloxy" represents a hetaryl group as defined above attached through an oxygen bridge (e.g., 2-pyridyloxy).

[0040] The term "arylalkyloxy" represents an arylalkyl group as defined above attached through an oxygen bridge (e.g., phenethyloxy and naphthylmethyloxy).

[0041] The term "hetarylalkyloxy" represents a hetarylalkyl group as defined above attached through an oxygen bridge (e.g., 2-pyridylmethyloxy).

- [0042] The term "alkyloxycarbonyl" represents an alkyloxy group as defined above attached through a carbonyl group (e.g., methylformiat and ethylformiat).
- [0043] The term "aryloxycarbonyl" represents an aryloxy group as defined above attached through a carbonyl group (e.g., phenylformiat and 2-thiazolylformiat).
- 5 [0044] The term "arylalkyloxycarbonyl" represents an "arylalkyloxy" group as defined above attached through a carbonyl group (e.g., benzylformiat and phenyletylformiat).
- [0045] The term "alkylthio" represents an alkyl group having the indicated number of carbon atoms attached through a sulphur bridge (e.g., methylthio and ethylthio).
- [0046] The term "arylthio" represents an aryl group as defined above attached through a sulphur bridge (e.g., benzenthio and naphthylthio).
- 10 [0047] The term "hetarylthio" represents a hetaryl group as defined above attached through a sulphur bridge (e.g., pyridine-2-thiol and thiazole-2-thiol).
- [0048] The term "arylthioalkyl" represents an arylthio group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., methylsulfanyl benzene, and ethylsulfanyl naphthalene).
- 15 [0049] The term "hetarylthioalkyl" represents a hetarylthio group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., 2-methylsulfanyl-pyridine and 1-ethylsulfanyl-isoquinoline).
- [0050] The term "hetaryloxyaryl" represents a hetaryloxy group as defined above attached through an aryl group as defined above (e.g., 1-phenoxy-isoquinolyl and 2-phenoxy-pyridyl).
- 20 [0051] The term "hetaryloxyhetaryl" represents a hetaryloxy group as defined above attached through a hetaryl group as defined above (e.g., 1-(2-pyridyloxy-isoquinoline) and 2-(imidazol-2-yloxy-pyridine)).
- [0052] The term "aryloxyalkyl" represents an aryloxy group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., phoxymethyl and naphthyloxyethyl).
- 25 [0053] The term "aryloxyaryl" represents an aryloxy group as defined above attached through an aryl group as defined above (e.g., 1-phenoxy-naphthalene and phenyloxy-phenyl).
- 30 [0054] The term "arylalkyloxyalkyl" represents an arylalkyloxy group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., ethoxymethyl-benzene and 2-methoxymethyl-naphthalene).
- [0055] The term "hetaryloxyalkyl" represents a hetaryloxy group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., 2-pyridyloxymethyl and 2-quinolyloxyethyl).
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[0056] The term "hetarylalkyloxyalkyl" represents a hetarylalkyloxy group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., 4-methoxymethyl-pyrimidine and 2-methoxymethyl-quinoline).

5 [0057] The term "alkylcarbonyl" represents an alkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group (e.g., octylcarbonyl, pentylcarbonyl, and 3-hexenylcarbonyl).

[0058] The term "arylcarbonyl" represents an aryl group as defined above attached through a carbonyl group (e.g., benzoyl).

10 [0059] The term "hetarylcarbonyl" represents a hetaryl group as defined above attached through a carbonyl group (e.g., 2-thiophenylcarbonyl, 3-methoxy-anthrylcarbonyl, and oxazolylcarbonyl).

[0060] The term "carbonylalkyl" represents a carbonyl group attached through an alkyl group having the indicated number of carbon atoms (e.g., acetyl).

15 [0061] The term "alkylcarbonylalkyl" represents an alkylcarbonyl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., propan-2-one and 4,4-dimethyl-pentan-2-one).

[0062] The term "arylcarbonylalkyl" represents a arylcarbonyl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., 1-phenylpropan-1-one and 1-(3-chloro-phenyl)-2-methyl-butan-1-one).

20 [0063] The term "hetarylcarbonylalkyl" represents a hetarylcarbonyl group as defined above attached through an alkyl group having the indicated number of carbon atoms (e.g., 1-pyridin-2-yl-propan-1-one and 1-(1-*H*-imidazol-2-yl)-propan-1-one).

[0064] The term "arylalkylcarbonyl" represents an arylalkyl group as defined above having the indicated number of carbon atoms attached through a carbonyl group (e.g., phenylpropylcarbonyl and phenylethylcarbonyl).

25 [0065] The term "hetarylalkylcarbonyl" represents a hetarylalkyl group as defined above wherein the alkyl group is in turn attached through a carbonyl (e.g., imidazolylpentylcarbonyl).

[0066] The term "alkylcarbonylamino" represents an "alkylcarbonyl" group as defined above wherein the carbonyl is in turn attached through the nitrogen atom of an amino group (e.g., methylcarbonylamino, cyclopentylcarbonyl-aminomethyl, and methylcarbonylaminophenyl). The nitrogen atom may itself be substituted with an alkyl or aryl group.

30 [0067] The term "alkylcarbonylaminoalkyl" represents an "alkylcarbonylamino" group attached through an alkyl group having the indicated number of carbon atoms (e.g. N-propylacetamide and N-butyl-propionamide).

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[0068] The term "arylalkylcarbonylamino" represents an "arylalkylcarbonyl" group as defined above attached through an amino group (e.g., phenylacetamide and 3-phenyl-propionamide).

5 [0069] The term "arylalkylcarbonylaminoalkyl" represents an "arylalkylcarbonylamino" group attached through an alkyl group having the indicated number of carbon atoms (e.g., N-ethyl-phenylacetamide and N-butyl-3-phenyl-propionamide).

[0070] The term "arylcarbonylamino" represents an "arylcarbonyl" group as defined above attached through an amino group (e.g., benzamide and naphthalene-1-carboxylic acid amide).

10 [0071] The term "arylcarbonylaminoalkyl" represents an "arylcarbonylamino" group attached through an alkyl group having the indicated number of carbon atoms (e.g., N-propyl-benzamide and N-Butyl-naphthalene-1-carboxylic acid amide).

[0072] The term "alkylcarboxy" represents an alkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge (e.g., heptylcarboxy, cyclopropyl-carboxy, and 3-pentenylcarboxy).

[0073] The term "arylcarboxy" represents an arylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge (e.g., benzoic acid).

20 [0074] The term "alkylcarboxyalkyl" represents an alkylcarboxy group as defined above wherein the oxygen is attached via an alkyl bridge (e.g., heptylcarboxymethyl, propylcarboxy *tert*-butyl, and 3-pentylcarboxyethyl).

[0075] The term "arylalkylcarboxy" represents an arylalkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge (e.g., benzylcarboxy and phenylpropylcarboxy).

25 [0076] The term "arylalkylcarboxyalkyl" represents an arylalkylcarboxy group as defined above wherein the carboxy group is in turn attached through an alkyl group having the indicated number of carbon atoms (e.g., benzylcarboxymethyl and phenylpropylcarboxypropyl).

[0077] The term "hetarylcarboxy" represents a hetarylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge (e.g., pyridine-2-carboxylic acid).

30 [0078] The term "hetarylalkylcarboxy" represents a hetarylalkylcarbonyl group as defined above wherein the carbonyl is in turn attached through an oxygen bridge (e.g., (1-*H*-imidazol-2-yl)-acetic acid and 3-pyrimidin-2-yl-propionic acid).

35 [0079] The term "alkylSO_m" represents an alkyl group having the number of indicated carbon atoms, wherein the alkyl group is in turn attached through a sulphur bridge wherein the sulphur is substituted with *m* oxygen atoms (e.g., ethylsulfonyl and ethylsulfiny).

[0080] The term "aryISO_m" represents an aryl group as defined above, wherein the aryl group is in turn attached through a sulphur bridge wherein the sulphur is substituted with m oxygen atoms (e.g., phenylsulfinyl and naphthyl-2-sulfonyl).

5 [0081] The term "hetaryISO_m" represents a hetaryl group as defined above, wherein the hetaryl group is in turn attached through a sulphur bridge wherein the sulphur is substituted with m oxygen atoms (e.g., thiazol-2-sulfinyl and pyridine-2-sulfonyl).

[0082] Certain of the above defined terms may occur more than once in the structural formulae, and upon such occurrence each term shall be defined independently of the other.

10 [0083] The term "optionally substituted" as used herein means that the groups in question are either unsubstituted or substituted with one or more of the substituents specified. When the groups in question are substituted with more than one substituent, the substituents may be the same or different.

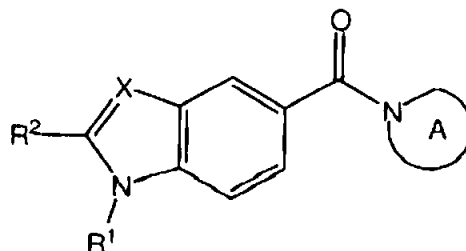
[0084] The term "treatment" or "treating" is defined as the management and care of a patient for the purpose of combating or alleviating the disease, condition, or disorder, and the term
15 includes the administration of the active compound to prevent or delay the onset of the symptoms or complications; alleviating (both temporary and permanent) the symptoms or complications; and/or eliminating the disease, condition, or disorder. Thus, "treatment" or "treating" includes prevention and/or prophylaxis of the disease, condition, or disorder.

20 [0085] The term "pharmaceutically acceptable" is defined as being suitable for administration to humans without adverse events.

[0086] The term "prodrug" is defined as a chemically modified form of the active drug, said prodrug being administered to the patient and subsequently being converted to the active drug. Techniques for development of prodrugs are well known in the art.

25 DETAILED DESCRIPTION OF THE INVENTION

[0087] [1] Thus in an embodiment, the present invention provides for the novel use of a substituted amide, a prodrug thereof, or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture or any tautomeric forms, wherein the substituted amide or a prodrug thereof is of formula I:



[0088] wherein:

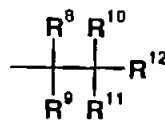
[0089] X is selected from CR⁵ and nitrogen;

5

[0090] R¹ is selected from H and C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

[0091] R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

10



[0092] alternatively, R¹ and R² are, independently,

[0093] Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

15

[0094] Ring A is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

20

[0095] R⁵ is selected from hydrogen, C₁-C₆alkyl, -C(=O)R¹³, and cyano;

[0096] R⁶ is selected from cyano, C₃-C₁₀cycloalkyl, 3-10 membered hetcycloalkyl, aryl, hetaryl, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸F¹⁹, -C(=NR¹⁵)NR¹⁵, -N(R¹⁸)C(=O)R¹³, -N(R¹⁸)C(=O)-C₃-C₁₀cycloalkyl, -N(R¹⁸)C(=O)-3-10 membered hetcycloalkyl, -N(R¹⁸)C(=O)-aryl, -N(R¹⁸)C(=O)-hetaryl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R¹⁶;

25

[0097] R⁷ is selected from halo, hydroxy, oxo, cyano, and C₁-C₆alkyl;

30

[0098] R⁸, R⁹, R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁-C₆alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C₁-C₆alkyloxy, wherein the C₁-C₆alkyl and C₁-C₆alkyloxy are substituted with 0-3 R¹⁷;

[0099] alternatively, R^8 and R^9 together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_3 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

[00100] alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

[00101] alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy, and hetaryl C_1 - C_6 alkyloxy;

[00102] R^{12} is selected from H, OH, $NR^{18}R^{19}$, C_3 - C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, and $-C(=NR^{15})NR^{16}$; wherein the cycloalkyl and heterocycloalkyl groups are substituted with 0-3 R^{17} ;

[00103] R^{13} is selected from OH, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, C_1 - C_8 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

[00104] R^{14} is selected from halo, hydroxy, oxo, and cyano;

[00105] R^{15} and R^{16} are independently selected from H, C_1 - C_8 alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R^{20} ;

23

[00106] R^{17} is selected from halo, OH, oxo, nitro, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $NR^{18}R^{19}$, C_1-C_8 alkyl, C_1-C_6 alkyloxy, and aryloxy;

5 [00107] R^{18} and R^{19} are independently selected from H, C_1-C_8 alkyl, C_1-C_6 alkyloxy, aryl, hetaryl, aryl- C_1-C_6 alkylene, and hetaryl- C_1-C_6 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R^{20} ;

10 [00108] alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1-C_8 alkyl, aryl, hetaryl, aryl- C_1-C_6 alkylene, hetaryl- C_1-C_6 alkylene, hydroxy, oxo, C_1-C_6 alkyloxy, aryl- C_1-C_6 alkyloxy, hetaryl- C_1-C_6 alkyloxy, C_1-C_6 alkyloxy- C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, arylcarbonyl, hetarylcarbonyl, aryl- C_1-C_6 alkylcarbonyl, hetaryl- C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarboxy, arylcarboxy, 15 hetarylcarboxy, aryl- C_1-C_6 alkyl-carboxy, and hetaryl- C_1-C_6 alkylcarboxy;

[00109] R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkyloxy, $NR^{21}R^{22}$, methylenedioxy, dihalomethylenedioxy, trihalomethyl, and trihalomethyloxy;

20 [00110] R^{21} and R^{22} are independently selected from H, C_1-C_8 alkyl, and aryl- C_1-C_6 alkyl;

[00111] R^{23} is selected from H and C_1-C_6 alkyl;

25 [00112] n is selected from 0, 1, and 2;

[00113] Y is selected from O and S;

30 [00114] or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

[00115] [2] In another embodiment, the present invention provides the novel use of compounds of formula I, wherein:

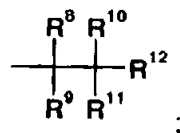
zh

[00116] R^1 is selected from H and C_1 - C_4 alkyl- R^6 , wherein the alkyl group is substituted with 0-1 R^7 ;

[00117] R^2 is selected from hydrogen, C_1 - C_6 alkyl, and $-C(=O)R^{13}$;

5

[00118] alternatively, R^1 and R^2 are, independently,



[00119] Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen and 7-10 carbon atoms;

10

[00120] Ring A is substituted with 0-3 groups selected from C_1 - C_4 alkyl, halo, hydroxy, and C_1 - C_6 alkyloxy;

[00121] R^5 is selected from hydrogen and C_1 - C_4 alkyl;

15

[00122] R^6 is selected from cyano, C_3 - C_6 cycloalkyl, 3-6 membered hetcycloalkyl, aryl, hetaryl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$, $-C(=NR^{15})NR^{15}$, $-N(R^{18})C(=O)R^{13}$, $-N(R^{18})C(=O)-C_3$ - C_6 cycloalkyl, $-N(R^{18})C(=O)$ -3-6 membered hetcycloalkyl, $-N(R^{18})C(=O)$ -aryl, $-N(R^{18})C(=O)$ -hetaryl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R^{18} ;

20

[00123] R^7 is selected from halo and C_1 - C_4 alkyl;

[00124] R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen and C_1 - C_4 alkyl;

25

[00125] alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms and 1-4 additional carbon atoms, wherein this ring is substituted with 0-1 groups selected from halo, trihalomethyl, hydroxyl, and C_1 - C_6 alkyl;

30

[00126] R^{12} is selected from H, OH, and $NR^{18}R^{19}$;

29

[00127] R^{13} is selected from OH, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, C_1 - C_4 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

5 [00128] R^{15} and R^{16} are independently selected from H, C_1 - C_4 alkyl, 3-6 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-1 R^{20} ;

10 [00129] R^{18} and R^{19} are independently selected from H, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, aryl, hetaryl, aryl C_1 - C_4 alkylene, and hetaryl C_1 - C_4 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-1 R^{20} ;

15 [00130] alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-5 carbon atoms, and 0-1 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-1 C_1 - C_4 alkyl, aryl, hetaryl, aryl C_1 - C_4 alkylene, hetaryl C_1 - C_4 alkylene, hydroxy, and C_1 - C_4 alkyloxy;

20 [00131] R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, $NR^{21}R^{22}$, trihalomethyl, and trihalomethoxy;

[00132] R^{21} and R^{22} are independently selected from H, C_1 - C_4 alkyl, and aryl C_1 - C_4 alkyl;

[00133] R^{23} is selected from H and C_1 - C_6 alkyl;

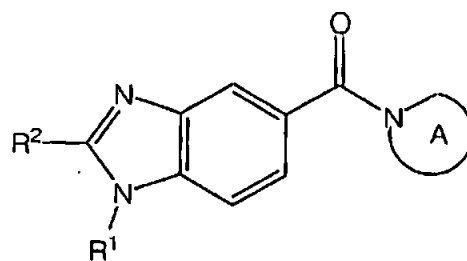
25 [00134] n is selected from 0, 1, and 2; and,

[00135] Y is selected from O and S.

30 [00136] [3] In another embodiment, the present invention provides the novel use of compounds wherein the substituted amide or prodrug thereof is of formula IA:

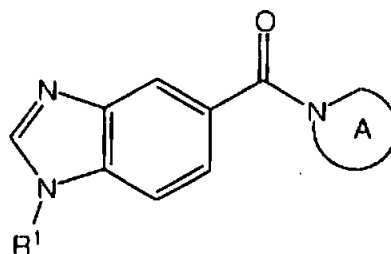
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16



IA.

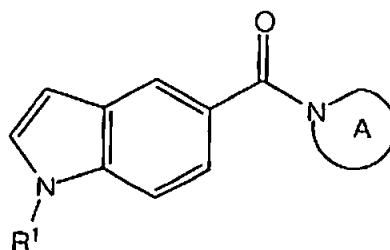
- 5 [00137] [4] In another embodiment, the present invention provides the novel use of compounds wherein the substituted amide or prodrug thereof is of formula IB:



IB.

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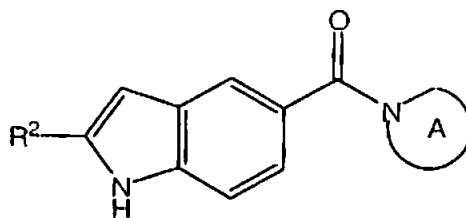
- [00138] [5] In another embodiment, the present invention provides the novel use of compounds wherein the substituted amide or prodrug thereof is of formula IC:



IC.

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[00139] [6] In another embodiment, the present invention provides the novel use of compounds wherein the substituted amide or prodrug thereof is of formula ID:

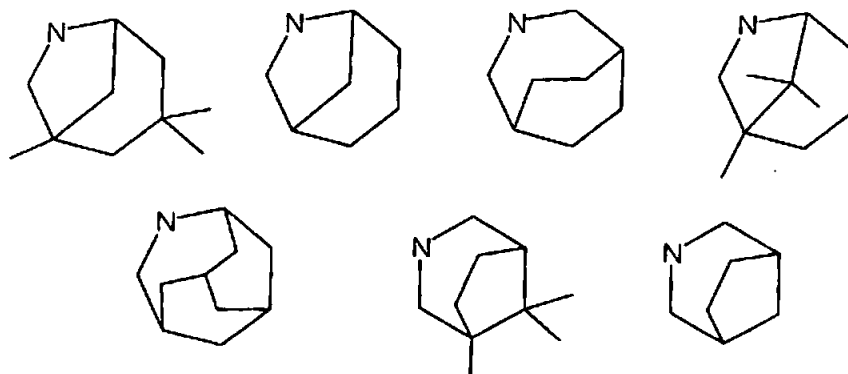


ID.

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[00140] [7] In another embodiment, the present invention provides the novel use of compounds of formula I, wherein:

10 [00141] Ring A is selected from:

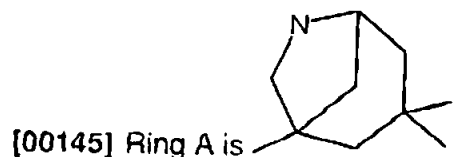


[00142] Ring A is substituted with 0-2 R^{24} ; and,

15 [00143] R^{24} is selected from C_1 - C_8 alkyl, halo, hydroxy, oxo, cyano, and C_1 - C_6 alkyloxy.

[00144] [8] In another embodiment, the present invention provides the novel use of compounds of formula I, wherein:

20



[00145] Ring A is

[00146] [9] In another embodiment, the present invention provides the novel use of compounds of formula I, wherein the substituted amide or a prodrug thereof is of the selected from the group:

5

- 1 Furan-2-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-1 1-Acetyl-piperidine-4-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-2 2-Methoxy-*N*-{2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide
- 1-3 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-isonicotinamide
- 1-4 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide
- 1-5 {2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-carbamic acid *tert*-butyl ester
- 1-6 Isoxazole-5-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-7 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-benzamide
- 2 3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
- 3 3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid
- 4 2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
- 5 2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
- 5-1 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
- 5-2 2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
- 5-3 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-

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- benzimidazol-1-yl]-propionic acid
- 5-4 2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
- 6 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 7 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-1 [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid *tert*-butyl ester
- 7-2 [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid
- 7-3 1-Morpholin-4-yl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propan-1-one
- 7-4 1-Morpholin-4-yl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-ethanone
- 7-5 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 7-6 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-7 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid methyl ester
- 7-8 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid methyl ester
- 7-9 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid
- 7-10 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-11 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 7-12 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester
- 7-13 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 7-14 3-[5-(4-Aza-tricyclo[4.3.1.1^{3,8}]*undecane-4-carbonyl)-indol-1-yl]-propionic

30

- acid ethyl ester
- 7-15 3-[5-(4-Aza-tricyclo[4.3.1.1*3,8*]undecane-4-carbonyl)-indol-1-yl]-propionic acid
- 8 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid ethyl ester
- 9 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid
- N*-Methoxy-*N*-methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- N*-Ethoxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- N*-Hydroxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- {1-[2-(2*H*-Tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- N*-(1*H*-Tetrazol-5-yl)-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- {1-[2-(2-Methyl-2*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(1-Methyl-1*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

[00147] or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 5 [00148] [10] In another embodiment, the present invention provides for the novel preparation of a pharmaceutical composition for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

[00149] [11] In another embodiment, the present invention provides for the novel preparation of a pharmaceutical composition, wherein: the conditions, disorders, and diseases that are influenced by intracellular glucocorticoid levels.

5 [00150] [12] In another embodiment, the present invention provides for the novel preparation of a pharmaceutical composition, wherein: the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), the progression from IGT to type 2 diabetes, the progression of the metabolic syndrome into type 2
10 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

[00151] [13] In another embodiment, the present invention provides for the novel preparation of a pharmaceutical composition, wherein: the pharmaceutical composition is
15 suitable for a route of administration selected from oral, nasal, buccal, transdermal, pulmonary, and parenteral.

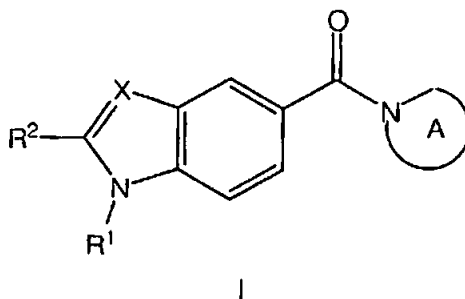
[00152] [14] In another embodiment, the present invention provides a novel method for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the
20 activity of 11 β HSD1 is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound of the present invention.

[00153] [15] In another embodiment, the present invention provides a novel method wherein the conditions, disorders, and diseases that are influenced by intracellular glucocorticoid
25 levels.

[00154] [16] In another embodiment, the present invention provides a novel method wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance
30 (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

[00155] [17] In another embodiment, the present invention provides a novel method wherein the administering is via a route selected from oral, nasal, buccal, transdermal, pulmonary, and parenteral.

- 5 [00156] [18] In another embodiment, the present invention provides for a novel compound of formula I:



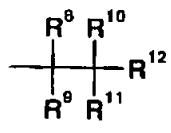
[00157] wherein:

[00158] X is selected from CR⁵ and nitrogen;

[00159] R¹ is selected from H and C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

[00160] R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

[00161] alternatively, R¹ and R² are, independently,



20 [00162] Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

25 [00163] Ring A is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

[00164] R⁵ is selected from hydrogen, C₁-C₆alkyl, -C(=O)R¹³, and cyano;

[00165] R^8 is selected from cyano, C_3 - C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, aryl, heteraryl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{13}R^{19}$, $-C(=NR^{15})NR^{15}$, $-N(R^{18})C(=O)R^{13}$, $-N(R^{18})C(=O)-C_3$ - C_{10} cycloalkyl, $-N(R^{18})C(=O)$ -3-10 membered heterocycloalkyl, $-N(R^{18})C(=O)$ -aryl, $-N(R^{18})C(=O)$ -heteraryl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteraryl groups are substituted with 0-3 R^{16} ;

[00166] R^7 is selected from halo, hydroxy, oxo, cyano, and C_1 - C_8 alkyl;

[00167] R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen, C_1 - C_6 alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C_1 - C_6 alkyloxy, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkyloxy are substituted with 0-3 R^{17} ;

[00168] alternatively, R^8 and R^9 together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, heteraryl, aryl- C_6 alkylene, heteraryl- C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl- C_6 alkyloxy or heteraryl- C_6 alkyloxy;

[00169] alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, heteraryl, aryl- C_6 alkylene, heteraryl- C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl- C_6 alkyloxy or heteraryl- C_6 alkyloxy;

[00170] alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, heteraryl, aryl- C_6 alkylene, heteraryl- C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl- C_6 alkyloxy, and heteraryl- C_6 alkyloxy;

[00171] R^{12} is selected from H, OH, $NR^{18}R^{19}$, C_3 - C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, and $-C(=NR^{15})NR^{16}$; wherein the cycloalkyl and heterocycloalkyl groups are substituted with 0-3 R^{17} ;

- 5 [00172] R^{13} is selected from OH, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, C_1 - C_8 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, heteroaryloxy, and $NR^{18}R^{19}$;

[00173] R^{14} is selected from halo, hydroxy, oxo, and cyano;

- 10 [00174] R^{15} and R^{16} are independently selected from H, C_1 - C_8 alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R^{20} ;

- [00175] R^{17} is selected from halo, OH, oxo, nitro, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$,
15 $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $NR^{18}R^{19}$, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, and aryloxy;

[00176] R^{18} and R^{19} are independently selected from H, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, aryl, hetaryl, aryl C_1 - C_6 alkylene, and heteroaryl C_1 - C_6 alkylene, wherein the alkyl/alkylene, aryl, and heteroaryl groups are independently substituted with 0-3 R^{20} ;

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- [00177] alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1 - C_8 alkyl, aryl, hetaryl,
25 aryl C_1 - C_6 alkylene, heteroaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_8 alkyloxy, aryl C_1 - C_6 alkyloxy, heteroaryl C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, arylcarbonyl, heteroarylcarbonyl, aryl C_1 - C_6 alkylcarbonyl, heteroaryl C_1 - C_6 alkylcarbonyl, C_1 - C_6 alkylcarboxy, arylcarboxy, heteroarylcarboxy, aryl C_1 - C_6 alkyl-carboxy, and heteroaryl C_1 - C_6 alkylcarboxy;

- 30 [00178] R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, $NR^{21}R^{22}$, methylenedioxy, dihalomethylenedioxy, trihalomethyl, and trihalomethyloxy;

[00179] R^{21} and R^{22} are independently selected from H, C_1 - C_8 alkyl, and aryl C_1 - C_6 alkyl;

- 35 [00180] R^{23} is selected from H and C_1 - C_8 alkyl;

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[00181] n is selected from 0, 1, and 2;

[00182] Y is selected from O and S;

5

[00183] or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

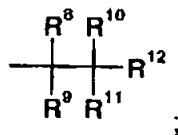
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[00184] [19] In another embodiment, the present invention provides the novel compound of formula I, wherein:

[00185] R¹ is selected from H and C₁-C₄alkyl-R⁶, wherein the alkyl group is substituted with 0-1 R⁷;

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[00186] R² is selected from hydrogen, C₁-C₆alkyl, and -C(=O)R¹³;



[00187] alternatively, R¹ and R² are, independently,

20

[00188] Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen and 7-10 carbon atoms;

[00189] Ring A is substituted with 0-3 groups selected from C₁-C₄alkyl, halo, hydroxy, and C₁-C₆alkoxy;

25

[00190] R⁵ is selected from hydrogen and C₁-C₄alkyl;

30

[00191] R⁶ is selected from cyano, C₃-C₆cycloalkyl, 3-6 membered hetcycloalkyl, aryl, hetaryl, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸R¹⁹, -C(=NR¹⁵)NR¹⁵, -N(R¹⁸)C(=O)R¹³, -N(R¹⁸)C(=O)-C₃-C₅cycloalkyl, -N(R¹⁸)C(=O)-3-6 membered hetcycloalkyl, -N(R¹⁸)C(=O)-aryl, -N(R¹⁸)C(=O)-hetaryl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R¹⁸;

[00192] R⁷ is selected from halo and C₁-C₄alkyl;

36

[00193] R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen and C_1 - C_4 alkyl;

5 [00194] alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms and 1-4 additional carbon atoms, wherein this ring is substituted with 0-1 groups selected from halo, trihalomethyl, hydroxyl, and C_1 - C_6 alkyl;

10 [00195] R^{12} is selected from H, OH, and $NR^{18}R^{19}$;

[00196] R^{13} is selected from OH, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, C_1 - C_4 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

15 [00197] R^{15} and R^{16} are independently selected from H, C_1 - C_4 alkyl, 3-6 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-1 R^{20} ;

20 [00198] R^{18} and R^{19} are independently selected from H, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, aryl, hetaryl, aryl C_1 - C_4 alkylene, and hetaryl C_1 - C_4 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-1 R^{20} ;

25 [00199] alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-5 carbon atoms, and 0-1 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-1 C_1 - C_4 alkyl, aryl, hetaryl, aryl C_1 - C_4 alkylene, hetaryl C_1 - C_4 alkylene, hydroxy, and C_1 - C_4 alkyloxy;

30 [00200] R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, $NR^{21}R^{22}$, trihalomethyl, and trihalomethyloxy;

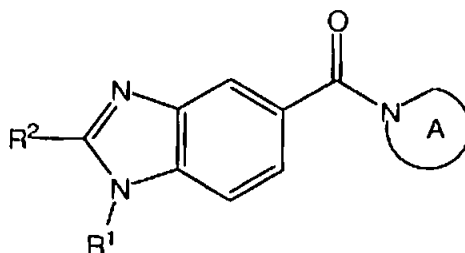
[00201] R^{21} and R^{22} are independently selected from H, C_1 - C_4 alkyl, and aryl C_1 - C_4 alkyl;

[00202] R^{23} is selected from H and C_1 - C_6 alkyl;

35 [00203] n is selected from 0, 1, and 2; and,

[00204] Y is selected from O and S.

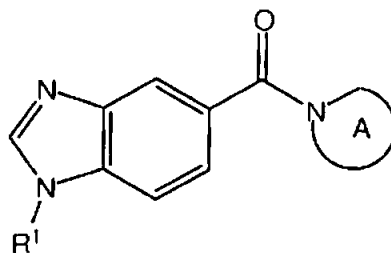
- 5 [00205] [20] In another embodiment, the present invention provides the novel compounds of formula IA:



IA.

10

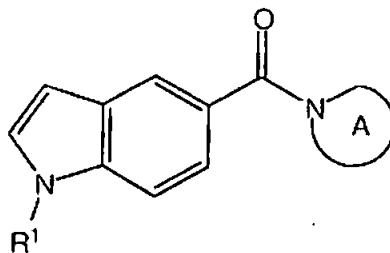
- [00206] [21] In another embodiment, the present invention provides the novel compounds of formula IB:



IB.

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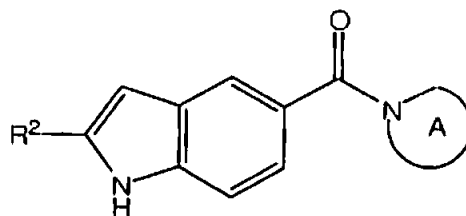
- [00207] [22] In another embodiment, the present invention provides the novel compounds of formula IC:



IC.

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[00208] [23] In another embodiment, the present invention provides the novel compounds of formula ID:

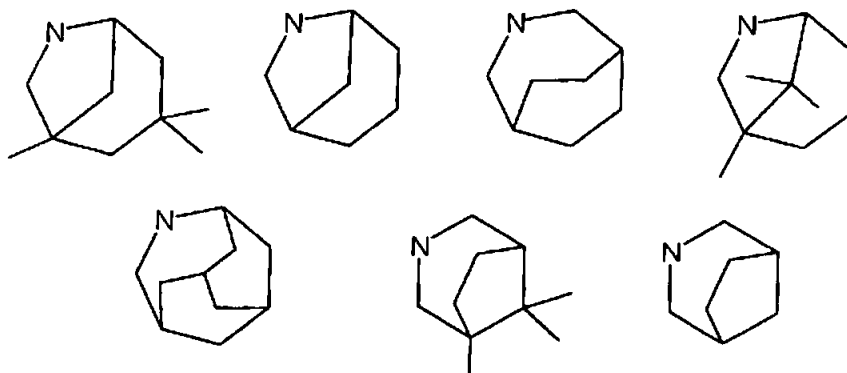


ID.

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[00209] [24] In another embodiment, the present invention provides the novel compounds of formula I, wherein:

10 [00210] Ring A is selected from:

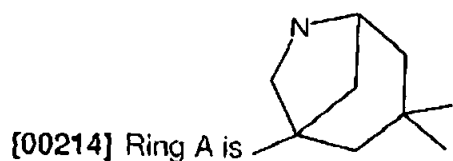


[00211] Ring A is substituted with 0-2 R^{24} ; and,

15 [00212] R^{24} is selected from C_1 - C_8 alkyl, halo, hydroxy, oxo, cyano, and C_1 - C_6 alkyloxy.

[00213] [25] In another embodiment, the present invention provides the novel compounds of formula I, wherein:

20



[00214] Ring A is

[00215] [26] In another embodiment, the present invention provides the novel compounds of formula I, selected from the group:

- 1 Furan-2-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-1 1-Acetyl-piperidine-4-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-2 2-Methoxy-*N*-{2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide
- 1-3 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-isonicotinamide
- 1-4 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide
- 1-5 {2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-carbamic acid *tert*-butyl ester
- 1-6 Isoxazole-5-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
- 1-7 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-benzamide
- 2 3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
- 3 3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid
- 4 2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
- 5 2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
- 5-1 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
- 5-2 2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
- 5-3 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid

MD

- 5-4 2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
- 6 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 7 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-1 [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid *tert*-butyl ester
- 7-2 [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid
- 7-3 1-Morpholin-4-yl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propan-1-one
- 7-4 1-Morpholin-4-yl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-ethanone
- 7-5 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 7-6 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-7 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid methyl ester
- 7-8 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid methyl ester
- 7-9 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid
- 7-10 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 7-11 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 7-12 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester
- 7-13 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 7-14 3-[5-(4-Aza-bicyclo[4.3.1.1*3,8*]undecane-4-carbonyl)-indol-1-yl]-propionic acid ethyl ester

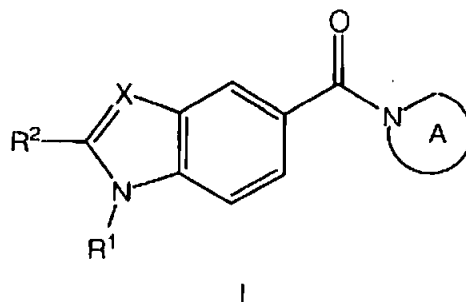
- 7-15 3-[5-(4-Aza-tricyclo[4.3.1.1*3,8*]undecane-4-carbonyl)-indol-1-yl]-propionic acid
- 8 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid ethyl ester
- 9 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid
- N*-Methoxy-*N*-methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- N*-Ethoxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- N*-Hydroxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- {1-[2-(2*H*-Tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- N*-(1*H*-Tetrazol-5-yl)-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- {1-[2-(2-Methyl-2*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(1-Methyl-1*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone
- {1-[2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

[00216] or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

- 5 [00217] In another embodiment, the present invention provides for a novel compound of formula I:

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sil



wherein:

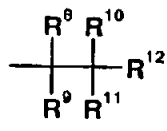
5 X is selected from CR⁵ and nitrogen;

R¹ is selected from C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

10

alternatively, R¹ and R² are, independently,



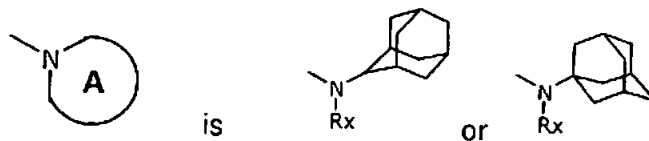
Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

15

Ring A is substituted with 0-3 groups selected from C₁-C₈alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

20

alternatively,



wherein Rx is selected from hydrogen and C₁-C₆alkyl;

25



is substituted with 0-3 groups selected from C₁-C₈alkyl, halo, hydroxy, -COOH,

43

-CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

5 R⁵ is selected from hydrogen, C₁-C₆alkyl, -C(=O)R¹³, and cyano;

R⁸ is selected from cyano, aryl, hetaryl, -oxoC₁-C₆alkyl-S(=O)_nR¹³, -C(=O)R¹³, -S(=O)_rR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸R¹⁹, -C(=NR¹⁵)NR¹⁵,
 10 -N(R¹⁶)C(=O)R¹³, -N(R¹⁶)C(=O)-C₃-C₁₀cycloalkyl, -N(R¹⁶)C(=O)-3-10 membered hetcycloalkyl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R¹⁵;

R⁷ is selected from C₁-C₆alkyl, halo, hydroxy, oxo and cyano;

15 R⁶, R⁹, R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁-C₆alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C₁-C₆alkyloxy, wherein the C₁-C₆alkyl and C₁-C₆alkyloxy are substituted with 0-3 R¹⁷;

alternatively, R⁸ and R⁹ together with the carbon atom to which they are attached form a
 20 saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy or hetarylC₁-C₆alkyloxy;

25 alternatively, R¹⁰ and R¹¹ together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy,
 30 oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy or hetarylC₁-C₆alkyloxy;

alternatively, R⁸ and R¹⁰ together with the two carbon atoms to which they are attached form
 35 a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and

sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy, and hetarylC₁-C₆alkyloxy;

- 5 R¹² is selected from H, OH, NR¹⁸R¹⁹, C₃-C₁₀cycloalkyl, 3-10 membered hetcycloalkyl, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, and -C(=NR¹⁵)NR¹⁶; wherein the cycloalkyl and hetcycloalkyl groups are substituted with 0-3 R¹⁷;

- 10 R¹³ is selected from OH, C₁-C₈alkyl, C₁-C₈alkyloxy, C₁-C₈alkyloxyC₁-C₄alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and NR¹⁸R¹⁹;

R¹⁴ is selected from halo, hydroxy, oxo, and cyano;

- 15 R¹⁵ and R¹⁶ are independently selected from H, C₁-C₈alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, -C(=O)R¹³, -S(=O)_nR¹³, S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R²⁰;

- 20 R¹⁷ is selected from halo, OH, oxo, nitro, cyano, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, NR¹⁸R¹⁹, C₁-C₈alkyl, C₁-C₈alkyloxy, and aryloxy;

R¹⁸ and R¹⁹ are independently selected from H, C₁-C₈alkyl, C₁-C₈alkyloxy, aryl, hetaryl, arylC₁-C₆alkylene, and hetarylC₁-C₆alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R²⁰;

- 25 alternatively, R¹⁸ and R¹⁹, together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C₁-C₈alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, arylC₁-C₆alkyloxy, hetarylC₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkyl, C₁-C₆alkylcarbonyl, arylcarbonyl, hetarylcarbonyl, arylC₁-C₆alkylcarbonyl, hetarylC₁-C₆alkylcarbonyl, C₁-C₆alkylcarboxy, arylcarboxy, hetarylcarboxy, arylC₁-C₆alkyl-carboxy, and hetarylC₁-C₆alkylcarboxy;
- 30

R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, $NR^{21}R^{22}$, methylendioxo, dihalomethylendioxo, trihalomethyl, and trihalomethyloxy;

R^{21} and R^{22} are independently selected from H, C_1 - C_6 alkyl, and aryl C_1 - C_6 alkyl;

5

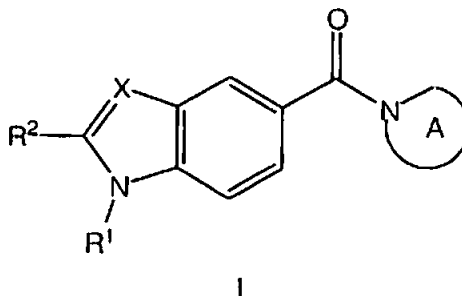
R^{23} is selected from H and C_1 - C_6 alkyl;

n is selected from 0, 1, and 2;

10 Y is selected from O and S;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

15 [00218] In another embodiment, the present invention provides for a novel compound of formula I:



wherein:

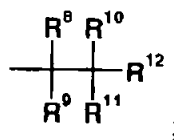
20

X is selected from CR^5 and nitrogen;

R^1 is selected from C_1 - C_6 alkyl- R^6 , wherein the alkyl group is substituted with 0-3 R^7 ;

25 R^2 is selected from hydrogen, halo, C_1 - C_6 alkyl, and $-C(=O)R^{13}$;

alternatively, R^1 and R^2 are, independently,



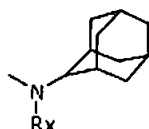
Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

- 5 Ring A is substituted with 0-3 groups selected from C_1 - C_6 alkyl, halo, hydroxy, $-COOH$, $-CONR^{16}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ oxo, cyano, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkylene, and C_1 - C_6 alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R^{14} ;

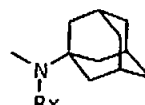
alternatively,



is



or



10

wherein R_x is selected from hydrogen and C_1 - C_6 alkyl;



is substituted with 0-3 groups selected from C_1 - C_6 alkyl, halo, hydroxy, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ oxo, cyano, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkylene, and C_1 - C_6 alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R^{14} ;

15

R^5 is selected from hydrogen, C_1 - C_6 alkyl, $-C(=O)R^{13}$, and cyano;

- 20 R^6 is selected from cyano, aryl, hetaryl, $-oxoC_1$ - C_6 alkyl- $S(=O)_nR^{13}$, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$, $-C(=NR^{15})NR^{15}$, $-N(R^{13})C(=O)R^{13}$, $-N(R^{18})C(=O)-C_3$ - C_{10} cycloalkyl, $-N(R^{18})C(=O)$ -3-10 membered heterocycloalkyl, wherein the cycloalkyl, heterocycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R^{16} ;

25

R^7 is selected from C_1 - C_6 alkyl, halo, hydroxy, oxo and cyano;

R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen, C_1 - C_6 alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C_1 - C_6 alkyloxy, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkyloxy are substituted with 0-3 R^{17} ;

30

alternatively, R^8 and R^9 together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy, and hetaryl C_1 - C_6 alkyloxy;

R^{12} is selected from H, OH, $NR^{18}R^{19}$, C_3 - C_{10} cycloalkyl, 3-10 membered hetcycloalkyl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, and $-C(=NR^{15})NR^{16}$; wherein the cycloalkyl and hetcycloalkyl groups are substituted with 0-3 R^{17} ;

R^{13} is selected from OH, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

R^{14} is selected from halo, hydroxy, oxo, and cyano;

R^{15} and R^{16} are independently selected from H, C_1 - C_6 alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R^{20} ;

R^{17} is selected from halo, OH, oxo, nitro, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$,

$-N(R^{18})S(=O)_nR^{13}$, $NR^{18}R^{19}$, C_1-C_8 alkyl, C_1-C_6 alkyloxy, and aryloxy;

R^{18} and R^{19} are independently selected from H, C_1-C_8 alkyl, C_1-C_6 alkyloxy, aryl, hetaryl, aryl- C_1-C_6 alkylene, and hetaryl- C_1-C_6 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R^{20} ;

alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1-C_8 alkyl, aryl, hetaryl, aryl- C_1-C_6 alkylene, hetaryl- C_1-C_6 alkylene, hydroxy, oxo, C_1-C_6 alkyloxy, aryl- C_1-C_6 alkyloxy, hetaryl- C_1-C_6 alkyloxy, C_1-C_6 alkyloxy- C_1-C_6 alkyl, C_1-C_6 alkylcarbonyl, arylcarbonyl, hetarylcarbonyl, aryl- C_1-C_6 alkylcarbonyl, hetaryl- C_1-C_6 alkylcarbonyl, C_1-C_6 alkylcarboxy, arylcarboxy, hetarylcarboxy, aryl- C_1-C_6 alkylcarboxy, and hetaryl- C_1-C_6 alkylcarboxy;

R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1-C_6 alkyl, C_1-C_6 alkyloxy, $NR^{21}R^{22}$, methylenedioxy, dihalomethylenedioxy, trihalomethyl, and trihalomethyloxy;

R^{21} and R^{22} are independently selected from H, C_1-C_8 alkyl, and aryl- C_1-C_6 alkyl;

R^{23} is selected from H and C_1-C_6 alkyl;

n is selected from 0, 1, and 2;

Y is selected from O and S;

provided that when X is CR^5 , then R^6 is $-C(=O)R^{13}$ wherein R^{13} is OH;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

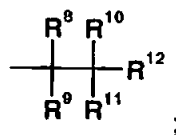
[00219] In another embodiment, the present invention provides for a novel compound of formula I, wherein:

X is selected from CR⁵ and nitrogen;

R¹ is selected from C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

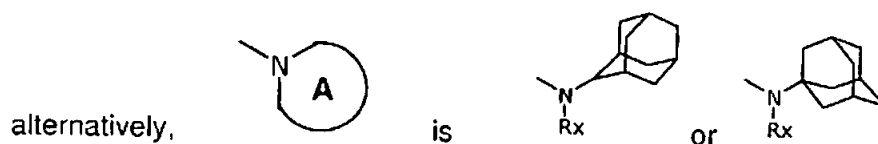
5 R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

alternatively, R¹ and R² are, independently,



10 Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

Ring A is substituted with 0-3 groups selected from C₁-C₈alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;



wherein Rx is selected from hydrogen and C₁-C₆alkyl;

20 is substituted with 0-3 groups selected from C₁-C₈alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

25 R⁵ is selected from hydrogen, C₁-C₆alkyl, -C(=O)R¹³, and cyano;

R⁶ is selected from cyano, aryl, hetaryl, -oxoC₁-C₆alkyl-S(=O)_nR¹³, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸R¹⁹, -C(=NR¹⁵)NR¹⁵,

$-N(R^{18})C(=O)R^{13}$, $-N(R^{18})C(=O)-C_3-C_{10}$ cycloalkyl, $-N(R^{18})C(=O)-3-10$ membered heterocycloalkyl, wherein the cycloalkyl, heterocycloalkyl, aryl, and heteraryl groups are substituted with 0-3 R^{16} ;

5 R^7 is selected from halo, hydroxy, oxo and cyano;

R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen, C_1-C_6 alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C_1-C_6 alkyloxy, wherein the C_1-C_6 alkyl and C_1-C_6 alkyloxy are substituted with 0-3 R^{17} ;

10

alternatively, R^8 and R^9 together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1-C_6 alkyl, aryl, heteraryl, aryl- C_1-C_6 alkylene, heteraryl- C_1-C_6 alkylene, hydroxy, 15 oxo, C_1-C_6 alkyloxy, aryloxy, aryl- C_1-C_6 alkyloxy or heteraryl- C_1-C_6 alkyloxy;

15

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1-C_6 alkyl, aryl, heteraryl, aryl- C_1-C_6 alkylene, heteraryl- C_1-C_6 alkylene, hydroxy, 20 oxo, C_1-C_6 alkyloxy, aryloxy, aryl- C_1-C_6 alkyloxy or heteraryl- C_1-C_6 alkyloxy;

20

alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1-C_6 alkyl, aryl, heteraryl, aryl- C_1-C_6 alkylene, heteraryl- C_1-C_6 alkylene, hydroxy, 25 oxo, C_1-C_6 alkyloxy, aryloxy, aryl- C_1-C_6 alkyloxy, and heteraryl- C_1-C_6 alkyloxy;

30

R^{12} is selected from H, OH, $NR^{18}R^{19}$, C_3-C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, and $-C(=NR^{15})NR^{16}$; wherein the cycloalkyl and heterocycloalkyl groups are substituted with 0-3 R^{17} ;

35

R^{13} is selected from OH, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, C_1 - C_8 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

R^{14} is selected from halo, hydroxy, oxo, and cyano;

5

R^{15} and R^{16} are independently selected from H, C_1 - C_8 alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R^{20} ;

10 R^{17} is selected from halo, OH, oxo, nitro, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $NR^{18}R^{19}$, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, and aryloxy;

R^{18} and R^{19} are independently selected from H, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, aryl, hetaryl, aryl C_1 - C_8 alkylene, and hetaryl C_1 - C_8 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R^{20} ;

15

alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from ni-

20 trogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1 - C_8 alkyl, aryl, hetaryl, aryl C_1 - C_8 alkylene, hetaryl C_1 - C_8 alkylene, hydroxy, oxo, C_1 - C_8 alkyloxy, aryl C_1 - C_8 alkyloxy, hetaryl C_1 - C_8 alkyloxy, C_1 - C_8 alkyloxy C_1 - C_8 alkyl, C_1 - C_8 alkylcarbonyl, arylcarbonyl, hetarylcarbonyl, aryl C_1 - C_8 alkylcarbonyl, hetaryl C_1 - C_8 alkylcarbonyl, C_1 - C_8 alkylcarboxy, arylcarboxy, hetarylcarboxy, aryl C_1 - C_8 alkylcarboxy, and hetaryl C_1 -

25 C_8 alkylcarboxy;

R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, $NR^{21}R^{22}$, methylenedioxy, dihalomethylenedioxy, trihalomethyl, and trihalomethyloxy;

30 R^{21} and R^{22} are independently selected from H, C_1 - C_8 alkyl, and aryl C_1 - C_8 alkyl;

R^{23} is selected from H and C_1 - C_8 alkyl;

n is selected from 0, 1, and 2;

35

Y is selected from O and S;

provided that when X is CR⁵, then R⁶ is -C(=O)R¹³ wherein R¹³ is OH;

- 5 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

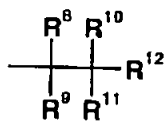
[00220] In another embodiment, the present invention provides for a novel compound of formula I, wherein

10

R¹ is C₁-C₄alkyl-R⁶, wherein the alkyl group is substituted with 0-1 R⁷;

R² is selected from hydrogen, C₁-C₆alkyl, and -C(=O)R¹³;

- 15 alternatively, R¹ and R² are, independently,



Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen and 7-10 carbon atoms;

- 20 Ring A is substituted with 0-3 groups selected from C₁-C₄alkyl, halo, hydroxy, oxo, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ and C₁-C₆alkyloxy;



- 25 wherein Rx is selected from hydrogen and C₁-C₆alkyl;



is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, -COOH,

-CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

5 R⁵ is selected from hydrogen and C₁-C₄alkyl;

R⁵ is selected from cyano, aryl, hetaryl, -oxoC₁-C₆alkyl-S(=O)_nR¹³, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸R¹⁹, -C(=NR¹⁵)NR¹⁵,
 10 -N(R¹⁸)C(=O)R¹³, -N(R¹⁸)C(=O)-C₃-C₆cycloalkyl, -N(R¹⁸)C(=O)-3-6 membered hetcycloalkyl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R¹⁶;

R⁷ is selected from halo;

15 R⁸, R⁹, R¹⁰ and R¹¹ are each independently selected from hydrogen and C₁-C₄alkyl;

alternatively, R⁸ and R¹⁰ together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms and 1-4 additional carbon atoms, wherein this ring is substituted with 0-1 groups selected
 20 from halo, trihalomethyl, hydroxyl, and C₁-C₆alkyl;

R¹² is selected from H, OH, and NR¹⁸R¹⁹;

25 R¹³ is selected from OH, C₁-C₄alkyl, C₁-C₄alkyloxy, C₁-C₄alkyloxyC₁-C₄alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and NR¹⁸R¹⁹;

R¹⁵ and R¹⁶ are independently selected from H, C₁-C₄alkyl, 3-6 membered cycloalkyl, halo, OH, cyano, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-1 R²⁰;

30 R¹⁸ and R¹⁹ are independently selected from H, C₁-C₄alkyl, C₁-C₄alkyloxy, aryl, hetaryl, arylC₁-C₄alkylene, and hetarylC₁-C₄alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-1 R²⁰;

alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-5 carbon atoms, and 0-1 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-1 C_1 - C_4 alkyl, aryl, hetaryl, aryl C_1 - C_4 alkylene, hetaryl C_1 - C_4 alkylene, hydroxy, and C_1 - C_4 alkyloxy;

R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_4 alkyl, C_1 - C_4 alkyloxy, $NR^{21}R^{22}$, trihalomethyl, and trihalomethyloxy;

R^{21} and R^{22} are independently selected from H, C_1 - C_4 alkyl, and aryl C_1 - C_4 alkyl;

R^{23} is selected from H and C_1 - C_5 alkyl;

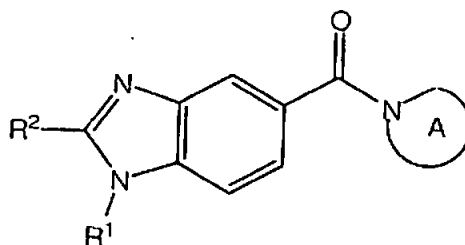
n is selected from 0, 1, and 2; and,

Y is selected from O and S;

provided that when X is CR^5 , then R^6 , is $-C(=O)R^{13}$ wherein R^{13} is OH;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

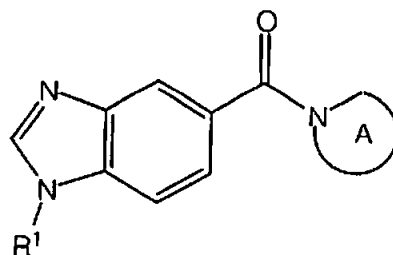
[00221] In another embodiment, the present invention provides for a novel compound of formula IA:



IA.

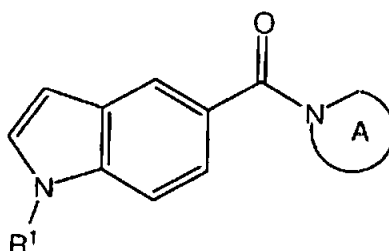
[00222] In another embodiment, the present invention provides for a novel compound of formula IB:

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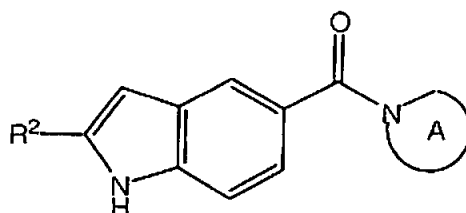
IB.

[00223] In another embodiment, the present invention provides for a novel compound of of
5 formula IC:



IC.

[00224] In another embodiment, the present invention provides for a novel compound of of
10 formula ID:



ID.

[00225] In another embodiment, the present invention provides for a novel compound of of
15 formula I wherein R^6 is selected from aryl, hetaryl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$, $-C(=NR^{15})NR^{15}$, $-N(R^{18})C(=O)$ -aryl, or $-N(R^{18})C(=O)$ -hetaryl, wherein the aryl, and hetaryl groups are substituted with 0-3 R^{16} .

[00226] In another embodiment, the present invention provides for a novel compound of of
20 formula I wherein R^6 is selected from aryl, hetaryl, $-oxoC_1-C_8alkyl-S(=O)_nR^{13}$, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$ or $-C(=NR^{15})NR^{15}$, wherein the aryl, and hetaryl groups are substituted with 0-3 R^{16} .

[00227] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^6 is selected from $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$ or $-C(=NR^{15})NR^{15}$.

5 [00228] In another embodiment, the present invention provides for a novel compound of formula I wherein R^6 is selected from $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, or $-N(R^{23})C(=Y)NR^{18}R^{19}$.

10 [00229] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^6 is selected from $-N(R^{23})C(=Y)NR^{18}R^{19}$.

[00230] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^7 is C_1 - C_6 alkyl.

15 [00231] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^7 is halo.

[00232] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^7 is hydroxy.

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[00233] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^7 is oxo.

25 [00234] In another embodiment, the present invention provides for a novel compound of formula I, wherein R^7 is cyano.

[00235] In another embodiment, the present invention provides for a novel compound of formula I, wherein Y is oxygen (O).

30 [00236] In another embodiment, the present invention provides for a novel compound of formula I, wherein

Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

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Ring A is substituted with 0-3 groups selected from C_1 - C_8 alkyl, halo, hydroxy, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ oxo, cyano, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkylene, and C_1 - C_6 alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R^{14} .

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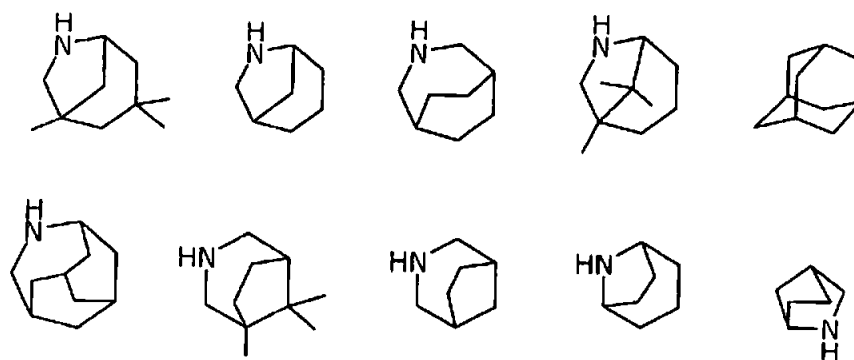
[00237] In another embodiment, the present invention provides for a novel compound of formula I, wherein

- 10 Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 1-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

Ring A is substituted with 0-3 groups selected from C_1 - C_4 alkyl, halo, hydroxy, oxo, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ and C_1 - C_6 alkyloxy.

15

[00238] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is selected from:



- 20 Ring A is substituted with 0-2 groups selected from C_1 - C_8 alkyl, halo, hydroxy, oxo, cyano, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ and C_1 - C_6 alkyloxy.

[00239] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is



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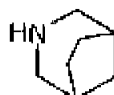
[00240] In another embodiment, the present invention provides for a novel compound of formula I wherein Ring A is



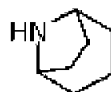
5 [00241] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is



10 [00242] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is



[00243] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is



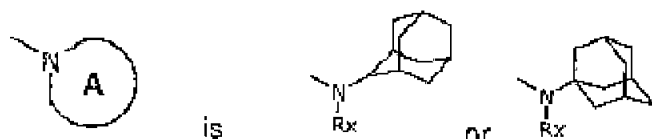
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[00244] In another embodiment, the present invention provides for a novel compound of formula I, wherein Ring A is

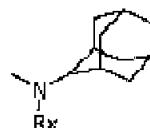


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[00245] In another embodiment, the present invention provides for a novel compound of formula I, wherein



is



Rx

or



Rx

wherein Rx is selected from hydrogen and C₁-C₆alkyl;

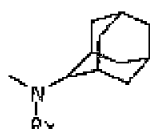


- 5 is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴.

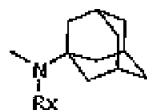
- 10 [00246] In another embodiment, the present invention provides for a novel compound of formula I, wherein



is



or



wherein Rx is selected from hydrogen and C₁-C₆alkyl;



- 15 is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, oxo, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ and C₁-C₆alkyloxy.

[00247] In another embodiment, the present invention provides for a novel compound, wherein the compound is of the selected from the group:

- 20 Furan-2-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
 1-Acetyl-piperidine-4-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide
 2-Methoxy-N-{2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide
 25 N-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-isonicotinamide
 N-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide

{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-ethyl}-
carbamic acid *tert*-butyl ester

Isoxazole-5-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-
benzimidazol-1-yl]-ethyl}-amide

5 *N*-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-ethyl}-
benzamide

3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-
propionic acid ethyl ester

10 3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-
propionic acid

2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-
cyclopropanecarboxylic acid ethyl ester

2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-
cyclopropanecarboxylic acid

15 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-
propionic acid ethyl ester

2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-
cyclopropanecarboxylic acid ethyl ester

20 3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-
propionic acid

2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-
cyclopropanecarboxylic acid

3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl
ester

25 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid

[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid *tert*-butyl
ester

[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid

30 1-Morpholin-4-yl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-
propan-1-one

1-Morpholin-4-yl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-
ethanone

2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-
propionic acid ethyl ester

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- 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid methyl ester
- 5 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid methyl ester
- 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid
- 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 10 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester
- 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 3-[5-(4-Aza-tricyclo[4.3.1.1^{3,8}]undecane-4-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 15 3-[5-(4-Aza-tricyclo[4.3.1.1^{3,8}]undecane-4-carbonyl)-indol-1-yl]-propionic acid
- 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-2-carboxylic acid ethyl ester
- 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-2-carboxylic acid
- [1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzoimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone
- 20 (3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1H-benzoimidazol-5-yl]-methanone
- trans*-1-(2-Methanesulfonyl-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- 25 *Cis*-1-(2-Methanesulfonyl-methoxy-ethyl)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- (3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1H-benzoimidazol-5-yl]-methanone
- 1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- 30 (3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-methanone
- (3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-methanone
- 35 [1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone

- 1-(2-Methanesulfonyl-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- (3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone
- 5 (Octahydro-quinolin-1-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone
- Trans-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- Cis-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- 10 3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- 4-Hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- 1-(2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl)-1H-benzimidazole-5-carboxylic acid
- 15 (5-hydroxy-adamantan-2-yl)-amide
- 1-(2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- 1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- Cis-1-[2-[(morpholine-4-carbonyl)-amino]-ethyl]-1H-benzo-imidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide
- Trans-1-[2-[(Morpholine-4-carbonyl)-amino]-ethyl]-1H-benzo-imidazole-5-carboxylic acid
- Cis-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- Trans-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo-[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- 1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- 3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide
- 1-(2-[5-(Octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethylcarbamoyl)-piperidine-4-carboxylic acid

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3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Cis-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Trans-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Endo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Exo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

1-{2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

1-{2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1-{2-[(3-Hydroxy-pyrrolidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Cis-1-{2-[5-(5-hydroxy-adamantan-2-ylcarbamoyl)-benzimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

Trans-1-{2-[5-(5-hydroxy-adamantan-2-ylcarbamoyl)-benzimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

1-{2-[5-(3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

N-Methoxy-*N*-methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

N-Ethoxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

5 *N*-Hydroxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

{1-{2-(2H-Tetrazol-5-yl)-ethyl}-1H-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

5 *N*-(1*H*-Tetrazol-5-yl)-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

{1-[2-(2-Methyl-2*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

10 {1-[2-(1-Methyl-1*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone;

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

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[00248] In another embodiment, the present invention provides for a novel compound of formula I, which is an agent useful for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

20 [00249] In another embodiment, the present invention provides for a use of a compound of formula I, for the preparation of a pharmaceutical composition for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

25 [00250] In another embodiment, the present invention provides for a use of a compound of formula I for the preparation of a pharmaceutical composition for the treatment of conditions, disorders, or diseases, wherein the conditions, disorders, and diseases are influenced by intracellular glucocorticoid levels.

30 [00251] In another embodiment, the present invention provides for a use of a compound of formula I for the preparation of a pharmaceutical composition for the treatment of conditions, disorders, or diseases, wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), the progression
35 from IGT to type 2 diabetes, the progression of the metabolic syndrome into type 2 diabetes,

diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

5 [00252] In another embodiment, the present invention provides for a method for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11β HSD1 is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound of formula I.

10 [00253] In another embodiment, the present invention provides for a method for the treatment of conditions, disorders or diseases, wherein the conditions, disorders, and diseases are influenced by intracellular glucocorticoid levels, the method comprising administering to a subject in need thereof an effective amount of a compound of formula I.

15 [00254] In another embodiment, the present invention provides for a method for the treatment of conditions, disorders or diseases, wherein the conditions, disorders or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

20 [00255] [27] In another embodiment, the present invention provides a novel compound, which is an agent useful for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11β HSD1 is beneficial.

25 [00256] [28] In another embodiment, the present invention provides a novel method wherein the conditions, disorders, and diseases that are influenced by intracellular glucocorticoid levels

30 [00257] [29] In another embodiment, the present invention provides a novel method wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative

and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

5 [00258] [30] In another embodiment, the present invention provides a novel method pharmaceutical composition comprising, as an active ingredient, at least one compound according of the present invention together with one or more pharmaceutically acceptable carriers or excipients.

10 [00259] [31] In another embodiment, the present invention provides a novel pharmaceutical composition, which is suitable for oral, nasal, buccal, transdermal, pulmonal, or parenteral administration.

15 [00260] The compounds of the present invention may have asymmetric centers and may occur as racemates, racemic mixtures, and as individual enantiomers or diastereoisomers, with all isomeric forms being included in the present invention as well as mixtures thereof.

[00261] The present invention also encompasses pharmaceutically acceptable salts of the present compounds. Such salts include pharmaceutically acceptable acid addition salts, pharmaceutically acceptable base addition salts, pharmaceutically acceptable metal salts, ammonium and alkylated ammonium salts. Acid addition salts include salts of inorganic acids as well as organic acids. Representative examples of suitable inorganic acids include hydrochloric, hydrobromic, hydroiodic, phosphoric, sulfuric, and nitric acids. Representative examples of suitable organic acids include formic, acetic, trichloroacetic, trifluoroacetic, propionic, benzoic, cinnamic, citric, fumaric, glycolic, lactic, maleic, malic, malonic, mandelic, oxalic, picric, pyruvic, salicylic, succinic, methanesulfonic, ethanesulfonic, tartaric, ascorbic, pantoic, bismethylene salicylic, ethanedisulfonic, gluconic, citraconic, aspartic, stearic, palmitic, EDTA, glycolic, p-aminobenzoic, glutamic, benzenesulfonic, p-toluenesulfonic acids, sulphates, nitrates, phosphates, perchlorates, borates, acetates, benzoates, hydroxynaphthoates, glycerophosphates, and ketoglutarates. Further examples of pharmaceutically acceptable inorganic or organic acid addition salts include the pharmaceutically acceptable salts listed in J. Pharm. Sci., 66, 2 (1977), which is incorporated herein by reference. Examples of metal salts include lithium, sodium, potassium, barium, calcium, magnesium, zinc, and calcium salts. Examples of amines and organic amines include ammonium, methylamine, dimethylamine, trimethylamine, ethylamine, diethylamine, propylamine, butylamine, tetramethylamine, ethanolamine, diethanolamine, triethanolamine, meglumine, ethylenediamine, choline, N,N'-dibenzylethylenediamine, N-benzylphenylethylamine, N-

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methyl-D-glucamine, and guanidine. Examples of cationic amino acids include lysine, arginine, and histidine.

[00262] Further, some of the compounds of the present invention may form solvates with water or common organic solvents. Such solvates are encompassed within the scope of the invention.

[00263] The pharmaceutically acceptable salts are prepared by reacting a compound of the present invention with 1 to 4 equivalents of a base such as sodium hydroxide, sodium methoxide, sodium hydride, potassium *tert*-butoxide, calcium hydroxide, and magnesium hydroxide, in solvents such as ether, THF, methanol, *tert*-butanol, dioxane, and isopropanol, ethanol. Mixtures of solvents may be used. Organic bases such as lysine, arginine, diethanolamine, choline, guanidine and their derivatives etc. may also be used. Alternatively, acid addition salts wherever applicable are prepared by treatment with acids such as hydrochloric acid, hydrobromic acid, nitric acid, sulfuric acid, phosphoric acid, *p*-toluenesulphonic acid, methanesulfonic acid, acetic acid, citric acid, maleic acid, salicylic acid, hydroxynaphthoic acid, ascorbic acid, palmitic acid, succinic acid, benzoic acid, benzenesulfonic acid, and tartaric acid in solvents such as ethyl acetate, ether, alcohols, acetone, THF, and dioxane. Mixture of solvents may also be used.

[00264] The stereoisomers of the compounds forming part of this invention may be prepared by using reactants in their single enantiomeric form in the process wherever possible or by conducting the reaction in the presence of reagents or catalysts in their single enantiomer form or by resolving the mixture of stereoisomers by conventional methods. Some of the preferred methods include use of microbial resolution, enzymatic resolution, resolving the diastereomeric salts formed with chiral acids such as mandelic acid, camphorsulfonic acid, tartaric acid, and lactic acid, wherever applicable or chiral bases such as brucine, (*R*)- or (*S*)-phenylethylamine, cinchona alkaloids and their derivatives. Commonly used methods are compiled by Jaques et al. in "Enantiomers, Racemates and Resolution" (Wiley Interscience, 1981). More specifically the compound of the present invention may be converted to a 1:1 mixture of diastereomeric amides by treating with chiral amines, aminoacids, aminoalcohols derived from aminoacids; conventional reaction conditions may be employed to convert acid into an amide; the diastereomers may be separated either by fractional crystallization or chromatography and the stereoisomers of compound of formula I may be prepared by hydrolysing the pure diastereomeric amide.

[00265] Various polymorphs of the compounds forming part of this invention may be prepared by crystallization of said compounds under different conditions. For example, using different solvents commonly used or their mixtures for recrystallization, crystallizations at dif-

ferent temperatures; various modes of cooling, ranging from very fast to very slow cooling during crystallizations. Polymorphs may also be obtained by heating or melting the compound followed by gradual or fast cooling. The presence of polymorphs may be determined by solid probe NMR spectroscopy, IR spectroscopy, differential scanning calorimetry, powder X-ray diffraction or such other techniques.

[00266] The invention also encompasses prodrugs of the present compounds, which on administration undergo chemical conversion by metabolic processes before becoming active pharmacological substances. In general, such prodrugs will be functional derivatives of the present compounds, which are readily convertible *in vivo* into the required compound of the present invention. Conventional procedures for the selection and preparation of suitable prodrug derivatives are described, for example, in "Design of Prodrugs", ed. H. Bundgaard, Elsevier, 1985.

[00267] It is a well known problem in drug discovery that compounds, such as enzyme inhibitors, may be very potent and selective in biochemical assays, yet be inactive *in vivo*.

This lack of so-called bioavailability may be ascribed to a number of different factors such as lack of or poor absorption in the gut, first pass metabolism in the liver and/or poor uptake in cells. Although the factors determining bioavailability are not completely understood, there are many examples in the scientific literature - well known to those skilled in the art - of how to modify compounds, which are potent and selective in biochemical assays but show low or no activity *in vivo*, into drugs that are biologically active.

[00268] It is within the scope of the invention to modify the compounds of the present invention, termed the 'original compound', by attaching chemical groups that will improve the bioavailability of said compounds in such a way that the uptake in cells or mammals is facilitated.

[00269] Examples of said modifications, which are not intended in any way to limit the scope of the invention, include changing of one or more carboxy groups to esters (for instance methyl esters, ethyl esters, *tert*-butyl, acetoxymethyl, pivaloyloxymethyl esters or other acyloxymethyl esters). Compounds of the invention, original compounds, such modified by attaching chemical groups are termed 'modified compounds'.

[00270] The invention also encompasses active metabolites of the present compounds.

[00271] The compounds according to the invention alter, and more specifically, reduce the level of active intracellular glucocorticoid and are accordingly useful for the treatment of conditions, disorders, and diseases in which such a modulation or reduction is beneficial.

[00272] Accordingly, the present compounds may be applicable for the treatment of the metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes,

impaired glucose tolerance (IGT), impaired fasting glucose (IFG), Latent Autoimmune Diabetes in the Adult (LADA), type 1 diabetes, diabetic late complications including cardiovascular diseases, cardiovascular disorders, disorders of lipid metabolism, neurodegenerative and psychiatric disorders, dysregulation of intraocular pressure including glaucoma, immune disorders, inappropriate immune responses, musculo-skeletal disorders, gastrointestinal disorders, polycystic ovarie syndrome (PCOS), reduced hair growth or other diseases, disorders or conditions that are influenced by intracellular glucocorticoid levels, adverse effects of increased blood levels of active endogenous or exogenous glucocorticoid, and any combination thereof, adverse effects of increased plasma levels of endogenous active glucocorticoid, Cushing's disease, Cushing's syndrome, adverse effects of glucocorticoid receptor agonist treatment of autoimmune diseases, adverse effects of glucocorticoid receptor agonist treatment of inflammatory diseases, adverse effects of glucocorticoid receptor agonist treatment of diseases with an inflammatory component, adverse effects of glucocorticoid receptor agonist treatment as a part of cancer chemotherapy, adverse effects of glucocorticoid receptor agonist treatment for surgical/post-surgical or other trauma, adverse effects of glucocorticoid receptor agonist therapy in the context of organ or tissue transplantation or adverse effects of glucocorticoid receptor agonist treatment in other diseases, disorders or conditions where glucocorticoid receptor agonists provide clinically beneficial effects. Also the present compounds may be applicable for the treatment of visceral fat accumulation and insulin resistance in HAART (highly active antiretroviral treatment)-treated patients.

[00273] More specifically the present compounds may be applicable for the treatment of the metabolic syndrome, type 2 diabetes, diabetes as a consequence of obesity, insulin resistance, hyperglycemia, prandial hyperglycemia, hyperinsulinemia, inappropriately low insulin secretion, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), increased hepatic glucose production, type 1 diabetes, LADA, pediatric diabetes, dyslipidemia, diabetic dyslipidemia, hyperlipidemia, hypertriglyceridemia, hyperlipoproteinemia, hypercholesterolemia, decreased HDL cholesterol, impaired LDL/HDL ratio, other disorders of lipid metabolism, obesity, visceral obesity, obesity as a consequence of diabetes, increased food intake, hypertension, diabetic late complications, micro-/macroalbuminuria, nephropathy, retinopathy, neuropathy, diabetic ulcers, cardiovascular diseases, arteriosclerosis, atherosclerosis, coronary artery disease, cardiac hypertrophy, myocardial ischemia, heart insufficiency, congestional heart failure, stroke, myocardial infarction, arrhythmia, decreased blood flow, erectile dysfunction (male or female), myopathy, loss of muscle tissue, muscle wasting, muscle catabolism, osteoporosis, decreased linear growth, neurodegenerative and psychiatric disorders. Alzheimers disease, neuronal death, impaired cognitive function, depression,

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anxiety, eating disorders, appetite regulation, migraine, epilepsy, addiction to chemical substances, disorders of intraocular pressure, glaucoma, polycystic ovary syndrome (PCOS), inappropriate immune responses, inappropriate T helper-1/T helper-2 polarisation, bacterial infections, mycobacterial infections, fungal infections, viral infections, parasitic infestations, suboptimal responses to immunizations, immune dysfunction, partial or complete baldness, or other diseases, disorders or conditions that are influenced by intracellular glucocorticoid levels and any combination thereof, adverse effects of glucocorticoid receptor agonist treatment of allergic-inflammatory diseases such as asthma and atopic dermatitis, adverse effects of glucocorticoid receptor agonist treatment of disorders of the respiratory system e.g., asthma, cystic fibrosis, emphysema, bronchitis, hypersensitivity, pneumonitis, eosinophilic pneumonias, pulmonary fibrosis, adverse effects of glucocorticoid receptor agonist treatment of inflammatory bowel disease such as Crohn's disease and ulcerative colitis; adverse effects of glucocorticoid receptor agonist treatment of disorders of the immune system, connective tissue and joints e.g., reactive arthritis, rheumatoid arthritis, Sjögren's syndrome, systemic lupus erythematosus, lupus nephritis, Henoch-Schönlein purpura, Wegener's granulomatosis, temporal arteritis, systemic sclerosis, vasculitis, sarcoidosis, dermatomyositis-polymyositis, pemphigus vulgaris; adverse effects of glucocorticoid receptor agonist treatment of endocrinological diseases such as hyperthyroidism, hypoadosteronism, hypopituitarism; adverse effects of glucocorticoid receptor agonist treatment of hematological diseases e.g., hemolytic anemia, thrombocytopenia, paroxysmal nocturnal hemoglobinuria; adverse effects of glucocorticoid receptor agonist treatment of cancer such as spinal cord diseases, neoplastic compression of the spinal cord, brain tumours, acute lymphoblastic leukemia, Hodgkin's disease, chemotherapy-induced nausea, adverse effects of glucocorticoid receptor agonist treatment of diseases of muscle and at the neuro-muscular joint e.g., myasthenia gravis and hereditary myopathies (e.g., Duchenne muscular dystrophy), adverse effects of glucocorticoid receptor agonist treatment in the context of surgery & transplantation e.g., trauma, post-surgical stress, surgical stress, renal transplantation, liver transplantation, lung transplantation, pancreatic islet transplantation, blood stem cell transplantation, bone marrow transplantation, heart transplantation, adrenal gland transplantation, tracheal transplantation, intestinal transplantation, corneal transplantation, skin grafting, keratoplasty, lens implantation and other procedures where immunosuppression with glucocorticoid receptor agonists is beneficial; adverse effects of glucocorticoid receptor agonist treatment of brain abscess, nausea/vomiting, infections, hypercalcemia, adrenal hyperplasia, autoimmune hepatitis, spinal cord diseases, saccular aneurysms or adverse effects to glucocorticoid receptor

agonist treatment in other diseases, disorders and conditions where glucocorticoid receptor agonists provide clinically beneficial effects.

[00274] Accordingly, in a further aspect the invention relates to a compound according to the invention for use as a pharmaceutical composition.

5 [00275] The invention also relates to pharmaceutical compositions comprising, as an active ingredient, at least one compound according to the invention together with one or more pharmaceutically acceptable carriers or diluents.

[00276] The pharmaceutical composition is preferably in unit dosage form, comprising from about 0.05 mg/day to about 2000 mg/day, preferably from about 0.1 mg/day to about 1000
10 mg/day, and more preferably from about 0.5 mg/day to about 500 mg/day of a compound according to the invention.

[00277] In another embodiment, the patient is treated with a compound according to the invention for at least about 1 week, for at least about 2 weeks, for at least about 4 weeks, for at least about 2 months or for at least about 4 months.

15 [00278] In yet another embodiment, the pharmaceutical composition is for oral, nasal, buccal, transdermal, pulmonal or parenteral administration.

[00279] Furthermore, the invention relates to the use of a compound according to the invention for the preparation of a pharmaceutical composition for the treatment of disorders and diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

20 [00280] The invention also relates to a method for the treatment of disorders and diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound according to the invention.

[00281] In a preferred embodiment of the invention the present compounds are used for the
25 preparation of a medicament for the treatment of any diseases and conditions that are influenced by intracellular glucocorticoid levels as mentioned above.

[00282] Thus, in a preferred embodiment of the invention the present compounds are used for the preparation of a medicament for the treatment of conditions and disorders where a decreased level of active intracellular glucocorticoid is desirable, such as the conditions and
30 diseases mentioned above.

[00283] In yet a preferred embodiment of the invention the present compounds are used for the preparation of a medicament for the treatment of metabolic syndrome, insulin resistance, dyslipidemia, hypertension obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of the
35 metabolic syndrome into type 2 diabetes, diabetic late complications (e.g., cardiovascular

diseases, arteriosclerosis, and atherosclerosis), neurodegenerative and psychiatric disorders, and, the adverse effects of glucocorticoid receptor agonist treatment or therapy.

[00284] In another embodiment of the present invention, the route of administration may be any route which effectively transports a compound according to the invention to the appropriate or desired site of action, such as oral, nasal, buccal, transdermal, pulmonary, or parenteral.

[00285] In still a further aspect of the invention the present compounds are administered in combination with one or more further active substances in any suitable ratios. Such further active substances may e.g., be selected from antiobesity agents, antidiabetics, agents modifying the lipid metabolism, antihypertensive agents, glucocorticoid receptor agonists, agents for the treatment and/or prevention of complications resulting from or associated with diabetes and agents for the treatment and/or prevention of complications and disorders resulting from or associated with obesity.

[00286] Thus, in a further aspect of the invention the present compounds may be administered in combination with one or more antiobesity agents or appetite regulating agents.

[00287] Such agents may be selected from the group consisting of CART (cocaine amphetamine regulated transcript) agonists, NPY (neuropeptide Y) antagonists, MC4 (melanocortin 4) agonists, orexin antagonists, TNF (tumor necrosis factor) agonists, CRF (corticotropin releasing factor) agonists, CRF BP (corticotropin releasing factor binding protein) antagonists, urocortin agonists, $\beta 3$ agonists, MSH (melanocyte-stimulating hormone) agonists, MCH (melanocyte-concentrating hormone) antagonists, CCK (cholecystokinin) agonists, serotonin re-uptake inhibitors, serotonin and noradrenaline re-uptake inhibitors, mixed serotonin and noradrenergic compounds, 5HT (serotonin) agonists, bombesin agonists, galanin antagonists, growth hormone, growth hormone releasing compounds, TRH (thyrotropin releasing hormone) agonists, UCP 2 or 3 (uncoupling protein 2 or 3) modulators, leptin agonists, DA agonists (bromocriptin, doprexin), lipase/amylase inhibitors, PPAR (peroxisome proliferator-activated receptor) modulators, RXR (retinoid X receptor) modulators, TR β agonists, AGRP (Agouti related protein) inhibitors, H3 histamine antagonists, opioid antagonists (such as naltrexone), exendin-4, GLP-1 and ciliary neurotrophic factor.

[00288] In one embodiment of the invention the antiobesity agent is leptin; dexamphetamine or amphetamine; fenfluramine or dexfenfluramine; sibutramine; orlistat; mazindol or phentermine.

[00289] Suitable antidiabetic agents include insulin, insulin analogues and derivatives such as those disclosed in EP 792 290 (Novo Nordisk A/S), e.g., N^{B29}-tetradecanoyl d ϵ s (B30) human insulin, EP 214 826 and EP 705 275 (Novo Nordisk A/S), e.g., Asp^{B28} human insulin,

US 5,504,188 (Eli Lilly), e.g., Lys^{B28} Pro^{B29} human insulin, EP 368 187 (Aventis), eg Lantus, which are all incorporated herein by reference, GLP-1 (glucagon like peptide-1) and GLP-1 derivatives such as those disclosed in WO 98/08871 to Novo Nordisk A/S, which is incorporated herein by reference as well as orally active hypoglycaemic agents.

- 5 [00290] The orally active hypoglycaemic agents preferably comprise sulphonylureas, biguanides, meglitinides, glucosidase inhibitors, glucagon antagonists such as those disclosed in WO 99/01423 to Novo Nordisk A/S and Agouron Pharmaceuticals, Inc., GLP-1 agonists, potassium channel openers such as those disclosed in WO 97/26265 and WO 99/03851 to Novo Nordisk A/S which are incorporated herein by reference, DPP-IV (dipeptidyl peptidase-IV) inhibitors, inhibitors of hepatic enzymes involved in stimulation of gluconeogenesis and/or glycogenolysis, glucose uptake modulators, compounds modifying the lipid metabolism such as antihyperlipidemic agents and antilipidemic agents as PPAR α modulators, PPAR δ modulators, cholesterol absorption inhibitors, HSL (hormone-sensitive lipase) inhibitors and HMG CoA inhibitors (statins), nicotinic acid, fibrates, anion exchangers, compounds lowering food intake, bile acid resins, RXR agonists and agents acting on the ATP-dependent potassium channel of the β -cells.

- 10 [00291] In one embodiment, the present compounds are administered in combination with insulin or an insulin analogue or derivative, such as N^{B29}-tetradecanoyl des (B30) human insulin, Asp^{B29} human insulin, Lys^{B28} Pro^{B29} human insulin, Lantus®, or a mix-preparation comprising one or more of these.

20 [00292] In a further embodiment the present compounds are administered in combination with a sulphonylurea e.g., tolbutamide, glibenclamide, glipizide or glicazide.

[00293] In another embodiment the present compounds are administered in combination with a biguanide e.g., metformin.

- 25 [00294] In yet another embodiment the present compounds are administered in combination with a meglitinide e.g., repaglinide or senaglinide.

[00295] In still another embodiment the present compounds are administered in combination with a thiazolidinedione e.g., troglitazone, ciglitazone, pioglitazone, rosiglitazone or compounds disclosed in WO 97/41097 such as 5-[[4-[3-Methyl-4-oxo-3,4-dihydro-2-quinazolinyl]methoxy]phenyl-methyl]thiazolidine-2,4-dione or a pharmaceutically acceptable salt thereof, preferably the potassium salt.

30 [00296] In yet another embodiment the present compounds may be administered in combination with the insulin sensitizers disclosed in WO 99/19313 such as (-) 3-[4-[2-Phenoxazin-

10-yl)ethoxy]phenyl]-2-ethoxypropanoic acid or a pharmaceutically acceptable salt; thereof, preferably the arginine salt.

[00297] In a further embodiment the present compounds are administered in combination with an α -glucosidase inhibitor e.g., miglitol or acarbose.

5 [00298] In another embodiment the present compounds are administered in combination with an agent acting on the ATP-dependent potassium channel of the β -cells e.g., tolbutamide, glibenclamide, glipizide, glicazide or repaglinide.

[00299] Furthermore, the present compounds may be administered in combination with nateglinide.

10 [00300] In still another embodiment the present compounds are administered in combination with an antihyperlipidemic agent or antilipidemic agent e.g., cholestyramine, colestipol, clofibrate, gemfibrozil, fenofibrate, bezafibrate, tesaglitazar, EML-4156, LY-818, MK-767, atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin, acipimox, probucol, ezetimibe or dextrothyroxine.

15 [00301] In a further embodiment the present compounds are administered in combination with more than one of the above-mentioned compounds e.g., in combination with a sulphonylurea and metformin, a sulphonylurea and acarbose, repaglinide and metformin, insulin and a sulphonylurea, insulin and metformin, insulin, insulin and lovastatin, etc.

[00302] Further, the present compounds may be administered in combination with one
20 or more antihypertensive agents. Examples of antihypertensive agents are β -blockers such as alprenolol, atenolol, timolol, pindolol, propranolol, metoprolol, bisoprolol fumarate, esmolol, acebutolol, metoprolol, acebutolol, betaxolol, celiprolol, nebivolol, tertatolol, oxprenolol, amosolalol, carvedilol, labetalol, β 2-receptor blockers e.g., S-atenolol, OPC-1085, ACE (angiotensin converting enzyme) inhibitors such as quinapril, lisinopril, enalapril, captopril, benazepril, perindopril,trandolapril, fosinopril, ramipril, cilazapril, delapril, imidapril, moexipril, spirapril, temocapril, zofenopril, S-5590, fasidotril, Hoechst-Marion Roussel;
25 100240 (EP 00481522), omapatrilat, gemopatrilat and GW-660511, calcium channel blockers such as nifedipine, felodipine, nocardipine, isradipine, nimodipine, diltiazem, amlodipine, nitrendipine, verapamil, lacidipine, lercanidipine, aranidipine, cilnidipine,
30 clevidipine, azelnidipine, barnidipine, efendipine, lasidipine, lemidipine, lercanidipine, manidipine, nilvadipine, pranidipine, furnidipine, α -blockers such as doxazosin, urapidil, prazosin, terazosin, bunazosin and OPC-28326, diuretics such as thiazides/sulphonamides (e.g., bendroflumetazide, chlorothalidone, hydrochlorothiazide and clopamide), loop-diuretics (e.g., bumetanide, furosemide and torasemide) and potassium sparing diuretics (e.g.,

amiloride, spironolactone), endothelin ET-A antagonists such as ABT-546, ambrisentan, atrasentan, SB-234551, CI-1034, S-0139 and YM-598, endothelin antagonists e.g., bosentan and J-104133, renin inhibitors such as aliskiren, vasopressin V1 antagonists e.g., OPC-21268, vasopressin V2 antagonists such as tolvaptan, SR-121463 and OPC-31260, B-type natriuretic peptide agonists e.g., Nesiritide, angiotensin II antagonists such as irbesartan, candesartancilexetil, losartan, valsartan, telmisartan, eprosartan, candesartan, CL-329167, eprosartan, losartan, olmesartan, prazosartan, TA-606, and YM-358, 5-HT₂ agonists e.g., fenoldopam and ketanserin, adenosine A₁ antagonists such as naftopidil, N-0861 and FK-352, thromboxane A₂ antagonists such as KT2-962, endopeptidase inhibitors e.g., ecadotril, nitric oxide agonists such as LP-805, dopamine D₁ antagonists e.g., MYD-37, dopamine D₂ agonists such as nalmefene, n-3 fatty acids e.g., omacor, prostacyclin agonists such as treprostinil, beraprost, PGE₁ agonists e.g., ecraprost, Na⁺/K⁺ ATPase modulators e.g., PST-2238, Potassium channel activators e.g., KR-30450, vaccines such as PMD-3117, Indapamides, CGRP-unigene, guanylate cyclase stimulators, hydralazines, methyl dopa, docarpace, moxonidine, CoAprovel, MondoBiotech-811.

[00303] Further reference can be made to Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

[00304] Furthermore, the present compounds may be administered in combination with one or more glucocorticoid receptor agonists. Examples of such glucocorticoid receptor agonists are betametasone, dexamethasone, hydrocortisone, methylprednisolone, prednisolone, prednisone, beclomethasone, butixicort, clobetasol, flunisolide, flucatisone (and analogues), momethasone, triamcinolonacetone, triamcinolonhexacetone GW-685698, NXC-1015, NXC-1020, NXC-1021, NS-126, P-4112, P-4114, RU-24858 and T-25 series.

[00305] It should be understood that any suitable combination of the compounds according to the invention with one or more of the above-mentioned compounds and optionally one or more further pharmacologically active substances are considered to be within the scope of the present invention.

PHARMACEUTICAL COMPOSITIONS

[00306] The compounds of the present invention may be administered alone or in combination with pharmaceutically acceptable carriers or excipients, in either single or multiple doses. The pharmaceutical compositions according to the invention may be formulated with pharmaceutically acceptable carriers or diluents as well as any other known adjuvants and excipients in accordance with conventional techniques such as those disclosed in Remington:

The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

[00307] The pharmaceutical compositions may be specifically formulated for administration by any suitable route such as the oral, rectal, nasal, pulmonary, topical (including buccal and sublingual), transdermal, intracisternal, intraperitoneal, vaginal and parenteral (including subcutaneous, intramuscular, intrathecal, intravenous and intradermal) route, the oral route being preferred. It will be appreciated that the preferred route will depend on the general condition and age of the subject to be treated, the nature of the condition to be treated and the active ingredient chosen.

[00308] Pharmaceutical compositions for oral administration include solid dosage forms such as hard or soft capsules, tablets, troches, dragees, pills, lozenges, powders and granules. Where appropriate, they can be prepared with coatings such as enteric coatings or they can be formulated so as to provide controlled release of the active ingredient such as sustained or prolonged release according to methods well-known in the art.

[00309] Liquid dosage forms for oral administration include solutions, emulsions, suspensions, syrups and elixirs.

[00310] Pharmaceutical compositions for parenteral administration include sterile aqueous and non-aqueous injectable solutions, dispersions, suspensions or emulsions as well as sterile powders to be reconstituted in sterile injectable solutions or dispersions prior to use. Depot injectable formulations are also contemplated as being within the scope of the present invention.

[00311] Other suitable administration forms include suppositories, sprays, ointments, crèmes, gels, inhalants, dermal patches, implants etc.

[00312] A typical oral dosage is in the range of from about 0.001 to about 100 mg/kg body weight per day, preferably from about 0.01 to about 50 mg/kg body weight per day, and more preferred from about 0.05 to about 10 mg/kg body weight per day administered in one or more dosages such as 1 to 3 dosages. The exact dosage will depend upon the frequency and mode of administration, the sex, age, weight and general condition of the subject treated, the nature and severity of the condition treated and any concomitant diseases to be treated and other factors evident to those skilled in the art.

[00313] The formulations may conveniently be presented in unit dosage form by methods known to those skilled in the art. A typical unit dosage form for oral administration one or more times per day such as 1 to 3 times per day may contain from 0.05 to about 2000 mg, e.g., from about 0.1 to about 1000 mg, from about 0.5 mg to about 500 mg., from about 1 mg to about 200 mg, e.g., about 100 mg.

[00314] For parenteral routes, such as intravenous, intrathecal, intramuscular and similar administration, typically doses are in the order of about half the dose employed for oral administration.

5 [00315] The compounds of this invention are generally utilized as the free substance or as a pharmaceutically acceptable salt thereof. Examples are an acid addition salt of a compound having the utility of a free base and a base addition salt of a compound having the utility of a free acid. The term "pharmaceutically acceptable salts" refers to non-toxic salts of the compounds for use according to the present invention which are generally prepared by reacting the free base with a suitable organic or inorganic acid or by reacting the acid with a suitable organic or inorganic base. When a compound for use according to the present invention, contains a free base such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable acid. When a compounds for use according to the present invention, contains a free acid such salts are prepared in a conventional manner by treating a solution or suspension of the compound with a chemical equivalent of a pharmaceutically acceptable base. Physiologically acceptable salts of a compound with a hydroxy group include the anion of said compound in combination with a suitable cation such as sodium or ammonium ion. Other salts which are not pharmaceutically acceptable may be useful in the preparation of compounds for use according to the present invention and these form a further aspect of the present invention.

20 [00316] For parenteral administration, solutions of the present compounds in sterile aqueous solution, aqueous propylene glycol or sesame or peanut oil may be employed. Such aqueous solutions should be suitable buffered if necessary and the liquid diluent first rendered isotonic with sufficient saline or glucose. The aqueous solutions are particularly suitable for intravenous, intramuscular, subcutaneous and intraperitoneal administration. The sterile aqueous media employed are all readily available by standard techniques known to those skilled in the art.

30 [00317] Suitable pharmaceutical carriers include inert solid diluents or fillers, sterile aqueous solution and various organic solvents. Examples of suitable carriers are water, salt solutions, alcohols, polyethylene glycols, polyhydroxyethoxylated castor oil, peanut oil, olive oil, syrup, phospholipids, gelatine, lactose, terra alba, sucrose, cyclodextrin, amylose, magnesium stearate, talc, gelatin, agar, pectin, acacia, stearic acid or lower alkyl ethers of cellulose, silicic acid, fatty acids, fatty acid amines, fatty acid monoglycerides and diglycerides, pentaerythritol fatty acid esters, polyoxyethylene, hydroxymethylcellulose and polyvinylpyrrolidone. Similarly, the carrier or diluent may include any sustained release material known in the art, such as glyceryl monostearate or glyceryl distearate, alone or mixed with a wax. The

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formulations may also include wetting agents, emulsifying and suspending agents, preserving agents, sweetening agents or flavouring agents.

5 [00318] The pharmaceutical compositions formed by combining the compounds of the invention and the pharmaceutically acceptable carriers are then readily administered in a variety of dosage forms suitable for the disclosed routes of administration. The formulations may conveniently be presented in unit dosage form by methods known in the art of pharmacy.

10 [00319] Formulations of the present invention suitable for oral administration may be presented as discrete units such as capsules or tablets, each containing a predetermined amount of the active ingredient, and which may include a suitable excipient. These formulations may be in the form of powder or granules, as a solution or suspension in an aqueous or non-aqueous liquid, or as an oil-in-water or water-in-oil liquid emulsion.

15 [00320] Compositions intended for oral use may be prepared according to any known method, and such compositions may contain one or more agents selected from the group consisting of sweetening agents, flavouring agents, colouring agents, and preserving agents in order to provide pharmaceutically elegant and palatable preparations. Tablets may contain the active ingredient in admixture with non-toxic pharmaceutically-acceptable excipients which are suitable for the manufacture of tablets. These excipients may be for example, inert diluents, such as calcium carbonate, sodium carbonate, lactose, calcium phosphate or sodium phosphate; granulating and disintegrating agents, for example corn starch or alginic acid; binding agents, 20 for example, starch, gelatine or acacia; and lubricating agents, for example magnesium stearate, stearic acid or talc. The tablets may be uncoated or they may be coated by known techniques to delay disintegration and absorption in the gastrointestinal tract and thereby provide a sustained action over a longer period. For example, a time delay material such as glyceryl monostearate or glyceryl distearate may be employed. They may also be coated by the 25 techniques described in U.S. Patent Nos. 4,356,108; 4,166,452; and 4,265,874, incorporated herein by reference, to form osmotic therapeutic tablets for controlled release.

[00321] Formulations for oral use may also be presented as hard gelatine capsules where the active ingredient is mixed with an inert solid diluent, for example, calcium carbonate, calcium phosphate or kaolin, or a soft gelatine capsule wherein the active ingredient is mixed with water 30 or an oil medium, for example peanut oil, liquid paraffin, or olive oil.

[00322] Aqueous suspensions may contain the active compounds in admixture with excipients suitable for the manufacture of aqueous suspensions. Such excipients are suspending agents, for example sodium carboxymethylcellulose, methylcellulose, hydroxypropylmethylcellulose, sodium alginate, polyvinylpyrrolidone, gum tragacanth and gum acacia; dispersing or wetting 35 agents may be a naturally-occurring phosphatide such as lecithin, or condensation products of

an alkylene oxide with fatty acids, for example polyoxyethylene stearate, or condensation products of ethylene oxide with long chain aliphatic alcohols, for example, heptadecaethyleneglycerol, or condensation products of ethylene oxide with partial esters derived from fatty acids and a hexitol such as polyoxyethylene sorbitol monooleate, or condensation products of ethylene oxide with partial esters derived from fatty acids and hexitol anhydrides, for example polyethylene sorbitan monooleate. The aqueous suspensions may also contain one or more colouring agents, one or more flavouring agents, and one or more sweetening agents, such as sucrose or saccharin.

5 [00323] Oily suspensions may be formulated by suspending the active ingredient in a vegetable oil, for example arachis oil, olive oil, sesame oil or coconut oil, or in a mineral oil such as a liquid paraffin. The oily suspensions may contain a thickening agent, for example beeswax, hard paraffin or cetyl alcohol. Sweetening agents such as those set forth above, and flavouring agents may be added to provide a palatable oral preparation. These compositions may be preserved by the addition of an anti-oxidant such as ascorbic acid.

10 [00324] Dispersible powders and granules suitable for preparation of an aqueous suspension by the addition of water provide the active compound in admixture with a dispersing or wetting agent, suspending agent and one or more preservatives. Suitable dispersing or wetting agents and suspending agents are exemplified by those already mentioned above. Additional excipients, for example, sweetening, flavouring, and colouring agents may also be present.

15 [00325] The pharmaceutical compositions comprising a compound for use according to the present invention may also be in the form of oil-in-water emulsions. The oily phase may be a vegetable oil, for example, olive oil or arachis oil, or a mineral oil, for example a liquid paraffin, or a mixture thereof. Suitable emulsifying agents may be naturally-occurring gums, for example gum acacia or gum tragacanth, naturally-occurring phosphatides, for example soy bean, lecithin, and esters or partial esters derived from fatty acids and hexitol anhydrides, for example sorbitan monooleate, and condensation products of said partial esters with ethylene oxide, for example polyoxyethylene sorbitan monooleate. The emulsions may also contain sweetening and flavouring agents.

20 [00326] Syrups and elixirs may be formulated with sweetening agents, for example glycerol, propylene glycol, sorbitol or sucrose. Such formulations may also contain a demulcent, preservative and flavouring and colouring agent. The pharmaceutical compositions may be in the form of a sterile injectable aqueous or oleaginous suspension. This suspension may be formulated according to the known methods using suitable dispersing or wetting agents and suspending agents described above. The sterile injectable preparation may also be a sterile injectable solution or suspension in a non-toxic parenterally-acceptable diluent or solvent, for ex-

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ample as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution. In addition, sterile, fixed oils are conveniently employed as solvent or suspending medium. For this purpose, any bland fixed oil may be employed using synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of injectables.

5 [00327] The compositions may also be in the form of suppositories for rectal administration of the compounds of the present invention. These compositions can be prepared by mixing the drug with a suitable non-irritating excipient which is solid at ordinary temperatures but liquid at the rectal temperature and will thus melt in the rectum to release the drug. Such materials include cocoa butter and polyethylene glycols, for example.

10 [00328] For topical use, creams, ointments, jellies, solutions of suspensions, etc., containing the compounds of the present invention are contemplated. For the purpose of this application, topical applications shall include mouth washes and gargles.

[00329] The compounds for use according to the present invention may also be administered in the form of liposome delivery systems, such as small unilamellar vesicles, large unilamellar vesicles, and multilamellar vesicles. Liposomes may be formed from a variety of phospholipids, such as cholesterol, stearylamine, or phosphatidylcholines.

15 [00330] In addition, some of the compounds for use according to the present invention may form solvates with water or common organic solvents. Such solvates are also encompassed within the scope of the present invention.

20 [00331] Thus, in a further embodiment, there is provided a pharmaceutical composition comprising a compound for use according to the present invention, or a pharmaceutically acceptable salt, solvate, or prodrug thereof, and one or more pharmaceutically acceptable carriers, excipients, or diluents.

25 [00332] If a solid carrier is used for oral administration, the preparation may be tableted, placed in a hard gelatine capsule in powder or pellet form or it can be in the form of a troche or lozenge. The amount of solid carrier will vary widely but will usually be from about 25 mg to about 1 g. If a liquid carrier is used, the preparation may be in the form of a syrup, emulsion, soft gelatine capsule or sterile injectable liquid such as an aqueous or non-aqueous liquid suspension or solution.

30 [00333] A typical tablet which may be prepared by conventional tableting techniques may contain:

[00334] Core:

[00335] Active compound (as free compound or salt thereof) 5.0 mg

35 [00336] Lactosum PH. Eur. 67.8 mg



	[00337]	Cellulose, microcryst. (Avicel)	31.4 mg
	[00338]	Amberlite® IRP88*	1.0 mg
	[00339]	Magnesii stearas PH. Eur.	q.s.
5	[00340]	Coating:	
	[00341]	Hydroxypropyl methylcellulose	approx. 9 mg
	[00342]	Mywacett 9-40 T**	approx. 0.9 mg
	[00343]	Polacrillin potassium NF, tablet disintegrant, Rohm and Haas.	
10	[00344]	** Acylated monoglyceride used as plasticizer for film coating.	

[00345] The compounds of the invention may be administered to a patient which is a mammal, especially a human in need thereof. Such mammals include also animals, both domestic animals, e.g., household pets, and non-domestic animals such as wildlife.

15 [00346] Any novel feature or combination of features described herein is considered essential to this invention.

[00347] The present invention also relate to the below methods of preparing the compounds of the invention.

[00348] The present invention is further illustrated in the following representative
20 examples which are, however, not intended to limit the scope of the invention in any way.

EXAMPLES

[00349] The following examples and general procedures refer to intermediate compounds and final products for general formula (I) identified above. The preparation of the compounds of general formula (I) of the present invention is described in detail using the following examples. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, which is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may easily be prepared from known starting materials. The structures of the compounds are confirmed by either elemental analysis or nuclear magnetic resonance (NMR),
35

where peaks assigned to characteristic protons in the title compounds are presented where appropriate. ¹H NMR shifts (δ_H) are given in parts per million (ppm) down field from tetramethylsilane as internal reference standard. M.p.: is melting point and is given in °C and is not corrected. Column chromatography was carried out using the technique described by W.C. Still *et al.*, *J. Org. Chem.* 43: 2923 (1978) on Merck silica gel-60 (Art. 9385). HPLC analyses are performed using 5 μ m C18 4 x 250 mm column eluted with various mixtures of water and acetonitrile, flow = 1 ml/min, as described in the experimental section.

[00350] Microwave oven synthesis: The reaction was heated by microwave irradiation in sealed microwave vessels in a single mode Emrys Optimizer EXP from Personal Chemistry®.

[00351] Preparative HPLC: Column: 1.9 x 15 cm Waters XTerra RP-18 Buffer: linear gradient 5 – 95 % in 15 min, MeCN, 0.1 % TFA, flow rate of 15 ml/min. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated *in vacuo* until the MeCN is removed, and then frozen and freeze dried.

[00352] ABBREVIATIONS

[00353] d=day(s)

[00354] g=gram(s)

[00355] h=hour(s)

[00356] Hz=hertz

[00357] L=liter(s)

[00358] M=molar

[00359] mg=milligram(s)

[00360] min=minute(s)

[00361] mL=milliliter(s)

[00362] mmol=millimole(s)

[00363] mol=mole(s)

[00364] ppm=parts per million

[00365] psi=pounds per square inch

[00366] ESI=electrospray ionization

[00367] m/z=mass to charge ratio

[00368] mp=melting point

[00369] MS=mass spectrometry

[00370] HPLC=high pressure liquid chromatography

[00371] RP=reverse phase



[00372] HPLC-MS=high pressure liquid chromatography-mass spectrometry

[00373] NMR=nuclear magnetic resonance spectroscopy

[00374] rt=room temperature

[00375] TLC=thin layer chromatography

5 [00376] DCM=dichloromethane, CH_2Cl_2 , methylenechloride

[00377] DIPEA=*N,N*-diisopropylethylamine

[00378] DMF=*N,N*-dimethylformamide

[00379] DMSO=dimethylsulfoxide

[00380] EDAC=1-ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride

10 [00381] Et_2O =diethyl ether

[00382] EtOAc=ethyl acetate

[00383] HOBt=1-hydroxybenzotriazole

[00384] MeCN=acetonitrile

[00385] MeOH=methanol

15 [00386] NMP=*N*-methylpyrrolidin-2-one

[00387] TEA=triethylamine

[00388] TFA=trifluoroacetic acid

[00389] THF=tetrahydrofuran

[00390] CDCl_3 =deuterio chloroform

20 [00391] CD_3OD =tetra-deuterio methanol

[00392] $\text{DMSO}-d_6$ =hexa-deuterio dimethylsulfoxide

[00393] ANALYSIS

[00394] NMR

25 [00395] NMR spectra were recorded at 300 and 400 MHz on a Bruker DRX300, DRX400 or AV400 instrument equipped with 5 mm selective-inverse (SEI, ^1H and ^{13}C), 5 mm broad-band inverse (BBI, ^1H , broad-band) and 5 mm quadro nuclear (QNP, ^1H , ^{13}C) probeheads, respectively. Shifts (δ) are given in parts per million (ppm) down field from tetramethylsilane as internal reference standard.

30

[00396] HPLC-MS

[00397] HPLC-MS method

[00398] The RP-analysis was performed on an Agilent HPLC system (1100 degasser, 1100 pump, 1100 injector and a 1100 DAD) fitted with an Agilent MS detector system Model VL
35 (MW 0-1000) and a S.E.D.E.R.E Model Sedex 55 ELS detector system using a Waters X-

terra MS C18 column (5 μ m, 3.0 mm x 50 mm) with gradient elution, 5 % to 95 % solvent B (0.05 % TFA in acetonitrile) in solvent A (0.05 % TFA in water) within 3 min, 2.7 mL/min, temperature 40°C.

5 [00399] PREPARATIVE TECHNIQUES

[00400] HPLC

[00401] HPLC method Z3

[00402] The RP-purification was performed on a Gilson system (3 Gilson 306 pumps, Gilson 170 DAD detector and a Gilson 215 liquid handler) using a Waters X-terra RP (10 μ m, 30 mm x 150 mm) with gradient elution, 5 % to 95 % solvent B (0.05 % TFA in acetonitrile) in solvent A (0.05 % TFA in water) within 15 min, 40 mL/min, detection at 210 nm, temperature rt. The pooled fractions are either evaporated to dryness *in vacuo*, or evaporated *in vacuo* until the acetonitrile is removed, and then frozen and freeze dried.

15 [00403] GENERAL

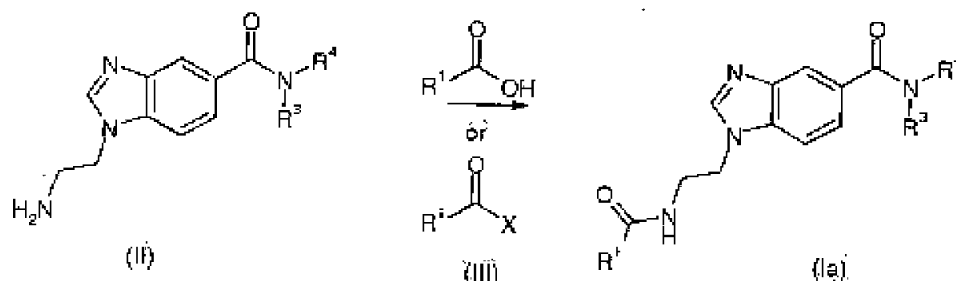
[00404] The following examples and general procedures refer to intermediate compounds and final products for general formula (I) identified in the specification and in the synthesis schemes. The preparation of the compounds of general formula (I) of the present invention is described in detail using the following examples. Occasionally, the reaction may not be applicable as described to each compound included within the disclosed scope of the invention. The compounds for which this occurs will be readily recognised by those skilled in the art. In these cases the reactions can be successfully performed by conventional modifications known to those skilled in the art, which is, by appropriate protection of interfering groups, by changing to other conventional reagents, or by routine modification of reaction conditions. Alternatively, other reactions disclosed herein or otherwise conventional will be applicable to the preparation of the corresponding compounds of the invention. In all preparative methods, all starting materials are known or may be prepared by a person skilled in the art in analogy with the preparation of similar known compounds or by the General procedures A through D described herein. The structures of the compounds are confirmed by either elemental analysis or nuclear magnetic resonance (NMR), where peaks assigned to characteristic protons in the title compounds are presented where appropriate.



[00405] GENERAL PROCEDURES

[00406] General procedure (A)

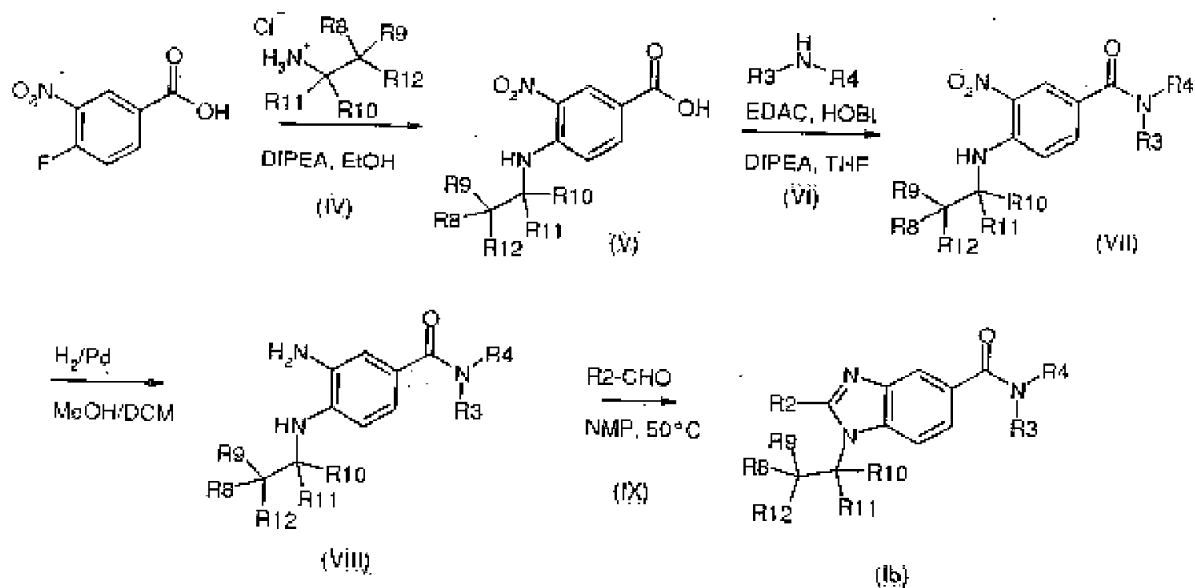
[00407] Compounds of the formula (Ia) according to the invention wherein R^1 , R^3 , and R^4 are as defined for formula (I), with NR^3R^4 corresponding to ring A, can be prepared as outlined below:



[00408] A benzimidazole of formula (II) wherein NR^3R^4 corresponds to ring A defined above may be reacted with a carboxylic acid in the presence of coupling reagents (e.g., EDAC and HOBt) or an activated carboxylic acid of the formula (III) wherein R^1 is as defined above. This reaction may be carried out in a suitable solvent (e.g., dichloromethane) in the presence of a base (e.g., DIPEA) at ambient temperature.

[00409] General procedure (B)

[00410] Compounds of the formula (Ib) according to the invention wherein R^2 , R^3 , R^4 , R^8 , R^9 , R^{10} , R^{11} , and R^{12} are as defined for formula (I), with NR^3R^4 corresponding to ring A, can be prepared as outlined below:

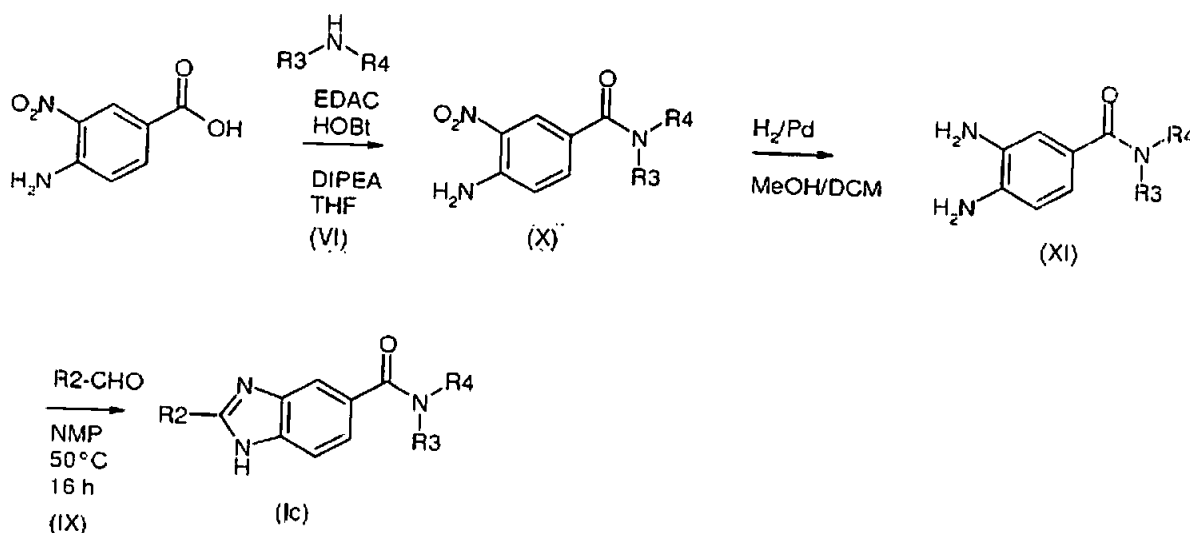


[00411] 4-Fluoro-3-nitrobenzoic acid may be reacted with an amine of formula (IV) wherein R^5 , R^8 , R^{10} , R^{11} and R^{12} are as defined above. This reaction may be carried out in a suitable

solvent (e.g., ethanol) in the presence of a base (e.g., DIPEA) at ambient temperature forming the secondary aniline of formula (V). The carboxylic acid of formula (V) then can be activated with HOBT and EDAC and reacted with an amine of the formula (VI) wherein NR^3R^4 is ring A as defined above. This reaction may be carried out in a suitable solvent (e.g., THF) in the presence of a base (e.g., DIPEA) at ambient temperature forming the compound of formula (VII). The nitro group of compounds of formula (VII) may be reduced by hydrogen under pressure in a suitable solvent (e.g., methanol/dichloromethane) in presence of a catalyst (e.g., palladium on activated carbon) at ambient temperature to form the diamine of formula (VIII). Compounds of formula (VIII) may be reacted with an aldehyde of formula (IX) wherein R^2 is as defined above. This reaction may be carried out in a suitable solvent (e.g., NMP) in the presence of a drying agent (e.g., molecular sieve 4 Å) at 50 °C to form compounds of formula (Ib).

[00412] General procedure (C)

[00413] Compounds of the formula (Ic) according to the invention wherein R^2 , R^3 , and R^4 are as defined for formula (I), with NR^3R^4 corresponding to ring A, can be prepared as outlined below:

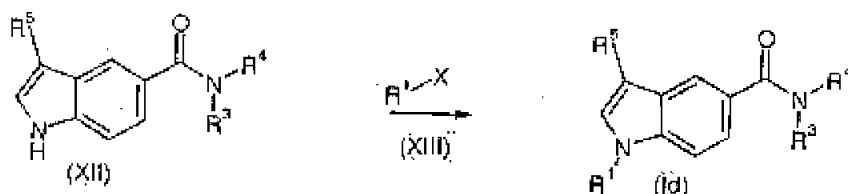


[00414] 4-Amino-3-nitrobenzoic acid can be activated with HOBT and EDAC and reacted with an amine of the formula (VI) wherein NR^3R^4 is ring A as defined above. This reaction may be carried out in a suitable solvent (e.g., THF) in the presence of a base (e.g., DIPEA) at ambient temperature to form the compound of formula (X). The nitro group of the formula (X) may be reduced by hydrogen under pressure in a mixture of methanol and dichloromethane in presence of a catalyst (e.g., palladium on activated carbon) at ambient tempera-

lure to form the diamine of the formula (XI). (XI) may be reacted with an aldehyde of the formula (IX) wherein R^2 is as defined above. This reaction may be carried out in NMP in the presence of a drying agent (e.g., molecular sieve 4 Å) at 50 °C to form target product (Ic).

5 [00415] General procedure (D)

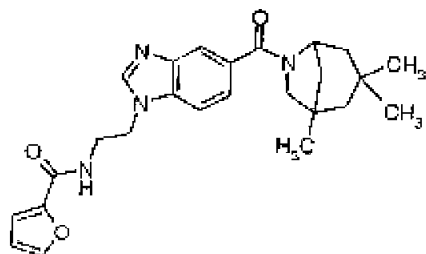
[00416] Compounds of the formula (Id) according to the invention wherein R^1 , R^3 , R^4 , and R^5 are as defined for formula (I), with NR^3R^4 corresponding to ring A, can be prepared as outlined below:



- 10 [00417] An indole of formula (XII) wherein R^3 , R^4 , and R^5 are as defined above, with NR^3R^4 corresponding to ring A, may be reacted with an alkyl/benzyl halide of the formula (XIII) wherein R^1 is as defined above in the presence of base (e.g., sodium hydride). This reaction may be carried out in a suitable solvent (e.g., DMF) at a temperature of up to reflux.

15 [00418] Example 1 (General procedure (A))

Furan-2-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

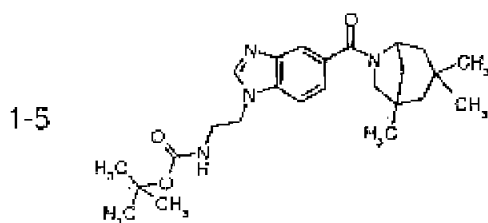


- 20 [00419] To a solution of 2-furoic acid (37 mg, 0.33 mmol) in dry THF (2 mL) at room temperature under an inert atmosphere of nitrogen were added HOBt (49 mg, 0.36 mmol) and EDAC (82 mg, 0.43 mmol), and the resulting solution was stirred for 30 min. [1-(2-Amino-ethyl)-1H-benzoimidazol-5-yl]-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone trifluoroacetate (150 mg, 0.33 mmol) was added to the solution followed by TEA (0.184 mL, 1.32 mmol), and the reaction mixture was stirred for 16 h at room temperature. The volatiles were evaporated *in vacuo* and the resulting solid was purified by preparative HPLC, dried *in vacuo* at 50 °C affording 100 mg (70%) of the title compound as a solid. MS-ESI m/z 435; ^1H NMR (400 MHz, DMSO- d_6) δ 0.88-0.99 (m, 6H), 1.07 (d, 3H), 1.29-1.41 (m, 4H), 1.50-
- 25

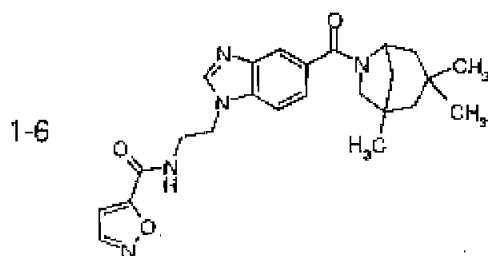
1.52 (m) and 2.10-2.11 (m, 1H), 1.76-1.79 (m, 1H), 9.02 (d), 3.13 (d), 3.32 (d) and 3.47 (d, 2H), 3.69 (t, 2H), 3.87-3.89 (m) and 4.39-4.41 (m, 1H), 4.56 (t, 2H), 6.58 (s, 1H), 6.98 (d, 1H), 7.48 (dd, 1H), 7.77-7.82 (m, 2H), 7.89 (t, 1H), 8.54-8.58 (m, 1H), 9.07 (d, 1H).

- 5 [00420] The following compounds were synthesised employing a similar method to the one described in Example 1 above:

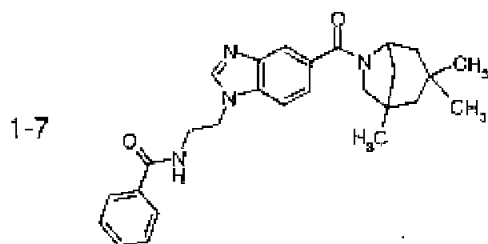
Ex.	Structure	MW	IUPAC Name	MS-ESI m/z
1-1		493.65	1-Acetyl-piperidine-4-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	494
1-2		412.53	2-Methoxy-N{2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide	413
1-3		445.57	N{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-isonicotinamide	446
1-4		382.51	N{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl}-acetamide	383



440.59 [2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-ethyl]-carbamic acid *tert*-butyl ester 441



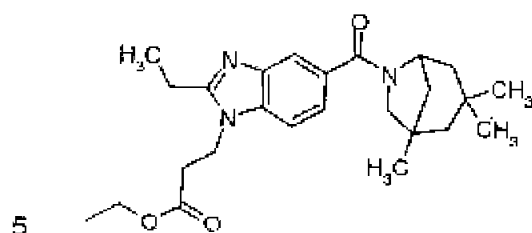
435.53 Isoxazole-5-carboxylic acid [2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-ethyl]-amide 436



444.58 *N*-[2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-ethyl]-benzamide 445

[00421] Example 2 (General procedure (B))

3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester



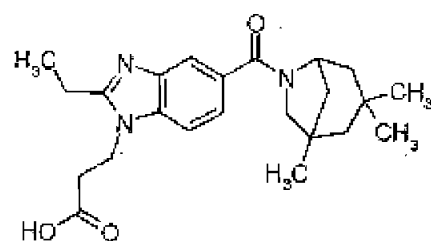
[00422] To a solution of 3-[2-amino-4-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-phenylamino]-propionic acid ethyl ester (250 mg, 0.645 mmol) in dry NMP (10 mL) at room temperature under an inert atmosphere of nitrogen was added approx. 200 mg of molecular sieve 4 Å followed by acetaldehyde (93 μ L, 1.29 mmol). The mixture was stirred for 16 hrs at 50°C. The reaction was quenched by the addition of water (100 mL) followed by extraction with diethyl ether (3 x 100 mL). The combined organic phases were washed with brine (4 x 200 mL), dried (MgSO_4), filtered, and evaporated *in vacuo*. The resulting oil was purified by preparative HPLC, dried *in vacuo* at 50°C affording 104 mg (38%) of the title compound as brown oil. MS-ESI m/z 426; ^1H NMR (400 MHz, CDCl_3) δ 0.88-1.06 (m, 6H),

1.11-1.23 (m, 7H), 1.24-1.28 (m) and 1.55-1.65 (m, 1H), 1.36-1.45 (m, 2H), 1.50 (t, 3H), 1.74-1.81 (m, 1H), 2.23-2.30 (m) and 3.12-3.20 (m, 1H), 2.81 (t, 2H), 2.96 (q, 2H), 3.22-3.35 (m, 1H), 3.32 (dd) and 3.62 (dd, 1H), 4.03-4.07 (m) and 4.63-4.67 (m, 1H), 4.13 (q, 2H), 4.45 (dt, 2H), 7.32-7.46 (m, 2H), 7.84 (d, 1H).

5

[00423] Example 3

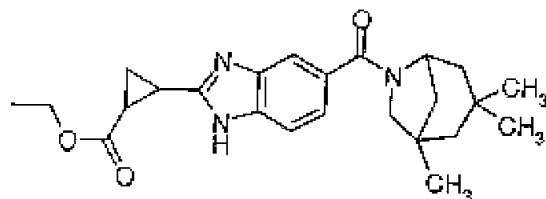
3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid



- 10 [00424] To a solution of 3-[2-ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester (104 mg, 0.244 mmol) in 96% ethanol (5 mL) at room temperature under an inert atmosphere of nitrogen was added 1N NaOH (aq) (0.3 mL, 0.3 mmol). The mixture was stirred for 2 hrs at room temperature. The reaction was quenched by the addition of water (5 mL) and acidified to pH 2 with 1N HCl followed by ex-
- 15 traction with diethyl ether (2 x 10 mL). The combined organic phases were washed with water (2 x 10 mL), brine (10 mL), dried (MgSO₄), filtered, and evaporated *in vacuo* affording 11 mg (11%) of the title compound as yellow oil. MS-ESI *m/z* 398; ¹H NMR (400 MHz, CDCl₃) δ 0.83-1.06 (m, 6H), 1.12-1.22 (m, 7H), 1.24-1.28 (m) and 1.46-1.54 (m, 1H), 1.30-1.39 (m, 2H), 1.33 (t, 3H), 1.63-1.74 (m, 1H), 2.22-2.32 (m) and 3.15-3.27 (m, 1H), 2.26 (t, 2H), 2.85 (t, 2H), 3.51 (q, 2H), 7.25-7.35 (m, 2H), 7.56 (d) and 7.74 (d, 1H).
- 20

[00425] Example 4 (General procedure (C))

2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester



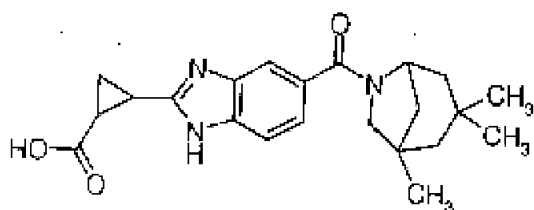
25

- [00426] To a solution of (3,4-diaminophenyl)-(1,3,3-trimethyl-6-azabicyclo[3.2.1]oct-6-yl)-methanone (500 mg, 1.74 mmol) in dry NMP (25 mL) at room temperature under an inert

atmosphere of nitrogen was added approx. 500 mg of molecular sieve 4 Å followed by ethyl 2-formyl-1-cyclopropanecarboxylate (0.51 mL, 3.86 mmol). The mixture was stirred for 16 hrs at 50°C. The reaction was quenched by the addition of water (100 mL) followed by extraction with diethyl ether (3 x 100 mL). The combined organic phases were washed with water (3 x 100 mL), brine (100 mL), dried (MgSO₄), filtered, and evaporated *in vacuo*. The resulting oil was purified by preparative HPLC, dried *in vacuo* at 50°C affording 60 mg (8%) of the title compound as a solid. MS-ESI *m/z* 410; ¹H NMR (400 MHz, CDCl₃) δ 0.88-1.06 (m, 6H), 1.07-1.20 (m, 4H), 1.25 (t, 3H), 1.27-1.34 (m) and 1.49-1.66 (m, 3H), 1.36-1.48 (m, 2H), 1.72-1.84 (m, 2H), 2.36-2.48 (m, 1H), 2.66-2.76 (m, 1H), 3.18-3.27 (m, 1H), 3.30 (d) and 3.65 (d, 1H), 4.00-4.06 (m) and 4.57-4.65 (m, 1H), 4.14 (q, 2H), 7.18-7.30 (m, 2H), 7.57 (d, 1H), 10.37 (br s, 1H).

[00427] Example 5

2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-cyclopropanecarboxylic acid



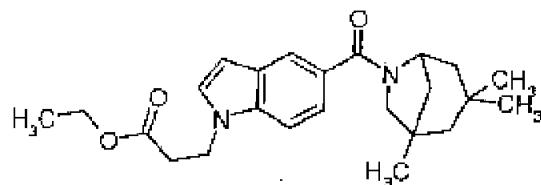
[00428] To a solution of 2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester (60 mg, 0.147 mmol) in 96% ethanol (3 mL) at room temperature under an inert atmosphere of nitrogen was added 1*N* NaOH (aq) (0.36 mL, 0.36 mmol). The mixture was stirred for 16 hrs at 50 °C. The reaction was quenched by the addition of water (3 mL) and acidified to pH 2 with 1*N* HCl followed by extraction with diethyl ether (2 x 5 mL). The combined organic phases were washed with water (2 x 5 mL), brine (5 mL), dried (MgSO₄), filtered, and evaporated *in vacuo* affording 49 mg (88%) of the title compound as a solid. MS-ESI *m/z* 382; ¹H NMR (400 MHz, CDCl₃) δ 0.87-1.06 (m, 6H), 1.08-1.20 (m, 4H), 1.30-1.38 (m, 1H), 1.39-1.45 (m) and 1.48-1.64 (m, 3H), 1.70-1.90 (m, 2H), 1.91-2.01 (m, 1H), 2.18-2.30 (m) and 2.43-2.61 (m) and 2.85-3.02 (m, 2H), 3.15 (t) and 3.66 (t, 1H), 3.20-3.34 (m, 1H), 3.88-4.01 (m) and 4.54-4.65 (m, 1H), 7.39-7.50 (m, 1H), 7.69-7.85 (m, 2H).

[00429] The following compounds were synthesised employing a similar method to the ones described in Examples 2, 3, 4 and 5 above:

Ex.	Structure	MW	IUPAC Name	MS-ESI <i>m/z</i>
5-1		411.54	3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester	412
5-2		437.58	2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester	438
5-3		383.49	3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid	384
5-4		409.53	2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid	410

[00430] Example 6 (General procedure (D))

3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester

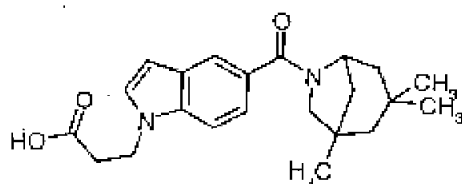


[00431] To a solution of (1*H*-indol-5-yl)-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone (250 mg, 0.84 mmol) in dry DMF (5 mL) at room temperature under an inert atmosphere of nitrogen was added sodium hydride (30 mg, 1.26 mmol, 60% dispersion in oil), and after stirring for 30 min ethyl bromopropionate (168 mg, 0.93 mmol) was added, and the

reaction mixture was stirred for 16 h at 60°C. The reaction was quenched by the addition of water (20 mL) followed by extraction with DCM (3 x 100 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting solid was purified by silica gel chromatography using a mixture of ethyl acetate and heptane (1:1) as eluent. Pure fractions were collected, the solvent evaporated *in vacuo* and dried *in vacuo* at 50°C affording 125 mg (37%) of the title compound as a solid. MS-ESI *m/z* 397; ¹H NMR (400 MHz, CDCl₃) δ 0.95 (d, 3H), 1.03 (d, 3H), 1.13-1.22 (m, 7H), 1.25-1.43 (m, 2H), 1.45 (s, 1H), 1.62-1.68 (m, 1H), 1.76-1.80 (m, 1H), 2.29-2.33 (m, 1H), 2.82 (t, 2H), 3.28-3.35 (m) and 3.63 (d, 1H), 4.12-4.14 and 4.64-4.66 (m, 1H), 4.11 (q, 2H), 4.47 (t, 2H), 6.52 (d, 1H), 7.18 (d, 1H), 7.32-7.39 (m, 2H), 7.74 (d, 1H).

[00432] Example 7

3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid



[00433] To a solution of 3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester (80 mg, 0.2 mmol) in ethanol (2 mL) was added 1N aqueous sodium hydroxide solution (2 mL), and the resulting solution stirred for 2 h. The solution was acidified with 1N hydrochloric acid solution before the organic volatiles were removed *in vacuo*, and the aqueous residues were extracted with DCM (3 x 5 mL). The combined organic phases were dried (MgSO₄), filtered, and evaporated *in vacuo*. The resulting solid was purified by preparative HPLC, dried *in vacuo* at 50°C affording 55 mg (74%) of the title compound as a solid. MS-ESI *m/z* 369; ¹H NMR (400 MHz, DMSO-*d*₆) δ 0.94 (d, 3H), 1.04 (d, 3H), 1.13-1.17 (m, 4H), 1.28-1.38 (m, 2H), 1.43-1.45 (m, 1H), 1.60-1.63 (m, 1H), 1.75-1.79 (m, 1H), 2.24-2.32 and 3.25-3.26 (m, 1H), 2.74 (t, 2H), 3.27-3.35 (m) and 3.62-3.65 (m, 1H), 4.08-4.10 and 4.62-4.63 (m, 1H), 4.39 (t, 2H), 6.47-6.48 (m, 1H), 7.17-7.23 (m, 3H), 7.70 (d, 1H).

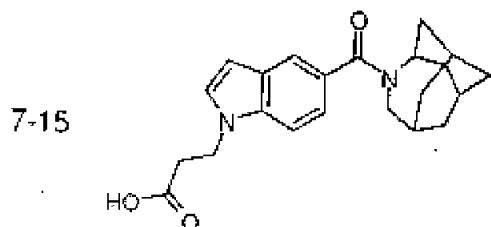
[00434] The following compounds were synthesised employing a similar method to the ones described in examples 6 and 7 above:

MS-
ESI
m/z

Ex.	Structure	MW	IUPAC Name	
7-1		410.56	[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid <i>tert</i> -butyl ester	411
7-2		354.45	[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid	355
7-3		437.58	1-Morpholin-4-yl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propan-1-one	438
7-4		423.56	1-Morpholin-4-yl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-ethanone	424
7-5		424.58	2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester	425
7-6		396.53	2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid	397

7-7		396.53	2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid methyl ester	397
7-8		396.53	3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid methyl ester	397
7-9		382.50	3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid	383
7-10		382.50	2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid	383
7-11		430.55	3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid	431
7-12		444.57	4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester	445
7-13		430.55	4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid	431
7-14		394.51	3-[5-(4-Aza-tricyclo[4.3.1.1*3,8*]-undecane-4-carbonyl)-indol-1-yl]-propionic acid ethyl ester	395

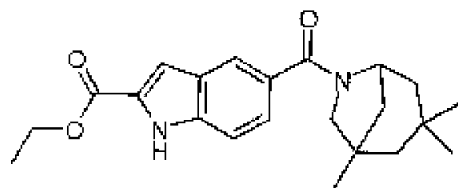
db



366.46 3-[5-(4-Aza-tricyclo[4.3.1.1*3,8*]-undecane-4-carbonyl)-indol-1-yl]-propionic acid 367

[00435] Example 8

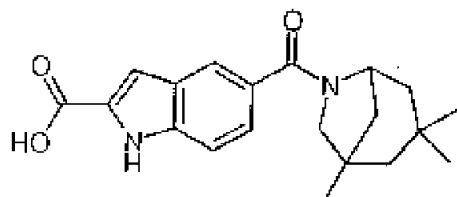
5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-2-carboxylic acid ethyl ester



[00436] To a solution of 1H-Indole-2,5-dicarboxylic acid 2-ethyl ester (890 mg, 3.8 mmol) in dry DMF (10 mL) at room temperature under an inert atmosphere of nitrogen was added HOBt (570 mg, 4.2 mmol) and EDAC (951 mg, 4.9 mmol), and the resulting solution was stirred for 30 min. 1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane hydrochloride (796 mg, 4.2 mmol) was added to the solution followed by DIPEA (1.98 mL, 11.4 mmol), and the reaction mixture was stirred for 16 h at room temperature. The reaction was quenched by the addition of water (20 mL) followed by extraction with DCM (3 x 50 mL). The combined organic phases were dried (MgSO₄), filtered, and evaporated *in vacuo*. The resulting solid was purified by silica gel chromatography using a mixture of ethyl acetate and heptane (1:2) as eluent. Pure fractions were collected, the solvent evaporated *in vacuo* and dried *in vacuo* at 50°C affording 800 mg (57%) of the title compound as a solid. MS-ESI *m/z* 369; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (d, 3H), 1.04 (d, 3H), 1.14-1.19 (m, 4H), 1.24-1.29 (m, 2H), 1.39-1.45 (m, 4H), 1.58-1.63 (m, 1H), 1.76-1.79 (m, 1H), 3.25-3.30 (m, 1H), 3.35 (d) and 3.65 (d, 1H), 4.06-4.09 (m) and 4.64-4.67 (m, 1H), 4.42 (q, 2H), 7.27 (s, 1H), 7.39-7.46 (m, 2H), 7.82 (d, 1H), 9.05 (s, 1H).

Example 9

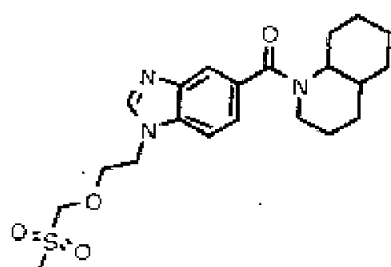
5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-2-carboxylic acid



[00437] To a solution of 5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-indole-2-carboxylic acid ethyl ester (500 mg, 1.35 mmol) in ethanol (10 mL) was added 1N aqueous sodium hydroxide solution (10 mL), and the resulting solution stirred for 16 h. The solution was acidified with 1N hydrochloric acid solution before the organic volatiles were removed *in vacuo* and the aqueous residues were extracted with DCM (3 x 5 mL). The combined organic phases were dried (MgSO₄), filtered and evaporated *in vacuo*. The resulting solid was dried *in vacuo* at 50°C affording 460 mg (100%) of the title compound as a solid. MS-ESI *m/z* 341; ¹H NMR (300 MHz, DMSO-*d*₆) δ 0.88-0.99 (m, 6H), 1.07 (d, 3H), 1.16-1.19 (m, 1H), 1.27-1.50 (m, 4H), 1.74-1.77 (m, 1H), 3.10-3.19 (m, 1H), 3.40-3.48 (m, 1H), 3.99-4.07 (m) and 4.38-4.40 (m, 1H), 7.16 (s, 1H), 7.32-7.37 (m, 1H), 7.42-7.48 (m, 1H), 7.77 (d, 1H), 11.93 (s, 1H), 13.04 (s, 1H).

Example 10

[1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone



Step-A:

4-(2-Hydroxyethylamino)-3-nitro-benzoic acid methyl ester:

4-Fluoro-3-nitro-benzoic acid methyl ester (3 g, 15.64 mmol) was dissolved in DMF (20 ml) and DIPEA (5.8 g, 18.07 mmol) was added. 2-Aminoethanol (1.1 g, 18.07 mmol) was then added slowly by maintaining the temperature <20°C. Stirring continued at ambient temperature for 1 h. After checking the completion of reaction by TLC, the reaction mixture was

added onto the ice cold water. The yellow solid which separated out was filtered, washed with cold water and finally washed with hexane affording 3.3 g (92%) of 4-(2-hydroxyethylamino)-3-nitro-benzoic acid methyl ester. ¹H NMR(300 MHz, CDCl₃) δ 3.5 (q, 2H), 3.7 (q, 2H), 3.9 (s, 3H), 5.1 (t, 1H), 7.2 (d, 1H), 8.0 (d, 1H), 8.6 (s, 1H).

5

Step-B:

3-Amino-4-(2-hydroxy-ethylamino)-benzoic acid methyl ester:

To a solution of 4-(2-hydroxy-ethylamino)-3-nitro-benzoic acid methyl ester (3.0 g, 12.4 mmol) in methanol was added 10% Pd/C (800 mg). The mixture was hydrogenated at 1 atmospheric pressure for 2 h. The catalyst was filtered off and the methanol evaporated to give 2.6 g (99%) of 3-amino-4-(2-hydroxyethylamino)-benzoic acid methyl ester.

10

Step-C:

1-(2-Hydroxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

3-Amino-4-(2-hydroxy-ethylamino)-benzoic acid methyl ester (2.6 g, 12.0 mmol) was dissolved in formic acid (20 mL). The solution was heated at 45°C for 1 h. After checking the completion of reaction by TLC, formic acid was evaporated at <40°C under reduced pressure and the resulting solid was recrystallized from EtOAc. The above solid was dissolved in 3N HCl, stirred at ambient temperature for 1 h, basified back with saturated sodium bicarbonate solution and extracted with EtOAc. The organic layer was evaporated to give 2.1 g (78%) of 1-(2-hydroxy-ethyl)-1H-benzimidazole-5-carboxylic acid methyl ester. MS-ESI *m/z* 221 (M+1): ¹H NMR(300 MHz, DMSO-d₆) δ 3.7 (q, 2H), 3.9 (s, 3H), 4.3 (t, 3H), 5.0 (t, 1H), 7.7 (d, 1H), 7.9 (dd, 1H), 8.25 (s, 1H), 8.35 (s, 1H).

20

25 Step-D:

1-(2-Methylsulfanylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

A solution of 1-(2-hydroxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (0.5 g, 2.27 mmol) in a mixture of dry THF:DME (25 mL : 15 mL) was cooled to 5°C. NaH (0.031 g, 3.4 mmol) was added and stirred for 30 min at the same temperature. A mixture of chloromethyl methyl sulphide (0.285 g, 2.95 mmol) and NaI (0.408 g, 2.95 mmol) was then added slowly followed by TBAI (0.087 g, 0.22 mmol). The reaction was allowed to stir for overnight at ambient temperature. It was then quenched with saturated ammonium chloride solution and extracted with EtOAc. The organic layer was evaporated to give 0.53 g (83%) of 1-(2-methylsulfanylmethoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester. ¹H NMR(300

30

MHz, CDCl₃) δ 1.9 (s, 3H), 3.9 (t, 2H), 3.95 (s, 3H), 4.4 (t, 2H), 4.6 (s, 2H), 7.45 (d, 1H), 8.05 (m, 2H), 8.5 (d, 1H)

Step-E:

- 5 1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

A solution of 1-(2-methylsulfonylmethoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (3.0 g, 10.7mmoles) in methanol (30 mL) was cooled to 0°C and to this was added a solution of oxone (4.88 g, 7.94 mmoles) in water. The solution was stirred at the ambient temperature for 12 h. It was quenched with 5% sodium bicarbonate solution and extracted with EtOAc. Removal of solvent gave 2.0 g (60%) of 1-(2-methane-sulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid methyl ester. MS-ESI *m/z* 313(M+1); ¹H NMR(300 MHz,DMSO-d₆) δ 2.9 (s, 3H), 4.0 (s, 3H), 4.25 (t, 2H), 4.65 (t, 2H), 4.75 (s, 2H), 7.85 (d, 2H), 8.0 (dd, 1H), 8.35 (s, 1H), 8.5 (s, 1H)

- 15 Step-F:

1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid:

1-(2-Methanesulfonylmethoxyethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (1.0 g, 3.2 mmoles) was dissolved in THF (5 mL). A solution of LiOH (0.38 g, 16 mmol) in water was added and the mixture stirred vigorously for 1 h. The reaction was acidified with 2N HCl to pH 2 at 5-10° C. It was then filtered to give 0.8 g (84%) of 1-(2-methanesulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid. ¹H NMR(300 MHz,DMSO-d₆) δ 2.9 (s, 3H), 4.2 (t, 2H), 4.5 (t, 2H), 4.65 (s, 2H), 7.75 (d, 1H), 7.9 (dd, 1H), 8.25 (d, 1H), 8.35 (s, 1H), 12.7 (s, 1H)

- 25 Step-G:

[1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone:

To a solution of 1-(2-methanesulfonylmethoxyethyl)-1H-benzimidazole-5-carboxylic acid (0.5 g, 1.677mmol) in DMF (5mL) was added decahydroquinoline (0.257g, 1.845 mmol) followed by HOBT (0.25 g, 1.845 mmol) and DIPEA (0.65 g, 5 mmol). The reaction mixture was cooled to 0° C and EDCI.HCl (0.354 g, 1.845 mmol) was added. It was gradually raised to ambient temperature and stirring continued for 12 h. The solvent was then evaporated, the residue diluted with water (5 mL) and extracted with CH₂Cl₂ (3x25 mL). The combined organic phases were washed with brine solution, dried (Na₂SO₄) and the solvent evaporated affording the crude amide which was purified by preparative HPLC to give 0.3 g (43%) of [1-

(2-methanesulfonylmethoxy-ethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)-methanone. MS-ESI m/z 420 ($M+1$): ^1H NMR (300 MHz, DMSO- d_6) δ 1.1-1.9 (br. 13H), 2.8 (s, 3H), 3.0-3.3 (m, 2H), 4.15 (t, 2H), 4.5 (t, 2H), 4.65 (s, 2H), 7.3 (m, 1H), 7.6 (m, 1H), 7.7 (d, 1H), 8.3 (s, 1H)

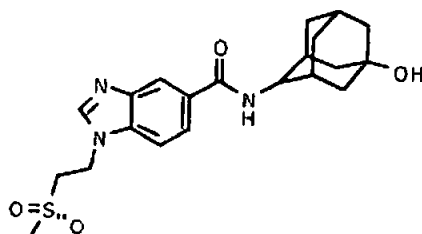
5

[00438] The following compounds were synthesised employing a similar method to the ones described in example 10 above:

Ex.	Structure	MW	IUPAC Name	MS-ESI m/z
10-1		407.49	(3-Hydroxy-8-aza-bicyclo-[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1H-benzoimidazol-5-yl]-methanone	408
10-2		447.56	<i>trans</i> -1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	448
10-3		447.56	<i>Cis</i> -1-(2-Methanesulfonylmethoxy-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	448
10-4		407.49	(3-Hydroxy-8-aza-bicyclo-[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1H-benzoimidazol-5-yl]-methanone	408

10 Example 11

1-(2-Methanesulfonyl-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide



Step A:

2-(2-Methylsulfonyl-ethyl)isoindol-1,3-dione:

To a solution of N-bromoethylphthalimide (1g, 3.953 mmol) in methanol (25 mL), was added NaOMe (0.415 g, 5.929 mmol) under N₂ atmosphere at 0°C. The reaction mixture was allowed to stir at ambient temperature for 2 h. The reaction mass was concentrated, diluted with water and extracted with EtOAc (3x25 mL). The organic layer was washed with brine solution and dried over anhydrous Na₂SO₄ and concentrated to give 2-(2-Methylsulfonyl-ethyl)isoindol-1,3-dione (0.88 g, 80%). MS-ESI *m/z* 222 (M+1); ¹H NMR (300 MHz, CDCl₃) δ 7.7 (m, 2H), 7.9 (m, 2H), 3.9 (t, 1H), 2.8 (t, 2H), 2.2 (s, 3H).

Step-B:

2-(2-Methanesulfonyl-ethyl)-isoindole-1,3-dione:

To a solution of 2-(2-methylsulfonyl-ethyl)-isoindole-1,3-dione (2.5 g, 11.30 mmol) in acetic acid (10 mL) was added 30% hydrogen peroxide (6 mL) at 0°C. The reaction mixture was brought to room temp and stirred for 2 h. Excess hydrogen peroxide in the reaction mixture was quenched with a saturated solution of sodium sulphite, and the resulting solution extracted with CHCl₃. The organic layer was washed with brine, dried over Na₂SO₄ and evaporated to give 2-(2-Methanesulfonyl-ethyl)-isoindole-1,3-dione (2.3 g, 83%). ¹H NMR (300 MHz, CDCl₃) δ 7.9 (m, 2H), 7.8 (m, 2H), 4.2 (t, 1H), 3.4 (t, 1H), 3.1 (s, 3H).

Step-C:

2-Methanesulfonyl-ethylamine:

Hydrazine hydrate (15 mL) was added to a solution of 2-(2-methanesulfonyl-ethyl)-isoindole-1,3-dione (3.123 g, 12.344 mmol) in a mixture of CHCl₃-ethanol (1:1) at 0°C. It was then stirred overnight at room temperature. It was filtered and the filtrate concentrated to give 2-Methanesulfonyl-ethylamine (1.2 g, 80%). ¹H NMR (300 MHz, CDCl₃) δ 3.05 (t, 2H), 3.15 (t, 2H), 3.0 (s, 3H).

Step-D:

4-(2-Methanesulfonyl-ethylamino)-3-nitro-benzoic acid methyl ester:

To a solution of 2-methanesulfonyl-ethylamine (1.3 g, 10.56 mmol) and DIPEA (3.5 mL, 31.69 mmol) in DMF (15 mL) was added 4-fluoro-3-nitro-benzoic acid methyl ester (1.2 g, 15.84 mmol) in portions. The reaction mixture was allowed to stir for 15 h at room temperature. It was then diluted with water and extracted with EtOAc. The organic layers were washed with water, brine and concentrated to give 4-(2-methanesulfonyl-ethylamino)-3-nitro-benzoic acid methyl ester (83%). ¹H NMR (300 MHz, CDCl₃) δ 8.9 (d, 1H), 8.6 (t, 1H), 8.2 (d, 1H), 6.9 (d, 1H), 4.0 (q, 2H), 3.9 (s, 3H), 3.4 (t, 2H), 3.0 (s, 3H).

Step-E:

1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid methyl ester:

4-(2-Methanesulfonyl-ethylamino)-3-nitro-benzoic acid methyl ester (1.63 g, 5.40 mmol) was dissolved in methanol, and 10% Pd/C (150mg) was added to it under N₂ atmosphere. The reaction mixture was then hydrogenated at 1 atmospheric pressure at room temp for 2 h. It was filtered through celite and the filtrate concentrated to yield the desired product. The crude material (1.32 g, 4.85 mmol) was taken in formic acid (10 mL) and allowed to stir at 50° C for 4 h. The reaction mass was concentrated, diluted with water and extracted with EtOAc. The organic layers were washed with saturated NaHCO₃, brine, dried over Na₂SO₄ and concentrated to give 1-(2-methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (77%). ¹H NMR (300 MHz, DMSO-d₆) δ 8.45 (s, 1H), 8.3 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 4.75 (t, 2H), 3.9 (s, 3H), 3.8 (t, 2H), 3.0 (s, 3H).

Step F:

1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid:

To a solution of 1-(2-methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid methyl ester (0.2 g, 7.09 mmol) in methanol was added LiOH (50mg) followed by water (1 mL). The reaction mixture was allowed to stir at room temp for 2h. it was then concentrated to remove methanol and the aqueous layer was acidified with citric acid. The precipitated product was filtered to give 1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid (90%). MS-ESI *m/z* 269 (M+1); ¹H NMR (300 MHz, DMSO-d₆) δ 12.6 (br, 1H), 8.4 (s, 1H), 8.2 (s, 1H), 7.9 (d, 1H), 7.8 (d, 1H), 4.8 (t, 2H), 3.8 (t, 2H), 3.0 (s, 3H).

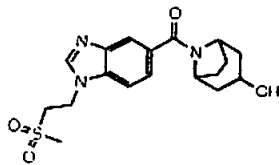
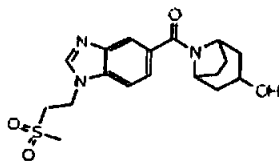
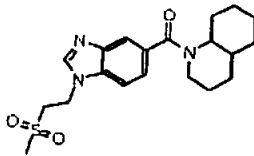
Step G:

103

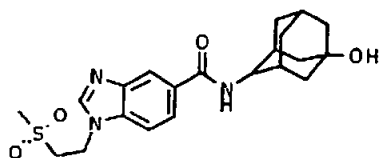
1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide:

To a solution of 1-(2-methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid (0.2 g, 0.74 mmol) in DMF (5 mL) was added HOBt (0.15 g, 0.89 mmol), DIPEA (0.4 mL, 2.23 mmol), 4-aminoadamantan-1-ol (0.15 g 0.89 mmol) and EDCI (0.21 g, 1.11 mmol) successively under N₂ atmosphere. The reaction mixture was allowed to stir over night at room temperature. It was diluted with water and extracted with CHCl₃. The organic layer was washed with saturated NaHCO₃ solution, brine and dried over anhydrous Na₂SO₄. Concentration of the organic layer gave 1-(2-methanesulfonyl-ethyl)-1H-benzoimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide (0.05 g). MS-ESI *m/z* 418 (M+1); ¹H NMR (300 MHz, CDCl₃) δ 8.2 (s, 1H), 8.1 (s, 1H), 7.9 (d, 1H), 7.5 (d, 1H), 6.4 (d, 1H), 4.8 (t, 2H), 4.2 (m, 1H), 3.6 (t, 2H), 2.7 (s, 3H), 2.4 (s, 2H), 2.3 (m, 1H), 1.8 (m, 11H).

[00439] The following compounds were synthesised employing a similar method to the ones described in example 11 above:

Ex.	Structure	MW	IUPAC Name	MS-ESI <i>m/z</i>
11-1		377,47	(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-methanone	378
11-2		377.47	(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-methanone	378
11-3		389,52	[1-(2-Methanesulfonyl-ethyl)-1H-benzoimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone	390

11-4



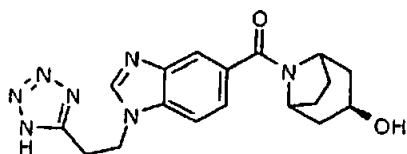
417,53

1-(2-Methanesulfonyl-ethyl)-
1H-benzimidazole-5-
carboxylic acid (5-hydroxy-
adamantan-2-yl)-amide

418

Example 12

(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone



5

Step-A:

4-(2-Cyano-ethylamino)-3-nitro-benzoic acid methyl ester:

To a solution of 4-fluoro-3-nitro-benzoic acid methyl ester (4.95 g, 24.8 mmol) in DMF (25 ml) was added 3-aminopropionitrile fumarate (3.18 g, 12.4 mmol) and DIPEA (15 ml, 84.3 mmol). The mixture was stirred at room temperature for 2 h. The solvent was evaporated under vacuum and the residue diluted with water (50 mL). It was extracted with EtOAc (3x100 mL) and the organic phase washed with brine solution and dried (Na₂SO₄). Removal of solvent gave 4-(2-cyanoethylamino)-3-nitro-benzoic acid methyl ester (6.19 g, 98.5%). MS-ESI *m/z* 250 (M+1); ¹H NMR (300 MHz, CDCl₃) δ 2.8 (t, 2H), 3.8 (m, 2H), 6.9 (d, 1H), 8.2 (m, 1H), 8.5 (t, 1H), 8.9 (s, 1H)

Step-B:

3-Amino-4-(2-cyanoethylamino)-benzoic acid methyl ester:

To a solution of ammonium chloride (21.7 g, 406.3 mmol) in water (200 mL) was added 4-(2-cyanoethylamino)-3-nitro-benzoic acid methyl ester (6.1 g, 24.5 mmol) followed by zinc powder (42.8 g, 655.9 mmol). The mixture was heated to 60° C for 3 h. It was filtered hot and washed with EtOAc. The filtrate was further extracted with EtOAc and the combined organic phase washed with brine solution. The organic layer was evaporated to give 4.1 g (75%) of 3-amino-4-(2-cyano-ethylamino)-benzoic acid methyl ester. MS-ESI *m/z* 220 (M+1); ¹H NMR (300 MHz, CDCl₃) δ 2.7 (t, 2H), 3.6 (m, 2H), 3.8 (s, 3H), 4.3 (bs, 1H), 6.6 (d, 1H), 7.45 (d, 1H), 7.6 (d, 1H)

Step-C:

1-(2-Cyano-ethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

To 3-amino-4-(2-cyano-ethylamino)-benzoic acid methyl ester (4.0 g) was added formic acid (25 ml) and the mixture heated to 50° C for 3 h. It was then concentrated and the residue
5 recrystallised from EtOAc to afford 4.0 g (95%) of 1-(2-cyanoethyl)-1H-benzimidazole-5-carboxylic acid methyl ester. MS-ESI m/z 230 ($M+1$); ^1H NMR (300 MHz, $CDCl_3$) δ 2.95 (t, 2H), 4.0 (s, 3H), 4.55 (t, 2H), 7.4 (d, 1H), 8.1 (m, 1H), 8.15 (s, 1H), 8.55 (s, 1H)

Step-D:

10 1-(2-Cyanoethyl)-1H-benzimidazole-5-carboxylic acid:

To a solution of 1-(2-cyanoethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (4.0 g, 17.4 mmol) in THF (30 mL) was added LiOH (1.67 g, 69.79 mmol) in water (8 mL) followed by MeOH (2 mL). Stirring continued at the ambient temperature for 1 h. It was then concentrated and acidified with 2N HCl. The solids formed were filtered and dried which afforded 1-
15 (2-cyanoethyl)-1H-benzimidazole-5-carboxylic acid (3.5 g, 95%). ^1H NMR (300 MHz, $DMSO-d_6$) δ 3.1 (t, 2H), 4.6 (t, 2H), 7.8 (d, 1H), 7.9 (dd, 1H), 8.25 (d, 1H), 8.42 (s, 1H)

Step-E:

3-[5-(3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-propionitrile:

20 To a solution of 1-(2-cyanoethyl)-1H-benzimidazole-5-carboxylic acid (0.25 g, 1.16 mmol) in DMF (2.5 mL) was added with stirring HOBt (0.17 g, 1.27 mmol) followed by exo-nortropinol hydrochloride (0.21 g, 1.27 mmol), DIPEA (0.45 g, 3.48 mmol). EDCI.HCl was then added and it was stirred at room temperature for 12 h. The solvent was then evaporated and to the residue diluted with water (5 mL) and extracted with CH_2Cl_2 . The organic
25 phase was washed with brine solution, dried (Na_2SO_4) and the solvent evaporated. The residue was purified by preparative HPLC which afforded 0.26 g (67%) of 3-[5-(3-Hydroxy-8-aza-bicyclo [3.2.1] octane-8-carbonyl)-benzimidazol-1-yl]-propionitrile. MS-ESI m/z 325 ($M+1$).

30 Step-F:

3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone:

To a solution of 3-[5-(3-Hydroxy-8-aza-bicyclo [3.2.1] octane-8-carbonyl)-benzimidazol-1-yl]-propionitrile (250 mg, 0.7 mmol) in DMF (5 mL) was added sodium azide (184 mg, 2.83
35 mmol) and ammonium chloride (152 mg, 2.83 mmol) and heated to 100°C for 12 h. The sol-

vent was evaporated completely; methanol (20 mL) was added and filtered. The filtrate was concentrated and the residue purified by preparative HPLC to give 36 mg (13 %) of 3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzoimidazol-5-yl}-methanone. MS-ESI m/z 368 (M+1); ^1H NMR (300 MHz, DMSO- d_6) δ 1.3-2.0 (m, 8H), 3.15 (s, 1H), 3.5 (t, 2H), 3.9-4.0 (m, 2H), 4.6 (br, 1H), 4.75 (t, 2H), 7.4 (dd, 1H), 7.6-7.7 (m, 2H), 8.25 (s, 1H).

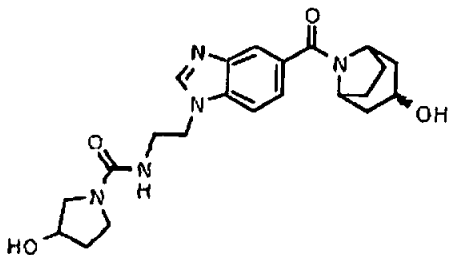
[00440] The following compounds were synthesised employing a similar method to the ones described in example 11 above:

Ex.	Structure	MW	IUPAC Name	MS-ESI m/z
12-1		379,41	(Octahydro-quinolin-1-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzoimidazol-5-yl}-methanone	380
12-2		407,48	Trans-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	355
12-3		477.48	Cis-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	438

10

Example 13

3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide



Step-A:

4-Fluoro-3-nitro-benzoic acid methyl ester:

To a solution of 4-fluoro-3-nitrobenzoic acid (16.0 g, 0.0864 mol) in dry DMF (100 mL) was added with stirring potassium carbonate (59.0 g, 0.43 mol) followed by methyl iodide (24.5 g, 0.173 mol) and the mixture was stirred for 3 h at ambient temperature. The reaction mixture was diluted with ice water (500 mL), extracted with EtOAc (3x100 mL) and the combined organic phases were washed with water (3x100 mL) and saturated brine solution (100 mL). The organic phase was dried (Na_2SO_4) and the solvent evaporated affording 17.0 g (99%) of 4-fluoro-3-nitro-benzoic acid methyl ester.

10

Step-B:

4-(2-Chloroethylamino)-3-nitro-benzoic acid methyl ester:

To a solution of 4-fluoro-3-nitro-benzoic acid methyl ester (10.0 g, 0.0502 mol) in dry DMF (100 mL) was added with stirring potassium carbonate (59.0 g, 0.43 mol) followed by 2-chloroethylamine hydrochloride (8.7 g, 0.075 mol) and the mixture was stirred for 15 h at ambient temperature. The reaction mixture was diluted with ice water (500 mL) and the solid precipitated was filtered, washed with water and dried under vacuum to get a yellow solid (12.7 g, 98%). MS-ESI m/z 259 ($M+1$).

15

20 Step-C:

3-Amino-4-(2-chloroethylamino)-benzoic acid methyl ester:

To a solution of 4-(2-chloroethylamino)-3-nitro-benzoic acid methyl ester (12.7 g, 0.0492 mol) in methanol (500 mL) was added 10% Pd/C (1.3 g) under a N_2 atmosphere. The reaction mixture was hydrogenated in a Parr apparatus at 3 kg pressure for 2 h. The catalyst was filtered over celite and the filtrate was concentrated affording 11.0 g (98 %) of 3-amino-4-(2-chloroethylamino)-benzoic acid methyl ester as a solid.

25

Step-D:

30 1-(2-Chloroethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

To 3-amino-4-(2-chloroethylamino)-benzoic acid methyl ester (11.0 g, 0.0482 mol) was added HCO_2H (30 mL) and heated at 100°C for 1 h. The reaction was cooled to ambient temperature and diluted with ice water (100 mL). The pH of the reaction mixture was adjusted to 7 with NaHCO_3 and the solid precipitated was filtered, washed with water and dried

30

under vacuum to get a pale green solid (9.9 g, 86%) of 1-(2-chloroethyl)-1H-benzimidazole-5-carboxylic acid methyl ester. MS-ESI m/z 239 ($M+1$).

Step-E:

5 1-(2-Azidoethyl)-1H-benzimidazole-5-carboxylic acid methyl ester:

To a solution of 1-(2-chloroethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (9.9 g, 0.0416 mol) in dry DMSO (90 mL) was added with stirring NaN_3 (5.4 g, 0.0832 mol) and the mixture was stirred for 15 h at 75° C. The reaction mixture was cooled to ambient temperature and diluted with ice water (500 mL) and the solid precipitated was filtered, washed with water and dried under vacuum affording 9.3 g (91%) of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid methyl ester as a solid. MS-ESI m/z 246 ($M+1$); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.8 (t, 2H), 3.9 (s, 3H), 4.5 (t, 2H), 7.8 (d, 1H), 7.9 (dd, 1H), 8.25 (s, 1H), 8.4 (s, 1H).

15 Step-F:

1-(2-Azido-ethyl)-1H-benzimidazole-5-carboxylic acid:

To a solution of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid methyl ester (5.0 g, 0.0204 mol) in THF/water 1:1 (100 mL) was added with stirring LiOH (0.73 g, 0.0306 mol) and the mixture was stirred for 5 h at ambient temperature. The solvent was evaporated and to the residue was added ice water (100 mL). The pH of the reaction mixture was adjusted to 5 with 1N HCl and the mixture extracted with EtOAc (5x100 mL). The combined organic phases were washed with saturated brine solution (100 mL), dried (Na_2SO_4) and the solvent evaporated affording 4.2 g (89%) of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid as an ash coloured solid. MS-ESI m/z 232 ($M+1$); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 3.8 (t, 2H), 4.5 (t, 2H), 7.8 (d, 1H), 7.9 (d, 1H), 8.25 (s, 1H), 8.4 (s, 1H).

Step-G:

[1-(2-Azidoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)methanone:

To a solution of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid (0.82 g, 0.00357 mol) in dry DMF (8.0 mL) was added with stirring HOBt (0.578 g, 0.00428 mol), DIPEA (1.9 mL, 0.0107 mol), 8-azabicyclo[3.2.1]octan-3-ol (0.5 g, 0.00393 mol) and the mixture was cooled to 0° C. To the resulting mixture was added EDCI (0.82 g, 0.00428 mol) and stirred for 15 h at ambient temperature. The reaction mixture was then diluted with ice water (100 mL), extracted with EtOAc (3x50 mL) and the combined organic phases were washed with water (3x50 mL) and saturated brine solution (50 mL). The organic phase was dried (Na_2SO_4) and

the solvent evaporated affording (1.1 g, 98%) of [1-(2-azidoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)methanone. MS-ESI m/z 341 ($M+1$).

Step-H:

- 5 [1-(2-Amino-ethyl)-1H-benzoimidazol-5-yl]-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-methanone:

To a solution of [1-(2-azidoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)methanone (1.1 g, 0.0035 mol) in methanol (15 mL) was added 10% Pd/C (0.17 g) and the mixture hydrogenated at 3 kg pressure for 1 h. The catalyst was filtered over celite and
10 the filtrate was concentrated to give [1-(2-aminoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)methanone (0.87 g, 86%). MS-ESI m/z 315 ($M+1$).

Step-I:

- 15 3-Hydroxypyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}amide:

A) 3-Hydroxypyrrolidine-1-carbonyl chloride:

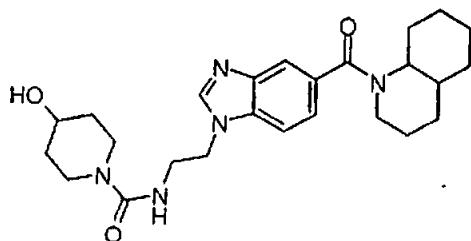
To a solution of pyrrolidin-3-ol (0.083 g, 0.955 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) and cooled 0° C. To the resulting mixture was added triphosgene (0.127 g, 0.429 mmol) and the mixture was stirred for 2 h at an ambient temperature.
20

B) To a solution of [1-(2-aminoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)methanone (0.25 g, 0.79 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0° C. To this reaction mixture was added compound A slowly and stirred for 3 days at an ambient temperature. The solvent was evaporated and the residue
25 purified by preparative HPLC to afford 175 mg (54 %) of 3-hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide. MS-ESI m/z 428 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ 1.5 (t, 1H), 1.9 (m, 6H), 2.1 (m, 3H), 3.2 (m, 2H), 3.5 (t, 2H), 4.2 (m, 2H), 4.4 (m, 1H), 4.5 (t, 2H), 4.8 (s, 1H), 7.45 (dd, 1H), 7.7 (d, 1H), 7.8 (s, 1H), 8.25 (s, 1H),
30

Example 14

4-Hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

MO



Steps A-F is similar to those used in example 13 above.

Step-G:

- 5 [1-(2-azidoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone:

To a solution of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid (1 g, 0.00433 mol) in dry DMF (7.0 mL) was added with stirring HOBt (0.876 g, 0.00649 mol), DIPEA (2.25 mL, 0.0129 mol), decahydroquinoline (0.902 g, 0.00649 mol) at 0° C. To the resulting mixture was added EDCI (1.24 g, 0.00649 mol) and stirred for 15 h at an ambient temperature. The reaction mixture was diluted with ice water (100 mL) and extracted with EtOAc (3x50 mL). The combined organic phases were washed with water, dried (Na₂SO₄) and the solvent evaporated to give [1-(2-azidoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone (1.5 g, 98%).

- 15 Step-H:

[1-(2-Aminoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone:

To a solution of [1-(2-azidoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone (1.8 g, 0.0051 mol) in methanol (10 mL) was added 10% Pd/C (0.2 g). The reaction mixture was hydrogenated at 3 kg pressure for 2 h. The catalyst was filtered over celite and the filtrate was concentrated to give [1-(2-aminoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone (1.5 g, 90%).

Step-I:

- 25 4-Hydroxypiperidine-1-carboxylic acid {2-[5-(octahydroquinoline-1-carbonyl)benzimidazol-1-yl]ethyl}amide:

A) 4-Hydroxypiperidine-1-carbonyl chloride:

To a solution of piperidin-4-ol (0.074 g, 0.73 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0° C. To the resulting mixture was added triphosgene (0.076 g, 2.1 mmol) and stirred for 2 h at ambient temperature.

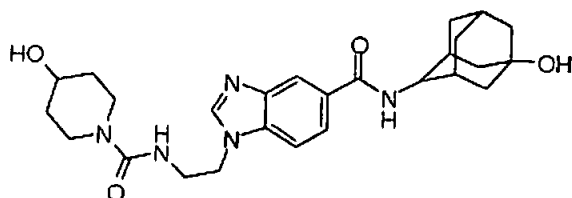
B) To a solution of [1-(2-aminoethyl)-1H-benzimidazol-5-yl]-(octahydroquinolin-1-yl)methanone (0.2 g, 0.613 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0° C. To this reaction mixture was added compound A slowly and stirred for 2 h at ambient temperature. The solvent was evaporated and the residue purified by preparative HPLC affording cis and trans isomers of 4-hydroxypiperidine-1-carboxylic acid [2-[5-(octahydroquinoline-1-carbonyl)-benzimidazol-1-yl]ethyl]amide.

Isomer I (12 mg): MS-ESI m/z 454 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ 1.30-1.80 (m, 13H), 2.0 (m, 3H), 2.9 (m, 2H), 3.2 (m, 2H), 3.55 (t, 2H), 3.7 (m, 3H), 4.5 (t, 2H), 7.35 (d, 1H), 7.7 (m, 2H), 8.25 (s, 1H). HPLC (VERYPOL.M): t_r = 7.73 min (95 %).

Isomer II (8 mg): MS-ESI m/z 454 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ 1.2 (m, 3H), 1.4 (m, 8H), 1.7 (m, 6H), 3.0 (m, 2H), 3.6 (t, 2H), 3.7 (m, 3H), 4.4 (t, 2H), 7.4 (dd, 1H), 7.65 (d, 1H), 7.7 (s, 1H), 8.3 (s, 1H). HPLC (VERYPOL.M): t_r = 7.86 min (94 %).

Example 15

1-{2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide



Steps A-F is similar to those used in example 14 above.

Step-G:

1-(2-Azidoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide:

To a solution of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid (0.65 g, 0.0028 mol) in dry DMF (5.0 mL) was added with stirring HOBt (0.46 g, 0.0034 mol), DIPEA (2.5 mL, 0.014 mol), 4-aminoadamantan-1-ol (0.685 g, 0.0034 mol) at 0°C. To the resulting mixture was added EDCI (0.65 g, 0.0034 mol) and stirred for 15 h at ambient temperature. The reaction mixture was diluted with ice water (100 mL) and extracted with EtOAc (3x50 mL) and the combined organic phases were washed with water, dried (Na_2SO_4) and the solvent evaporated affording (1.0 g, 93.5%) of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide. MS-ESI m/z 381 ($M+1$).

Step-H:

1-[(2-Aminoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)]-amide:

To a solution of 1-(2-azidoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide (1.0 g, 0.00263 mol) in methanol (20 mL) was added 10% Pd/C (200 mg). The reaction mixture was hydrogenated at 3 kg pressure for 1 h. The catalyst was filtered over celite and the filtrate was concentrated to give 1-(2-aminoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide (0.7 g, 75%).

Step-I:

1-{2-[(4-Hydroxypiperidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide:

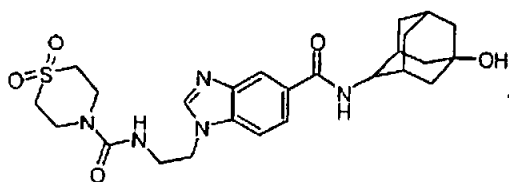
To a solution of 1-(2-aminoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide (0.35 g, 0.988 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0°C. To this reaction mixture was added 4-hydroxypiperidine-1-carbonyl chloride slowly and stirred for 2 h at ambient temperature. The solvents were evaporated and the residue purified by preparative HPLC cis and trans isomers of 1-{2-[(4-hydroxypiperidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide.

Isomer I (0.008 g): MS-ESI m/z 482 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 1.4 (m, 3H), 1.6 (d, 3H), 1.8 (m, 9H), 2.0 (d, 2H), 2.2 (s, 1H), 2.4 (s, 2H), 2.9 (m, 2H), 3.5-3.8 (m, 5H), 4.0 (s, 1H), 4.5 (t, 2H), 7.65 (d, 1H), 7.8 (d, 1H), 7.95 (d, 1H), 8.15 (s, 1H), 8.25 (s, 1H). HPLC (VERYPOL.M): t_r = 6.59 min (95 %).

Isomer II (0.022 g): MS-ESI m/z 482 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD): δ 1.4 (m, 3H), 1.5 (d, 2H), 1.8 (m, 5H), 1.9 (d, 2H), 2.1 (d, 2H), 2.2 (brs, 1H), 2.3 (d, 2H), 2.9 (m, 2H), 3.55 (t, 2H), 3.7 (m, 3H), 4.1 (s, 1H), 4.4 (t, 2H), 4.6 (s, 1H), 7.65 (d, 1H), 7.8 (dd, 1H), 8.15 (d, 1H), 8.25 (s, 1H). HPLC (VERYPOL.M): t_r = 6.12 min (98 %).

Example 16

1-{2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide



Steps A-F is similar to those used in example 15 above.

5 Step-I:

A) 1,1-Dioxo-thiomorpholine-4-carbonyl chloride:

To a solution of thiomorpholine 1,1-dioxide (0.181 g, 0.00105 mol) in dry THF (5mL) was added DIPEA (0.3 mL, 0.00191 mol) at 0° C. To the resulting mixture was added triphosgene (0.11 g, 0.00037mol) and the mixture was stirred for 2 h at ambient temperature.

10

B) To a solution of 1-(2-aminoethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide (0.25 g, 0.706 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0° C. To this reaction mixture was added compound A slowly and stirred for 2 h at ambient temperature. The solvents were evaporated and the residue purified by preparative HPLC affording cis and trans isomers of 1-[2-[(1,1-dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxyadamantan-2-yl)-amide.

15

Isomer I (15 mg): MS-ESI m/z 516 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ 1.5 (d, 2H), 1.8 (d, 4H), 1.9 (d, 2H), 2.1 (m, 3H), 2.3 (s, 2H), 2.7 (t, 4H), 3.6 (t, 2H), 4.1 (s, 1H), 4.5 (t, 2H), 7.6 (d, 1H), 7.8 (d, 1H), 8.2 (s, 1H), 8.35 (s, 1H). HPLC (VERYPOL.M): t_r = 6.54 min (98 %).

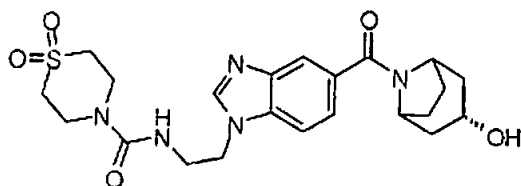
20

Isomer II (17 mg): MS-ESI m/z 516 ($M+1$); $^1\text{H-NMR}$ (300 MHz, CD_3OD) δ 1.6 (d, 2H), 1.8 (d, 6H), 2.1 (d, 2H), 2.2 (m, 1H), 2.4 (s, 2H), 2.7 (t, 4H), 3.6 (t, 2H), 3.7 (t, 4H), 4.0 (s, 1H), 4.5 (t, 2H), 7.6 (d, 1H), 7.8 (dd, 1H), 8.2 (s, 1H), 8.3 (s, 1H). HPLC (VERYPOL.M): t_r = 6.84 min (94 %).

25

Example 17

1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide



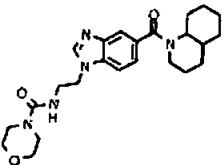
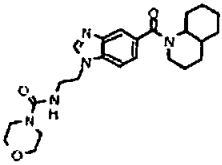
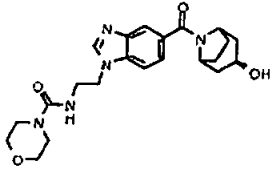
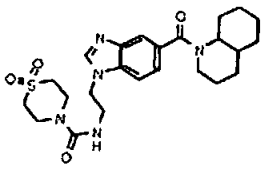
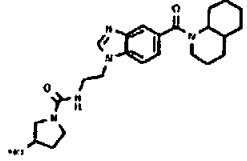
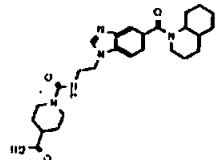
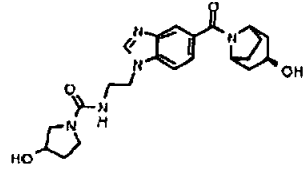
Steps A-F is similar to those used in example 16 above.

5 Step-I:

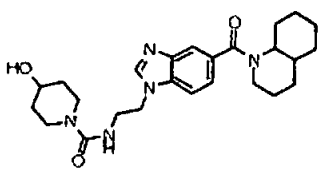
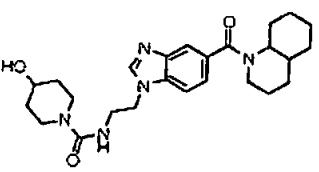
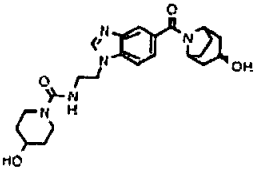
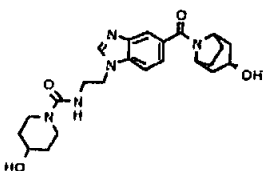
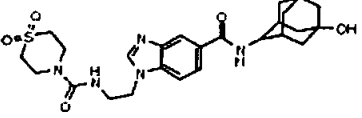
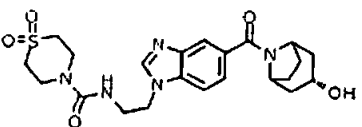
To a solution of [1-(2-aminoethyl)-1H-benzimidazol-5-yl]-(3-hydroxy-8-azabicyclo[3.2.1]oct-8-yl)-methanone (0.2 g, 0.636 mmol) in dry THF (5 mL) was added DIPEA (0.3 mL, 1.91 mmol) at 0° C. To this reaction mixture was added 1,1-dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carboxyl)-benzoimidazol-1-yl]-ethyl}-amide (0.007 g, 2.3%). MS-ESI m/z 476 (M+1); ¹H-NMR (300 MHz, CD₃OD) δ 1.5 (t, 1H), 1.8 (m, 4H), 2.1 (brs, 3H), 2.8 (s, 4H), 3.6 (t, 2H), 3.8 (s, 4H), 4.2 (m, 2H), 4.5 (t, 2H), 4.7 (s, 1H), 7.5 (d, 1H), 7.7 (d, 1H), 7.85 (s, 1H), 8.3 (s, 1H). HPLC (VERYPOL.M): t_r = 6.24 min (97 %).

[00441] The following compounds were synthesised employing a similar method to the ones described in examples 13-17 above:

Ex.	Structure	MW	IUPAC Name	MS-ESI m/z
17-1		467,57	Cis-1-{2-[(morpholine-4-carboxyl)-amino]-ethyl}-1H-benzo-imidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	458
17-2		467,57	Trans-1-{2-[(morpholine-4-carboxyl)-amino]-ethyl}-1H-benzo-imidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	458

17-3		439,56	Cis-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	440
17-4		439,56	Trans-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	440
17-5		427,51	Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	428
17-6		487,63	1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	488
17-7		439,56	3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	440
17-8		481,60	1-{2-[5-(Octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid	482
17-9		427,51	3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	428

116

17-10		453,59	Cis-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	454
17-11		453,59	Trans-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	454
17-12		441,53	Endo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	442
17-13		441,53	Exo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-azabicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	442
17-14		515,64	1-{2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl}-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	516
17-15		475,57	1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide	476

17-16		481,60	1-{2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	482
17-17		467,57	1-{2-[(3-Hydroxy-pyrrolidine-1-carbonyl)-amino]-ethyl}-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide	463
17-18		427,51	Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide	428
17-19		509,61	Cis-1-{2-[5-(5-Hydroxy-adamantan-2-ylcarbamoyl)-benzimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid	510
17-20		509,61	Trans-1-{2-[5-(5-Hydroxy-adamantan-2-ylcarbamoyl)-benzimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid	510
17-21		469,55	1-{2-[5-(3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl-carbamoyl}-piperidine-4-carboxylic acid	470

[00442] PHARMACOLOGICAL METHODS**[00443] 11 β HSD1 enzyme assay****[00444] Materials**

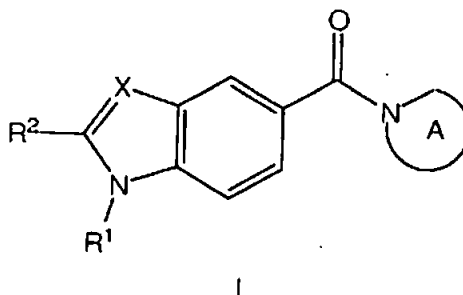
5 **[00445]** ^3H -cortisone and anti-rabbit Ig coated scintillation proximity assay (SPA) beads were purchased from Amersham Pharmacia Biotech, β -NADPH was from Sigma and rabbit anti-cortisol antibodies were from Fitzgerald. An extract of yeast transformed with h-11 β HSD1 (Hult et al., FEBS Lett., 441, 25 (1998)) was used as the source of enzyme. The test compounds were dissolved in DMSO (10 mM). All dilutions were performed in a buffer containing 50 mM TRIS-HCl (Sigma Chemical Co), 4 mM EDTA (Sigma Chemical Co), 0.1% BSA (Sigma Chemical Co), 0.01% Tween-20 (Sigma Chemical Co) and 0.005% bacitracin (Novo Nordisk A/S), pH=7.4. Optiplate 96 wells plates were supplied by Packard. The amount of ^3H -cortisol bound to the SPA beads was measured on TopCount NXT, Packard.

[00446] Methods

15 **[00447]** h-11 β HSD1, 120 nM ^3H -cortisone, 4 mM β -NADPH, antibody (1:200), serial dilutions of test compound and SPA particles (2 mg/well) were added to the wells. The reaction was initiated by mixing the different components and was allowed to proceed under shaking for 60 min at 30°C. The reaction was stopped by the addition of 10 fold excess of a stopping buffer containing 500 μM carbenoxolone and 1 μM cortisone. Data was analysed using GraphPad Prism software.

WHAT IS CLAIMED:

1. A compound of the formula I:



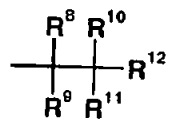
5 wherein:

X is selected from CR⁵ and nitrogen;

10 R¹ is selected from C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

alternatively, R¹ and R² are, independently,



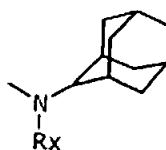
15 Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

20 Ring A is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

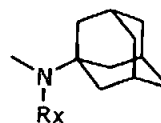
alternatively,



is



or



25

wherein Rx is selected from hydrogen and C₁-C₆alkyl;



is substituted with 0-3 groups selected from C_1 - C_6 alkyl, halo, hydroxy, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ oxo, cyano, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkylene, and C_1 - C_6 alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R^{14} ;

R^5 is selected from hydrogen, C_1 - C_6 alkyl, $-C(=O)R^{13}$, and cyano;

R^6 is selected from cyano, aryl, hetaryl, $-oxoC_1$ - C_6 alkyl- $S(=O)_nR^{13}$, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$, $-C(=NR^{15})NR^{15}$, $-N(R^{16})C(=O)R^{13}$, $-N(R^{18})C(=O)-C_3$ - C_{10} cycloalkyl, $-N(R^{18})C(=O)$ -3-10 membered hetcycloalkyl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R^{16} ;

R^7 is selected from C_1 - C_6 alkyl, halo, hydroxy, oxo and cyano;

R^8 , R^9 , R^{10} and R^{11} are each independently selected from hydrogen, C_1 - C_6 alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C_1 - C_6 alkyloxy, wherein the C_1 - C_6 alkyl and C_1 - C_6 alkyloxy are substituted with 0-3 R^{17} ;

alternatively, R^8 and R^9 together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

alternatively, R^{10} and R^{11} together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy or hetaryl C_1 - C_6 alkyloxy;

alternatively, R^8 and R^{10} together with the two carbon atoms to which they are attached form a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryloxy, aryl C_1 - C_6 alkyloxy, and hetaryl C_1 - C_6 alkyloxy;

R^{12} is selected from H, OH, $NR^{18}R^{19}$, C_3 - C_{10} cycloalkyl, 3-10 membered heterocycloalkyl, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, and $-C(=NR^{15})NR^{16}$, wherein the cycloalkyl and heterocycloalkyl groups are substituted with 0-3 R^{17} ;

R^{13} is selected from OH, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_4 alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and $NR^{18}R^{19}$;

R^{14} is selected from halo, hydroxy, oxo, and cyano;

R^{15} and R^{16} are independently selected from H, C_1 - C_6 alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R^{20} ;

R^{17} is selected from halo, OH, oxo, nitro, cyano, $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $NR^{18}R^{19}$, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, and aryloxy;

R^{18} and R^{19} are independently selected from H, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, aryl, hetaryl, aryl C_1 - C_6 alkylene, and hetaryl C_1 - C_6 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R^{20} ;

alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1 - C_6 alkyl, aryl, hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryl C_1 - C_6 alkyloxy, hetaryl C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, arylcarbonyl, hetarylcarbonyl, aryl C_1 - C_6 alkylcarbonyl, hetaryl C_1 - C_6 alkylcarbonyl, C_1 -

C₆alkylcarboxy, arylcarboxy, hetarylcarboxy, arylC₁-C₅alkyl-carboxy, and hetarylC₁-C₆alkylcarboxy;

5 R²⁰ is selected from H, OH, oxo, halo, cyano, nitro, C₁-C₆alkyl, C₁-C₆alkyloxy, NR²¹R²², methylendioxo, dihalomethylendioxo, trihalomethyl, and trihalomethyloxy;

R²¹ and R²² are independently selected from H, C₁-C₈alkyl, and arylC₁-C₆alkyl;

10 R²³ is selected from H and C₁-C₅alkyl;

n is selected from 0, 1, and 2;

Y is selected from O and S;

15 or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

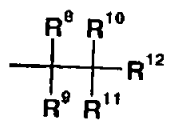
20 2. A compound according to claim 1 wherein:

X is selected from CR⁵ and nitrogen;

R¹ is selected from C₁-C₆alkyl-R⁶, wherein the alkyl group is substituted with 0-3 R⁷;

25 R² is selected from hydrogen, halo, C₁-C₆alkyl, and -C(=O)R¹³;

alternatively, R¹ and R² are, independently,

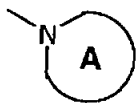


30 Ring A is a saturated or partially saturated bicyclic or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from nitrogen, oxygen, and sulphur;

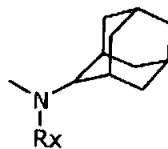
Ring A is substituted with 0-3 groups selected from C₁-C₈alkyl, halo, hydroxy, -COOH,

-CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

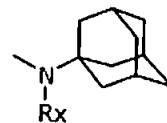
5 alternatively,



is



or



wherein Rx is selected from hydrogen and C₁-C₆alkyl;



10 is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

15 R⁵ is selected from hydrogen, C₁-C₆alkyl, -C(=O)R¹³, and cyano;

R⁶ is selected from cyano, aryl, hetaryl, -oxoC₁-C₆alkyl-S(=O)_nR¹³, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, -N(R²³)C(=Y)NR¹⁸R¹⁹, -C(=NR¹⁵)NR¹⁵, -N(R¹⁸)C(=O)R¹³, -N(R¹⁸)C(=O)-C₃-C₁₀cycloalkyl, -N(R¹⁸)C(=O)-3-10 membered hetcycloalkyl, wherein the cycloalkyl, hetcycloalkyl, aryl, and hetaryl groups are substituted with 0-3 R¹⁶;

R⁷ is selected from C₁-C₆alkyl, halo, hydroxy, oxo and cyano;

25 R⁸, R⁹, R¹⁰ and R¹¹ are each independently selected from hydrogen, C₁-C₆alkyl, F, trihalomethyl, trihalomethoxy, hydroxy, and C₁-C₆alkyloxy, wherein the C₁-C₆alkyl and C₁-C₆alkyloxy are substituted with 0-3 R¹⁷;

alternatively, R⁸ and R⁹ together with the carbon atom to which they are attached form a saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, triha-

lomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy or hetarylC₁-C₆alkyloxy;

alternatively, R¹⁰ and R¹¹ together with the carbon atom to which they are attached form a
 5 saturated or partially saturated ring consisting of the carbon atom shown, 2-5 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy or hetarylC₁-C₆alkyloxy;

alternatively, R⁸ and R¹⁰ together with the two carbon atoms to which they are attached form
 a saturated or partially saturated ring consisting of the two shown carbon atoms, 1-4
 additional carbon atoms, and 0-2 heteroatoms selected from nitrogen, oxygen, and
 sulphur, wherein this ring is substituted with 0-3 groups selected from halo, trihalomethyl, C₁-C₆alkyl, aryl, hetaryl, arylC₁-C₆alkylene, hetarylC₁-C₆alkylene, hydroxy, oxo, C₁-C₆alkyloxy, aryloxy, arylC₁-C₆alkyloxy, and hetarylC₁-C₆alkyloxy;

R¹² is selected from H, OH, NR¹⁸R¹⁹, C₃-C₁₀cycloalkyl, 3-10 membered hetcycloalkyl,
 -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, and -C(=NR¹⁵)NR¹⁶;
 20 wherein the cycloalkyl and hetcycloalkyl groups are substituted with 0-3 R¹⁷;

R¹³ is selected from OH, C₁-C₈alkyl, C₁-C₈alkyloxy, C₁-C₈alkyloxyC₁-C₄alkylene, aryl, hetaryl, aryloxy, hetaryloxy, and NR¹⁸R¹⁹;

25 R¹⁴ is selected from halo, hydroxy, oxo, and cyano;

R¹⁵ and R¹⁶ are independently selected from H, C₁-C₈alkyl, 3-10 membered cycloalkyl, halo, OH, cyano, -C(=O)R¹³, -S(=O)_nR¹³, S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, aryl, and hetaryl, wherein the alkyl and cycloalkyl groups are substituted with 0-3 R²⁰;

30 R¹⁷ is selected from halo, OH, oxo, nitro, cyano, -C(=O)R¹³, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹, -N(R¹⁸)S(=O)_nR¹³, NR¹⁸R¹⁹, C₁-C₈alkyl, C₁-C₈alkyloxy, and aryloxy;

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R^{18} and R^{19} are independently selected from H, C_1 - C_8 alkyl, C_1 - C_8 alkyloxy, aryl, hetaryl, aryl C_1 - C_6 alkylene, and hetaryl C_1 - C_6 alkylene, wherein the alkyl/alkylene, aryl, and hetaryl groups are independently substituted with 0-3 R^{20} ;

- 5 alternatively, R^{18} and R^{19} , together with the nitrogen atom to which they are attached, form a saturated or partially saturated monocyclic, bicyclic, or tricyclic ring consisting of the shown nitrogen, 4-10 carbon atoms, and 0-2 additional heteroatoms selected from ni-
trogen, oxygen, and sulfur, wherein this ring is substituted with 0-3 C_1 - C_8 alkyl, aryl,
hetaryl, aryl C_1 - C_6 alkylene, hetaryl C_1 - C_6 alkylene, hydroxy, oxo, C_1 - C_6 alkyloxy, aryl C_1 -
10 C_6 alkyloxy, hetaryl C_1 - C_6 alkyloxy, C_1 - C_6 alkyloxy C_1 - C_6 alkyl, C_1 - C_6 alkylcarbonyl, aryl-
carbonyl, hetarylcarbonyl, aryl C_1 - C_6 alkylcarbonyl, hetaryl C_1 - C_6 alkylcarbonyl, C_1 -
 C_6 alkylcarboxy, arylcarboxy, hetarylcarboxy, aryl C_1 - C_6 alkyl-carboxy, and hetaryl C_1 -
 C_6 alkylcarboxy;
- 15 R^{20} is selected from H, OH, oxo, halo, cyano, nitro, C_1 - C_6 alkyl, C_1 - C_6 alkyloxy, $NR^{21}R^{22}$, me-
thylendioxo, dihalomethylendioxo, trihalomethyl, and trihalomethyloxy;

R^{21} and R^{22} are independently selected from H, C_1 - C_8 alkyl, and aryl C_1 - C_6 alkyl;

- 20 R^{23} is selected from H and C_1 - C_6 alkyl;

n is selected from 0, 1, and 2;

Y is selected from O and S;

25

provided that when X is CR^5 , then R^6 , is $-C(=O)R^{13}$ wherein R^{13} is OH;

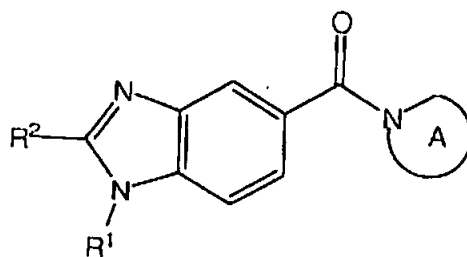
or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or
mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

30

3. The compound according to Claim 1, wherein the compound is of formula IA:

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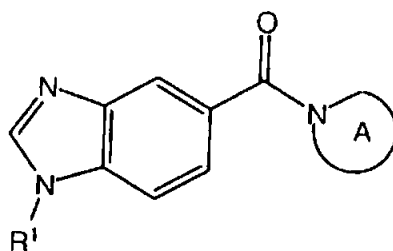
126



IA.

5

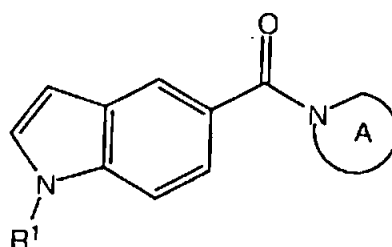
4. The compound according to Claim 1, wherein the compound is of formula IB:



IB.

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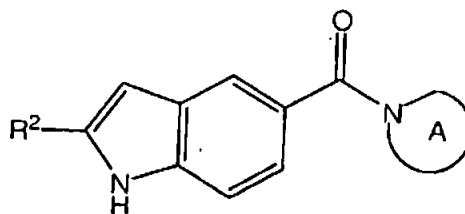
5. The compound according to Claim 1, wherein the compound is of formula IC:



IC.

15

6. The compound according to Claim 1, wherein the compound is of formula ID:



ID.

7. The compound according to Claim 1, wherein R^6 is selected from $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, $-N(R^{18})S(=O)_nR^{13}$, $-N(R^{23})C(=Y)NR^{18}R^{19}$ or $-C(=NR^{15})NR^{15}$.

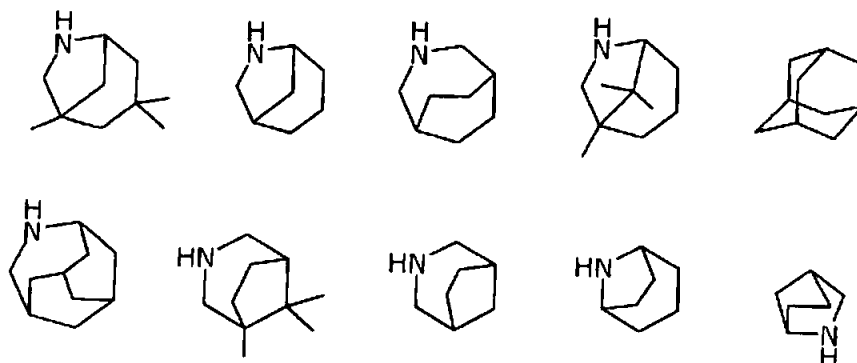
5 8. The compound according to Claim 1, wherein R^6 is selected from $-C(=O)R^{13}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$, or $-N(R^{23})C(=Y)NR^{18}R^{19}$.

9. The compound according to Claim 1, wherein R^6 is selected from $-N(R^{23})C(=Y)NR^{18}R^{19}$.

10

10. The compound according to Claim 1, wherein Y is oxygen (O).

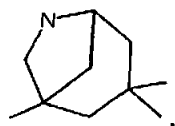
11. The compound according to claim 1, wherein Ring A is selected from:



15

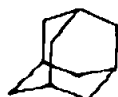
Ring A is substituted with 0-2 groups selected from C_1 - C_8 alkyl, halo, hydroxy, oxo, cyano, $-COOH$, $-CONR^{18}R^{19}$, $-S(=O)_nR^{13}$, $-S(=O)_nNR^{18}R^{19}$ and C_1 - C_8 alkyloxy.

12. The compound according to claim 11, wherein Ring A is



20

13. The compound according to claim 11, wherein Ring A is

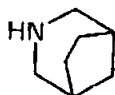


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14. The compound according to claim 11, wherein Ring A is

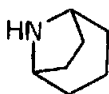


15. The compound according to claim 11, wherein Ring A is



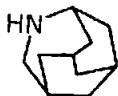
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16. The compound according to claim 11, wherein Ring A is



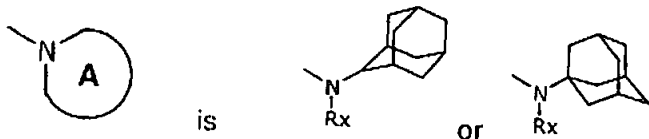
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17. The compound according to claim 11, wherein Ring A is



18. The compound according to claim 1, wherein

15



is

or

wherein Rx is selected from hydrogen and C₁-C₆alkyl;



is substituted with 0-3 groups selected from C₁-C₆alkyl, halo, hydroxy, -COOH, -CONR¹⁸R¹⁹, -S(=O)_nR¹³, -S(=O)_nNR¹⁸R¹⁹ oxo, cyano, C₁-C₆alkyloxy, C₁-C₆alkyloxyC₁-C₆alkylene, and C₁-C₆alkylcarbonyl, wherein each alkyl/alkylene group is substituted with 0-3 R¹⁴;

20

19. A compound selected from the group :

Furan-2-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-

benzoimidazol-1-yl]-ethyl)-amide
1-Acetyl-piperidine-4-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-amide
2-Methoxy-N-{2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-acetamide
N-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-isonicotinamide
N-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-acetamide
{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-carbamic acid *tert*-butyl ester
Isoxazole-5-carboxylic acid {2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-amide
N-{2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzoimidazol-1-yl]-ethyl)-benzamide
3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
3-[2-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid
2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
2-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid ethyl ester
2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid ethyl ester
3-[2-Methyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-benzimidazol-1-yl]-propionic acid
2-[1-Ethyl-5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1H-benzimidazol-2-yl]-cyclopropanecarboxylic acid
3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid

- [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid *tert*-butyl ester
- [5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-acetic acid 1-Morpholin-4-yl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propan-1-one
- 1-Morpholin-4-yl-2-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-ethanone
- 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 2,2-Dimethyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid methyl ester
- 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid methyl ester
- 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-butyric acid
- 2-Methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionic acid
- 3-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid methyl ester
- 4-[5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-ylmethyl]-benzoic acid
- 3-[5-(4-Aza-tricyclo[4.3.1.1^{3,8}]*undecane-4-carbonyl)-indol-1-yl]-propionic acid ethyl ester
- 3-[5-(4-Aza-tricyclo[4.3.1.1^{3,8}]*undecane-4-carbonyl)-indol-1-yl]-propionic acid
- 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid ethyl ester
- 5-(1,3,3-Trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-1*H*-indole-2-carboxylic acid *N*-Methoxy-*N*-methyl-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide
- N*-Ethoxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

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N-Hydroxy-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

{1-[2-(2H-Tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(3-Cyclopropyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(3-Methyl-[1,2,4]oxadiazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

N-(1*H*-Tetrazol-5-yl)-3-[5-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]octane-6-carbonyl)-indol-1-yl]-propionamide

{1-[2-(2-Methyl-2H-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(1-Methyl-1*H*-tetrazol-5-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

{1-[2-(5-Methyl-[1,2,4]oxadiazol-3-yl)-ethyl]-1*H*-indol-5-yl}-(1,3,3-trimethyl-6-aza-bicyclo[3.2.1]oct-6-yl)-methanone

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

20. A compound selected from the group :

[1-(2-Methanesulfonylmethoxy-ethyl)-1*H*-benzoimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone

(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1*H*-benzoimidazol-5-yl]-methanone

trans-1-(2-Methanesulfonyl-methoxy-ethyl)-1*H*-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Cis-1-(2-Methanesulfonyl-methoxy-ethyl)-1*H*-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonylmethoxy-ethyl)-1*H*-benzoimidazol-5-yl]-methanone

1-(2-Methanesulfonyl-ethyl)-1*H*-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1*H*-benzoimidazol-5-yl]-methanone

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(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-[1-(2-methanesulfonyl-ethyl)-1H-benzimidazol-5-yl]-methanone

[1-(2-Methanesulfonyl-ethyl)-1H-benzimidazol-5-yl]-(octahydro-quinolin-1-yl)-methanone

1-(2-Methanesulfonyl-ethyl)-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

(3-Hydroxy-8-aza-bicyclo[3.2.1]oct-8-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone

(Octahydro-quinolin-1-yl)-{1-[2-(1H-tetrazol-5-yl)-ethyl]-1H-benzimidazol-5-yl}-methanone

Trans-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Cis-1-[2-(1H-Tetrazol-5-yl)-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

4-Hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

1-[2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1-[2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Cis-1-[2-[(morpholine-4-carbonyl)-amino]-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Trans-1-[2-[(morpholine-4-carbonyl)-amino]-ethyl]-1H-benzimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Cis-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Trans-morpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzimidazol-1-yl]-ethyl}-amide

1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

1-{2-[5-(Octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

3-Hydroxy-pyrrolidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

Cis-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

Trans-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(octahydro-quinoline-1-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

Endo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]-octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

Exo-4-hydroxy-piperidine-1-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]-octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

1-{2-[(1,1-Dioxo-thiomorpholine-4-carbonyl)-amino]-ethyl}-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1,1-Dioxo-thiomorpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]-octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

1-{2-[(4-Hydroxy-piperidine-1-carbonyl)-amino]-ethyl}-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

1-{2-[(3-Hydroxy-pyrrolidine-1-carbonyl)-amino]-ethyl}-1H-benzoimidazole-5-carboxylic acid (5-hydroxy-adamantan-2-yl)-amide

Morpholine-4-carboxylic acid {2-[5-(3-hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethyl}-amide

Cis-1-{2-[5-(5-Hydroxy-adamantan-2-ylcarbamoyl)-benzoimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

Trans-1-{2-[5-(5-Hydroxy-adamantan-2-ylcarbamoyl)-benzoimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

1-{2-[5-(3-Hydroxy-8-aza-bicyclo[3.2.1]octane-8-carbonyl)-benzoimidazol-1-yl]-ethylcarbamoyl}-piperidine-4-carboxylic acid

or a salt thereof with a pharmaceutically acceptable acid or base, or any optical isomer or mixture of optical isomers, including a racemic mixture, or any tautomeric forms.

21. A compound according to any one of the claims 1-20, which is an agent useful for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

5 22. The compound according to claim 21, wherein the conditions, disorders, and diseases are influenced by intracellular glucocorticoid levels.

10 23. The compound according to claim 21, wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

15 24. A pharmaceutical composition comprising, as an active ingredient, at least one compound according to any one of the claims 1-20 together with one or more pharmaceutically acceptable carriers or excipients.

20 25. The pharmaceutical composition according to claim 24 which is suitable for oral, nasal, buccal, transdermal, pulmonal, or parenteral administration.

25 26. Use of a compound according to any of the claims 1-20 for the preparation of a pharmaceutical composition for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial.

27. The use according to claim 26, wherein the conditions, disorders, and diseases that are influenced by intracellular glucocorticoid levels.

30 28. The use according to claim 26, wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), the progression from IGT to type 2 diabetes, the progression of the metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

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29. The use according to any of the claims 26-28, wherein the pharmaceutical composition is suitable for a route of administration selected from oral, nasal, buccal, transdermal, pulmonal, and parenteral.

5 30. A method for the treatment of conditions, disorders, or diseases wherein a modulation or an inhibition of the activity of 11 β HSD1 is beneficial, the method comprising administering to a subject in need thereof an effective amount of a compound according to any of claims 1-20.

10 31. The method according to claim 30, wherein the conditions, disorders, and diseases that are influenced by intracellular glucocorticoid levels.

15 32. The method according to claim 30, wherein the conditions, disorders, or diseases are selected from metabolic syndrome, insulin resistance, dyslipidemia, hypertension, obesity, type 2 diabetes, impaired glucose tolerance (IGT), impaired fasting glucose (IFG), progression from IGT to type 2 diabetes, progression of metabolic syndrome into type 2 diabetes, diabetic late complications, neurodegenerative and psychiatric disorders, and the adverse effects of glucocorticoid receptor agonist treatment or therapy.

20 33. The method according to any of claims 30-32, wherein the administering is via a route selected from oral, nasal, buccal, transdermal, pulmonal, and parenteral.

USO FARMACÉUTICO DE AMIDAS SUSTITUIDAS

CAMPO DEL INVENTO

5 El presente invento se relaciona con el uso de amidas sustituidas y composiciones farmacéuticas que comprenden las mismas para tratar trastornos donde se desea modular la actividad de la deshidrogenasa de 11β - hidroxiesteroide tipo 1 (11β HSD1). El presente invento también se relaciona con amidas sustituidas novedosas, con su uso en terapia, con composiciones farmacéuticas que comprenden las mismas, con el uso de dichos compuestos en la fabricación de
10 medicamentos, y con métodos terapéuticos que comprenden la administración de los compuestos. Estos compuestos modulan la actividad de la deshidrogenasa 11β - hidroxiesteroide tipo 1 (11β HSD1) y por consiguiente son útiles en el tratamiento de enfermedades en las cuales tal modulación es benéfica, tal como el síndrome metabólico.

15 FUNDAMENTO DEL INVENTO

El síndrome metabólico es un problema principal global de salud. En los Estados Unidos, la prevalencia en la población adulta actualmente se estima en 25% aproximadamente, y continúa creciendo tanto en los Estados Unidos como a nivel mundial. El síndrome metabólico se caracteriza por una combinación de resistencia a insulina, dislipidemia, obesidad e hipertensión
20 llevando a morbilidad y mortalidad aumentadas de enfermedades cardiovasculares. Las personas con síndrome metabólico están en riesgo aumentado de desarrollar diabetes tipo 2 evidente, la prevalencia de la cual igualmente está creciendo.

En diabetes tipo 2, la obesidad y dislipidemia son altamente prevalentes y aproximadamente 70% de las personas con diabetes tipo 2 adicionalmente tienen hipertensión
25 una que otra vez llevando a mortalidad aumentada de enfermedades cardiovasculares.

En el ambiente clínico, es bien conocido que los glucocorticoides pueden inducir todas las características cardinales del síndrome metabólico y diabetes tipo 2.

La deshidrogenasa 11β - hidroxiesteroide tipo 1 (11β HSD1) cataliza la generación local de glucocorticoide activo en varios tejidos y organismos incluyendo predominantemente el
30 hígado y tejido adiposo, pero también ej., músculo esquelético, hueso, páncreas, endotelio, tejido ocular y ciertas partes del sistema nervioso central. Por lo tanto, 11β HSD1 sirve como un

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regulador local de acciones glucocorticoides en los tejidos y órganos donde se expresa (Tannin, J. Biol. Chem. 266, 16653 (1991) ; Bujalska, *Endocrinología*, 140, 3188 (1999) ; Whorwood et al., J Clin Endocrinol Metab., 86, 2296 (2001) ; cooper et al., Bone, 27, 375 (2000) ; Davani et al., J. Biol. Chem., 275, 34841 (2000) ; Brem et al., Hipertensión, 31, 459 (1998); Rauz et al., Invest. Ophthalmol. Vis. Sci., 42, 2037 (2001) ; Moisan et al., Endocrinology, 127, 1450 (1990)) .

El rol de 11 β HSD1 en el síndrome metabólico y diabetes tipo 2 está soportada por varias líneas de evidencia. En humanos, el tratamiento con el inhibidor 11 β HSD1 no específico carbenoxolona mejora la sensibilidad de insulina en voluntarios delgados saludables y personas con diabetes tipo 2. Igualmente, los ratones *knock-out* 11 β HSD1 son resistentes a resistencia a insulina inducida por obesidad y estrés. Adicionalmente, los ratones *knock-out* presentan un perfil lipídico anti aterogénico de triglicéridos VLDL disminuidos y colesterol HDL aumentado. A la inversa, los ratones que sobre- expresan 11 β HSD1 en adipocitos desarrollan resistencia a insulina, hiperlipidemia y obesidad visceral, un fenotipo que se asemeja al síndrome metabólico humano Andrews et al., J, Clin, Endocrinol, Metab., 88, 285 (2003) ; Walter et al., J. Clin, Endocrinol. Metab., 80, 3155(1995) ; Morton et al., J. Biol. Chem., 276, 41293 (2001) ; Kotelevtsev et al., Proc. Natl. Acad. Sci. USA, 94, 14924 (1997) ; Masuzaki et al., Science, 294, 2166 (2001)) .

Los aspectos más mecanísticos de la modulación 11 β HSD1 y con eso la modulación de niveles intracelulares de glucocorticoide activo se han investigado en varios modelos roedores y diferentes sistemas celulares. 11 β HSD1 promueve las características del síndrome metabólico aumentando la expresión hepática de las enzimas limitantes de tasa en gluconeogénesis, a saber carboxiquinasa de fosfoenolpiruvato y glucosa- 6- fosfatasa, promoviendo la diferenciación de preadipocitos en adipocitos facilitando así la obesidad, directa e indirectamente estimulando la secreción VLDL hepática, disminuyendo la absorción LDL hepática y aumentando la contractilidad de vasos sanguíneos (Kotelevtsev et al., Proc. Natl. Acad. Sci. USA, 94, 14924 (1997) ; Morton et al., J. Biol. Chem. 276, 41293 (2001) ; Bujalska et al., Endocrinology, 140, 3188 (1999) ; Soumess et al., Steroids, 67, 195 (2002) , Brindley & Salter, Prog. Lipid Res., 30, 349 (1991)) .

WO 01/90090, WO 01/90091, WO 01/90092, WO 01/90093 y WO 01/90094 divulgan varias tiazol- sulfonamidas como inhibidores de la enzima deshidrogenasa 11 beta- hidroxisteroide humana tipo 1, y además afirman que dichos compuestos pueden ser útiles para tratar diabetes,

obesidad, glaucoma, osteoporosis, trastornos cognitivos, trastornos inmunes y depresión.

Ahora hemos encontrado amidas sustituidas que modulan la actividad de 11β HSD1 llevando a concentraciones intracelulares alteradas de glucocorticoide activo. Más específicamente, los presentes compuestos inhiben la actividad de 11β HSD1 llevando a concentraciones intracelulares disminuidas de glucocorticoide activo. Por lo tanto, el presente compuesto se puede utilizar para tratar trastornos donde se desea un nivel disminuido de glucocorticoide intracelular, tal como ej., el síndrome metabólico, diabetes tipo 2, intolerancia a la glucosa (IGT), alteración de la glucosa en ayunas (IFG), dislipidemia, obesidad, hipertensión, complicaciones diabéticas tardías, enfermedades cardiovasculares, arteriosclerosis, aterosclerosis, miopatía, agotamiento muscular, osteoporosis, trastornos neurodegenerativos y psiquiátricos, y efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

Un objetivo del presente invento es proporcionar compuestos, composiciones farmacéuticas y uso de compuestos que modulan la actividad de 11β HSD1.

15 DEFINICIONES

En las siguientes fórmulas estructurales y en toda la presente especificación, los siguientes términos tiene el significado idéntico. Los ejemplos proporcionados en las definiciones presentes en esta especificación son no inclusivos a menos que se indique lo contrario. Estos incluyen pero no están limitados a los ejemplos citados.

20 El término "halo" incluye fluor, cloro, bromo y yodo.

El término "trihalometilo" incluye trifluorometilo, triclorometilo, tribromometilo, y triyodometilo.

El término "trihalometoxilo" incluye trifluorometoxilo, triclorometoxilo, tribromometoxilo, y triyodometoxilo.

25 El término "alquilo" incluye grupos hidrocarburos alifáticos de metileno y saturados de cadena lineal C1- C8 y grupos hidrocarburos saturados ramificados C3- C8 con el número especificado de átomos. Por ejemplo, esta definición incluye metilo (Me), etilo (Et), propilo (Pr), butilo (Bu), pentilo, hexilo, isopropilo (i- Pr), isobutilo (i- Bu), tert- butilo (t- BU), sec- butilo (s- Bu), isopentilo, neopentilo.

30 El término "alquénilo" incluye grupos hidrocarburos alifáticos no saturados de cadena lineal C2- C6 y grupos hidrocarburos alifáticos no saturados C3- C6 ramificados con el número

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especificado de átomos de carbono. Por ejemplo, esta definición incluye etenilo, propenilo, butenilo, pentenilo, hexenilo, metilpropenilo, y metilbutenilo.

5 El término "alquínilo" incluye grupos hidrocarburos alifáticos no saturados de cadena lineal C2- C6 y grupos hidrocarburos alifáticos no saturados ramificados C4- C6 con el número especificado de átomos de carbono. Por ejemplo, esta definición incluye etinilo, propinilo, butinilo, pentinilo, hexinilo, y metilbutinilo.

10 El término "sistema monocíclico, bicíclico o tricíclico saturado o parcialmente saturado" representa pero no está limitado a aziridinilo, azepanilo, azocanilo, pirrolinilo, pirrolidinilo, 2-imidazolinilo, imidazolidinilo, 2- pirazolinilo, morfolinilo, piperidinilo, tiomorfolinilo, piperazinilo, ftalimida, 1,2,3,4- tetrahidro- quinolinilo, 1,2,3,4- tetrahidro- isoquinolinilo, 1,2,3,4- tetrahidro- quinoxalinilo, indolinilo, 1,6- aza- biciclo[3.2.1]octano, 2- aza- biciclo[4.1.1]octano, 2- aza- biciclo[3.2.1]octanilo, 7- aza- biciclo[4.1.1]octanilo, 9- aza- biciclo[3.3.2]decanilo, 4- aza- triciclo[4.3.1.1^{3,8}]undecanilo, 9- aza- triciclo[3.3.2.0^{3,7}]decanilo

15 El término "anillo saturado o parcialmente saturado" representa ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclobutenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclodecenilo, tetrahidrofurano, y tetrahidropirano.

El término "anillo aromático saturado o parcialmente saturado" representa ciclopentilo, ciclohexilo, ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclodecenilo, tetrahidrofurano, fenilo, piridilo, y pirimidinilo.

20 El término "cicloalquilo" representa un grupo saturado, mono- , bi- , o tri- o espirocarbocíclico con el número especificado de átomos de carbono (e. g., ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, cicloheptilo, ciclooctilo, ciclodecenilo, ciclodecilo, biciclo[3.2.1]octilo, Spiro[4.5]decilo, norpinilo, norbonilo, norcarilo, y adamantilo) .

25 El término "cicloalquilalquilo" representa un grupo cicloalquilo como se definió anteriormente fijado a través de cualquier grupo alquilo con el número indicado de átomos de carbono o grupo alquilo sustituido como se definió anteriormente (ej., ciclopropilmetilo, ciclobutiletilo, y adamantilmetilo) .

30 El término "cicloalquenilo" representa un grupo mono- , bi- , tri- , o espirocarbocíclico parcialmente saturado con el número especificado de átomos de carbono (ej., ciclobutenilo, ciclopentenilo, ciclohexenilo, cicloheptenilo, ciclooctenilo, ciclodecenilo, y ciclodecenilo) .

El término "cicloalquilcarbonilo" representa un grupo cicloalquilo como se definió

anteriormente con el número indicado de átomos de carbono fijados a través de un grupo carbonilo (ej., ciclopropilcarbonilo y ciclohexilcarbonilo).

El término "cicloalquilalquilcarbonilo" representa un grupo cicloalquilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono o grupo alquilo sustituido como se definió anteriormente (ej., ciclohexilmetilcarbonilo y cicloheptiletilcarbonilo).

El término "hetcicloalquilo" representa un grupo mono-, bi-, tri-, o espirocarbocíclico saturado con el número especificado de átomos con 1-4 del número especificado como heteroátomos o grupos seleccionados de nitrógeno, oxígeno, azufre, SO, y SO₂ (ej., tetrahydrofuranilo, tetrahydropiranilo, tetrahydrotiopiranilo, piperidina y piridazina).

El término "hetcicloalquilalquilo" representa un grupo hetcicloalquilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., tetrahydrofuranilmetilo, tetrahydropiraniletilo, y tetrahydrotiopiranilmetilo).

El término "hetcicloalquilcarbonilo" representa un grupo hetcicloalquilo como se definió anteriormente con el número indicado de átomos de carbono fijados a través de un grupo carbonilo (ej., 1- piperidin- 4- il- carbonilo y 1- (1,2,3,4- tetrahydro- isoquinolil- 6- il) carbonilo).

El término "alquiloxilo" representa un grupo alquilo con el número indicado de átomos de carbono fijados a través de un puente de oxígeno (ej., metoxilo, etoxilo, propiloxilo, aliloxilo, y ciclohexiloxilo).

El término "alquiloxialquilo" representa un grupo alquiloxilo como se definió anteriormente fijado a través de un grupo alquilo que tiene el número indicado de átomos de carbono (ej., metiloximetilo).

El término "arilo" incluye un anillo aromático carbocíclico que es monocíclico, bicíclico, o policíclico, tal como fenilo, bifenilo, naftilo, antracenilo, fenantrenilo, fluorenilo, indenilo, pentalenilo, azuleno, y bifenilenilo. Arilo también incluye los derivados parcialmente hidrogenados de los aromáticos carbocíclicos enumerados anteriormente. Ejemplos de derivados parcialmente hidrogenados incluyen 1,2,3,4- tetrahydro-naftilo y 1,4- dihydro-naftilo.

El término "arilo1" incluye fenilo, bifenilo, naftilo, antracenilo, fenantrenilo, y fluorenilo.

El término "arilo2" incluye fenilo, bifenilo, y naftilo.

El término "hetarilo" incluye marla 8.pirrolil(2- pirrolil) , pirazolil(3- pirazolil) , imidazolil(1- imidazolilo, 2- imidazolilo, 4- imidazolilo, 5- imidazolilo) , triazol(1,2,3- tirazol- 1-

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- il, 1,2,3- triazol- 2- il, 1,2,3- triazol- 4- il, 1,2,4- triazol- 3- il) , oxazolil(2- oxazolilo) , 4- oxazolilo, 5- oxazolilo) , isoxazolil(3- isoxazolilo, 4- isoxazolilo, 5- isoxazolilo) , tiazolil(2- tiazolilo, 4- tiazolilo, 5- tiazolilo) , tiofenil(2- tiofenilo, 3- tiofenilo, 4- tiofenilo, 5- tiofenilo) , furanil(2- furanilo, 3- furanilo, 4- furanilo, 5- furanilo) , piridil(2- piridilo, 3- piridilo, 4- piridilo, 5- piridilo) , 5- tetrazolilo, pirimidinil(2- pirimidinilo, 4- pirimidinilo, 6- pirimidinilo) , pirazinilo, piridazinilo (3- piridazinilo, 5- piridazinilo) , quinolil(2- quinolilo, 3- quinolilo, 4- quinolilo, 5- quinolilo, 6- quinolilo, 7- quimililo, 8- quinolilo) , isoquinolil(1- isoquinolilo, 3- isoquinolilo, 4- isoquinolilo, 5- isoquinolilo, 6- isoquinolilo, 7- isoquinolilo, 8- isoquinolilo) , benzo[b]furanil(2- benzo[b]furanilo, 3- benzo[b]furanilo, 4- benzo[b]furanilo, 5- benzo[b]furanilo, 6- benzo[b]furanilo, 7- benzo[b]furanilo) , 2,3- dihidro- benzo[b]furanilo, (2- (2,3- dihidro- benzo[b]furanilo) , 3- (2,3- dihidro- benzo[b]furanilo) , 4- (2,3- dihidro- benzo[b]furanilo) , 5- (2,3- dihidro- benzo[b]furanilo) , 6- (2,3- dihidro- benzo[b]furanilo) , 7- (2,3- dihidro- benzo[b]furanilo)) , 1,4- benzodioxin (2- (1,4- benzodioxino) , 3- (1,4- benzodioxino) , 5- (1,4- benzodioxino) , 6- (1,4- benzodioxino)) , benzo[b]tiofenilo, 6- benzo[b]tiofenilo, 7- benzo[b]tiofenilo, 2,3- dihidro- benzo[b]tiofenil (2- (2,3- dihidro- benzo[b]tiofenilo) , 3- (2,3- dihidro- benzo[b]tiofenilo) , 4- (2,3- dihidrobenzo[b]tiofenilo) , 5- (2,3- dihidro- benzo[b]tiofenilo) , 6- (2,3- dihidro- benzo[b]tiofenilo) , 7- (2,3- dihidro- benzo[b]tiofenilo)) , 4,5,6,7- tetrahidro- benceno[b]tiofenil (2- (4,5,6,7- tetrahidro- benceno[b]tiofenilo) , 3- (4,5,6,7- tetrahidro- benceno[b]tiofenilo) , 4- (4,5,6,7- tetrahidro- benceno[b]tiofenilo) , 5- (4,5,6,7- tetrahidro- benceno[b]tiofenilo) , 6- (4,5,6,7- tetrahidro- benceno[b]tiofenilo) , 7- (4,5,6,7- tetrahidro- benceno[b]tiofenilo)) , tieno[2,3- b]tiofenilo, 4,5,6,7- tetrahidro- tieno[2,3- c]piridil(4- (4,5,6,7- tetrahidro- tieno[2,3- c]piridilo) , 5- (4,5,6,7- tetrahidro- tieno[2,3- c]piridilo) , 6- (4,5,6,7- tetrahidro- tieno[2,3- c]piridilo) , 7- (4,5,6,7- tetrahidro- tieno[2,3- c]piridilo)) , indolil (1- indolil, 2- indolilo, 3- indolilo, 4- indolilo, 5- indolilo, 6- indolilo, 7- indolilo) , isoindolil (1- isoindolilo, 2- isoindolilo, 3- isoindolilo, 4- isoindolilo, 5- isoindolilo, 6- isoindolilo, 7- isoindolilo) , 1,3- dihidro- isoindolilo (1- (1,3- dihidro- isoindolilo) , 2- (1,3- dihidro- isoindolilo) , 3- (1,3- dihidro- isoindolilo) , 4- (1,3- dihidro- isoindolilo) , 5- (1,3- dihidro- isoindolilo) , 6- (1,3- dihidro- isoindolilo) , 7- (1,3- dihidro- isoindolilo)) , indazole (1- indazolilo, 3- indazolilo, 4- indazolilo, 5- indazolilo, 6- indazolilo, 7- indazolilo) , benzimidazolil (1- benzimidazolilo, 2- benzimidazolilo, 4- benzimidazolilo, 5- benzimidazolilo, 6- benzimidazolilo, 7- benzimidazolilo, 8- benzimidazolilo) , benzoxazolil (1- benzoxazolilo, 2-

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benzoxazolilo), benzotiazolil (1- benzotiazolilo, 2- benzotiazolilo, 4- benzotiazolilo, 5- benzotiazolilo, 6- benzotiazolilo, 7- benzotiazolilo), benzo- [1,2,5]oxadiazolilo, (4- benzo- [1,2,5]oxadiazol, 5- benzo- [1,2,5]oxadiazol), carbazolilo (1- carbazolilo, 2- carbazolilo, 3- carbazolilo, 4- carbozililo), piperidinil (2- piperidinilo, 3- piperidinilo, 4- piperidinilo), y
5 pirrolidinil (1- pirrolidinilo, 2- pirrolidinilo, 3- pirrolidinilo).

El término "arilaquilo" representa un grupo arilo como se definió anteriormente a través de un grupo alquilo con el numero indicado de átomos de carbono (ej., bencilo, feniletilo, 3- fenilpropilo, 1- naftilmetilo, y 2- (1- naftil) etilo).

El término "hetarilaquilo" o "hetaralquilo" representa un grupo hetarilo como se definió
10 anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., (2- furil) metilo, (3- furil) metilo, (2- tienil) metilo, (3- tienil) metilo, (2- piridil) metilo, y 1- metil- 1- (2- pirimidil) etilo).

El término "ariloxihetarilo" representa un grupo ariloxilo como se definió anteriormente fijado a través de un grupo hetarilo (ej., 2- fenoxi- piridilo).

15 El término "ariloxilo" representa un grupo arilo como se definió anteriormente fijado a través de un puente de oxígeno (ej., fenoxilo y naftiloxilo).

El término "hetariloxilo" representa un grupo hetarilo como se definió anteriormente a través de un puente de oxígeno (ej., 2- piridiloxilo).

20 El término "arilalquiloxilo" representa un grupo arilalquilo como se definió anteriormente fijado a través de un puente de oxígeno (ej., fenetiloxilo y naftilmetiloxilo).

El término "hetarilalquiloxilo" representa un grupo hetarilalquilo como se definió anteriormente fijado a través de un puente de oxígeno (ej., 2- piridilmetiloxilo).

El término "alquiloxicarbonilo" representa un grupo alquiloxilo como se definió anteriormente fijado a través de un grupo carbonilo (ej., metilformiat y etilformiat).

25 El término "ariloxicarbonilo" representa un grupo ariloxilo como se definió anteriormente fijado a través de un grupo carbonilo (ej., fenilformiat y 2- tiazolilformiat).

El término "arilalquiloxicarbonilo" representa un grupo "arilalquiloxilo" como se definió anteriormente fijado a través de un grupo carbonilo (ej., benzilformiat y feniletilformiat).

30 El término "alquiltio" representa un grupo alquilo con el número indicado de átomos de carbono fijados a través de un puente de azufre (ej., metilito y etiltio).

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El término "ariltio" representa un grupo arilo como se definió anteriormente fijado a través de un puente de azufre (ej., benzentiol y naftiltiol) .

El término "hetariltio" representa un grupo hetarilo como se definió anteriormente fijado a través de un puente de azufre (ej., piridina- 2- tiol y tiazol- 2- tiol) .

5 El término "ariltioalquilo" representa un grupo ariltio como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., metilsulfanilbenceno, y etilsulfanilnaftaleno) .

10 El término "hetariltioalquilo" representa un grupo hetariltio como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., 2- metilsulfanilpiridina y 1- etilsulfanilisoquinolina) .

El término "hetariloxiarilo" representa un grupo hetariloxilo como se definió anteriormente fijado a través de un grupo arilo como se definió anteriormente (ej., 1- fenoxi- isoquinolilo y 2- fenoxipiridilo) .

15 El término "hetariloxihetarilo" representa un grupo hetariloxilo como se definió anteriormente fijado a través de un grupo hetarilo como se definió anteriormente (ej., 1- (2- piridiloxi- isoquinolina) y 2- (imidazol- 2- iloxi- piridina)) .

El término "ariloxialquilo" representa un grupo ariloxilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., fenoximetilo y naftiloxietilo) .

20 El término "ariloxiarilo" representa un grupo ariloxilo como se definió anteriormente fijado a través de un grupo arilo como se definió anteriormente (ej., 1- fenoxi- naftaleno y feniloxi- fenilo) .

25 El término "arilalquiloxialquilo" representa un grupo arilalquiloxilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., etoxi- metil- benceno y 2- metoximetil- naftaleno) .

El término "hetariloxialquilo" representa un grupo hetariloxilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., 2- piridiloximetilo y 2- quinoliloxietilo) .

30 El término "hetarilalquiloxialquilo" representa un grupo hetarilalquiloxilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., 4- metoximetil- pirimidina y 2- metoximetil- quinolina) .

El término “alquilcarbonilo” representa un grupo alquilo como se definió anteriormente con el número indicado de átomos de carbono fijados a través de un grupo carbonilo (ej., octilcarbonilo, pentilcarbonilo, y 3- hexenilcarbonilo) .

El término “arilcarbonilo” representa un grupo arilo como se definió anteriormente fijado a través de un grupo carbonilo (ej., benzoilo) .

El término “hetarilcarbonilo” representa un grupo hetarilo como se definió anteriormente fijado a través de un grupo carbonilo (ej., 2- tiofenilcarbonilo, 3- metoxi- antrilcarbonilo, y oxazolilcarbonilo) .

El término “carbonilalquilo” representa un grupo carbonilo fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., acetilo) .

El término “alquilcarbonilalquilo” representa un grupo alquilcarbonilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., propan- 2- ona y 4,4- dimetil- pentan- 2- ona) .

El término “arilcarbonilalquilo” representa un grupo arilcarbonilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., 1- fenil- propan- 1- ona y 1- (3- cloro- fenil) - 2- metil- butan- 1- ona) .

El término “hetarilcarbonilalquilo” representa un grupo hetarilcarbonilo como se definió anteriormente fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., 1- piridin- 2- il- propan- 1- ona y 1- (1- H- imidazol- 2- il) - propan- 1- ona) .

El término “arilalquilcarbonilo” representa un grupo arilalquilo como se definió anteriormente con el número indicado de átomos de carbono fijado a través de un grupo carbonilo (ej., fenilpropilcarbonilo y feniletilcarbonilo) .

El término “hetarilalquilcarbonilo” representa un grupo hetarilalquilo como se definió anteriormente en donde el grupo alquilo es a su vez fijado a través de un carbonilo (ej., imidazolilpentilcarbonilo) .

El término “alquilcarbonilamino” representa un grupo “alquilcarbonilo” como se definió anteriormente en donde el carbonilo es a su vez fijado a través del átomo de nitrógeno de un grupo amino (ej., metilcarbonilamino, ciclopentilcarbonil- aminometilo, y metilcarbonilaminofenilo) . El átomo de nitrógeno se puede así mismo sustituir con un grupo alquilo o arilo.

El término "alquilcarbonilaminoalquilo" representa un grupo "alquilcarbonilamino" fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., N-propilacetamida y N-butil-propionamida).

El término "arilalquilcarbonilamino" representa un grupo "arilalquilcarbonilo" como se definió anteriormente fijado a través de un grupo amino (ej., fenilacetamida y 3-fenilpropionamida).

El término "arilalquilcarbonilaminoalquilo" representa un grupo "arilalquilcarbonilamino" fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., N-etil-fenilacetamida y N-butil-3-fenil-propionamida).

El término "arilcarbonilamino" representa un grupo "arilcarbonilo" como se definió anteriormente fijado a través de un grupo amino (ej., benzamida y amida del ácido naftalen-1-carboxílico).

El término "arilcarbonilaminoalquilo" representa un grupo "arilcarbonilamino" fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., N-propilbenzamida y amida del ácido N-butil-naftalen-1-carboxílico).

El término "alquilcarboxilo" representa un grupo alquilcarbonilo como se definió anteriormente en donde el carbonilo a su vez es fijado a través de un puente de oxígeno (ej., heptilcarboxilo, ciclopropilcarboxilo, y 3-pentilcarboxilo).

El término "arilcarboxilo" representa un grupo arilcarbonilo como se definió anteriormente en donde el carbonilo a su vez es fijado a través de un puente de oxígeno (ej., ácido benzoico).

El término "alquilcarboxialquilo" representa un grupo alquilcarboxilo como se definió anteriormente en donde el oxígeno es fijado a través de un puente de alquilo (ej., heptilcarboximetilo, propilcarboxi-*tert*-butilo, y 3-pentilcarboxietilo).

El término "arilalquilcarboxilo" representa un grupo arilalquilcarbonilo como se definió anteriormente en donde el carbonilo a su vez está fijado a través de un puente de oxígeno (ej., benzilcarboxilo y fenilpropilcarboxilo).

El término "arilalquilcarboxialquilo" representa un grupo arilalquilcarboxilo como se definió anteriormente en donde el grupo carboxilo a su vez es fijado a través de un grupo alquilo con el número indicado de átomos de carbono (ej., benzilcarboximetilo y fenilpropilcarboxipropilo).

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El término “hetarilcarboxilo” representa un grupo hetarilcarbonilo como se definió anteriormente en donde el carbonilo es a su vez fijado a través de un puente de oxígeno (ej., ácido piridina- 2- carboxílico) .

5 El término “hetarilalquilcarboxilo” representa un grupo hetarilalquilcarbonilo como se definió anteriormente en donde el carbonilo a su vez es fijado a través de un puente de oxígeno (ej., (ácido 1- H- imidazol- 2- il) - acético y ácido 3- pirimidin- 2- il- propiónico) .

El término “alquilSOM” representa un grupo alquilo con el número de átomos de carbono indicados, en donde el grupo alquilo es a su vez fijado a través de un puente de azufre en donde el azufre es sustituido con m átomos de oxígeno (ej., etilsulfonilo y etilsulfinilo) .

10 El término “arilSOM” representa un grupo arilo como se definió anteriormente, en donde el grupo arilo a su vez es fijado a través de un puente de azufre en donde el azufre es sustituido como m átomos de oxígeno (ej., fenilsulfinilo y naftil- 2- sulfonilo) .

15 El término “hetarilSOM” representa un grupo hetarilo como se definió anteriormente, en donde el grupo hetarilo a su vez es fijado a través de un puente de azufre en donde el azufre es sustituido con m átomos de oxígeno (ej., tiazol- 2- sulfinilo y piridina- 2- sulfonilo) .

Ciertos términos definidos anteriormente pueden ocurrir más de una vez en las formulas estructurales, y ante tal ocurrencia cada término se definirá independientemente de los demás.

20 El término “opcionalmente sustituido” como se utiliza en la presente significa que los grupos en cuestión son sustituidos o no sustituidos con uno o más sustituyentes especificados. Cuando los grupos en cuestión son sustituidos con más de un sustituyente, los sustituyentes pueden ser iguales o diferentes.

25 El término “tratamiento” o “tratar” se define como el manejo y atención de un paciente para el propósito de combatir o aliviar la enfermedad, condición, o trastorno, y el término incluye la administración del compuesto activo para prevenir o retardar el comienzo de los síntomas o complicaciones; aliviar los síntomas o complicaciones; y/o eliminar la enfermedad, condición, o trastorno. Por lo tanto, “tratamiento” o “tratar” incluye prevención y/o profilaxis de la enfermedad, condición, o trastorno.

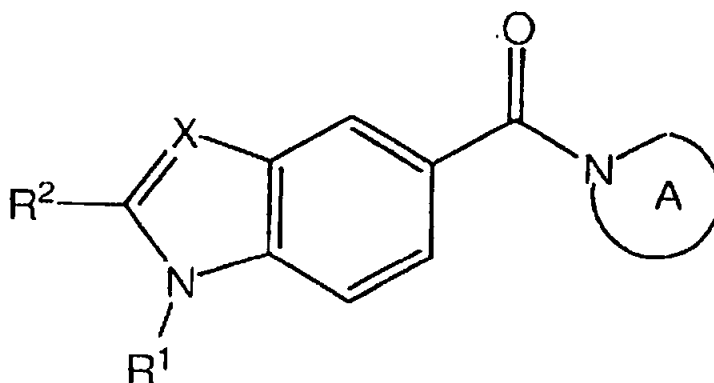
El término “farmacéuticamente aceptable” se define como apropiado para administración a humanos sin eventos adversos.

30 El término “profármaco” se define como una forma químicamente modificada del fármaco activo, dicho profármaco es administrado al paciente y subsecuentemente convertido al

fármaco activo. Las técnicas para el desarrollo de profármacos son bien conocidas en el estado de la técnica.

DESCRIPCION DETALLADA DEL INVENTO

- 5 Así en una realización, el presente invento proporciona el uso novedoso de una amida sustituida, un profármaco de la misma, o una sal de la misma con un ácido o base farmacéuticamente aceptables, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica o cualquiera de las formas tautoméricas, en donde la amida sustituida o un profármaco de la misma es de la formula I:

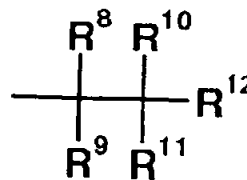


10 en donde:

X es seleccionada de CR_5 y nitrógeno;

- 15 R_1 es seleccionado de H y $C1-C6$ alquil-, R_6 , en donde el grupo alquilo es sustituido con 0-3 R_7 ;

R_2 es seleccionado de hidrógeno, halo, $C1-C6$ alquilo, y $-C(=O)R_{13}$;



Alternativamente, R_1 y R_2 son, independientemente,

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El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

5 El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquil/alquilenos es sustituido con 0- 3 R14;

R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;

10

R6 es seleccionado de ciano, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, arilo, hetarilo, - C(=O) R¹³, - S(=O) nR¹³, - S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, - N(R²³) C(=Y) NR¹⁸R¹⁹, - C(=NR¹⁵) NR¹⁵, - N(R¹⁸) C(=O) R¹³, - N(R¹⁸) C(=O) - C3- C10 cicloalquilo, - N(R¹⁸) C(=O) - hetcicloalquilo 3- 10 miembros, - N(R¹⁸) C(=O) - arilo, - N(R¹⁸) C(=O) - hetarilo en donde los grupos cicloalquilo, hetcicloalquilo, arilo y hetarilo son sustituidos con 0- 3 R16;

15

R7 es seleccionado de halo, hidroxilo, oxo, ciano, y C1- C6alquilo;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1- C6alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1- C6alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

20

Alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

25

Alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

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Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1-4 átomos de carbono adicionales, y 0-2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0-3 grupos seleccionados de halo, trihalometilo, C1-C6alquilo, arilo, hetarilo, arilC1-C6alquilenos, hetarilC1-C6alquilenos, hidroxilo, oxo, C1-C6alquiloxilo, ariloxilo, arilC1-C6alquiloxilo, y hetarilC1-C6alquiloxilo;

R12 es seleccionado de H, OH, NR18R19, C3-C10cicloalquilo, hetcicloalquilo de 3-10 miembros, -C(=O)R13, -S(=O)nR13, S(=O)nNR18R19, -N(R18)S(=O)nR13, y -C(=NR15)NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0-3 R17;

R13 es seleccionado de OH, C1-6alquilo, C1-C6alquiloxilo, C1-C8alquiloxiC1-C4alquilenos, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

R15 y R16 son independientemente seleccionados de H, C1-C6alquilo, cicloalquilo de 3-10 miembros, halo, OH, ciano, -C(=O)R13, -S(=O)nR13, S(=O)nNR18R19, -N(R18)S(=O)nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0-3 R20;

R17 es seleccionado de halo, OH, oxo, nitro, ciano, -C(=O)R13, -S(=O)nR13, S(=O)nR18R19, -N(R18)S(=O)nR13, NR18R19, C1-C6alquilo, C1-C6alquiloxilo, y ariloxilo;

R18 y R19 son independientemente seleccionados de H, C1-C6alquilo, C1-C8alquiloxilo, arilo, hetarilo, arilC1-C6alquilenos, y hetarilC1-C6alquilenos, en donde los grupos alquilo/alquilenos, arilo, y hetarilo son independientemente sustituidos por 0-3 R20;

Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4-10 átomos de carbono, y 0-2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0-3 C1-C8alquilo, arilo, hetarilo, arilC1-C6alquilenos, hetarilC1-C6alquilenos, hidroxilo, oxo, C1-C6alquiloxilo, arilC1-C6alquiloxilo, hetarilC1-C6alquiloxilo, C1-C6alquiloxiC1-C6alquiloxiC1-C6alquilo, C1-C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1-C6carbonilo, hetarilC1-C6alquilcarbonilo, C1-C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1-C6alquil-carboxilo, y hetarilC1-C6alquilcarboxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1-C6alquilo, C1-C6alquiloxilo, NR21R22, metilendioxo, dihalometilendioxo, trihalometilo, y trihalometiloxilo;

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R21 y R22 son independientemente seleccionados de H, C1- C6alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

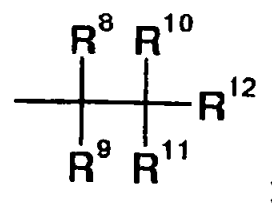
5 Y es seleccionado de O y S;

O una sal del mismo con un ácido o base farmacéuticamente aceptable o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

10 En otra realización, el presente invento proporciona el uso novedoso de compuestos de la formula I, en donde:

R1 se selecciona de H y C1- C4alquilo- R6, en donde el grupo alquilo es sustituido con 0- 1 R7;

R2 es seleccionado de hidrógeno, C1- C6alquilo, y -C(=O) R13;



Alternativamente, R1 y R2 son, independientemente,

15 El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado y 7- 10 átomos de carbono;

El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C4alquilo, halo, hidroxilo, y C1- C6alquiloxilo;

20 R5 es seleccionado de hidrógeno y C1- C4alquilo;

R6 es seleccionado de ciano, C3- C6cicloalquilo, hetcicloalquilo de 3- 6 miembros, arilo, hetarilo, - C(=O)=R13, - S(=O) nR13, - S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, - N(R²³) C(=Y) NR¹⁸R¹⁹, - C(=NR¹⁵) NR¹⁵, - N(R¹⁸) C(=O) R¹³, - N(R¹⁸) C(=O) - C3- C10 cicloalquilo, - N(R¹⁸) C(=O) - hetcicloalquilo 3- 10 miembros, - N(R¹⁸) C(=O) - arilo, - N(R¹⁸) C(=O) - hetarilo, en donde los grupos cicloalquilo, hetcicloalquilo, arilo, hetarilo son sustituidos con 0- 3 R16;

25 R7 es seleccionado de halo y C1- C4alquilo;

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R8, R9, R10, y R11 son cada uno independientemente seleccionados de hidrógeno y C1-C4alquilo;

5 Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono mostrados y 1- 4 átomos de carbono adicionales, en donde este anillo es sustituido con 0- 1 grupos seleccionados de halo, trihalometilo, hidroxilo, y C1- C6alquilo;

R12 es seleccionado de H, OH, y NR¹⁸R¹⁹;

R13 es seleccionado de OH, C1- C4alquilo, C1- C4alquiloxilo, C1- C4alquiloxiC1-C4alquileno, arilo, hetarilo, ariloxilo, hetariloxi, y NR¹⁸R¹⁹;

10 R15 y R16 son independientemente seleccionados de H, C1- C4alquilo, cicloalquilo de 3- 6 miembros, halo, OH, ciano, - C(=O) R¹³, - S(=O) nR¹³, S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 1 R20;

15 R18 y R19 son independientemente seleccionados de H, C1- C4alquiloxilo, arilo, hetarilo, arilC1- C4alquileno, y hetarilC1- C4alquileno, en donde los grupos alquilo/alquileno, arilo, y hetarilo son independientemente sustituidos con 0- 1 R20;

20 Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados, forman un anillo monocíclico, bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 5 átomos de carbono, y 0- 1 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre, en donde este anillo es sustituido con 0- 1 C1- C4alquilo, arilo, hetarilo, arilC1- C4alquileno, hetarilC1- C4alquileno, hidroxilo, y C1- C4alquiloxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C4alquilo, C1- C4alquiloxilo, NR²¹R²², trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C4alquilo, y arilC1-C4alquilo;

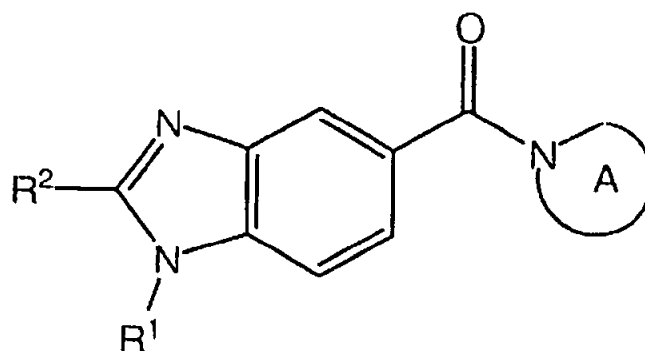
25 R23 es seleccionado de H y C1- C6alquilo;

N es seleccionado de 0, 1, y 2; y,

Y es seleccionado de O y S.

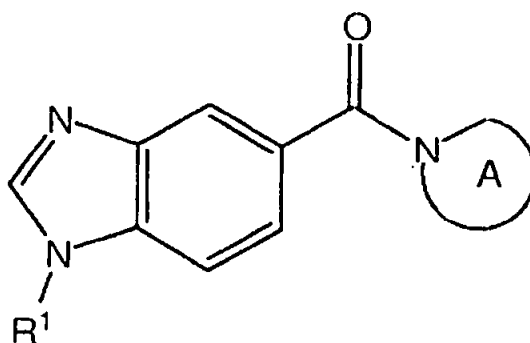
En otra realización, el presente invento proporciona el uso novedoso de compuestos en donde la amida sustituida o profármaco de la misma es de la fórmula IA:

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IA.

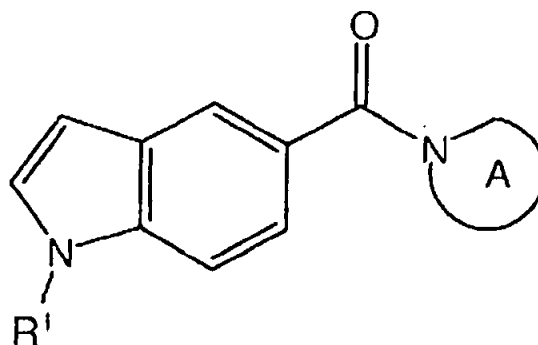
En otra realización, el presente invento proporciona el uso novedoso de compuestos en donde la amida sustituida o profármaco de la misma es de la formula IB:



IB.

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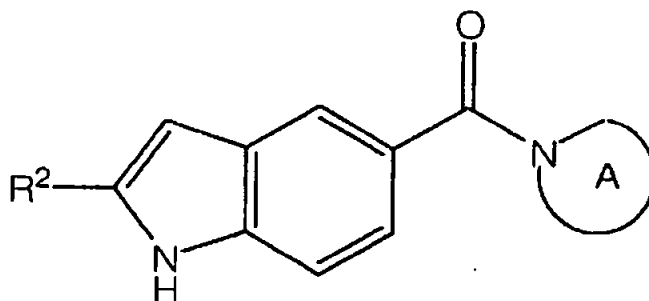
En otra realización, el presente invento proporciona el uso novedoso de compuestos en donde la amida sustituida o profármaco de la misma es de la formula IC:



IC.

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En otra realización, el presente invento proporciona el uso novedoso de compuestos en donde la amida sustituida o profármaco de la misma es de la formula ID:

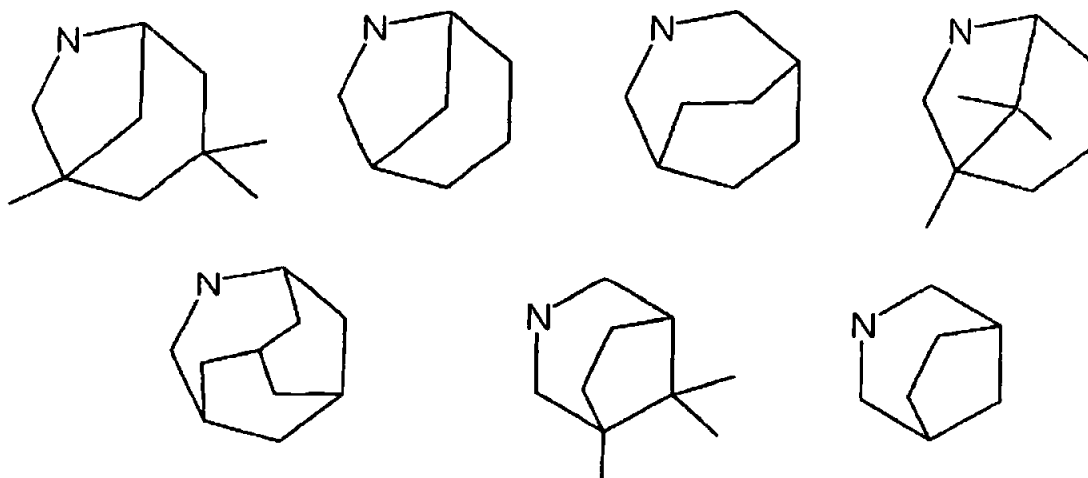


ID.

5

En otra realización, el presente invento proporciona el uso novedoso de compuestos de la formula I, en donde:

El anillo A es seleccionado de:



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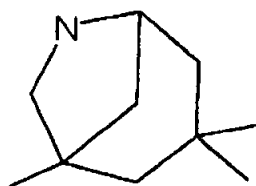
El anillo A es sustituido por 0- 2 R24; y,

R24 se selecciona de C1- C6alquilo, halo, hidroxilo, oxo, ciano, y C1- C6alquilo.

En otra realización, el presente invento proporciona el uso novedoso de compuestos de la formula I, en donde:

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El anillo A es

En otra realización, el presente invento proporciona el uso novedoso de compuestos de la formula 1, en donde la amida sustituida o un profármaco de la misma se seleccionan del grupo:

- 5 {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}amida del ácido furan- 2- carboxílico
- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}amida del ácido 1- acetil- piperidina- 4- carboxílico
- 10 2- metoxi- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil- acetamida
- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}-isonicotinamida
- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}-acetamida
- 15 Éster tert- butílico del ácido {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}carbámico
- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}-amida del ácido isoxazole- 5- carboxílico
- 20 N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}-benzamida
- Éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- Ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- 25 Éster etílico del ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - III- benzimidazol- 2- il]- ciclopropanocarboxílico

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- Acido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]-
ciclopropanocarboxílico
- Éster etílico del ácido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
benzimidazol- 1- il]- propiónico
- 5 Éster etílico del ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- Ácido de 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
benzimidazol- 1- il]- propiónico
- Acido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H-
10 benzimidazol- 2- il]- ciclopropanocarboxílico
- Éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1-
il]- propiónico
- Acido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster tert- butílico del ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
15 1- il]- acético
- Acido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- 1- morfolin- 4- il- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propan- 1- ona
- 1- morfolin- 4- il- 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
20 etanona
- Éster etílico del ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6-
carbonil) - indol- 1- il]- propiónico
- Acido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propiónico
- 25 Éster metílico del ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil)
- indol- 1- il]- propiónico
- Éster metílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
1- il]- butírico
- Acido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico
- 30 Acido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propiónico

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- Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- Éster metílico del ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- 5 Ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- Éster etílico del ácido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- Ácido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- 10 Éster etílico de ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- Ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- N- metoxi- N- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- 15 N- etoxi- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- N- hidroxí- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- {1- [2- (2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 20 {1- [2- (3- ciclopropil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 25 N- (1H- tetrazol- 5- il) - 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- {1- [2- (2- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- {1- [2- (1- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 30

CA

{1-[2-(5-metil-[1,2,4]oxadiazol-3-il)-etil]-1H-indol-5-il)-(1,3,3-trimetil-6-aza-biciclo[3.2.1]oct-6-il) metanona

5 o una sal del mismo con un ácido o base farmacéuticamente aceptable, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

En otra realización, el presente invento proporciona la preparación novedosa de una composición farmacéutica para el tratamiento de condiciones, trastornos, o enfermedades en donde una modulación o una inhibición de la actividad de 11 β HSD1 es benéfica.

10 En otra realización, el presente invento proporciona la preparación novedosa de una composición farmacéutica, en donde: las condiciones, trastornos, y enfermedades están influenciadas por niveles glucocorticoides intracelulares.

15 En otra realización, el presente invento proporciona la preparación novedosa de una composición farmacéutica, en donde: las condiciones, trastornos, o enfermedades son seleccionadas de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa (IGT), alteración de la glucosa en ayunas (IFG), la progresión desde IGT a diabetes tipo 2, la progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

20 En otra realización, el presente invento proporciona la preparación novedosa de una composición farmacéutica, en donde: la composición farmacéutica es apropiada para una ruta de administración seleccionada de oral, nasal, bucal, transdérmica, pulmonar y parenteral.

25 En otra realización, el presente invento proporciona un método novedoso para el tratamiento de condiciones, trastornos, o enfermedades en donde una modulación o una inhibición de la actividad de 11 β HSD1 es benéfica, el método comprendiendo la administración a un sujeto en necesidad del mismo de una cantidad efectiva de un compuesto del presente invento.

En otra realización, el presente invento proporciona un método novedoso en donde las condiciones, trastornos, y enfermedades están influenciadas por niveles glucocorticoides intracelulares.

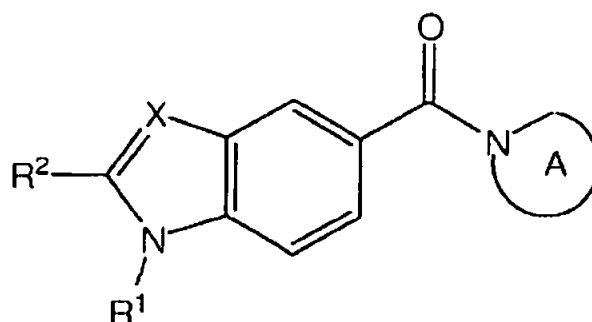
30 En otra realización, el presente invento proporciona un método novedoso en donde las condiciones, trastornos, o enfermedades se seleccionan de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa, (IGT),

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alteración de la glucosa en ayunas (IFG) , progresión desde IGT a diabetes tipo 2, progresión de síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

5 En otra realización, el presente invento proporciona un método novedoso en donde la administración se realiza a través de una ruta seleccionada entre oral, nasal, bucal, transdérmica, pulmonar, y parenteral.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I:

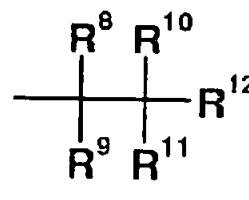


en donde:

X se selecciona de CR⁵ y nitrógeno;

15 R¹ se selecciona de H y C₁- C₆alquil- R₆, en donde el grupo alquilo es sustituido con 0- 3 R⁷;

R² es seleccionado de hidrógeno, halo, C₁- C₆alquilo, y -C(=O) R₁₃;



Alternativamente, R¹ y R² son independientemente,

20 El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre;

El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R14;

R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;

5 R6 es seleccionado de ciano, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, arilo, hetarilo, - C(=O) R¹³, - S(=O) nR¹³, - S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, - N(R²³) C(=Y) NR¹⁸R¹⁹, - C(=NR¹⁵) NR¹⁵, - N(R¹⁸) C(=O) R¹³, - N(R¹⁸) C(=O) - C3- C10 cicloalquilo, - N(R¹⁸) C(=O) - hetcicloalquilo 3- 10 miembros, - N(R¹⁸) C(=O) - arilo, - N(R¹⁸) C(=O) - hetarilo en donde los grupos cicloalquilo, hetcicloalquilo, arilo y hetarilo son sustituidos con 0- 3 R16;

10 R7 es seleccionado de halo, hidroxilo, oxo, ciano, y C1- C6alquilo;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1- C6alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1- C6alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

15 Alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

20 Alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

25 Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados formar un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono, 1- 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

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R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

5 R13 es seleccionado de OH, C1- 6alquilo, C1- C6alquiloxilo, C1- C8alquiloxiC1- C4alquilenos, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

R15 y R16 son independientemente seleccionados de H, C1- C6alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

10 R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C6alquilo, C1- C6alquiloxilo, y ariloxilo;

R18 y R19 son independientemente seleccionados de H, C1- C6alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C6alquilenos, y hetarilC1- C6alquilenos, en donde los grupos alquilo/alquilenos, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

15 Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, arilC1- C6alquiloxilo, hetarilC1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquiloxiC1- C6alquilo, C1- C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1- C6carbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

20 R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquiloxilo, NR21R22, metilendioxo, dihalometilendioxo, trihalometilo, y trihalometiloxilo;

25 R21 y R22 son independientemente seleccionados de H, C1- C6alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

30 Y es seleccionado de O y S;

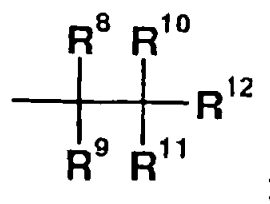
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o una sal del mismo con un ácido o base farmacéuticamente aceptable o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

En otra realización, el presente invento proporciona el compuesto novedoso de la fórmula 1, en donde:

R1 es seleccionado de H y C1- C4alquilo- R6, en donde el grupo alquilo es sustituido con 0- 1 R7;

R2 es seleccionado de hidrógeno, C1- C6alquilo, y -C(=O) R13;



Alternativamente, R1 y R2 son independientemente,

El anillo A es un anillo bicyclico o tricyclico saturado o parcialmente saturado que consta del nitrógeno mostrado y 7- 10 átomos de carbono;

R5 es seleccionado de hidrógeno y C1- C4alquilo;

R6 es seleccionado de ciano, C3- C10cicloalquilo, heterocicloalquilo de 3- 10 miembros, arilo, heterarilo, - C(=O) R¹³, - S(=O) nR¹³, - S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, - N(R²³) C(=Y) NR¹⁸R¹⁹, - C(=NR¹⁵) NR¹⁵, - N(R¹⁸) C(=O) R¹³, - N(R¹⁸) C(=O) - C3- C6 cicloalquilo, - N(R¹⁸) C(=O) - heterocicloalquilo 3- 6 miembros, - N(R¹⁸) C(=O) - arilo, - N(R¹⁸) C(=O) - heterarilo en donde los grupos cicloalquilo, heterocicloalquilo, arilo y heterarilo son sustituidos con 0- 3 R16;

R7 es seleccionado de halo y C1- C4alquilo;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1- C4alquilo;

Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, en donde este anillo es sustituido con 0- 1 grupos seleccionados de halo, trihalometilo, hidroxilo, y C1- C6alquilo;

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R12 es seleccionado de H, OH, y NR¹⁸R¹⁹;

R13 es seleccionado de OH, C1- 4alquilo, C1- C4alquiloxilo, C1- C4alquiloxiC1- C4alquileno, arilo, hetarilo, ariloxilo, hetariloxilo, y NR¹⁸R¹⁹;

5 R15 y R16 son independientemente seleccionados de H, C1- C4alquilo, cicloalquilo de 3- 6 miembros, halo, OH, ciano, - C(=O) R¹³, - S(=O) nR¹³, S(=O) nNR¹⁸R¹⁹, - N(R¹⁸) S(=O) nR¹³, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 1 R20;

R18 y R19 son independientemente seleccionados de H, C1- C4alquilo, C1- C4alquiloxilo, arilo, hetarilo, arilC1- C4alquileno, y hetarilC1- C4alquileno, en donde los grupos alquilo/alquileno, arilo, y hetarilo son independientemente sustituidos con 0- 1 R20;

10 Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados, forman un anillo monocíclico, bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 5 átomos de carbono, y 0- 1 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre, en donde este anillo es sustituido con 0- 1 C1- C4alquilo, arilo, hetarilo, arilC1- C4alquileno, hetarilC1- C4alquileno, hidroxilo, y C1- C4alquiloxilo;

15 R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C4alquilo, C1- C4alquiloxilo, NR²¹R²², trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C4alquilo, y arilC1- C4alquilo;

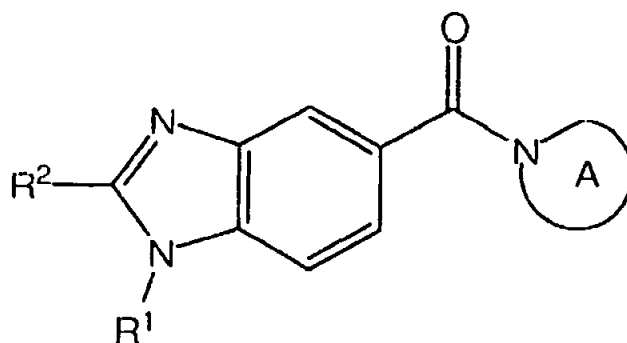
R23 es seleccionado de H y C1- C6alquilo;

20 n es seleccionado de 0, 1, y 2; y,

Y es seleccionado de O y S.

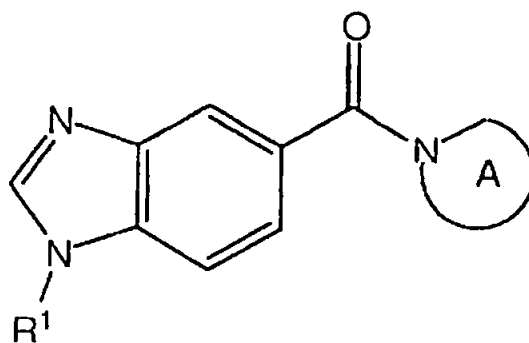
En otra realización, el presente invento proporciona los compuestos novedosos de la fórmula IA:

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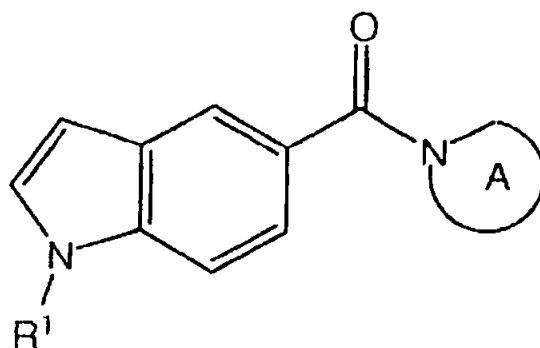
IA.

En otra realización, el presente invento proporciona los compuestos novedosos de la formula IB:



IB.

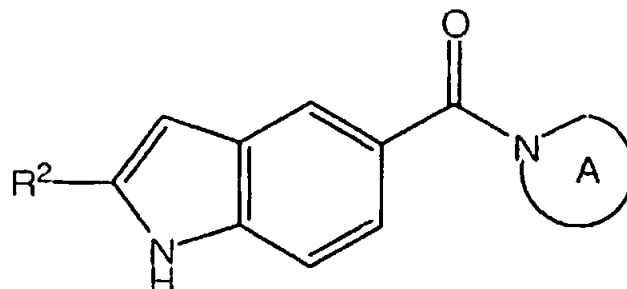
En otra realización, el presente invento proporciona los compuestos novedosos de la formula IC:



IC.

164

En otra realización, el presente invento proporciona los compuestos novedosos de la formula ID:

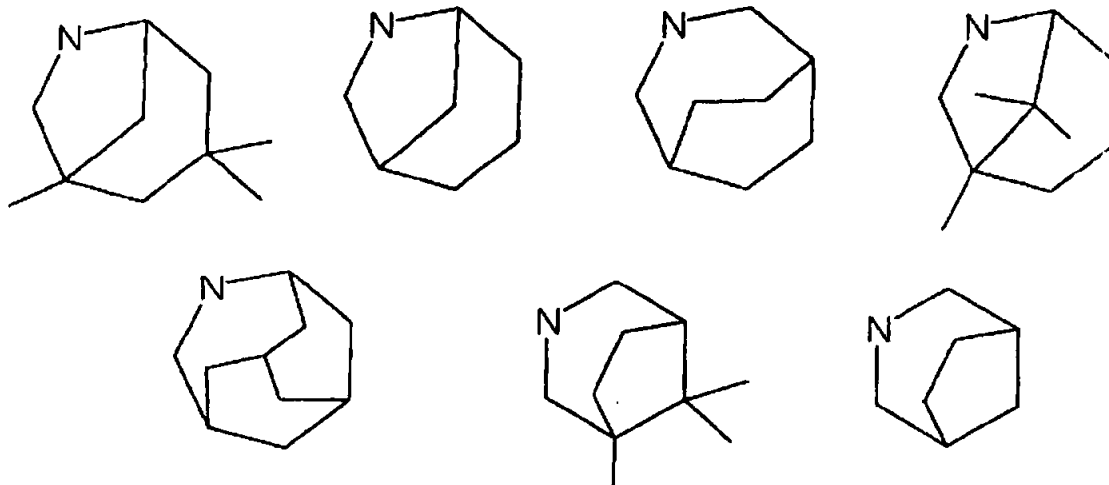


ID.

5

En otra realización, el presente invento proporciona los compuestos novedosos de la Formula I, en donde:

El anillo A es seleccionado de:



10

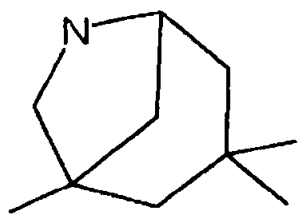
El Anillo A es sustituido con 0- 2 R24; y,

R24 es seleccionado de C1- C8alquilo, halo, hidroxilo, oxo, ciano, y C1- C6alquiloxilo.

15



En otra realización, el presente invento proporciona los compuestos novedosos de la formula I, en donde:



El Anillo A es

En otra realización, el presente invento proporciona los compuestos novedosos de la formula I, seleccionados del grupo:

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido furan- carboxílico

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida de 1- acetil- piperidina- 4- carboxílico

2- metoxi- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- isonicotinamida

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}acetamida

Éster tert- butilico del ácido {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}carbámico

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido isoxazole- 5- carboxílico

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}benzamida

Éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

Ácido de 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

166

- Éster etílico del ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- Ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- 5 Éster etílico del ácido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- Éster etílico del ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- Ácido de 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- 10 Ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- Éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- 15 Ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster tert- butílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- Ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- 1- morfolin- 4- il- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propan- 1- ona
- 20 1- morfolin- 4- il- 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- etanona
- Éster etílico del ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- 25 Ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster metílico del ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster metílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico
- 30 Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico

- Acido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propiónico
- Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]-
benzoico
- 5 Éster metílico del ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
1- ilmetil]- benzoico
- Acido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]-
benzoico
- Éster etílico del ácido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]-
10 propiónico
- Acido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- Éster etílico de ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2-
carboxílico
- Acido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- 15 N- metoxi- N- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1-
il]- propionamida
- N- etoxi- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propionamida
- N- hidroxí- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
20 propionamida
- {1- [2- (2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6-
il) metanona
- {1- [2- (3- ciclopropil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]oct- 6- il) metanona
- 25 {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]oct- 6- il) metanona
- N- (1H- tetrazol- 5- il) - 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
1- il]- propionamida
- {1- [2- (2- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
30 biciclo[3.2.1]oct- 6- il) metanona

100

{1- [2- (1- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]oct- 6- il) metanona

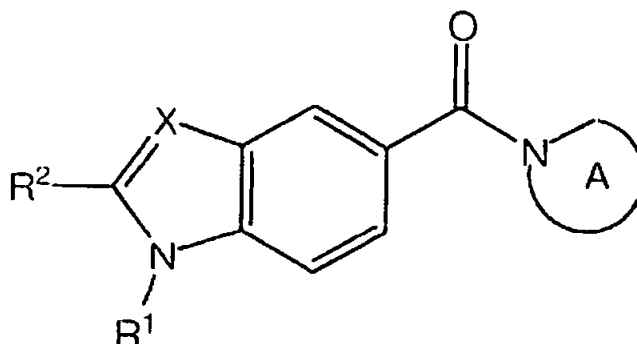
{1- [2- (5- metil- [1,2,4]oxadiazol- 3- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]oct- 6- il) metanona

5

o una sal del mismo con un ácido o base farmacéuticamente aceptable, o cualquier
isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma
tautomérica.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula

10 I:

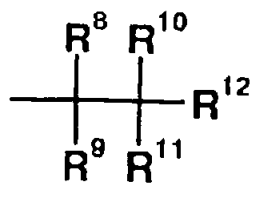


en donde:

15 X se selecciona de CR5 y nitrógeno;

R1 se selecciona de C1- C6alquil- R6, en donde el grupo alquilo es sustituido con 0- 3 R7;

R2 se selecciona de hidrógeno, halo, C1- C6alquilo, y -C(=O) R13;

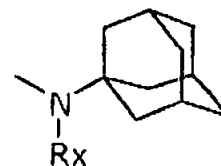
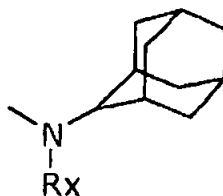
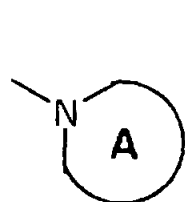


20 Alternativamente, R1 y R2 son, independientemente,

16

El Anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

- 5 El Anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R14;

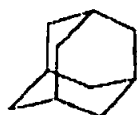


10 alternativamente,

es

ó

en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



- 15 es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R14;

R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;

- 20 R6 es seleccionado de ciano, arilo, hetarilo, - oxoC1- C6alquil- S(=O) R13, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) R13, - N(R18) C(=O) - C3- C10cicloalquilo, - N(R18) C(=O) - hetcicloalquilo de 3- 10 miembros, en donde los grupos cicloalquilo, hetcicloalquilo, arilo, y hetarilo son sustituidos con 0- 3 R16;

R7 es seleccionado de C1- C6alquilo, halo, hidroxilo, oxo y ciano;

120

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1-C6alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1- C6alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

5 Alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

10 Alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

15 Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

20 R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

25 R13 es seleccionado de OH, C1- 6alquilo, C1- C6alquiloxilo, C1- C8alquiloxiC1- C4alquileno, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

30 R15 y R16 son independientemente seleccionados de H, C1- C6alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

K1

R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C8alquilo, C1- C8alquiloxilo, y ariloxilo;

R18 y R19 son independientemente seleccionados de H, C1- C8alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C8alquilenos, y hetarilC1- C8alquilenos, en donde los grupos alquilo/alquilenos, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, arilC1- C6alquiloxilo, hetarilC1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilo, C1- C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1- C6carbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquiloxilo, NR21R22, metilendioxo, dihalometilendioxo, trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C8alquilo, y arilC1- C6alquilo;

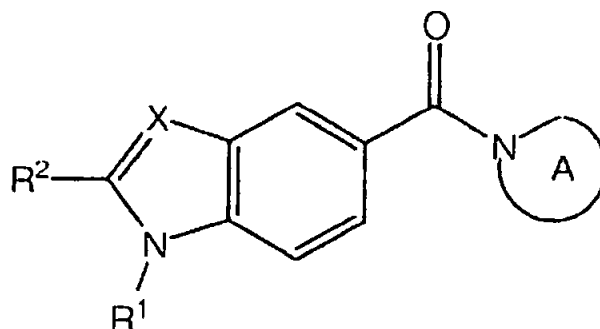
R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

Y es seleccionado de O y S;

o una sal del mismo con un ácido o base farmacéuticamente aceptable o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I:



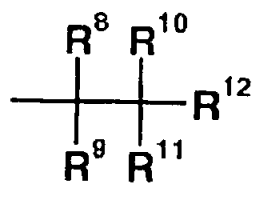
en donde:

5

X se selecciona de CR5 y nitrógeno;

R1 se selecciona de C1- C6alquil- R6, en donde el grupo alquilo es sustituido con 0- 3 R7;

R2 se selecciona de hidrógeno, halo, C1- C6alquilo, y -C(=O) R13;



10 alternativamente, R1 y R2 son, independientemente,

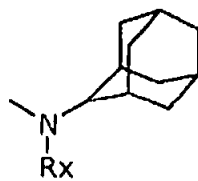
El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre;

15

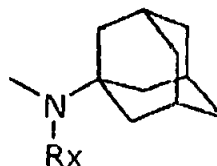
El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nNR18R19 oxo, ciano, C1- C6alquilo, C1- C6alquilo, C1- C6alquilo, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilo es sustituido con 0- 3 R14;



alternativamente,



es



6

en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



5 es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R14;

R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;

10 R6 es seleccionado de ciano, arilo, hetarilo, - oxoC1- C6alquil- S(=O) R13, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) R13, - N(R18) C(=O) - C3- C10cicloalquilo, - N(R18) C(=O) - hetcicloalquilo de 3- 10 miembros, en donde los grupos cicloalquilo, hetcicloalquilo, arilo, y hetarilo son sustituidos con 0- 3 R16;

15 R7 es seleccionado de C1- C6alquilo, halo, hidroxilo, oxo y ciano;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1- C8alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1- C8alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

20 alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

PH

alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

R13 es seleccionado de OH, C1- 8alquilo, C1- C8alquiloxilo, C1- C8alquiloC1- C4alquilenos, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

R15 y R16 son independientemente seleccionados de H, C1- C8alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C8alquilo, C1- C8alquiloxilo, y ariloxilo;

R18 y R19 son independientemente seleccionados de H, C1- C8alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C8alquilenos, y hetarilC1- C6alquilenos, en donde los grupos alquilo/alquilenos, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, arilC1-

C6alquilo, hetarilC1- C6alquilo, C1- C6alquilo, C1- C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1- C6carbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

5 R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquilo, NR21R22, metilendio, dihalometilendio, trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C8alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

10 n es seleccionado de 0, 1, y 2;

Y es seleccionado de O y S;

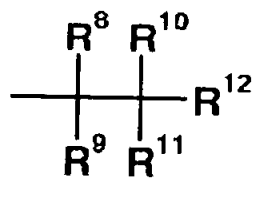
siempre que cuando X es CR5, entonces R6 es -C(=O) R13 en donde R13 es OH; o una sal del mismo con un ácido o base farmacéuticamente aceptables, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica o cualquier forma tautomérica.

15 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde:

X se selecciona de CR5 y nitrógeno;

R1 se selecciona de C1- C6alquil- R6, en donde el grupo alquilo es sustituido con 0- 3 R7;

20 R2 se selecciona de hidrógeno, halo, C1- C6alquilo, y -C(=O) R13;



alternativamente, R1 y R2 son, independientemente,

25 El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre;

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es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, -COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquileno, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquileno es sustituido con 0- 3 R14;

15

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R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1-C8alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1-C6alquiloxilo, en donde el C1-C8alquilo y C1-C6alquiloxilo son sustituidos con 0-3 R17;

20

alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1-

5 C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y

10 azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1-

15 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

R13 es seleccionado de OH, C1- 8alquilo, C1- C8alquiloxilo, C1- C8alquiloxiC1- C4alquilenos, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

25 R15 y R16 son independientemente seleccionados de H, C1- C8alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C8alquilo, C1- C6alquiloxilo, y ariloxilo;

3

R18 y R19 son independientemente seleccionados de H, C1- C8alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C6alquilenos, y hetarilC1- C6alquilenos, en donde los grupos alquilo/alquilenos, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

5 alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquilenos, hetarilC1- C6alquilenos, hidroxilo, oxo, C1- C6alquiloxilo, arilC1- C6alquiloxilo, hetarilC1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilo, C1- C6alquilcarbonilo, 10 arilcarbonilo, hetarilcarbonilo, arilC1- C6alquilcarbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquiloxilo, NR21R22, metilendioxo, dihalometilendioxo, trihalometilo, y trihalometiloxilo;

15 R21 y R22 son independientemente seleccionados de H, C1- C8alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

Y es seleccionado de O y S;

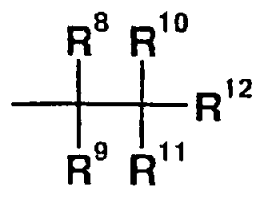
20 siempre que cuando X es CR5, entonces R6 es -C(=O) R13 en donde R13 es OH; o una sal del mismo con un ácido o base farmacéuticamente aceptables, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica o cualquier forma tautomérica.

25 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde:

R1 es C1- C6alquil- R6, en donde el grupo alquilo es sustituido con 0- 1 R7;

R2 se selecciona de hidrógeno, C1- C6alquilo, y -C(=O) R13;

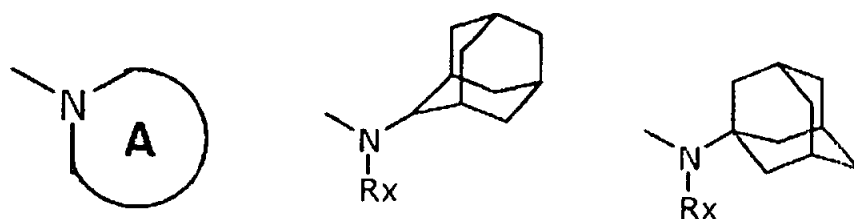
iv



alternativamente, R1 y R2 son, independientemente,

El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado y 7- 10 átomos de carbono;

- 5 El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C4alquilo, halo, hidroxilo, oxo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 y C1- C6alquilo; oxilo;



alternativamente,

es

ó

- 10 en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquilo; oxilo, C1- C6alquilo; oxilo, C1- C6alquilo; oxilo, y C1- C6alquilo; carbonilo, en donde cada grupo alquilo/alquilo es sustituido con 0- 3 R14;

15

R5 es seleccionado de hidrógeno y C1- C4alquilo;

R6 es seleccionado de ciano, arilo, hetarilo, - oxoC1- C6alquilo- S(=O) R13, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) R13, - N(R18) C(=O) - C3- C6cicloalquilo, - N(R18) C(=O) -

hetcicloalquilo de 3- 6 miembros, en donde los grupos cicloalquilo, hetcicloalquilo, arilo, y hetarilo son sustituidos con 0- 3 R16;

R7 es seleccionado de halo;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno y C1-

5 C4alquilo;

alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, en donde este anillo es sustituido con 0- 1 grupos seleccionados de halo, trihalometilo, hidroxilo, y C1- C6alquilo;

10 R12 es seleccionado de H, OH y NR18R19;

R13 es seleccionado de OH, C1- 4alquilo, C1- C4alquiloxilo, C1- C4alquiloC1- C4alquileno, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R15 y R16 son independientemente seleccionados de H, C1- C4alquilo, cicloalquilo de 3- 6 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 1 R20;

15 R18 y R19 son independientemente seleccionados de H, C1- C4alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C4alquileno, y hetarilC1- C4alquileno, en donde los grupos alquilo/alquileno, arilo, y hetarilo son independientemente sustituidos por 0- 1 R20;

20 alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 5 átomos de carbono, y 0- 1 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 1 C1- C4 alquilo, arilo, hetarilo, arilC1- C4alquileno, hetarilC1- C4alquileno, hidroxilo, y C1- C4alquiloxilo;

25 R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C4alquilo, C1- C4alquiloxilo, NR21R22, trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C4alquilo, y arilC1- C4alquilo;

R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

30 Y es seleccionado de O y S;

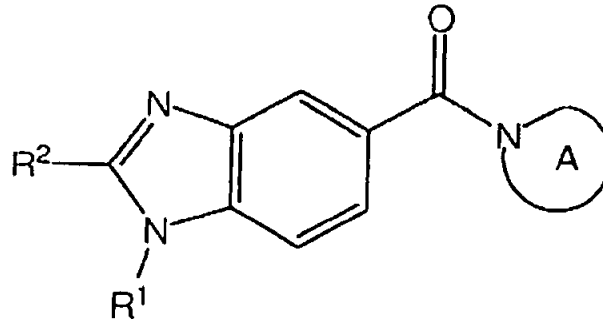
siempre que cuando X es CR5, entonces R6 es -C(=O) R13 en donde R13 es OH;

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o una sal del mismo con un ácido o base farmacéuticamente aceptables, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica o cualquier forma tautomérica.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula

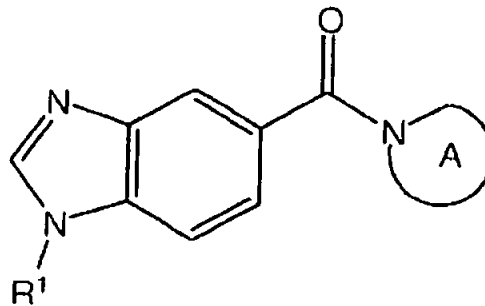
5 IA:



IA.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula

IB:

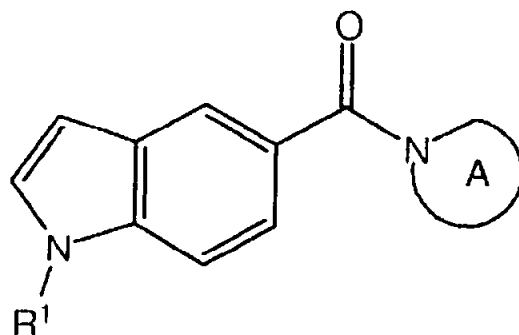


IB.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula

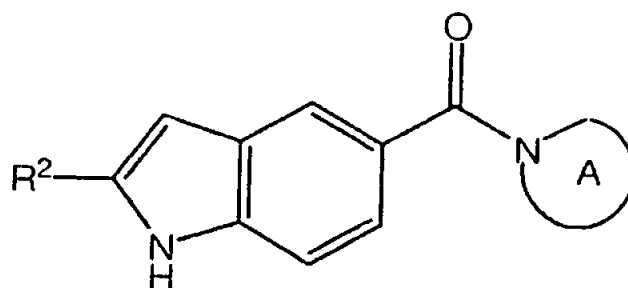
15 IC:

18a



IC.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula ID:



ID.

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En otra realización, el presente invento proporciona un compuesto novedoso de la formula I en donde R6 es seleccionado de arilo, hetarilo, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) - arilo, o -N(R18) C(=O) - hetarilo, en donde los grupos arilo, y hetarilo son sustituidos con 0- 3 R16.

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En otra realización, el presente invento proporciona un compuesto novedoso de la formula I en donde R6 es seleccionado de arilo, hetarilo, - oxoC1- C6alquil- S(=O) nR13, - C(=O) R13, - S(=O) nR13, - S(=O) nR18R19, - N(R18) S(=O) nR18, - N(R23) C(=Y) NR18R19 o -C(=NR15) NR15; en donde los grupos arilo y hetarilo son sustituidos con 0- 3 R16.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, donde R6 es seleccionado de -C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19 o -C(=NR15) NR15.

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En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I en donde R6 es seleccionado de $-C(=O)R_{13}$, $-S(=O)_nR_{13}$, $-S(=O)_nNR_{18}R_{19}$, o $N(R_{23})C(=Y)NR_{18}R_{19}$.

5 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R6 es seleccionado de $-N(R_{23})C(=Y)NR_{18}R_{19}$.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R7 es C1- C6alquilo.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R7 es halo.

10 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R7 es hidroxilo.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R7 es oxo.

15 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde R7 es ciano.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde Y es oxígeno (O).

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde

20

El Anillo A es un anillo bicíclico o tríciclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

25 El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, $-COOH$, $-CONR_{18}R_{19}$, $-S(=O)_nR_{13}$, $-S(=O)_nNR_{18}R_{19}$ oxo, ciano, C1- C6alquilo, C1- C6alquilo, C1- C6alquilo, C1- C6alquilo, y C1- C6alquilo, en donde cada grupo alquilo/alquilo es sustituido con 0- 3 R14.

En otra realización, el presente invento proporciona un compuesto novedoso de la Fórmula I, en donde

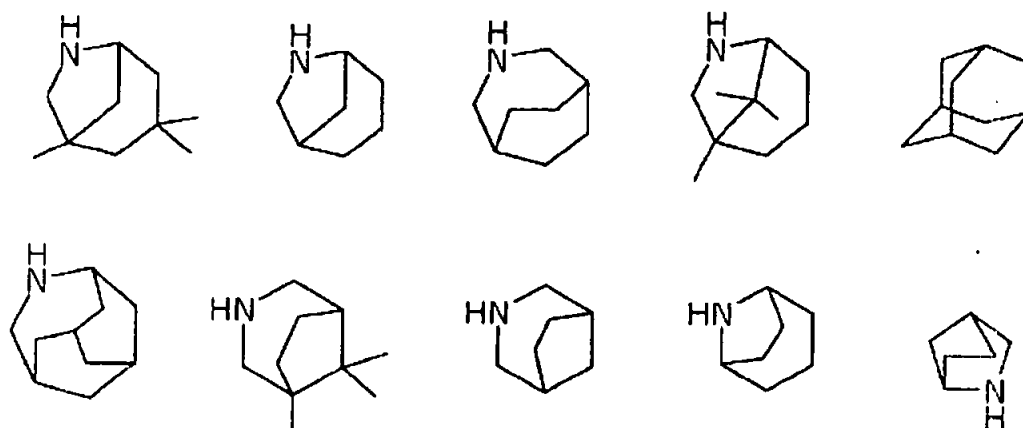
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1984

El Anillo A es un anillo bicíclico o tricíclico que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 1- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

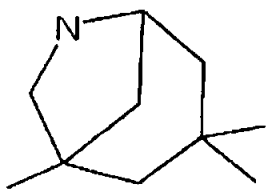
El anillo A es sustituido con 0- 3 grupos seleccionados de C1- C4alquilo, halo, hidroxilo, oxo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 y C1- C6alquiloxilo.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, en donde el Anillo A es seleccionado de:



10 El Anillo A es sustituido con 0- 2 grupos seleccionados de C1- C6alquilo, halo, hidroxilo, oxo, ciano, COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 y C1- C6alquiloxilo.

En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, en donde el Anillo A es



15 En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, en donde el Anillo A es

En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, en donde el Anillo A es

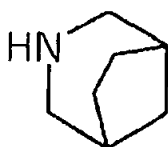
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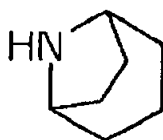
En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde el Anillo A es



5 En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde el anillo A es

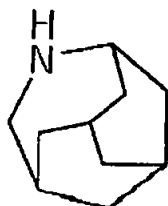


En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde el Anillo A es



10

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde el Anillo A es



sd



en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;

es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, -COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R14.

En otra realización, el presente invento proporciona un compuesto novedoso de la fórmula I, en donde



en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



es sustituido con 0- 3 grupos seleccionados de C1- C4alquilo, halo, hidroxilo, oxo, - COOH, - CONR¹⁸R¹⁹, - S(=O) nR¹³, - S(=O) nNR¹⁸R¹⁹ y C1- C6alquiloxilo.

En otra realización, el presente invento proporciona un compuesto novedoso, en donde el compuesto se selecciona del grupo:

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido furan- 2- carboxílico

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido 1- acetil- piperidina- 4- carboxílico

2- metoxi- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- acetamida

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- isonicotinamida

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- acetamida

Éster tert- butílico del ácido {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}carbámico

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido isoxazole- 5- carboxílico

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- benzamida

Éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

Ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

Éster etílico del ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico

Acido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico

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- Éster etílico del ácido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- Éster etílico del ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- 5 Ácido de 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico
- Ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- 10 Éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster tert- butílico del ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- Ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- 15 1- morfolin- 4- il- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propan- 1- ona
- 1- morfolin- 4- il- 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- etanona
- Éster etílico del ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- 20 Ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster metílico del ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- 25 Éster metílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico
- Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico
- Ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- 30 Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico

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- Éster metílico del ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- Acido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- 5 Éster etílico del ácido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- Acido 3- [5- (4- aza- triciclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- Éster etílico de ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- 10 Acido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- [1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona
- (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- metanona
- 15 (5- hidroxí- adamantan- 2- il) - amida del ácido trans- 1- (2- metanosulfonil- metoxi- etil) - 1H- benzoimidazol- 5- carboxílico
- (5- hidroxí- adamantan- 2- il) - amida del ácido Cis- 1- (2- metanosulfonil- metoxi- etil) - 1H- benzoimidazol- 5- carboxílico
- 20 (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- metanona
- (5- hidroxí- adamantan- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico
- (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- metanona
- 25 [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona
- (5- hidroxí- adamantan- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico
- 30 5- carboxílico

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- (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il}- metanona
- (octahidro- quinolin- 1- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il}- metanona
- 5 (5- hidroxí- adamantan- 2- il) - amida del ácido trans- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico
- (5- hidroxí- adamantan- 2- il) - amida del ácido cis- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida
- 10 del ácido 3- hidroxí- pirlidina- 1- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 4- hidroxí- piperidina- 1- carboxílico
- (5- hidroxí- adamantan- 2- il) - amida del ácido 1- {2- [(4- hidroxí- piperidina- 1- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- 15 (5- hidroxí- adamantan- 2- il) - amida del ácido 1- {2- [(1,1- dioxo- tiomorfolina- 4- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil} amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- (5- hidroxí- adamantan- 2- il) - amida del ácido cis- 1- {2- [(morfolina- 4- carbonil) - amino]etil}-
- 20 1H- benzo- imidazol- 5- carboxílico
- (5- hidroxí- adamantan- 2- il) - amida del ácido Trans- 1- {2- [(morfolina- 4- carbonil) - amino]etil}- 1H- benzo- imidazol- 5- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido cis- morfolina- 4- carboxílico
- 25 {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido trans- morfolina- 4- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido morfolina- 4- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- 30

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- {2- [5- (octahidro- quinolina- 1- carbonil) - benzo- imidazol- 1- il]- etil}- amida del ácido 3-
hidroxi- pirrolidina- 1- carboxílico
- Ácido 1- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etilcarbamoil}-
piperidina- 4- carboxílico
- 5 {2- [5- (3- hidroxi- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}-
amida del ácido 3- hidroxi- pirrolidina- 1- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzo- imidazol- 1- il]- etil}- amida del ácido cis- 4-
hidroxi- piperidina- 1- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido trans- 4-
10 hidroxi- piperidina- 1- carboxílico
- {2- [5- (3- hidroxi- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}-
amida del ácido endo- 4- hidroxi- piperidina- 1- carboxílico
- {2- [5- (3- hidroxi- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}-
amida del ácido exo- 4- hidroxi- piperidina- 1- carboxílico
- 15 (5- hidroxi- adamantan- 2- il) - amida del ácido 1- {2- [(1,1- dioxo- tiomorfolina- 4- carbonil) -
amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxi- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzo- imidazol- 1- il]- etil}-
amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- (5- hidroxi- adamantan- 2- il) - amida del ácido 1- {2- [(4- hidroxi- piperidina- 1- carbonil) -
20 amino]etil}- 1H- benzoimidazol- 5- carboxílico
- (5- hidroxi- adamantan- 2- il) - amida del ácido 1- {2- [(3- hidroxi- pirrolidina- 1- carbonil) -
amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxi- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}-
amida del ácido morfolina- 4- carboxílico
- 25 Ácido cis 1- {2- [5- (5- hidroxi- adamantan- 2- ilcarbamoil) - benzoimidazol- 1- il]-
etilcarbamoil}- piperidina- 4- carboxílico
- Ácido trans- 1- {2- [5- (5- hidroxi- adamantan- 2- ilcarbamoil) - benzoimidazol- 1- il]-
etilcarbamoil}- piperidina- 4- carboxílico
- Ácido 1- {2- [5- (3- hidroxi- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]-
30 etilcarbamoil}- piperidina- 4- carboxílico

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N- metoxi- N- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -indol- 1- il]- propionamida

N- etoxi- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -indol- 1- il]- propionamida

5 N- hidroxi- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -indol- 1- il]- propionamida

{1- [2- (2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}(1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) -metanona

10 {1- [2- (3- ciclopropil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}(1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) -metanona

{1- [2- (3- metil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}(1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) -metanona

N- (1H- tetrazol- 5- il) - 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -indol- 1- il]- propionamida

15 {1- [2- (2- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il} - (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- il) - metanona

{1- [2- (1- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il} - (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- il) - metanona

20 {1- [2- (5- metil- [1,2,4]oxadiazol- 3- il) - etil]- 1H- indol- 5- il} - (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- il) - metanona;

o una sal del mismo con un ácido o base farmacéuticamente aceptable, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

25 En otra realización, el presente invento proporciona un compuesto novedoso de la formula I, el cual es un agente útil para el tratamiento de condiciones, trastornos, o enfermedades en donde una modulación o inhibición de la actividad de 11 β HSD1 es benéfica.

30 En otra realización, el presente invento proporciona el uso de un compuesto de la formula I para la preparación de una composición farmacéutica para el tratamiento de condiciones, trastornos, o enfermedades, en donde las condiciones, trastornos, y enfermedades están influenciadas por niveles glucocorticoides intracelulares.

ca³

En otra realización, el presente invento proporciona el uso de un compuesto de la formula I para la preparación de una composición farmacéutica para el tratamiento de condiciones, trastornos, o enfermedades, en donde las condiciones, trastornos, o enfermedades se seleccionan de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa (IGT) , alteración de la glucosa en ayunas (IFG) , la progresión desde IGT a diabetes tipo 2, la progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

En otra realización, el presente invento proporciona un método para el tratamiento de condiciones, trastornos, o enfermedades en donde una modulación o una inhibición de la actividad de 11 β HSD1 es benéfica, el método comprendiendo administración a un sujeto en necesidad del mismo de una cantidad efectiva de un compuesto de la formula I.

En otra realización, el presente invento proporciona un método para el tratamiento de condiciones, trastornos o enfermedades, en donde las condiciones, trastornos, y enfermedades están influenciados por niveles glucocorticoides intracelulares, el método comprendiendo la administración a un sujeto en necesidad del mismo de una cantidad efectiva de un compuesto de la formula I.

En otra realización, el presente invento proporciona un método para el tratamiento de condiciones, trastornos o enfermedades, en donde las condiciones, trastornos o enfermedades se seleccionan de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa (IGT) , alteración de la glucosa en ayunas (IFG) , la progresión desde IGT a diabetes tipo 2, la progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

En otra realización, el presente invento proporciona un compuesto novedoso, el cual es un agente útil para el tratamiento de condiciones, trastornos, o enfermedades en donde una modulación o inhibición de la actividad de 11 β HSD1 es benéfica.

En otra realización, el presente invento proporciona un método novedoso en donde las condiciones, trastornos, y enfermedades están influenciadas por niveles glucocorticoides intracelulares.

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En otra realización, el presente invento proporciona un método novedoso en donde las condiciones, trastornos, o enfermedades se seleccionan de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa (IGT), alteración de la glucosa en ayunas (IFG), progresión de IGT a diabetes tipo 2, progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

En otra realización, el presente invento proporciona una composición farmacéutica de método novedoso que comprende, como un ingrediente activo, al menos un compuesto según el presente invento junto con uno o más vehículos farmacéuticamente aceptables o excipientes.

En otra realización, el presente invento proporciona una composición farmacéutica novedosa, la cual es apropiada para administración oral, nasal, bucal, transdérmica, pulmonar, o parenteral.

Los compuestos del presente invento pueden tener centros asimétricos y pueden ocurrir como racematos, mezclas racémicas, y como enantiómeros individuales o diastereoisómeros, con todas las formas isoméricas incluidas en el presente invento así como también mezclas de las mismas.

El presente invento también incluye sales farmacéuticamente aceptables de los presentes compuestos. Tales sales incluyen sales de adición ácida farmacéuticamente aceptables, sales de adición alcalina farmacéuticamente aceptables, sales metálicas farmacéuticamente aceptables, sales de amonio y de amonio alquiladas. Las sales de adición ácida incluyen sales de ácidos inorgánicos así como también ácidos orgánicos. Ejemplos representativos de ácidos inorgánicos incluyen ácidos clorhídrico, hidrobromico, hidroyódico, fosfórico, sulfúrico, y nítrico. Ejemplos representativos de ácidos orgánicos apropiados incluyen fórmico, acético, tricloroacético, propiónico, benzoico, cinámico, cítrico, fumárico, glicólico, láctico, maléico, málico, masónico, mandélico, oxálico, pícrico, pirúvico, salicílico, succínico, metanosulfónico, etanosulfónico, tartárico, ascórbico, pamóico, bismetilensalicílico, etanodisulfónico, glucónico, aspártico, esteárico, palmítico, EDTA, glicólico, p-aminobenzoico, glutámico, bencenosulfónico, p-toluensulfónico, sulfatos, nitratos, fosfatos, percloratos, boratos, acetatos, benzoatos, hidroxinaftoatos, glicerofosfatos, y cetoglutaratos. Ejemplos adicionales de sales de adición ácida orgánicas e inorgánicas farmacéuticamente aceptables incluyen las sales farmacéuticamente

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aceptables listadas en J. Pharm. Sci, 66, 2 (1977) , que se incorpora en la presente como referencia. Ejemplos de sales metálicas incluyen sales de litio, sodio, potasio, bario, calcio, magnesio, zinc, y calcio. Ejemplos de aminas y aminas orgánicas incluyen amonio, metilamina, dimetilamina, trimetilamina, etilamina, dietilamina, propilamina, butilamina, tetrametilamina, etanolamina, dietanolamina, trietanolamina, meglumina, etilendiamina, colina, N,N'-dibenziletildiamina, N- bencilfeniletilamina, N- metil- D- glucamina, y guanidina. Ejemplos de ácidos amino catiónicos incluyen lisina, arginina e histidina.

Además, algunos de los compuestos del presente invento pueden formar solvatos con agua o solventes orgánicos comunes. Tales solvatos están incluidos dentro del alcance del invento.

Las sales farmacéuticamente aceptables se preparan al reaccionar un compuesto del presente invento con 1 a 4 equivalentes de una base tal como hidróxido de sodio, metóxido de sodio, hidruro de sodio, tert- butóxido de potasio, hidróxido de calcio, e hidróxido de magnesio, en solventes tales como éter, THF, metanol, tert- butanol, dioxano, e isopropanol, etanol. Se pueden utilizar mezclas de solventes. También se pueden utilizar bases orgánicas tales como lisina, arginina, dietanolamina, colina, guandina, y sus derivados etc. Alternativamente, las sales de adición ácida donde son aplicables se preparan mediante tratamiento con ácidos tales como ácido clorhídrico, ácido hidrobromico, ácido nítrico, ácido sulfúrico, ácido fosfórico, ácido p-toluensulfónico, ácido metanosulfónico, ácido acético, ácido cítrico, ácido maleico y salicílico, ácido hidroxinaftóico, ácido ascórbico, ácido palmítico, ácido succínico, ácido benzóico, ácido bencenosulfónico, y ácido tartárico en solventes tales como acetato de etilo, éter, alcoholes, acetona, THF, y dioxano. También se puede utilizar mezcla de solventes.

Los estereoisómeros de los compuestos que forman parte del invento se pueden preparar utilizando reactivos en su forma enantiomérica simple en el proceso siempre que sea posible o al realizar la reacción en presencia de reactivos o catalizadores en su forma enantiomérica simple o mediante resolución de la mezcla de estereoisómeros mediante métodos convencionales. Algunos de los métodos preferidos incluyen el uso de resolución microbiana, resolución enzimática, resolviendo las sales diastereoméricas formadas con ácidos quirales tales como ácido mandélico, ácido canforsulfónico, ácido tartárico, y ácido láctico, donde sea aplicable o bases quirales tales como brucina, (R) o (S) - feniletilamina, alcaloides de cincona y sus derivados. Métodos comúnmente utilizados son compilados por Jaques, en "Enantiómeros, Racematos y Resolución" (Wiley Interscience, 1981) . Más específicamente el compuesto del presente invento se puede

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convertir a una mezcla 1:1 de amidas diastereoméricas al tratar con aminas quirales, aminoácidos, aminoalcoholes derivados a partir de aminoácidos; se pueden emplear condiciones de reacción convencionales para convertir ácido en una amida; los diastereoisómeros se pueden separar ya sea mediante cristalización fraccional o cromatografía y los estereoisómeros del compuesto de la formula I se pueden preparar al hidrolizar la amida diastereomérica pura.

Varios polimorfos de los compuestos que forman parte de este invento se pueden preparar mediante cristalización de dichos compuestos bajo diferentes condiciones. Por ejemplo, utilizando diferentes solventes comúnmente utilizados o sus mezclas para recrystalización; cristalizaciones a diferentes temperaturas; varios modos de enfriamiento, en el rango de enfriamiento desde muy rápido a muy lento durante cristalizaciones. Los polimorfos también se pueden obtener al calentar o fundir el compuesto seguido por enfriamiento gradual o rápido. La presencia de polimorfos se puede determinar mediante espectroscopia NMR de sonda sólida, o espectroscopia, calorimetría de exploración diferencial, difracción de polvo de Rayos- X u otras de estas técnicas.

El invento también incluye profármacos de los presentes compuestos, los cuales al ser administrados experimentan conversión química mediante procesos metabólicos antes de convertirse en sustancias farmacológicas activas. En general, tales profármacos serán derivados funcionales de los presentes compuestos, los cuales son fácilmente convertibles *in vivo* al compuesto requerido del presente invento. Los procedimientos convencionales para la selección y preparación de derivados de profármacos apropiados se describen, por ejemplo, en "*Design of Prodrugs*", ed. H. Bundgaard, Elsevier, 1985.

Un problema bien conocido en el descubrimiento de fármacos es que los compuestos, tales como inhibidores enzimáticos, pueden ser muy potentes y selectivos en ensayos bioquímicos, aún ser inactivos *in vivo*. Esta falta de la conocida biodisponibilidad se puede atribuir a un número de diferentes factores tales como falta de absorción o absorción pobre en el intestino, metabolismo de primer paso en el hígado y/o absorción pobre en las células. Aunque los factores que determinan la biodisponibilidad no están completamente entendidos, existen muchos ejemplos en la literatura científica – bien conocidos por aquellos con experiencia en el estado de la técnica – de cómo modificar compuestos, que son potentes y selectivos en ensayos bioquímicos pero que muestran actividad baja o nula *in vivo*, en fármacos que son biológicamente activos.

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Dentro del alcance del invento está modificar los compuestos del presente invento, denominados los “compuestos originales”, fijando grupos químicos que mejorarán la biodisponibilidad de dichos compuestos en forma tal que se facilita la absorción en las células o mamíferos.

5 Ejemplos de tales modificaciones, los cuales no tienen el propósito de limitar en forma alguna el alcance del invento, incluyen cambiar uno o más grupos carboxilos a ésteres (por ejemplo ésteres de metilo, ésteres de etilo, tert- butilo, acetoximetilo, ésteres de pivaloiloiloximetilo u otros ésteres de aciloximetilo) . Los compuestos del invento, compuestos originales, los cuales se modifican al fijar grupos químicos se denominan “compuestos modificados”.

10 El invento también incluye metabolitos activos de los presentes compuestos.

Los compuestos según el invento alteran, y más específicamente, reducen el nivel de glucocorticoide intracelular activo y por consiguiente son útiles para el tratamiento de condiciones, trastornos, y enfermedades en las cuales tal modulación o reducción es benéfica.

15 Por consiguiente, los presentes compuestos se pueden aplicar para el tratamiento del síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, tolerancia a glucosa deteriorado (IGT) , alteración de la glucosa en ayunas (IFG) , Diabetes Autoinmune Latente en el Adulto (LADA) , diabetes tipo 1, complicaciones diabéticas tardías incluyendo enfermedades cardiovasculares, trastornos cardiovasculares, trastornos de metabolismo lípido, trastornos neurodegenerativos y psiquiátricos, desregulación de presión

20 intraocular incluyendo glaucoma, trastornos inmunes, respuestas inmunes inapropiadas, trastornos músculo- esqueléticos, trastornos gastrointestinales, síndrome de ovario policístico (PCOS) , crecimiento capilar reducido u otras enfermedades, trastornos o condiciones que están influenciados por niveles glucocorticoides intracelulares, efectos adversos de niveles sanguíneos aumentados de glucocorticoide endógeno o exógeno activo, y cualquier combinación de los

25 mismos, efectos adversos de niveles de plasma aumentados de glucocorticoide endógeno activo, enfermedad de Cushing, síndrome de Cushing, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades autoinmunes, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades inflamatorias, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades con un componente

30 inflamatorio, efectos adversos de tratamiento con agonistas de receptores glucocorticoides como parte de quimioterapia para cáncer, efectos adversos de tratamiento con agonistas de receptores

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glucocorticoides para trauma quirúrgico/post- quirúrgico u otro trauma, efectos adversos de terapia con agonistas de receptores glucocorticoides en el contexto de transplante de órganos o tejidos o efectos adversos de tratamiento con agonistas de receptores glucocorticoides en otras enfermedades, trastornos o condiciones donde los agonistas de receptores glucocorticoides proporcionan efectos clínicamente benéficos. También los presentes compuestos pueden ser aplicables para el tratamiento de acumulación de grasa visceral y resistencia a insulina en paciente tratados con HAART (tratamiento antiretroviral altamente activo) .

Más específicamente los presentes compuestos se pueden aplicar para el tratamiento del síndrome metabólico, diabetes tipo 2, diabetes como una consecuencia de obesidad, resistencia a insulina, hiperglicemia, hiperglicemia prandial, hiperinsulinemia, secreción de insulina inadecuadamente baja, intolerancia a la glucosa (IGT) , alteración de la glucosa en ayunas (IFG) , producción de glucosa hepática aumentada, diabetes tipo 1, LADA, diabetes pediátrica, dislipidemia, dislipidemia diabética, hiperlipidemia, hipertrigliceridemia, hiperlipoproteinemia, hipercolesterolemia, colesterol HDL disminuido, proporción LDL/HDL deteriorada, otros trastornos de metabolismo lípido, obesidad, obesidad visceral, obesidad como una consecuencia de diabetes, absorción alimenticia aumentada, hipertensión, complicaciones diabéticas tardías, micro- /macro albuminuria, nefropatía, retinopatía, neuropatía, úlceras diabéticas, enfermedades cardiovasculares, arteriosclerosis, aterosclerosis, enfermedad arterial coronaria, hipertrofia cardíaca, isquemia miocárdica, insuficiencia cardíaca, falla cardíaca congestiva, apoplejía, infarto miocárdica, arritmia, flujo sanguíneo disminuido, disfunción eréctil (masculina o femenina) , miopatía, pérdida de tejido muscular, agotamiento muscular, catabolismo muscular, osteoporosis, crecimiento lineal disminuido, trastornos neurodegenerativos y psiquiátricos, enfermedad de Alzheimer, muerte neuronal, función cognitiva deteriorada, depresión, ansiedad, trastornos alimenticios, regulación del apetito, migraña, epilepsia, adicción a sustancias químicas, trastornos de presión intraocular, glaucoma, síndrome de ovario policístico (PCOS) , respuestas inmunes inapropiadas, polarización inadecuada de células T helper- 1 / T helper- 2, infecciones bacterianas, infecciones microbacterianas, infecciones micóticas, infecciones virales, infestaciones parasíticas, respuestas subóptimas a inmunizaciones, disfunción inmune, calvicie parcial o total, u otras enfermedades, trastornos o condiciones que están influenciadas por niveles glucocorticoides intracelulares y cualquier combinación de los mismos, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades alérgicas-

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inflamatorias tales como asma y dermatitis atópica, efectos adversos de tratamiento con agonistas de receptores glucocorticoides del sistema respiratorio ej., asma, fibrosis quística, enfisema, bronquitis, hipersensibilidad, neumonitis, neumonías eosinofílicas, fibrosis pulmonar, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedad intestinal inflamatoria tal como enfermedad de Crohn y colitis ulcerativa; efectos adversos de tratamiento con agonistas de receptores glucocorticoides de trastornos del sistema inmune, tejido conectivo y articulaciones ej., artritis reactiva, artritis reumatoide, síndrome de Sjögren, lupus eritematoso sistémico, nefritis lúpica, púrpura Henoch- Schönlein, granulomatosis de Wegener, arteritis temporal, esclerosis sistémica, vasculitis, sarcoidosis, dermatomiositis- polimiositis, pénfigo;

5 efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades endocrinológicas tales como hipertiroidismo, hipoaldosteronismo, hipopituitarismo; efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades hematológicas ej., anemia hemolítica, trombocitopenia, hemoglobinuria nocturna paroxismal;

10 efectos adversos de tratamiento con agonistas de receptores glucocorticoides de cáncer tal como enfermedades de la médula espinal, compresión neoplásica de la médula espinal, tumores cerebrales, leucemia linfoblástica aguda, enfermedad de Hodgking, náuseas inducidas por quimioterapia, efectos adversos de tratamiento con agonistas de receptores glucocorticoides de enfermedades musculares y sobre las articulaciones neuro- musculares ej., miastenia gravis y miopatías hereditarias (ej., distrofia muscular de Duchenne) , efectos adversos de tratamiento con

15 agonistas de receptores glucocorticoides en el contexto de cirugía & trasplantes ej., trauma, estrés post- quirúrgico, estrés quirúrgico, trasplante renal, trasplante hepático, trasplante pulmonar, trasplante de isletas pancreáticas, trasplante de células de tallo sanguíneo, trasplante de médula ósea, trasplante cardíaco, trasplante de glándula adrenal, trasplante traqueal, trasplante intestinal, trasplante córneo, injerto de piel, queratoplastia, implante de lentes y otros procedimientos donde

20 la inmunosupresión con agonistas de receptores glucocorticoides es benéfica; efectos adversos de tratamiento con agonistas de receptores glucocorticoides de absceso cerebral, náuseas/vómito, infecciones, hipercalcemia, hiperplasia adrenal, hepatitis autoinmune, enfermedades de la médula espinal, aneurismas saculares o efectos adversos de tratamiento con agonistas de receptores glucocorticoides en otras enfermedades, trastornos y condiciones donde los agonistas de

25 receptores glucocorticoides proporcionan efectos clínicamente benéficos.

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Por consiguiente, en un aspecto adicional el invento se relaciona con un compuesto según el invento para utilizar como una composición farmacéutica.

El invento también se relaciona con composiciones farmacéuticas que comprenden, como un ingrediente activo, al menos un compuesto según el invento junto con uno o más vehículos o diluyentes farmacéuticamente aceptables.

La composición farmacéutica preferiblemente está en forma de dosificación unitaria, comprendiendo entre 0.05 mg/día y 2000 mg/día aproximadamente, preferiblemente entre 0.1 mg/día y 1000 mg/día aproximadamente, y más preferiblemente entre 0.5 mg/día y 500 mg/día aproximadamente de un compuesto según el invento.

En otra realización, el paciente es tratado con un compuesto según el invento durante al menos una semana aproximadamente, durante al menos 2 semanas aproximadamente, durante al menos 4 semanas aproximadamente, durante al menos 2 meses aproximadamente o durante al menos 4 meses aproximadamente.

En aún otra realización, la composición farmacéutica es para administración oral, nasal, bucal, transdérmica, pulmonar, o parenteral.

Además, el invento se relaciona con el uso de un compuesto según el invento para la preparación de una composición farmacéutica para el tratamiento de trastornos y enfermedades en donde una modulación o una inhibición de la actividad de 11β HSD1 es benéfica.

El invento también se relaciona con un método para el tratamiento de trastornos y enfermedades en donde una modulación o una inhibición de la actividad de 11β HSD1 es benéfica, el método comprendiendo administración a un sujeto en necesidad del mismo una cantidad efectiva de un compuesto según el invento.

En una realización preferida del invento los presentes compuestos se utilizan para la preparación de un medicamento para el tratamiento de enfermedades y condiciones que están influenciadas por niveles glucocorticoides intracelulares como se mencionó anteriormente.

Así, en una realización preferida del invento los presentes compuestos se utilizan para la preparación de un medicamento para el tratamiento de condiciones o trastornos donde un nivel disminuido de glucocorticoide intracelular activo es deseable, tal como las condiciones y enfermedades anteriormente mencionadas.

En aún una realización preferida del invento los presentes compuestos se utilizan para la preparación de un medicamento para el tratamiento de síndrome metabólico, resistencia a

insulina, dislipidemia, obesidad de hipertensión, diabetes tipo 2, intolerancia a la glucosa (IGT) , glucosa en ayunas deteriorada (IFG) , progresión de IGT a diabetes tipo 2, progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías (ej., enfermedades cardiovasculares, arteriosclerosis, y aterosclerosis) , trastornos neurodegenerativos y psiquiátricos, y, los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

En otra realización del presente invento, la ruta de administración puede ser cualquier ruta que efectivamente transporte un compuesto según el invento hacia el sitio de acción apropiado o deseado, tal como oral, nasal, bucal, transdérmica, pulmonar, o parenteral.

En aún un aspecto adicional del invento los presentes compuestos son administrados en combinación con una o más sustancias activas adicionales en cualquier proporción apropiada. Tales sustancias activas adicionales se pueden por ejemplo seleccionar de agentes antiobesidad, antidiabéticos, agentes modificadores del metabolismo lípido, agentes antihipertensivos, agonistas de receptores glucocorticoides, agentes para el tratamiento y/o prevención de complicaciones que resultan de o están asociadas con diabetes y agentes para el tratamiento y/o prevención de complicaciones y trastornos que resultan o están asociados con obesidad.

Por lo tanto, en un aspecto adicional del invento, los presentes compuestos se pueden administrar en combinación con uno o más agentes antiobesidad o agentes reguladores del apetito.

Tales agentes se pueden seleccionar del grupo que consta de agonistas CART (transcripto regulado por anfetamina y cocaína) , antagonistas NPY (neuropéptido Y) , agonistas MC4 (melanocortina 4) , antagonistas de orexina, agonistas TNF (factor de necrosis tumoral) , agonistas CRF (factor de liberación de corticotropina) , antagonistas CRF BP (proteína de unión de factor de liberación de corticotropina) , agonistas de urocortina, agonistas $\beta 3$, agonistas MSH (hormona estimuladora de melanocitos) , antagonistas MCH (hormona concentradora de melanocitos) , agonistas CCK (colecistoquinina) , inhibidores de re- absorción de serotonina, inhibidores de re- absorción de serotonina y noradrenalina, serotonina mixta y compuestos no adrenérgicos, agonistas 5HT (serotonina) , agonistas de bombesina, antagonistas de galanina, hormona de crecimiento, compuestos liberadores de hormona de crecimiento, agonistas TRH (hormona liberadora de tirotrópina) , moduladores UCP 2 ó 3 (proteínas desacoplantes 2 ó 3) , agonistas de leptina, agonistas DA (bromocriptina, doprexina) , inhibidores de lipasa/amilasa,

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moduladores PPAR (receptor activado por proliferador de peroxisoma) , moduladores RXR (receptor retinoide X) , agonistas TR β , inhibidores AGRP (proteína Agouti relacionada) , antagonistas de histamina H3, antagonistas opioides (tal como naltrexona) , exendina- 4, GLP- 1 y factor neurotrófico ciliar.

5 En una realización del invento el agente antiobesidad es leptina; dexanfetamina o anfetamina; fenfluramina o dexfenfluramina, sibutramina; orlistat; mazindol o fentermina.

Agentes antidiabéticos apropiados incluyen insulina, análogos de insulina y derivados tales como aquellos divulgados en EP 792 290 (Novo Nordisk A/S) , ej., insulina humana N^{CH29} - tetradecanoil des (B30) , EP 214 826 y EP 705 275 (Novo Nordisk A/S) , ej., insulina humana Asp^{B28}, US 5.504.188 (Eli Lilly) , ej., insulina humana Lys^{B28} Pro^{B29}, EP 368 187 (Aventis) , eg 10 Lantus, las cuales se incorporan en la presente como referencia, GLP- 1 (péptido- 1 tipo glucagón) y derivados de GLP- 1 tales como aquellos divulgados en WO 98/08871 de Novo Nordisk A/S, el cual se incorpora en la presente como referencia así como también agentes hipoglicémicos oralmente activos.

15 Los agentes hipoglicémicos oralmente activos preferiblemente comprenden sulfonilureas, biguanidas, meglitinidas, inhibidores de glucosidasa, antagonistas de glucagón, tales como aquellos divulgados en WO 99/01423 de Novo Nordisk A/S y Agouron Pharmaceuticals, Inc., agonistas GLP- 1, abridores de canales de potasio, tales como aquellos divulgados en WO 97/26265 y WO 99/03861 de Novo Nordisk A/S los cuales se incorporan en la presente como 20 referencia, inhibidores DPP- IV (peptidasa- IV de dipeptidilo) , inhibidores de enzimas hepáticas involucradas en la estimulación de gluconeogénesis y/o glicogenolisis, moduladores de captación de glucosa, compuestos que modifican el metabolismo lípido tales como agentes antihiperlipidémicos y agentes antilipidémicos como moduladores PPAR α , moduladores PPAR δ , inhibidores de absorción de colesterol, inhibidores HSL (lipasa sensible a hormonas) e 25 inhibidores HMG CoA (estatinas) , ácido nicotínico, fibratos, intercambiadores aniónicos, compuestos que reducen absorción de alimentos, resinas de ácido biliar, agonistas RXR y agentes que actúan sobre el canal de potasio dependiente de ATP de células β .

En una realización, los presentes compuestos se administran en combinación con insulina o un análogo o derivado de insulina, tal como insulina humana N^{CH29}- tetradecanoil des (B30) , 30 insulina humana Asp^{B28}, insulina humana Lys^{B28} Pro^{B29}, Lantus®, o una preparación mixta que comprende una o más de estas.

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En una realización adicional los presentes compuestos se administran en combinación con una sulfonilurea ej., tolbutamida, glibenclamida, glipizida o glicazida.

En otra realización, los presentes compuestos se administran en combinación con una biguanida ej., metformina.

5 En aún otra realización los presentes compuestos se administran en combinación con una meglitinida ej., repaglinida o senaglinida.

En aún otra realización los presentes compuestos se administran en combinación con una tiazolidinediona ej., troglitazona, ciglitazona, pioglitazona, rosiglitazona, o compuestos divulgados en WO 97/41097 tal como 5- [[4- [3- metil- 4- oxo- 3,4- dihidro- 2- quinazolinil]metoxi]fenil- metil]tiazolidina- 2,4- diona o una sal farmacéuticamente aceptable del mismo, preferiblemente sal de potasio.

10 En aún otra realización los presentes compuestos se pueden administrar en combinación con los sensibilizadores de insulina divulgados en WO 99/19313 tal como (-) ácido 3- [4- [2- fenoxazin- 10- il) etoxi]fenil]- 2- etoxipropanoico o una sal farmacéuticamente aceptable del mismo, preferiblemente sal de arginina.

15 En una realización adicional, los presentes compuestos se administran en combinación con un inhibidor de α - glicosidasa ej., miglitol o acarbosa.

En otra realización los presentes compuestos se administran en combinación con un agente que actúa sobre el canal de potasio dependiente de ATP de las células β ej., tolbutamida, glibenclamida, glipizida, glicazida o repaglinida.

20 Además, los presentes compuestos se pueden administrar en combinación con nateglinida.

En aún otra realización los presentes compuestos se administran en combinación con un agente antihiperlipidémico o agente antilipidémico ej., colestiramina, colestipol, clofibrato, gemfibrozil, fenofibrato, benzaifibrato, tesaglitazar, EML- 4156, LY- 818, MK- 767, atorvastatina, fluvastatina, lovastatina, pravastatina, simvastatina, acipimox, probucol, ezetimibe o dextrotiroxina.

25 En una realización adicional los presentes compuestos se administran en combinación con más de uno de los compuestos antes mencionados ej., en combinación con sulfonilurea y metformina, una sulfonilurea y acarbosa, repaglinida y metformina, insulina y una sulfonilurea, insulina y metformina, insulina y lovastatina, etc.

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Además, los presentes compuestos se pueden administrar en combinación con uno o más agentes antihipertensivos. Ejemplos de agentes hipertensivos son β - bloqueadores tales como alprenolol, atenolol, timolol, pindolol, propanolol, metoprolol, bisoprololfumarato, esmolol, amisolalul, carvedilol, labetalol, bloqueadores de receptores β_2 , ej., S- agenolol, OPC- 1085, 5 inhibidores ACE (enzima convertidora de angiotensina) tales como quinapril, lisinopril, delapril, enalapril, captopril, benazepril, perindopril,trandolapril, fosinopril, ramipril, cilazapril, delapril, imidapril, moexipril, espirapril, temocapril, zofenopril, S- 5590, fasidotril, Hoechst- Marion Roussel; 100240 (EP 00481522) , omapatrilat, gemopatrilat y GW- 660511, bloqueadores de canales de calcio tales como nifedipina, felodipina, nicardipina, isradipina, nimodipina, diltiazem, 10 amlodipina, nitrendipina, verapamil, lacidipina, lercanidipina, aranidipina, cilnidipina, clevidipina, azelnidipina, barnidipina, efonodipina, lasididipina, iemildipina, iercanidipina, manidipina, nilvadipina, pranidipina, furnidipina, α - bloqueadores tales como doxazosina, urapidil, prazosina, terazosina, bunazosina y OPC- 28326, diuréticos tales como tiazidas/sulfonamidas (ej., bendroflumetazida, clorotalidona, hidroclorotiazida y clopamida) , 15 diuréticos de asa (ej., bumetanida, furosemida y torasemida) y diuréticos ahorradores de potasio (ej., amilorida, espironolactona) , antagonistas ET- A de endotelina tales como ABT- 546, ambrisentan, atrasentan, SB- 234551, CI- 1034, S- 0139 y YM- 598, antagonistas de endotelina ej., bosentan y J- 104133, inhibidores de renina tales como aliskiren, antagonistas de vasopresina V1 ej., OPC- 21268, antagonistas de vasopresina V2 tales como tolvaptan, SR- 121463 y OPC- 20 31260, agonistas de péptidos natriuréticos tipo B ej., Nesiritida, antagonistas de angiotensina II tales como irbesartan, candesartancilexetil, losartan, valsartan, telmisartan, eprosartan, candesartan, CL- 329167, eprosartan, iosartan, olmesartan, prazosartan, TA- 606 y YM- 358, agonistas 5HT2 ej., fenoldopam y quetanserina, antagonistas de adenosina A1 tales como naftopidil, N- 0861 y FK- 352, antagonistas de tromboxano A2 tales como KT2- 962, inhibidores 25 de endopeptidasa ej., ecadotril, agonistas de óxido nítrico tales como LP- 805, antagonistas de dopamina D1 ej., MYD- 37, agonistas de dopamina D2 tal como nolomirole, ácidos grasos n- 3 ej., omacor, agonistas de prostaciclina tales como treprostinil, beraprost, agonistas PGE1 ej., ecraprost, moduladores de Na⁺/K⁺ATPasa ej., PST- 2238, activadores de canales de potasio ej., KR- 30450, vacunas tales como PMD- 3117, indapamidas, CGRP- unigene, estimuladores de 30 guanilato ciclasa, hidralazinas, metildopa, docarpamina, moxonidina, CoAprovel, MondoBiotech- 811.

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Se puede hacer referencia adicional a Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

Además, los presentes compuestos se pueden administrar en combinación con uno o más agonistas de receptores glucocorticoides. Ejemplos de tales agonistas de receptores

5 glucocorticoides son betametasona, dexametasona, hidrocortisona, metilprednisolona, prednisolona, prednisona, beclometasona, butixicort, clobetasol, flunisolida, flucatisona (y análogos), mometasona, triamcinolonacetona, triamcinolonhexacetona GW- 685698, NXC- 1015, NXC- 1020, NXC- 1021, NS- 126, P- 4114, RU- 23858 y serie T- 25.

10 Se debe entender que cualquier combinación apropiada de los compuestos según el invento con uno o más de los compuestos antes mencionados y opcionalmente uno o más sustancias farmacológicamente activas se consideran dentro del alcance del presente invento.

COMPOSICIONES FARMACÉUTICAS

15 Los compuestos del presente invento se pueden administrar solos o en combinación con vehículos o excipientes farmacéuticamente aceptables, ya sea en dosis únicas o múltiples. Las composiciones farmacéuticas según el invento se pueden formular con vehículos o diluyentes farmacéuticamente aceptables así como también otros adyuvantes y excipientes conocidos según técnicas convencionales tales como aquellas divulgadas en Remington: The Science and Practice of Pharmacy, 19th Edition, Gennaro, Ed., Mack Publishing Co., Easton, PA, 1995.

20 Las composiciones farmacéuticas se pueden formular específicamente para administración mediante cualquier ruta apropiada tal como oral, rectal, nasal, pulmonar, tópica (incluyendo bucal y sublingual), transdérmica, intracisternal, intraperitoneal, vaginal y parenteral (incluyendo subcutánea, intramuscular, intrarectal, intravenosa e intradérmica), la ruta oral es la preferida. Se apreciará que la ruta oral dependerá de la condición general y la edad del sujeto a
25 ser tratado, la naturaleza de la condición a ser tratada y el ingrediente activo elegido.

Las composiciones farmacéuticas para administración oral incluyen formas de dosificación sólidas tales como cápsulas duras o suaves, tabletas, pastillas, grageas, píldoras, polvos y gránulos. Donde es apropiado, se pueden preparar con recubrimientos tales como recubrimientos entéricos o se pueden formular para proporcionar liberación controlada del
30 ingrediente activo tal como liberación sostenida o prolongada según los métodos bien conocidos en el estado de la técnica.

Las formas de dosificación líquida para administración oral incluyen soluciones, emulsiones, suspensiones, jarabes y elixires.

5 Las composiciones farmacéuticas para administración parenteral incluyen soluciones inyectables estériles acuosas y no acuosas, dispersiones, suspensiones o emulsiones así como también polvos estériles para ser reconstituídos en soluciones o dispersiones inyectables estériles antes de utilizar. Las formulaciones inyectables de depósito también se contemplan dentro del alcance del presente invento.

Otras formas de dosificación apropiadas incluyen supositorios, atomizaciones, ungüentos, cremas, geles, inhalantes, parches dérmicos, implantes etc.

10 Una dosificación oral típica está en el rango entre 0.001 y 100 mg/kg de peso corporal por día, preferiblemente entre 0.01 y 50 mg/kg de peso corporal por día, y más preferible entre 0.05 y 10 mg/kg de peso por día administrada en una o más dosificaciones tal como 1 a 3 dosificaciones. La dosificación exacta dependerá de la frecuencia y modo de administración, el sexo, edad, peso y condición general del sujeto tratado, la naturaleza y severidad de la condición tratada y
15 enfermedades concomitantes tratadas y otros factores evidentes para aquellos con experiencia en el estado de la técnica.

Las formulaciones se pueden presentar de manera conveniente en forma de dosificación unitaria mediante métodos conocidos por aquellos en el estado de la técnica. Una forma de dosificación unitaria típica para administración una o más veces por día tal como 1 a 3 veces por
20 día puede contener entre 0.05 y 2000 mg aproximadamente, ej., entre 0.1 y 1000 mg, entre 0.5 y 500 mg aproximadamente, entre 1 mg y 200 mg aproximadamente, ej., 100 mg aproximadamente.

Para rutas parenterales, tales como administración intravenosa, intratecal, intramuscular y similares, típicamente las dosis están en el orden de la mitad de la dosis empleada para
25 administración oral.

Los compuestos de este invento generalmente se utilizan como la sustancia libre o como una sal farmacéuticamente aceptable de la misma. Ejemplos son una sal de adición ácida de un compuesto que tiene la utilidad de una base libre y una sal de adición alcalina de un compuesto que tiene la utilidad de un ácido libre. El término "sales farmacéuticamente aceptables" se refiere
30 a sales no tóxicas de los compuestos para utilizar según el presente invento los cuales generalmente se preparan al reaccionar la base libre con un ácido orgánico o inorgánico

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apropiado o al reaccionar el ácido con una base orgánica o inorgánica apropiada. Cuando un compuesto para utilizar según el presente invento, contiene una base libre tales sales se preparan en una forma convencional al tratar una solución o suspensión del compuesto con un equivalente químico de un ácido farmacéuticamente aceptable. Cuando un compuesto para utilizar según el presente invento contiene un ácido libre tales sales se preparan en una forma convencional al tratar una solución o suspensión del compuesto con un equivalente químico de una base farmacéuticamente aceptable. Las sales fisiológicamente aceptables de un compuesto con un grupo hidroxilo incluyen el anión de dicho compuesto en combinación con un catión apropiado tal como el ion de sodio o amonio. Otras sales que no son farmacéuticamente aceptables pueden ser útiles en la preparación de compuestos para utilizar según el presente invento y estas forman un aspecto adicional del presente invento.

Para administración parenteral, las soluciones de los presentes compuestos en solución acuosa estéril, glicol de propileno acuoso o aceite de ajonjolí o cacahuete. Tales soluciones acuosas se deben amortiguar si es necesario y el diluyente líquido primero se hizo isotónico con suficiente solución salina o glucosa. Las soluciones acuosas son particularmente apropiadas para administración intravenosa, intramuscular, subcutánea e intraperitoneal. Los medios acuosos estériles son todos fácilmente disponibles mediante técnicas estándares conocidas por aquellos con experiencia en el estado de la técnica.

Los vehículos farmacéuticos apropiados incluyen diluyentes o rellenos sólidos inertes, solución acuosa estéril y varios solventes orgánicos. Ejemplos de vehículos apropiados son agua, soluciones salinas, alcoholes, glicoles de polietileno, aceite de ricino polihidroxietoxilado, aceite de cacahuete, aceite de oliva, jarabe, fosfolípidos, gelatina, lactosa, terra alba, sacarosa, ciclodextrina, amilasa, estearato de magnesio, talco, gelatina, agar, pectina, acacia, ácido esteárico o éteres de alquilo menores de celulosa, ácido silícico, ácidos grasos, aminas de ácidos grasos, monogliceridos de ácidos grasos y digliceridos, ésteres de ácidos grasos de pentaeritritol, polioxietileno, hidroximetilcelulosa, y polivinilpirrolidona. De manera similar, el vehículo o diluyente puede incluir cualquier material de liberación sostenida conocido en el estado de la técnica, tal como monoestearato de glicerilo o diestearato de glicerilo, solo o mezclado con una cera. Las formulaciones también pueden incluir agentes humectantes, agentes emulsificantes y de suspensión, agentes preservantes, agentes endulzantes o agentes saborizantes.

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Las composiciones farmacéuticas formadas al combinar los compuestos del invento y los vehículos farmacéuticamente aceptables luego se administran fácilmente en una variedad de formas de dosificación apropiadas para las rutas de administración divulgadas. Las formulaciones se pueden presentar de manera conveniente en forma de dosificación unitaria mediante métodos conocidos en el estado de la técnica de farmacia.

Las formulaciones del presente invento apropiadas para administración oral se pueden presentar como unidades discretas tales como cápsulas o tabletas, cada una conteniendo una cantidad predeterminada del ingrediente activo, y las cuales pueden incluir un excipiente apropiado. Estas formulaciones pueden estar en la forma de polvo o gránulos, como una solución o suspensión en un líquido acuoso o no acuoso, o como una emulsión de aceite en agua o agua en aceite.

Las composiciones diseñadas para uso oral se pueden preparar según cualquier método conocido, y tales composiciones pueden contener uno o más agentes seleccionados del grupo que consta de agentes endulzantes, agentes saborizantes, agentes colorantes, y agentes preservantes con el propósito de proporcionar preparaciones farmacéuticamente elegantes y de sabor agradable. Las tabletas pueden contener el ingrediente activo en mezcla con excipientes farmacéuticamente aceptables no tóxicos los cuales son apropiados para la fabricación de las tabletas. Estos excipientes por ejemplo pueden ser, diluyentes inertes, tales como carbonato de calcio, carbonato de sodio, lactosa, fosfato de calcio o fosfato de sodio; agentes granulantes y desintegrantes, por ejemplo almidón de maíz o ácido algínico; agentes aglomerantes, por ejemplo, almidón, gelatina o acacia; y agentes lubricantes, por ejemplo estearato de magnesio, ácido esteárico o talco. Las tabletas pueden estar sin recubrimiento o se pueden recubrir mediante técnicas conocidas para retardar la desintegración y absorción en el tracto gastrointestinal y así proporcionar una acción sostenida durante un periodo mayor. Por ejemplo, se puede emplear un material retardante de tiempo tal como monostearato de glicerilo o diestearato de glicerilo. También se pueden recubrir mediante las técnicas descritas en las Patentes U.S. No. 4.356.108; 4.166.452; y 4.265.874, las cuales se incorporan en la presente como referencia, para formar las tabletas terapéuticas osmóticas para liberación controlada.

Las formulaciones para uso oral también se pueden presentar como cápsulas de gelatina dura donde el ingrediente activo es mezclado con un diluyente sólido inerte, por ejemplo, carbonato de calcio, fosfato de calcio o caolina, o una cápsula de gelatina suave en donde el

ingrediente activo se mezcla con agua o un medio aceitoso, por ejemplo aceite de cacahuete, parafina líquida, o aceite de oliva.

5 Las suspensiones acuosas pueden contener los compuestos activos en mezcla con excipientes apropiados para la fabricación de suspensiones acuosas. Tales excipientes son agentes de suspensión, por ejemplo carboximetilcelulosa de sodio, metilcelulosa, hidroxipropilmetilcelulosa, alginato de sodio, polivinilpirrolidona, goma tragacanto y goma acacia; agentes de dispersión o humectantes pueden ser una fosfatida de ocurrencia natural tal como lecitina, o productos de condensación de un óxido de alquileo con ácidos grasos, por ejemplo estearato de polioxitileno, o productos de condensación de óxido de etileno con 10 alcoholes alifáticos de cadena larga, por ejemplo, heptadecaetilenoicetanol, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y un hexitol tal como monooleato de sorbitol de polioxitileno, o productos de condensación de óxido de etileno con ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitan de polietileno. Las suspensiones acuosas también pueden contener uno o más agentes 15 colorantes, uno o más agentes saborizantes, y uno o más agentes endulzantes, tal como sacarosa o sacarina.

Las suspensiones aceitosas se pueden formular al suspender el ingrediente activo en un aceite vegetal, aceite de oliva, aceite de ajonjolí o aceite de coco, o en un aceite mineral tal como una parafina líquida. Las suspensiones aceitosas pueden contener un agente espesante, por 20 ejemplo cera de abejas, parafina dura o alcohol cetílico. Se pueden agregar agentes endulzantes tales como aquellos divulgados anteriormente, y agentes saborizantes para proporcionar una preparación oral de sabor agradable. Estas composiciones se pueden preservar mediante la adición de un anti- oxidante tal como ácido ascórbico.

25 Polvos y gránulos dispersables apropiados para la preparación de una suspensión acuosa mediante la adición de agua proporcionan el compuesto activo en mezcla con un agente de dispersión o humectante, agente de suspensión y uno o más preservativos. Agentes humectantes o de dispersión apropiados y agentes de suspensión son ejemplificados por aquellos ya mencionados anteriormente. También pueden estar presentes excipientes adicionales, por ejemplo, agentes endulzantes, saborizantes, y colorantes.

30 Las composiciones farmacéuticas que comprenden un compuesto para utilizar según el presente invento también pueden estar en la forma de emulsiones de aceite en agua. La fase

aceitosa puede ser un aceite vegetal, por ejemplo, aceite de oliva o aceite de cacahuete, o un aceite mineral, por ejemplo una parafina líquida, o una mezcla del mismo. Agentes emulsificantes apropiados pueden ser gomas de ocurrencia natural, por ejemplo goma acacia o goma tragacanto, fosfatidas de ocurrencia natural, por ejemplo semilla de soya, lecitina, y ésteres o ésteres parciales derivados de ácidos grasos y anhídridos de hexitol, por ejemplo monooleato de sorbitan, y productos de condensación de dichos ésteres parciales con óxido de etileno, por ejemplo monooleato de sorbitan de polioxietileno. Las emulsiones también pueden contener agentes endulzantes y saborizantes.

Se pueden formular jarabes y elixires con agentes endulzantes, por ejemplo glicerol, glicol de propileno, sorbitol o sacarosa. Tales formulaciones también pueden contener un demulcente, preservativo y agente saborizante y colorante. Las composiciones farmacéuticas también pueden estar en la forma de una suspensión acuosa u oleaginosa inyectable estéril. Esta suspensión se puede formular según los métodos conocidos que utilizan agentes humectantes o de dispersión apropiados y los agentes de suspensión descritos anteriormente. La preparación inyectable estéril también puede ser una solución o suspensión inyectable estéril en un diluyente o solvente parenteralmente aceptable no tóxico, por ejemplo como una solución en 1,3- butanodiol. Entre los vehículos y solventes aceptables que se pueden emplear están agua, solución de Ringer, y solución de cloruro de sodio isotónico. Además, aceites fijos y estériles se emplean convenientemente como solvente o medio de suspensión. Para este propósito, cualquier aceite ligero blando se puede utilizar mono- o digliceridos sintéticos. Además, ácidos grasos tales como ácido oleico encuentran uso en la preparación de inyectables.

Las composiciones también pueden estar en la forma de supositorios para administración rectal de los compuestos del presente invento. Estas composiciones se pueden preparar al mezclar el fármaco con un excipiente no irritante apropiado el cual es sólido a temperaturas comunes pero líquido a la temperatura rectal y se fundirá en el recto para liberar el fármaco. Tales materiales incluyen por ejemplo manteca de cacao y glicoles de polietileno.

Para uso tópico, se contemplan cremas, ungüentos, jalcas, solución de suspensiones, que contienen los compuestos del presente invento. Para el propósito de esta solicitud, las aplicaciones tópicas deben incluir enjuagues bucales.

Los compuestos para utilizar según el presente invento también se pueden administrar en la forma de sistemas de liberación de liposomas, tal como vesículas unilaminares pequeñas.

vesículas unilaminares grandes y vesículas multilaminares. Los liposomas se pueden formar a partir de una variedad de fosfolípidos, tales como colesterol, estearilamina, o fosfatidilcolinas.

Además, algunos de los compuestos para utilizar según el presente invento pueden formar solvatos con agua o solventes orgánicos comunes. Tales solvatos también están incluidos dentro del alcance del presente invento.

Por lo tanto, en una realización adicional se proporciona una composición farmacéutica que comprende un compuesto para utilizar según el presente invento, o una sal farmacéuticamente aceptable, solvato o profármaco del mismo, y uno o más vehículos, excipientes, o diluyentes farmacéuticamente aceptables.

Si se utiliza un vehículo sólido para administración oral, la preparación se puede entabletar, colocar en una cápsula de gelatina dura en polvo o forma de pellet o puede estar en la forma de una gragea o pastilla. La cantidad de vehículo sólido variará ampliamente pero usualmente estará entre 25 mg y 1 g aproximadamente. Si se utiliza un vehículo líquido, la preparación puede estar en la forma de un jarabe, emulsión, capsula de gelatina suave o líquido inyectable estéril tal como una solución o suspensión líquida acuosa o no acuosa.

Una tableta típica la cual se puede preparar mediante técnicas convencionales de entabletado puede contener:

Núcleo:

	Compuesto activo (como compuesto libre o sal del mismo)	5.0 mg
20	Lactosum PH. Eur.	67.8 mg
	Celulosa, microcrist (Avicel)	31.4 mg
	Amberlite® IRP88*	1.0 mg
	Magnesii stearas PH. Eur.	q.s.

Recubrimiento:

	Metilcelulosa de hidroxipropilo	9 mg aprox.
	Mywacett 9- 40 T**	0.9 mg aprox.

Polacrilina de potasio NF, desintegrante de tabletas, Rohm y Haas.

**Monoglicerida acilada utilizado como plasticizador para recubrimiento de película.

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Los compuestos del invento se pueden administrar a un paciente el cual es un mamífero, especialmente un humano en necesidad del mismo. Tales mamíferos incluyen también animales, tanto domésticos, ej., mascotas, como animales no domésticos tales como animales salvajes.

5 Cualquier característica novedosa o combinación de características descritas en la presente se consideran esenciales para este invento.

El presente invento además se ilustra en los siguientes ejemplos representativos los cuales, sin embargo, no pretenden limitar el alcance del invento en forma alguna.

EJEMPLOS

10 Los siguientes ejemplos y procedimientos generales se refieren a compuestos intermedios y productos finales para la formula general (I) identificada anteriormente. La preparación de los compuestos de la fórmula general (I) del presente invento se describe en detalle utilizando los siguientes ejemplos. Ocasionalmente, la reacción puede no ser aplicable como se describió a cada compuesto incluido dentro del alcance del invento divulgado. Los compuestos para los cuales
15 esto ocurre serán fácilmente reconocidos por aquellos con experiencia en el estado de la técnica. En estos casos las reacciones se pueden realizar de manera exitosa mediante modificaciones convencionales conocidas por aquellos en el estado de la técnica, lo cual es, mediante protección apropiada de grupos de interferencia, al cambiar a otros reactivos convencionales, o mediante modificación común de condiciones de reacción. Alternativamente, otras reacciones divulgadas
20 en la presente o de otra manera convencionales serán aplicables a la preparación de los correspondientes compuestos del invento. En todos los métodos preparativos, todos los materiales de inicio son conocidos o se pueden preparar fácilmente a partir de materiales de inicio conocidos. Las estructuras de los compuestos se confirman ya sea mediante análisis elemental o resonancia magnética (NMR) , donde los picos asignados a protones característicos en los
25 compuestos del título son presentados donde sea apropiado. Los cambios ^1H NMR (δH) son dados en partes por millón (ppm) campo abajo de tetrametilsilano como estándar de referencia interna. M.p. es punto de fusión y es dado en $^{\circ}\text{C}$ y no es corregido. La cromatografía en columna se realizó utilizando la técnica descrita por W.C. Still, J. Org. Chem. 43:2923 (1978) sobre gel de sílice Merck (Art. 9385) . Los análisis HPLC son realizados utilizando la columna C18 4 x 250
30 mm de 5 μm eluida con varias mezclas de agua y acetonitrilo, flujo = 1 ml/min, como se describió en la sección experimental.

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Síntesis en horno microondas: La reacción se calentó mediante irradiación microondas en vasos microondas sellados en un Optimizador Emrys EXP de modo simple de PersonalChemistry®.

5 HPLC Preparativa: Columna: 1.9 x 15 cm Waters XTerra RP- 18. Buffer: gradiente lineal 5 – 95% en 15 min, MeCN, TFA al 0.1%, tasa de flujo de 15 ml/min. Las fracciones agrupadas son evaporadas hasta sequedad al vacío, o evaporadas al vacío hasta retirar MeCN, y luego congeladas y secadas por congelamiento.

ABREVIATURAS

10

d= día(s)

g=gramo(s)

h=hora(s)

Hz=hertz

L=litro(s)

15

M=molar

Mg=miligramo(s)

min=minuto(s)

mL=mililitro(s)

mmol= milimol(es)

20

mol=mol(es)

ppm=partes por millón

psi=libras por pulgada cuadrada

ESI=ionización de electroatomización

m/z=proporción masa a carga

25

mp=punto de fusión

MS=espectrometría de masa

HPLC= cromatografía líquida de alta presión

RP= fase inversa

HPLC- MS=cromatografía líquida de alta presión- espectrometría de masa

30

NMR=espectroscopia de resonancia magnética nuclear

rt=temperatura ambiente

TLC=cromatografía de capa delgada

DCM=diclorometano, CH_2Cl_2 , cloruro de metileno

DIPEA==N,N- diisopropiletilamina

DMF=N,N- dimetilformamida

5 DMSO=dimetilsulfóxido

EDAC=hidrocloruro de 1- etil- 3- (3- dimetilaminopropil) carbodiimida

Et₂O= éter dietílico

EtOAc=acetato de etilo

HOBt=1- hidroxibenzotriazol

10 MeCN=acetonitrilo

MeOH=metanol

NMP=N- metilpirrolidin- 2- ona

TEA=triethylamina

TFA=ácido trifluoroacético

15 THF=tetrahidrofurano

CDCl_3 =cloroformo deuterio

CD_3OD =metanol tetradeuterio

DMSO- d_6 =dimetilsulfóxido hexadeuterio

20 ANALISIS

NMR

Los espectros NMR se registraron a 300 y 400 MHz sobre un instrumento Broker

DRX300, DRX400 o AV400 equipado con cabezales de sonda selectiva- inversa de 5 mm (^1H y ^{13}C), inversa de banda ancha de 5mm (BBI, ^1H , banda ancha) y cuadro nuclear de 5 mm

25 (QNP, ^1H , ^{13}C), respectivamente. Los cambios (δ) son dados en partes por millón (ppm) campo abajo de tetrametilsilano como estándar de referencia interno.

HPLC- MS

Método HPLC- MS

El análisis RP se realizó sobre un sistema Agilent HPLC (degasificador 1100, bomba

30 1100, inyector 1100 y un DAD 1100) equipado con un sistema detector Agilent MS Modelo VL (MW 0- 1000) y un sistema detector S.E.D.E.R.E Modelo Sedex 55 ELS utilizando una columna

219

Waters X-terra MS C18 (5 μ m, 3.0 x 50 mm) con elusión de gradiente, solvente B de 5% a 95% (TFA al 0.05% en acetonitrilo) en solvente A (TFA al 0.05% en agua) dentro de 3 min, 2.7 mL/min, temperatura 40°C.

5 TECNICAS PREPARATIVAS

HPLC

Método HPLC Z3

La purificación RP se realizo sobre un sistema Wilson (bombas 3 Gilson 306, detector DAD Wilson 170 y un manejador de líquidos Wilson 215) utilizando una columna Waters X-terra RP (10 μ m, 30 mm x 150 mm) con elusión de gradiente, solvente B de 5% a 95% (TFA al 0.05% en acetonitrilo) en solvente A (TFA al 0.05% en agua) dentro de 15 min, 40 mL/min, detección a 210 nm, temperatura ambiente. Las fracciones agrupadas se evaporaron hasta sequedad *al vacío*, o se evaporaron *al vacío* hasta retirar el acetonitrilo, luego se congelaron y se secaron por congelamiento.

15

GENERAL

Los siguientes ejemplos y procedimientos generales se refieren a compuestos intermedios y productos finales para la formula general (I) identificada en la especificación y en los esquemas de síntesis. La preparación de los compuestos de la formula general (I) del presente invento se describe en detalle utilizando los siguientes ejemplos. Ocasionalmente, la reacción puede no ser aplicable como se describió a cada compuesto incluido dentro del alcance divulgado del invento. Los compuestos para los cuales ocurre esto serán fácilmente reconocidos por aquellos con experiencia en el estado de la técnica. En estos casos las reacciones se pueden realizar de manera exitosa mediante modificaciones convencionales conocidas por aquellos con experiencia en el estado de la técnica, lo cual es, mediante protección apropiada de grupos de interferencia, al cambiar a otros reactivos convencionales, o mediante modificación común de condiciones de reacción. Alternativamente, otras reacciones divulgadas en la presente o de otra manera convencionales serán aplicables a la preparación de los correspondientes compuestos del invento. En todos los métodos preparativos, todos los materiales de inicio son conocidos o los puede preparar una persona con experiencia en el estado de la técnica en analogía con la preparación de compuestos conocidos similares o mediante los procedimientos generales A a D

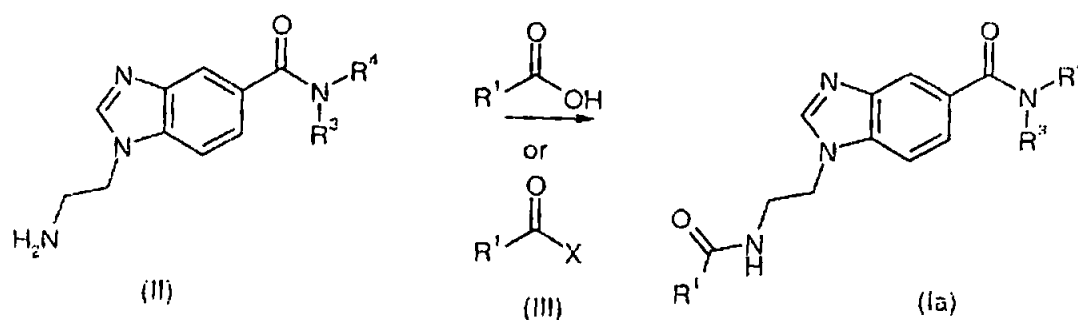
216

descritos en la presente.. Las estructuras de los compuestos se confirman ya sea mediante análisis elemental o resonancia magnética nuclear (NMR) , donde los picos asignados a protones característicos en los compuestos del título son presentados donde sea apropiado

5 PROCEDIMIENTOS GENERALES

Procedimiento General (A)

Los compuestos de la formula (Ia) según el invento en donde R1, R3, y R4 son como se definieron para la formula (I) , con NR3R4 correspondiendo al anillo A, se pueden preparar como se describe a continuación:



10

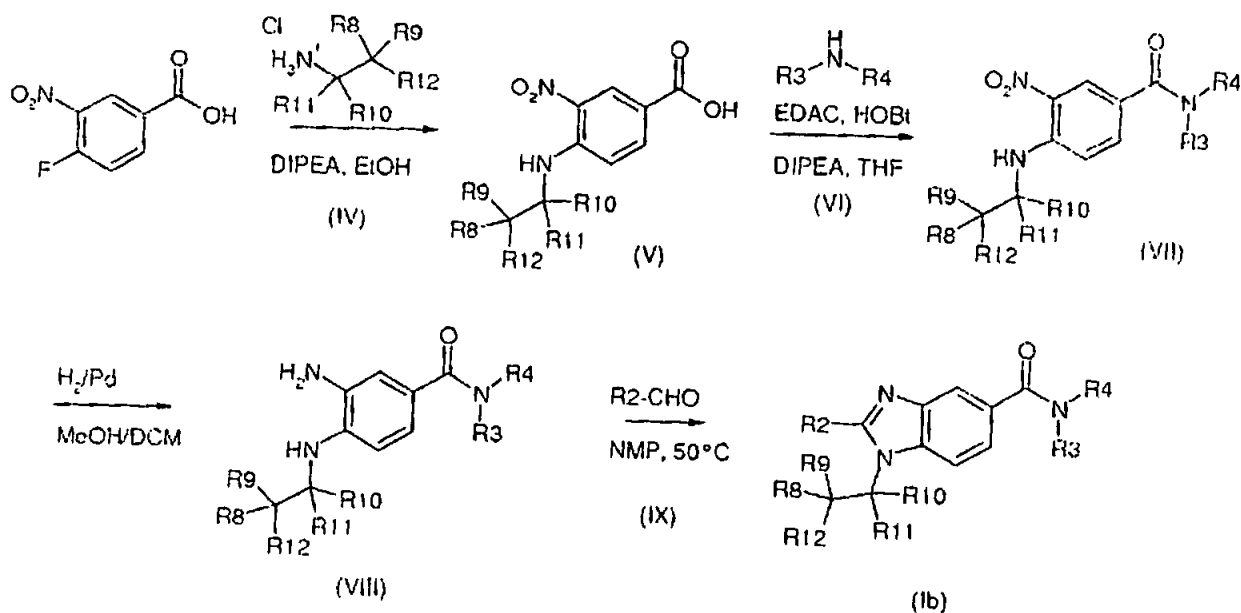
Un benzimidazol de la formula (II) en donde NR4R4 corresponde al anillo A definido anteriormente se puede hacer reaccionar con un ácido carboxílico en presencia de reactivos de acoplamiento (ej., EDAC y HOBt) o un ácido carboxílico activado de la formula (III) en donde R1 es como se definió anteriormente. Esta reacción se puede realizar en un solvente apropiado (ej., diclorometano) en presencia de una base (ej., DIPEA) a temperatura ambiente.

15

Procedimiento General (B)

Los compuestos de la formula (Ib) según el invento en donde R2, R3, R4, R8, R9, R10, R11, y R12 son como se definieron para la formula (I) , con NR3R4 correspondiendo al anillo A, se pueden preparar como se describe a continuación:

20

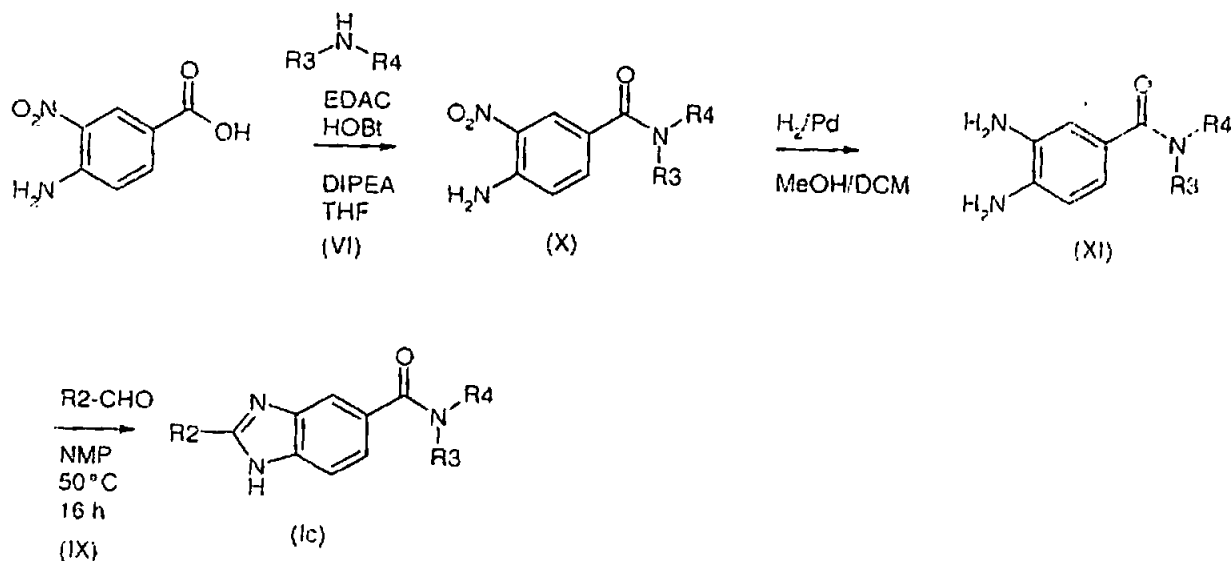


- 5 Acido 4- fluoro- 3- nitrobenzóico se puede hacer reaccionar con una amina de la formula (IV) en donde R8, R9, R10 R11 y R12 son como se definieron anteriormente. Esta reacción se puede realizar en un solvente apropiado (ej., etanol) en presencia de una base (ej., DIPEA) a temperatura ambiente formando la anilina secundaria de la formula (V) . Luego el ácido carboxílico de la formula (V) se puede activar con HOBt y EDAC y se puede hacer reaccionar con una amina de la formula (VI) en donde NR₃R₄ es el anillo A como se definió anteriormente. Esta reacción se puede realizar en un solvente apropiado (ej., THF) en presencia de una base (ej., DIPEA) a temperatura ambiente formando el compuesto de la formula (VII) . El grupo nitro de compuestos de la formula (VII) se puede reducir mediante hidrógeno bajo presión en un solvente apropiado (ej., metanol/diclorometano) en presencia de un catalizador (ej., paladio sobre carbón activado) a temperatura ambiente para formar la diamina de la formula (VIII) . Los compuestos de la formula (VIII) se pueden hacer reaccionar con un aldehído de la formula (IX) en donde R2 es como se definió anteriormente. Esta reacción se puede realizar en un solvente apropiado (ej., NMP) en presencia de un agente de secado (ej., tamiz molecular 4 Å) a 50°C para formar los compuestos de la formula (Ib) .
- 10
- 15

Procedimiento General (C)

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Los compuestos de la formula (Ic) según el invento en donde R2, R3, y R4 son como se definieron para la formula (I) , con NR3R4 correspondiendo al anillo A, se pueden preparar como se describe a continuación:



5

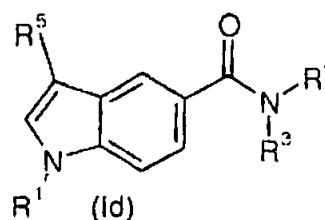
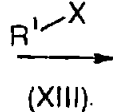
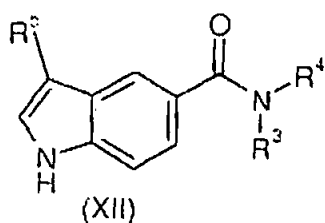
El ácido 4- amino- 3- nitrobenzónico se puede activar con HOBt y EDAC y se puede hacer reaccionar con una amina de la formula (VI) en donde NR3R4 es el anillo A como se definió anteriormente. Esta reacción se puede realizar en un solvente apropiado (ej., THF) en presencia de una base (ej., DIPEA) a temperatura ambiente para formar el compuesto de la formula (X) . El grupo nitro de la formula (X) se puede reducir mediante hidrógeno bajo presión en una mezcla de metanol y diclorometano en presencia de un catalizador (ej., paladio sobre carbón activado) a temperatura ambiente para formar la diamina de la formula (XI) . (XI) se puede hacer reaccionar con un aldehído de la formula (IX) en donde R2 es como se definió anteriormente. Esta reacción se puede realizar en NMP en presencia de un agente de secado (ej., tamiz molecular 4 Å) a $50^\circ C$ para formar el producto objetivo (Ic) .

15

Procedimiento General (D)

Los compuestos de la formula (Id) según el invento en donde R1, R3, R4, y R5 son como se definieron para la formula (I) , con NR3R4 correspondiendo al anillo A, se pueden preparar como se describe a continuación:

20

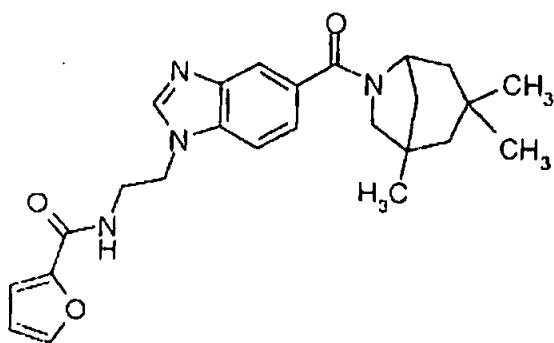


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Un indol de la formula (XII) en donde R3, R4, y R5 son como se definieron anteriormente, con NR3R4 correspondiendo al anillo A, se pueden hacer reaccionar con un haluro de alquilo/bencilo de la formula (XIII) en donde R1 es como se definió anteriormente en presencia de una base (ej., hidruro de sodio). Esta reacción se puede realizar en un solvente apropiado (ej., DMF) a una temperatura de hasta reflujo.

Ejemplo 1 (Procedimiento General) (A)

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-etil}amida del ácido furan- 2- carboxílico



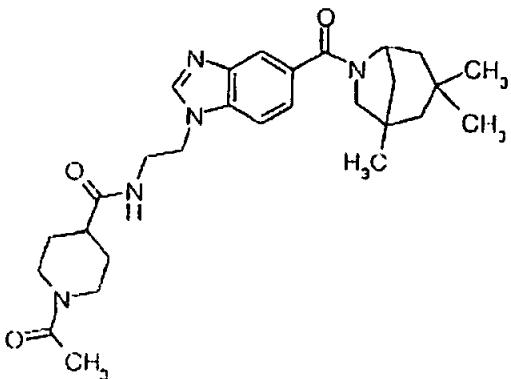
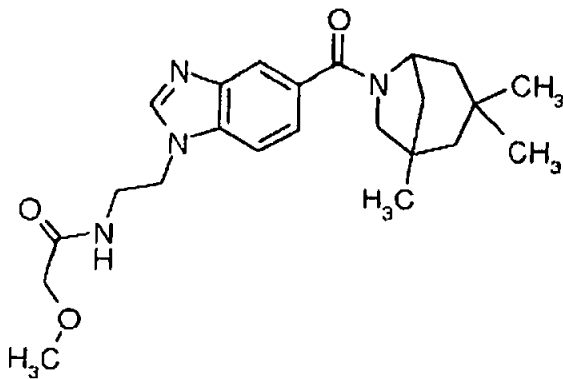
A una solución de ácido 2- furoico (37 mg, 0.33 mmol) en THF (2 mL) seco a temperatura ambiente bajo una atmósfera inerte de nitrógeno se agregó HOBt (49 mg, 0.36 mmol) y EDAC (82 mg, 0.43 mmol), y la solución resultante se agitó durante 30 minutos. Se agregó trifluoroacetato de [1- (2- amino- etil) - 1H- benzoimidazol- 5- il]- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6 il) - metanona (150 mg, 0.33 mmol) a la solución seguido por TEA (0.184 mL, 1.32 mmol), y la mezcla de reacción se agitó durante 16 horas a temperatura ambiente. Los volátiles se evaporaron al vacío y el sólido resultante se purificó mediante HPLC preparativa, se secó al vacío a 50°C proporcionando 100 mg (70%) del compuesto del título como un sólido. MS- ES1 m/z 435; ¹H NMR (400 MHz, DMSO- d6) δ 0.88- 0.99(m, 6H), 1.07 (d, 3H), 1.29 –

20

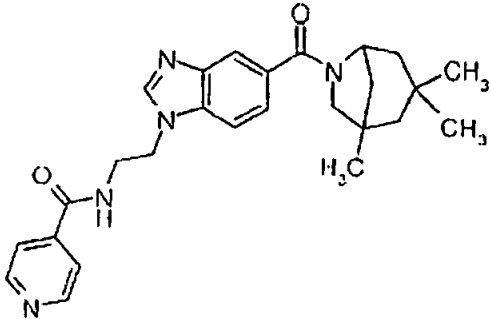
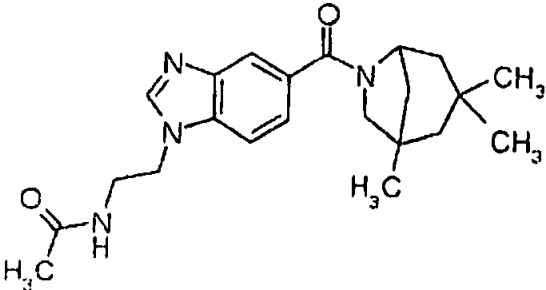
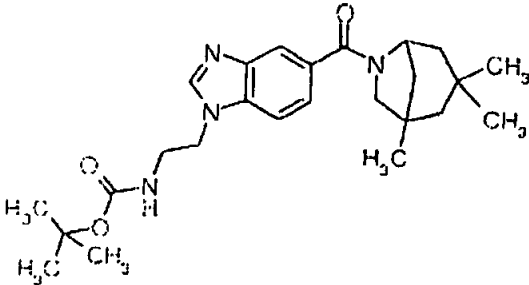
1.41 (m, 4H) , 1.50- 1.52 y 2.10 – 2.11 (m, 1H) , 1.76- 1.79 (m, 1H) , 3.02 (d) , 3.13 (d) , 3.32(d) y 3.47 (d, 2H) , 3.69 (t, 2H) , 3.87- 3.89 (m) y 4.39- 4.41 (m, 1H) , 4.56 (t, 2H) , 6.58 (s, 1H) , 6.98 (d, 1H) , 7.48 (dd, 1H) , 7.77- 7.82 (m, 2H) , 7.89 (t, 1H) , 8.54- 8.58 (m, 1H) , 9.07 (d, 1H) .

Los siguientes compuestos se sintetizaron empleando un método similar al descrito en el

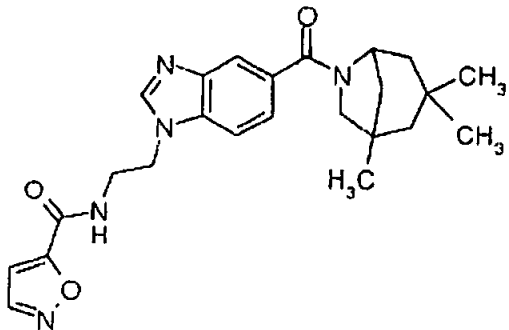
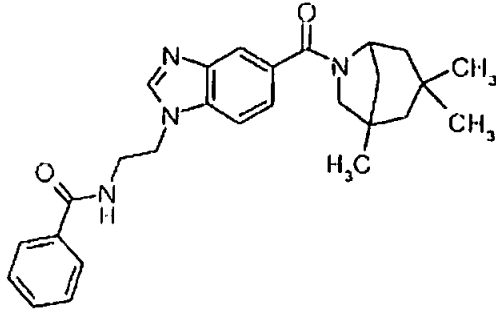
5 ejemplo 1 anterior:

Ejemplo	Estructura	PM	Nombre IUPAC	MS-ESI <i>m/z</i>
1- 1		493.65	{2- [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - benzoimidazol- 1-il]- etil}- amida del ácido 1- acetil-piperidina- 4-carboxílico	494
1- 2		412.53	2- metoxi- N- {2- [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - benzoimidazol- 1-il]- etil}- acetamida	413

221

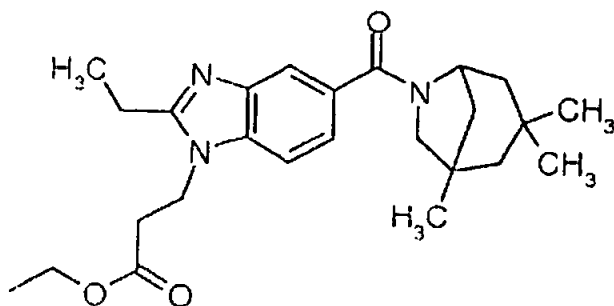
1-3		445.57	N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- isonicotinsmida	446
1-4		382.51	N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- acetamida	383
1-5		440.59	Éster butílico del ácido {2- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- carbámico	441

222

1- 6		435.53	{2- [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - benzoimidazol- 1-il]- etil}- amida del ácido isoxazol- 5- carboxílico	436
1- 7		444.58	N- {2- [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - benzoimidazol- 1-il]- etil}- benzamida	445

Ejemplo 2 (Procedimiento General (B))

Éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico.



5

A una solución de éster etílico del ácido 3- [2- amino- 4- (1,3,3- trimetil- 6- aza-biciclo[3.2.1]octano- 6- carbonil) - fenilamino]- propiónico (250 mg, 0.645 mmol) en NMP seco (10 mL.) a temperatura ambiente bajo una atmósfera inerte de nitrógeno se agregó aproximadamente 200 mg de tamiz molecular 4 Å seguido por acetaldehído (93 uL, 1.29 mmol) .

219

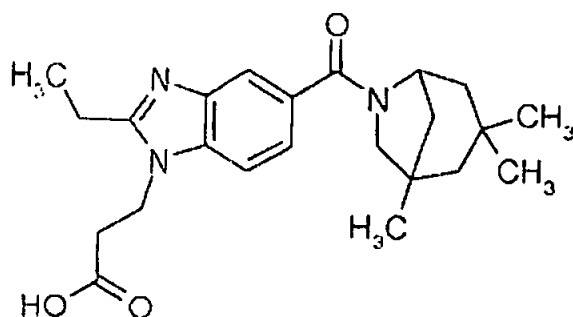
La mezcla se agito a temperatura ambiente durante 16 horas a 50°C. La reacción se apagó mediante la adición de agua (100 mL) seguido por extracción con éter dietílico (3 x 100 mL).

Las fases orgánicas combinadas fueron lavadas con salmuera (4 x 200 mL), secadas (MgSO₄), filtradas, y evaporadas al vacío. El aceite resultante fue purificado mediante HPLC preparativa,

5 secado al vacío a 50°C proporcionando 104 mg (38%) del compuesto del titulo como un aceite marrón. MS- ESI m/z 426; ¹H NMR (400 MHz, CDCl₃) δ 0.88- 1.06(m, 6H), 1.11- 1.23 (m, 7H), 1.24 – 1.28 (m) y 1.50- 1.55 - 1.65 (m, 1H), 1.36- 1.45 (m, 2H), 1.50 (t, 3H), 1.74- 1.81 (m, 1H), 2.23- 2.30 (m) y 3.12- 3.20 (m, 1H), 2.81 (t, 2H); 2.96 (q, 2H), 3.22- 3.35 (m, 1H), 3.32 (dd) y 3.62 (dd, 1H), 4.03- 4.07 (m) y 4.63- 4.97 (m, 1H), 4.13 (q, 2H), 4.45 (dt, 2H), 7.23- 10 7.46 (m, 2H), 7.84 (d, 1H).

Ejemplo 3

Acido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico.



15

A una solución de éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico (104 mg, 0.244 mmol) en etanol al 96% (5 mL) a temperatura ambiente bajo una atmósfera inerte de nitrógeno se agregó 1N NaOH (aq) (0.3 mL, 0.3 mmol). La mezcla se agito durante 2 horas a temperatura ambiente.

20 La reacción se apago mediante la adición de agua (5 mL) y se acidifico a pH 2 con 1N HCL seguido por extracción con éter dietílico (2 x 10 mL). Las fases orgánicas combinadas se lavaron con agua (2 x 10 mL), salmuera (10 mL), se secaron (MgSO₄), se filtraron y evaporaron al vacío proporcionando 11 mg (11%) del compuesto del titulo como un aceite amarillo. MS- ESI m/z 4398; ¹H NMR (400 MHz, CDCl₃) δ 0.83- 1.06(m, 6H), 1.12- 1.22 (m, 7H), 1.24 – 1.28 (m) y 1.46- 1.54 (m, 1H), 1.30- 1.39 (m, 2H), 1.33 (t, 3H), 1.63- 1.74 (m, 1H), 2.22- 2.32 (m)

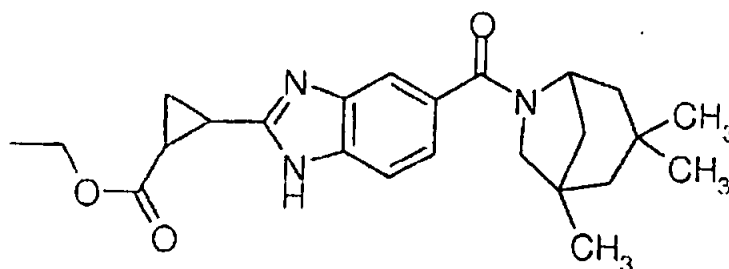
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y 3.15- 3.27 (m, 1H) , 2.26 (t, 2H) , 2.85 (t, 2H) , 3.51 (q, 2H) , 7.25- 7.35 (m, 2H) y 7.56 (d) y 7.74 (d, 1H) .

Ejemplo 4 (Procedimiento General (C))

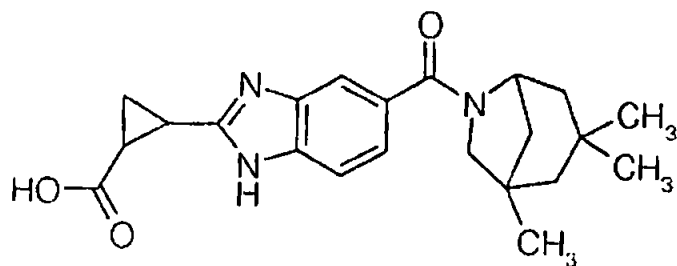
Éster etílico del ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 1- il]- ciclopropanocarboxílico



A una solución de (3,4- diaminofenil) - 1,3,3- trimetil- 6- azabicyclo[3.2.1]oct- 6- il) - metanona (500mg, 1.74 mmol) en NMP seco (25 mL) a temperatura ambiente bajo una atmósfera inerte de nitrógeno se agregó aproximadamente 500 mg de tamiz molecular 4 Å seguido por 2- formil- 1- ciclopropanocarboxilato de etilo (0.51 mL, 3.86 mmol) . La mezcla se agito durante 16 horas a 50°C. La reacción se apago mediante la adición de agua (100 mL) seguido por extracción con éter dietílico (3 x 100 mL) . Las fases orgánicas combinadas se lavaron con agua (3 x 100 mL) , salmuera (100 mL) , se secaron (MgSO₄) , filtraron, y evaporaron al vacío. El aceite resultante se purificó mediante HPLC preparativa, se seco al vacío a 50°C proporcionando 60 mg (8%) del compuesto del título como un sólido. MS- ESI m/z 410; ¹H NMR (400 MHz, CDCl₃) δ 0.88- 1.06 (m, 6H) , 1.07- 1.20 (m, 4H) , 1.25 (t, 3H) , 1.27- 1.34 (m) y 1.49- 1.66 (m, 3H) , 1.36- 1.48 (m, 2H) , 1.72- 1.84 (m, 2H) , 2.36- 2.48 (m, 1H) 2.66- 2.76 (m, 1H) , 3.18- 3.27 (m, 1H) , 3.30 (d) y 3.65 (d, 1H) , 4.00- 4.06 m) y 4.57- 4.65 (m, 1H) , 4.14 (q, 2H) , 7.18- 7.30 (m, 2H) , 7.57 (d, 1H) , 10.37 (br s, 1H) .

Ejemplo 5

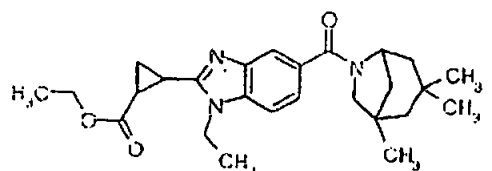
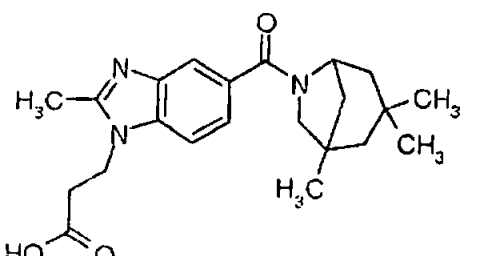
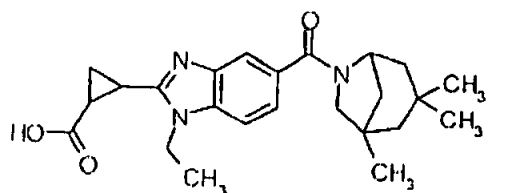
Acido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 1- il]- ciclopropanocarboxílico



- A una solución de éster dietílico del ácido 2- [5- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico (60mg,
1.74 mmol) en etanol al 96% (3 mL) a temperatura ambiente bajo una atmosfera inerte de
5 nitrógeno se agregó 1N NaOH (aq) (0.36 mmol) . La mezcla se agito durante 16 horas a 50°C. La
reacción se apagó mediante la adición de agua (3 mL) y se acidifico a pH 2 con 1N HCl seguido
por extracción con éter dietílico (2 x 5 mL) . Las fases orgánicas combinadas fueron lavadas con
agua (2 x 5 mL) , salmuera (5 mL) , se secaron (MgSO₄) , filtraron, y evaporaron al vacío
proporcionando 49 mg (88%) del compuesto del titulo como un sólido. MS- ESI m/z 382; ¹H
10 NMR (400 MHz, CDCl₃) δ 0.87- 1.06 (m, 6H) , 1.08- 1.20 (m, 4H) , 1.30- 1.38 (m, 1H) , 1.39-
1.45 (m) y 1.48- 1.64 (m, 3H) , 1.70- 1.90 (m, 2H) , 1.91- 2.01 (m, 1H) , 2.18- 2.30 (m) y 2.43-
2.61 (m) y 2.85- 3.02 (m, 2H) , 3.15 (t) y 3.66 (t, 1H) , 3.20- 3.34 (m, 1H) , 3.88- 4.01 (m) y
4.54- 4.65 (m, 1H) , 7.39- 7.50 (m, 1H) , 7.69- 7.85 (m, 2H) .
Los siguientes compuestos se sintetizaron utilizando un método similar a aquel descrito en los
15 ejemplos 2, 3, 4, y 5 anteriores

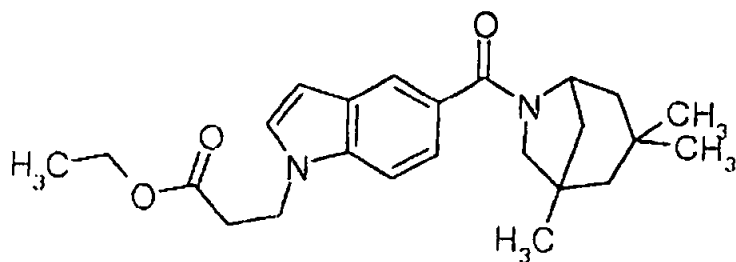
Ejemplo	Estructura	PM	Nombre IUPAC	MS - ESI m/z
5- 1		411.54	Éster etílico del ácido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]-	412

76

			propiónico	
5- 2		437.58	Éster etílico del ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - 1H- benzoimidazol- 2- il]- ciclopropanocarboxili co	438
5- 3		383.49	Acido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- propiónico	384
5- 4		409.53	Acido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - 1H- benzoimidazol- 2- il]- ciclopropanocarboxili co	410

Ejemplo 6 (Procedimiento General (D))

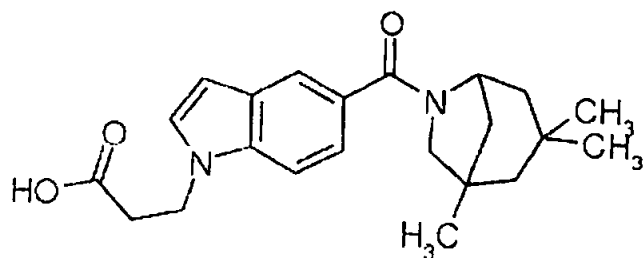
Éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1-
5 il]- propiónico



A una solución de (1H- indol- 5- il) - (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) - metanona (250mg, 0.84 mmol) en DMF seco (5 mL) a temperatura ambiente bajo una atmósfera inerte de nitrógeno se agregó hidruro de sodio (30 mg, 1.26 mmol, 60% de dispersión en aceite) , y después de agitar durante 30 minutos se agregó bromopropionato de etilo (168 mg, 0.93 mmol) , y la mezcla de reacción se agito durante 16 horas a 60°C. La reacción se apagó mediante la adición de agua (20 mL) seguido por extracción con DCM (3 x 100 mL) . Las fases orgánicas combinadas fueron secadas con (MgSO₄) , filtradas, y evaporadas al vacío. El sólido resultante se purificó mediante cromatografía de gel de sílice utilizando una mezcla de acetato de etilo y heptano (1:1) como eluyente. Las fracciones puras se recolectaron, el solvente se evaporó al vacío y se secó al vacío a 50°C proporcionando 125 mg (37%) del compuesto del título como un sólido. MS- ESI m/z 397; ¹H NMR (400 MHz, CDCl₃) δ 0.95 (d, 3H) , 1.03 (d, 3H) , 1.13- 1.22 (m, 7H) , 1.25- 1.43 (m, 2H) , 1.45 (s, 1H) , 1.62- 1.68 (m, 1H) , 1.76- 1.80 (m, 1H) , 2.29- 2.33 (m, 1H) y 2.82 (t, 2H) y 3.28- 3.35 (m) y 3.63 (d, 1H) , 4.12- 4.14 y 4.64- 4.66 (m, 1H) , 4.11 (q, 2H) , 4.47 (t, 2H) , 6.52 (d, 1H) , 7.18 (d, 1H) , 7.32- 7.39 (m, 2H) , 7.74 (d, 1H) .

Ejemplo 7

Acido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico



A una solución de éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico (80mg, 0.2 mmol) en etanol (2 mL) se agregó solución acuosa de hidróxido de sodio 1N (2 mL) , y la solución resultante se agito

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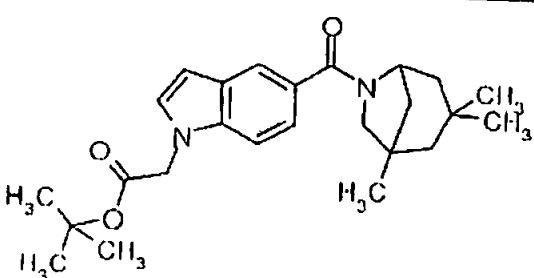
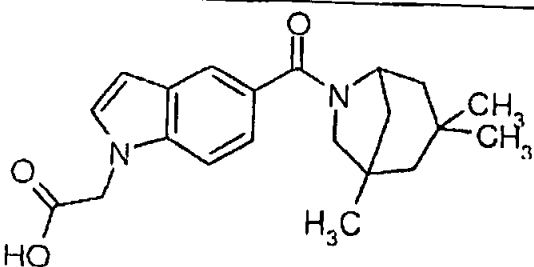
durante 2 horas. La solución se acidificó con una de solución 1N de ácido clorhídrico antes de retirar los volátiles orgánicos al vacío, y los residuos acuosos se extrajeron con DCM (3 X 5 mL). Las fases orgánicas combinadas fueron secadas con (MgSO₄), filtradas, y evaporadas al vacío.

El sólido resultante se purificó mediante HPLC preparativa, se secó al vacío a 50 °C

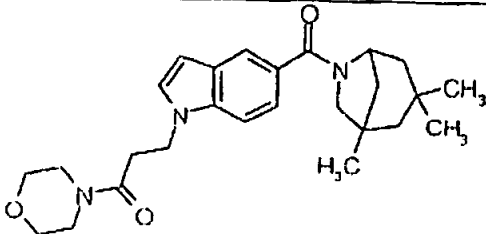
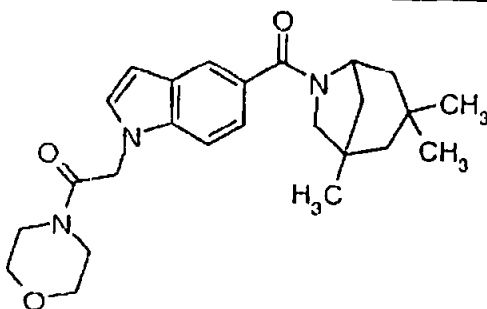
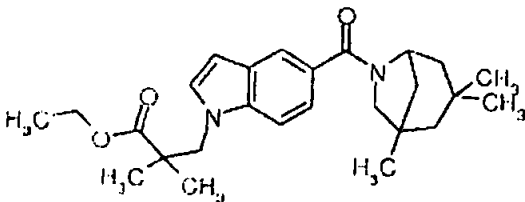
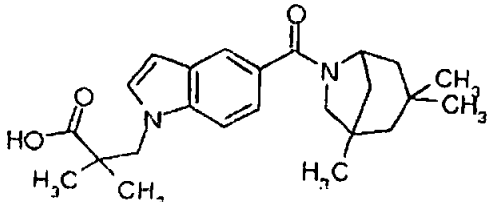
5 proporcionando 55 mg (74%) del compuesto del título como un sólido. MS- ESI m/z 369; ¹H NMR (400 MHz, CDCl₃) δ 0.94 (d, 3H), 1.04 (d, 3H), 1.13- 1.17 (m, 4H), 1.28- 1.38 (m, 2H), 1.43- 1.45 (m, 1H), 1.60- 1.63 (m, 1H), 1.75- 1.79 (m, 1H), 2.24- 2.32 y 3.25- 3.26 (m, 1H), 2.74 (t, 2H) y 3.27- 3.35 (m) y 3.62- 3.65 (m, 1H), 4.08- 4.10 y 4.62- 4.63 (m, 1H), 4.39 (t, 2H), 6.47- 6.48 (m, 1H), 7- 7.23 (m, 3H), 7.70 (d, 1H).

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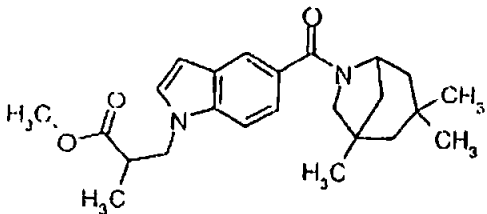
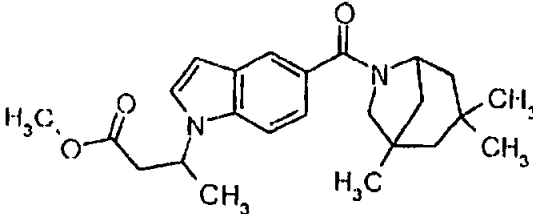
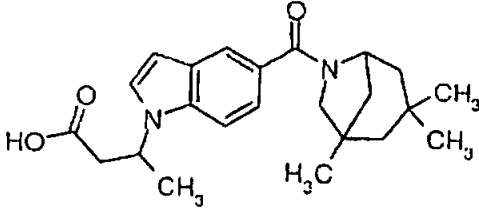
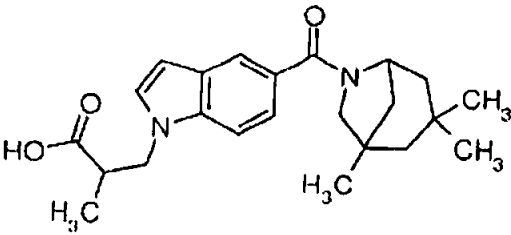
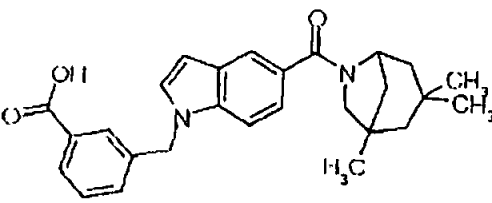
Los siguientes compuestos se sintetizaron utilizando un método similar a aquellos descritos en los ejemplos 6 y 7 anteriores:

Ejemplo	Estructura	PM	Nombre IUPAC	MS-ESI m/z
7-1		410.56	Éster tert- butílico del ácido [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - indol- 1-il]- acético	411
7-2		354.45	Ácido [5- (1,3,3-trimetil- 6- aza-biciclo-[3.2.1]octano- 6-carbonil) - indol- 1-il]- acético	355

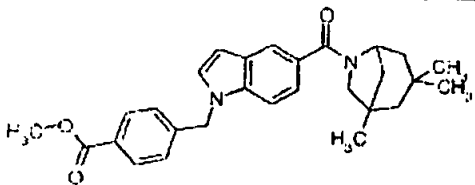
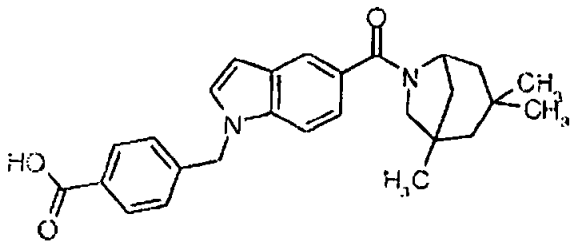
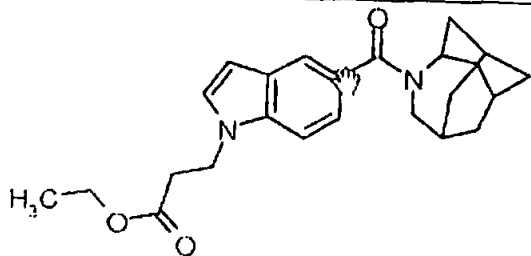
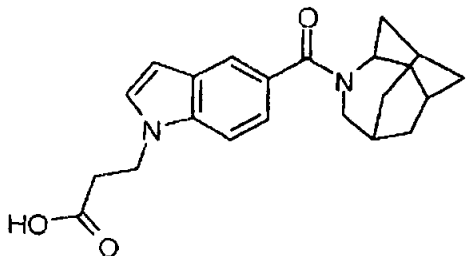
220

7-3		437.58	1- morfolin- 4- il- 3- [5- (1,3,3- trimetil- 6- aza- bicyclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- propan- 1- ona	438
7-4		423.56	1- morfolin- 4- il- 2- [5- (1,3,3- trimetil- 6- aza- bicyclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- etanona	424
7-5		424.58	Éster etílico del ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- bicyclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico	425
7-6		396.53	Ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- bicyclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico	397

290

7-7		396.53	Éster metílico del ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico	397
7-8		396.53	Éster metílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico	397
7-9		382.50	Ácido- 3- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico	383
7-10		382.50	Acido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico	383
7-11		430.55	Ácido- 3- [5- (1,3,3- trimetil- 6- aza- biciclo- [3.2.1]octano- 6- carbonil) - indol- 1-	431

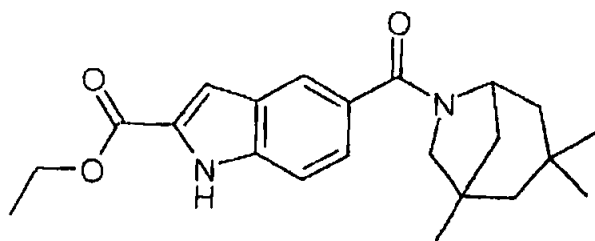
231

			ilmetil]- benzoico	
7- 12		444.57	Éster metílico del ácido 4- [5- (1,3,3-trimetil- 6- aza-biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico	445
7- 13		430.55	Ácido 4- [5- (1,3,3-trimetil- 6- aza-biciclo- [3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico	431
7- 14		394.51	Éster etílico del ácido 3- [5- (4- aza-triciclo[4.3.1.1 [*] . 3,8 [*]]- undecano- 4- carbonil) - indol- 1- il]- propiónico	395
7- 15		366.46	Ácido 3- [5- (4- aza-triciclo[4.3.1.1 [*] . 3,8 [*]]- undecano- 4- carbonil) - indol- 1- il]- propiónico	367

Ejemplo 8

Éster etílico del ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico.

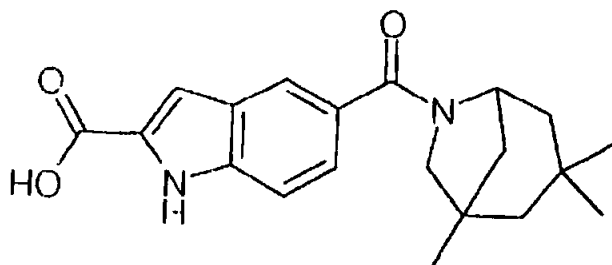
5



A una solución de éster 2- etílico del ácido 1H- indol- 2,5- dicarboxílico (890mg, 3.8 mmol) en DMF seco (10 mL) a temperatura ambiente bajo una atmosfera inerte de nitrógeno se agregó HOBt (570 mg, 4.2 mmol) y EDAC (951 mg, 4.9 mmol) y la solución resultante se agito durante 30 min. Se agregó hidrocloreuro de 1,3,3- trimetil- 6- aza- bicyclo[3.2.1]octano (796 mg, 4.2 mmol) a la solución seguido por DIPEA (1.98 mL, 11.4 mmol) , y la mezcla de reacción se agito durante 16 horas a temperatura ambiente. La reacción se apago mediante la adición de agua (20 mL.) seguido por la extracción con DCM (3 x 50 mL) . Las fases orgánicas combinadas se secaron con (MgSO₄) , filtraron, y evaporaron al vacío. El sólido resultante se purificó mediante cromatografía de gel de sílice utilizando una mezcla de acetato de etilo y heptano (1:2) como eluyente. Las fracciones puras se recolectaron, el solvente se evaporó al vacío y secó al vacío a 50 °C proporcionando 800 mg (57%) del compuesto del titulo como un sólido. MS- ESI m/z 369; ¹H NMR (300 MHz, CDCl₃) δ 0.94 (d, 3H) , 1.04 (d, 3H) , 1.14- 1.19 (m, 4H) , 1.24- 1.29 (m, 2H) , 1.39- 1.45 (m, 4H) , 1.58- 1.63 (m, 1H) , 1.76- 1.79 (m, 1H) , 3.25- 3.30 (m, 1H) 3.35 (d) y 3.65 (d, 1H) y 4.06- 4.09 (m) y 4.64- 4.67 (m, 1H) , 4.42 (q, 2H) , 7.27 (s, 1H) , 7.39- 7.46 (m, 2H) , 7.82 (d, 1H) , 9.05 (s, 1H) .

Ejemplo 9

Acido 5- (1,3,3- trimetil- 6- aza- bicyclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico.



A una solución de éster etílico del ácido 5- (1,3,3- trimetil- 6- aza- bicyclo[3.2.1]- octano- 6- carbonil- 1H- indol- 2- dicarboxílico (500mg, 1.35 mmol) en etanol (10 mL) se agregó

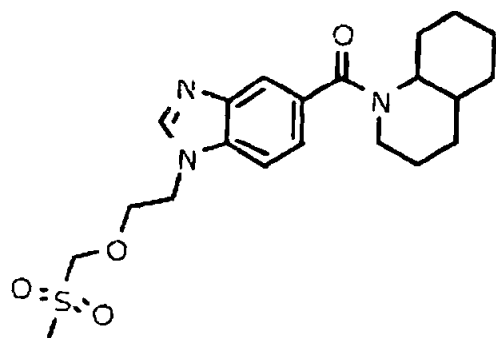
23

solución acuosa de hidróxido de sodio 1N (10 mL) y la solución resultante se agito durante 16 horas. La solución se acidificó con una solución 1N de ácido clorhídrico antes de retirar los volátiles orgánicos al vacío y los residuos acuosos se extrajeron con DCM (3 x 5 mL). Las fases orgánicas combinadas se secaron (MgSO₄), filtraron, y evaporaron al vacío. El sólido resultante se secó al vacío a 50°C proporcionando 460 mg (100%) del compuesto del título como un sólido. MS- ESI m/z 341; ¹H NMR (300 MHz, DMSO- d₆) δ 0.88- 0.99 (m, 6H), 1.07 (d, 3H), 1.16- 1.19 (m, 1H), 1.27- 1.50 (m, 4H), 1.74- 1.77 (m, 1H), 3.10- 3.19 (m, 1H), 3.40- 3.48 (m, 1H), 3.99- 4.07 (m) y 4.38- 4.40 (m, 1H) 7.16 (s, 1H) y 7.32- 7.37 (m, 1H), 7.42- 7.48 (m, 1H), 7.77 (d, 1H), 11.93 (s, 1H), 13.04 (s, 1H).

10

Ejemplo 10

[1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona



15 Paso A:

Éster metílico del ácido 4- (2- hidroxietilamino) - 3- nitro- benzoico:

Se disolvió éster metílico del ácido 4- fluoro- 3- nitro- benzoico (3 g, 15.64 mmol) en DMF (20 ml) y se agregó DIPEA (5.8 g, 18.07 mmol). Luego se agregó lentamente 2- aminoetanol (1.1 g, 18.07 mmol) manteniendo la temperatura a <20°C. La agitación continuó a temperatura ambiente durante 1 hora. Después de revisar la terminación de la reacción mediante TLC, la mezcla de reacción se agregó sobre el agua helada. El sólido amarillo separado se filtró, lavó con agua fría y finalmente se lavó con hexano proporcionando 3.3 g (92%) de éster metílico del ácido 4- (2- hidroxietilamino) - 3- nitro- benzoico. ¹H NMR (300 MHz, CDCl₃) δ 3.5 (q, 2H), 3.7 (q, 2H), 3.9 (s, 3H), 5.1 (t, 1H), 7.2 (d, 1H), 8.0 (d, 1H), 8.6 (s, 1H).

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23H

Paso B:

Éster metílico del ácido 3-amino-4-(2-hidroxi-etilamino)-benzoico:

A una solución de éster metílico del ácido 4-(2-hidroxi-etilamino)-3-nitro-benzoico (3.0 g, 12.4 mmol) en metanol se agregó Pd/C al 10% (800 mg). La mezcla se hidrogenó a presión atmosférica durante 2 horas. El catalizador se filtró y el metanol se evaporó para proporcionar 2.6 g (99%) de éster metílico del ácido 3-amino-4-(2-hidroxi-etilamino)-benzoico.

Paso C:

10 Éster metílico del ácido 1-(2-hidroxi-etil)-1H-benzimidazol-5-carboxílico:

Se disolvió éster metílico del ácido 3-amino-4-(2-hidroxi-etilamino)-benzoico (2.6 g, 12.0 mmol) en ácido fórmico (20 mL). La solución se calentó a 45°C durante 1 hora. Después de revisar la terminación de la reacción mediante TLC, el ácido fórmico se evaporó a <40°C bajo presión reducida y el sólido resultante se recrystalizó a partir de EtOAc. El sólido anterior se

15 disolvió en HCl 3N, se agitó a temperatura ambiente durante 1 hora, se basificó con solución saturada de bicarbonato de sodio y se extrajo con EtOAc. La capa orgánica se evaporó para proporcionar 2.1 g (78%) de éster metílico del ácido 1-(2-hidroxi-etil)-1H-benzimidazol-5-carboxílico: ¹H NMR (300 MHz, DMSO-d₆) δ 3.7 (q, 2H), 3.9 (s, 3H), 3.9 (s, 3H), 4.3 (t, 3H), 5.0 (t, 1H), 7.7 (d, 1H), 7.9 (dd, 1H), 8.25 (s, 1H), 8.35 (s, 1H).

20

Paso D:

Éster metílico del ácido 1-(2-metilsulfonilmetoxi-etil)-1H-benzimidazol-5-carboxílico:

Una solución de éster metílico del ácido 1-(2-hidroxi-etil)-1H-benzimidazol-5-carboxílico (0.5 g, 2.27 mmol) en una mezcla de THF seco:DME (25 mL : 15 mL) se enfrió a 5°C. Se
25 agregó NaH (0.081 g, 3.4 mmol) y se agitó durante 30 minutos a la misma temperatura. Luego se agregó lentamente una mezcla de metilsulfido de cloro-metilo (0.285 g, 2.95 mmol) y NaI (0.408 g, 2.95 mmol) seguido por TBAI (0.087 g, 0.22 mmol). La reacción se dejó agitar durante la noche a temperatura ambiente. Luego se apago con una solución saturada de cloruro de amonio y extrajo con EtOAc. La capa orgánica se evaporó para proporcionar 0.53 g (83%) de
30 éster metílico del ácido 1-(2-metilsulfonilmetoxietil)-1H-benzimidazol-5-carboxílico: ¹H

237

NNR (300 MHz, CDCl₃) δ 1.9 (s, 3H) , 3.9 (t, 2H) , 3.95 (s, 3H) , 4.4 (t, 2H) , 4.6 (s, 2H) , 7.45 (d, 1H) , 9.05 (m, 2H) , 8.5 (d, 1H) .

Paso E:

- 5 Éster metílico del ácido 1- (2- metilsulfonilmetoxi- etil) - 1H- benzoimidazol- 5- carboxílico:
Una solución de éster metílico del ácido 1- (2- metilsulfanilmetoxietil) - 1H- benzimidazol- 5- carboxílico (3.0 g, 10.7 mmoles) en metanol (30 mL) se enfrió a 0°C y a ésta se agregó una solución de oxono (4.88 g, 7.94 mmoles) en agua. La solución se agitó a temperatura ambiente durante 12 horas. Esta se apago con solución de bicarbonato de sodio al 5% y se extrajo con
- 10 EtOAc. El retiro del solvente proporcionó 2.0 g (60%) de éster metílico del ácido 1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- carboxílico: MS- ESI m/z 313 (M+1) : ¹H NNR (300 MHz, DMSO- d₆) δ 2.9 (s, 3H) , 4.0 (s, 3H) , 4.25 (t, 2H) , 4.65 (t, 2H) , 4.75 (s, 2H) , 7.85 (d, 2H) , 8.0 (dd, 1H) , 8.35 (s, 1H) , 8.5 (s, 1H)

15 Paso F:

- Ácido 1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- carboxílico:
Se disolvió éster metílico del ácido 1- (2- metanosulfonilmetoxietil) - 1H- benzoimidazol- 5- carboxílico (1.0 g, 3.2 mmoles) en THF (5 mL) . Se agregó una solución de LiOH (0.38 g, 16 mmol) en agua y la mezcla se agito vigorosamente durante 1 hora. La reacción se acidifico con
- 20 2N HCl a pH 2 a 5- 10°C. Luego esta se filtró para proporcionar 0.8 g (84%) de ácido 1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- carboxílico. ¹H NNR (300 MHz, DMSO- d₆) δ 2.9 (s, 3H) , 4.2 (t, 2H) , 4.5 (t, 2H) , 4.65 (s, 2H) , 7.75 (d, 1H) , 7.9 (dd, 1H) , 8.25 (d, 1H) , 8.35 (s, 1H) , 12.7 (s, 1H)

25 Paso G:

- [1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona:
A una solución de ácido 1- (2- metanosulfonilmetoxietil) - 1H- benzimidazol- 5- carboxílico (0.5 g, 1.677 mmol) en DMF (5 ml) se agregó decahidroquinolina (0.257g, 1.845 mmol) seguido
- 30 por HOBT (0.25 g, 1.845 mmol) y DIPEA (0.65 g, 5 mmol) . La mezcla de reacción se enfrió a 0°C y se agregó EDCI:HCl (0.354 g, 1.845 mmol) . La temperatura gradualmente se elevó a

276

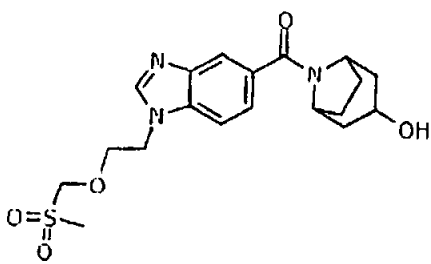
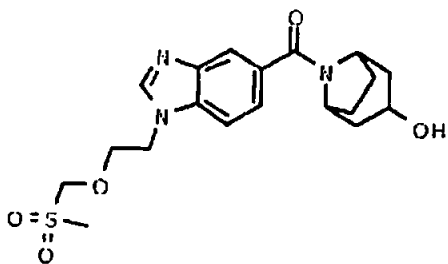
temperatura ambiente y la agitación continuó durante 12 horas. Luego el solvente se evaporó, el residuo se diluyó con agua (5 mL) y se extrajo con CH₂Cl₂ (3x25 mL). Las fases orgánicas combinadas se lavaron con solución de salmuera, se secaron (Na₂SO₄) y el solvente evaporó proporcionando la amida cruda la cual se purificó mediante HPLC preparativa para proporcionar 0.3 g (43%) de [1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]-

(octahidroquinolin- 1- il) - metanona. MS- ESI m/z 420 (M+1) : ¹H NMR (300 MHz, DMSO- d₆) δ 1.1- 1.9 (br, 13H) , 2.8 (s, 3H) , 3.0- 3.3 (m, 2H) , 4.15 (t, 2H) , 4.5 (t, 2H) , 4.65 (s, 2H) , 7.3 (m, 1H) , 7.6 (m, 1H) , 7.7 (d, 1H) , 8.3 (s, 1H)

10 Los siguientes compuestos se sintetizaron utilizando un método similar a aquel descrito en el ejemplo 10 anterior:

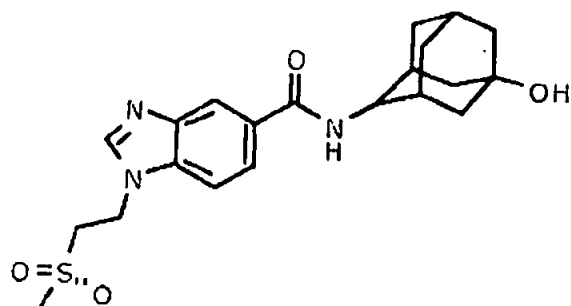
Ejemplo	Estructura	PM	Nombre IUPAC	MS- ESI m/z
10- 1		407.49	(3- hidroxí- 8- aza- bíciclo- [3.2.1]oct- 8- il) - [1- (2- metano- sulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- metanona	408
10- 2		447.56	(5- hidroxí- adamantan- 2- il) - amida del ácido trans- 1- (2- metanosulfonil- metoxi- etil) - 1H- benzo- imidazol- 5- carboxílico	448

237

10- 3		447.56	(5- hidroxí- adamantán- 2- il) - amida del ácido cis- 1- (2- metanosulfonil- metoxi- etil) - 1H- benzo- imidazol- 5- carboxílico	448
10- 4		407.49	(3- hidroxí- 8- aza- biciclo- [3.2.1]oct- 8- il) - [1- (2- metano- sulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- metanona	408

Ejemplo 11

- 5 (5- hidroxí- adamantán- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico



Paso A:

2- (2- metilsulfoniletil) isoindol- 1,3- diona

- 10 A una solución de N- bromoetilftalimida (1g, 3.953 mmol) en metanol (25 mL) , se agregó NaSMc (0.415 g, 5.929 mmol) bajo atmosfera N₂ a 0°C. La mezcla de reacción se dejó agitar a temperatura ambiente durante 2 horas. La masa de reacción se concentró, se diluyó con agua y se

970

extrajo con EtOAc (3x25 mL). La capa orgánica se lavó con solución de salmuera y se seco sobre Na₂SO₄ anhidro y se concentro para proporcionar 2- (2- metilsulfaniletíl) isoindol- 1,3- diona (0.88 g, 80%). MS- ESI m/z 222 (M+1) : ¹H NNR (300 MHz, CDCl₃) δ 7.7 (m, 2H) , 7.9 (m, 2H) , 3.9 (t, 1H) , 2.8 (t, 2H) , 2.2 (s, 3H) .

5

Paso B:

2- (2- metanosulfonil- etil) - isoindol- 1,3- diona

A una solución de 2- (2- metilsulfaniletíl) isoindol- 1,3- diona (2.5 g, 11.30 mmol) en ácido acético (10 mL) se agregó peróxido de hidrógeno al 30% (6 mL) a 0°C. La mezcla de reacción se llevó a temperatura ambiente y se agitó durante 2 horas. El exceso de peróxido de hidrógeno en la mezcla de reacción se apago con una solución saturada de sulfito de sodio, y la solución resultante se extrajo con CHCl₃. La capa orgánica se lavó con salmuera, se seco sobre Na₂SO₄ y se evaporó para proporcionar 2- (2- metanosulfonil- etil) isoindol- 1,3- diona (2.3 g, 83%). ¹H NNR (300 MHz, CDCl₃) δ 7.9 (m, 2H) , 7.8 (m, 2H) , 4.2 (t, 1H) , 3.4 (t, 1H) , 3.1 (s, 3H) .

15

Paso C:

2- metanosulfonil- etilamino:

Se agregó hidrato de hidrazina (15 mL) a una solución de 2- (2- metanosulfoniletíl) - isoindol- 1,3- diona (3.123 g, 12.344 mmol) en una mezcla de CHCl₃- etanol (1:1) a 0°C. Luego se agito durante la noche a temperatura ambiente. Se filtró y el filtrado se concentro para proporcionar 2- metanosulfoniletilamina (1.2 g, 80%). ¹H NNR (300 MHz, CDCl₃) δ 3.05 (t, 2H) , 3.15 (t, 2H) , 3.0 (s, 3H) .

20

Paso D:

25 Éster metílico del ácido 4- (2- metilsulfonil- etilamino) - 3- nitro- benzoico:

A una solución de 2- metanosulfoniletilamino (1.3 g, 10.56 mmol) y DIPEA (3.5 mL, 31.69 mmol) en DMF (15 mL) se agregó éster metílico del ácido 4- fluoro- 3- nitro- benzoico (1.2 g, 15.84 mmol) en porciones. La mezcla de reacción se dejo agitar durante 15 horas a temperatura ambiente. Luego se diluyo con agua y se extrajo con EtOAc. Las capas orgánicas se lavaron con agua, salmuera y se concentraron para proporcionar éster metílico del ácido 4- (2-

30

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metanosulfonil- etilamino) - 3- nitro- benzoico (83%) . ^1H NMR (300 MHz, CDCl_3) δ 8.9 (d, 1H) , 8.6 (t, 1H) , 8.2 (d, 1H) , 6.9 (d, 1H) , 4.0 (q, 2H) , 3.9 (s, 3H) , 3.4 (t, 2H) , 3.0 (s, 3H) .

Paso E.

- 5 Éster metílico del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico:
Se disolvió éster metílico del ácido 4- (2- metanosulfonil- etilamino) - 3- nitro- benzoico (1.63 g, 5.40 mmol) en metanol, y se agregó 10% Pd/C (150 mg) bajo una atmosfera de N_2 . Luego la mezcla de reacción se hidrogenó a presión atmosférica a temperatura ambiente durante 2 horas. Se filtró a través de Celite y el filtrado se concentro para proporcionar el producto del residuo. El
- 10 material crudo (1.32 g, 4.85 mmol) se tomó en ácido fórmico (10 mL) y se dejo agitar a 50°C durante 4 horas. La masa de reacción se concentró, se diluyó con agua y se extrajo con EtOAc. Las capas orgánicas se lavaron con NaHCO_3 saturado, salmuera, se secaron sobre Na_2SO_4 y se concentraron para proporcionar éster metílico del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico (77%) . ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 8.45 (s, 1H) , 8.3 (s, 1H) , 7.9 (d, 1H) , 7.8 (d, 1H) , 4.75 (t, 2H) , 3.9 (s, 3H) , 3.8 (t, 2H) , 3.0 (s, 3H) .
- 15

Paso F:

Acido 1- (2- metilsulfonil- etil) - 1H- benzoimidazol- 5- carboxílico

- A una solución de éster metílico del ácido 1- (2- metanosulfoniletil) - 1H- benzoimidazol- 5- carboxílico (0.2 g, 7.09 mmol) en metanol se agregó LiOH (50 mg) seguido por agua (1 mL) .
- 20 La mezcla de reacción se dejo agitar a temperatura ambiente durante 2 horas. Luego se concentro para retirar el metanol y la capa acosa se acidificó con ácido cítrico. El producto precipitado se filtró para proporcionar acido 1- (2- metilsulfonil- etil) - 1H- benzoimidazol- 5- carboxílico (90%) . MS- ESI m/z 269 (M+1) ; ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 12.6 (br, 1H) , 8.4 (s, 1H) , 8.2 (s, 1H) , 7.9 (d, 1H) , 7.8 (d, 1H) , 4.8 (t, 2H) , 3.8 (t, 2H) , 3.0 (s, 3H) .
- 25

Paso G:

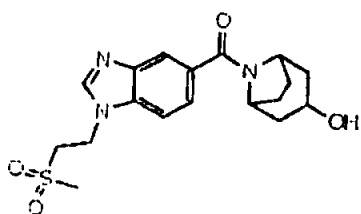
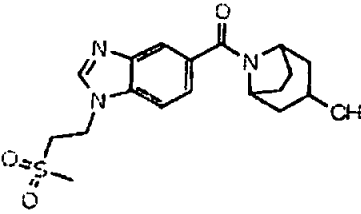
(5- hidroxí- adamantan- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico

- 30 A una solución del ácido 1- (2- metanosulfoniletil) - 1H- benzoimidazol- 5- carboxílico (0.2 g, 0.74 mmol) en DMF (5 mL) se agregó HOBt (0.15 g, 0.89 mmol) , DIPEA (0.4 mL, 2.23 mmol)

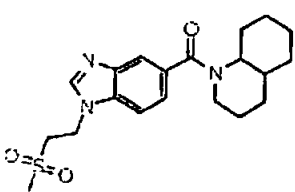
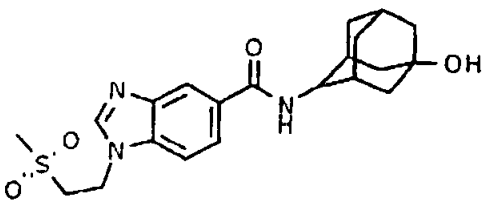
210

, 4- aminoadamantan- 1- ol (0.15g, 0.89 mmol) y EDCI (0.21 g, 1.11mmol) sucesivamente bajo atmosfera N₂. La mezcla de reacción se dejó agitar durante la noche a temperatura ambiente. Se diluyó con agua y se extrajo con CHCl₃. la capa orgánica se lavó con solución de NaHCO₃ saturado, salmuera y se secó sobre Na₂SO₄ anhidro. La concentración de la capa orgánica proporcionó (5- hidroxiadamantan- 2- il) - amida del ácido 1- (2- metanosulfoniletil) - 1H- benzoimidazol- 5- carboxílico (0.05 g) . MS- ESI m/z 418 (M+1) ; ¹H NMR (300 MHz, CDCl₃) δ 8.2 (s, 1H) , 8.1 (s, 1H) , 7.9 (d, 1H) , 7.5 (d, 1H) , 6.4 (d, 1H) , 4.8 (t, 2H) , 4.2 (m, 1H) , 3.6 (t, 2H) . 2.7 (s, 3H) , 2.4 (s, 2H) , 2.3 (m, 1H) , 1.8 (m, 11H) .

10 Los siguientes compuestos se sintetizaron utilizando un método similar a aquel descrito en el ejemplo 11 anterior:

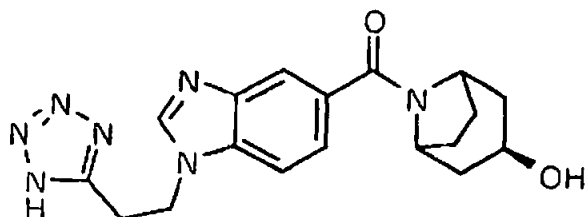
Ejemplo	Estructura	PM	Nombre IUPAC	MS-ESI m/z
11- 1		377.47	(3- hidroxi- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- metanona	378
11- 2		377.47	(3- hidroxi- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- metanona	378

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11-3		389.52	[1-(2-metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona	390
11-4		417.53	(5- hidroxí- adamantán- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- carboxílico	418

Ejemplo 12

(3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H-
5 benzoimidazol- 5- il}- metanona



Paso A:

Éster metílico del ácido 4- (2- ciano- etilamino) - 3- nitro- benzóico

A una solución de éster metílico del ácido 4- fluoro- 3- nitro- benzoico (4.95 g, 24.8 mmol) en
10 DMF (25 mL) se agregó fumarato de 3- aminopropionitrilo (3.18 g, 12.4 mmol) y DIPEA (15 mL, 84.3 mmol) . La mezcla se agito a temperatura ambiente durante 2 horas. El solvente se evaporó al vacío y el residuo se diluyó con agua (50 mL) . Se extrajo con EtOAc (3x100 mL) y la capa orgánica se lavó con solución de salmuera y se secó con (Na₂SO₄) . El retiro del solvente proporcionó éster metílico del ácido 4- (2- cianoetilamino) - 3- nitro- benzóico (6.19 g, 98.5%) .

22

MS- ESI m/z 250 (M+1) ; ^1H NMR (300 MHz, CDCl_3) δ 2.8 (t, 1H) , 3.8 (m, 2H) , 6.9 (d, 1H) , 8.2 (m, 1H) , 8.5 (t, 1H) , 8.9 (s, 1H) .

Paso B:

- 5 Éster metílico del ácido 3- amino- 4- (2- cianoetilamino) - benzoico:

A una solución de cloruro de amonio (21.7 g, 406.3 mmol) en agua (200 mL) se agregó éster metílico del ácido 4- (2- cianoetilamino) - 3- nitro- benzoico (6.1 g, 24.5 mmol) seguido por polvo de zinc (42.8g, 655.9 mmol) . La mezcla se calentó a 60°C durante 3 horas. Se filtró caliente y se lavó con EtOAc. El filtrado se extrajo adicionalmente con EtOAc y la fase orgánica

- 10 combinada se lavó con solución de salmuera. La capa orgánica se evaporó para proporcionar 4.1 g (75%) de éster metílico del ácido 3- amino- 4- (2- ciano- etilamino) - benzoico MS- ESI m/z 220 (M+1) ; ^1H NMR (300 MHz, CDCl_3) δ 2.7 (t, 2H) , 3.6 (m, 2H) , 3.8 (s, 3H) , 4.3 (bs, 1H) , 6.6 (d, 1H) , 7.45 (d, 1H) , 7.6 (d, 1H)

- 15 Paso C:

Éster metílico del ácido 1- (2- ciano- etil) - 1H- benzoimidazol- 5- carboxílico:

A éster metílico del ácido 3- amino- 4- (2- ciano- etilamino) - benzoico (4.0 g) se agregó ácido fórmico (25 mL) y la mezcla se calentó a 50°C durante 3 horas. Luego se concentró y el residuo se recrystalizó a partir de EtOAc para proporcionar 4.0 g (95%) de éster metílico del ácido 1- (2-

- 20 cianoetil) - 1H- benzoimidazol- 5- carboxílico MS- ESI m/z 230 (M+1) ; ^1H NMR (300 MHz, CDCl_3) δ 2.95 (t, 2H) , 4.0 (s, 3H) , 4.55 (t, 2H) , 7.4 (d, 1H) , 8.1 (m, 1H) , 8.15 (d, 1H) . 8.55 (s, 1H)

Paso D:

- 25 Ácido 1- (2- cianoetil) - 1H- benzoimidazol- 5- carboxílico:

A una solución de éster metílico del ácido 1- (2- cianoetil) - 1H- benzimidazol- 5- carboxílico (4.0 g, 17.4 mmol) en THF (30 mL) se agregó LiOH (1.67 g, 69.79 mmol) en agua (8 mL) seguido por MeOH (2 mL) . La agitación continuó a temperatura ambiente durante 1 hora. Luego se concentró y acidificó con HCl 2N. Los sólidos formados fueron filtrados y secados lo cual

30 proporcionó el ácido 1- (2- cianoetil) - 1H- benzoimidazol- 5- carboxílico (3.5 g, 95%) . ^1H NMR

213

(300 MHz, DMSO- D6) δ 3.1 (t, 2H) , 3.1 (T, 2H) , 4.6 (t, 2H) , 7.8 (d, 1H) , 7.9 (dd, 1H) , 8.25 (d, 1H) , 8.42 (s, 1H)

Paso E:

5 3- [5- (3- hidrox- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- propionitrilo:
A una solución de ácido 1- (2- cianoetil) - 1H- benzimidazol- 5- carboxílico (0.25 g, 1.16 mmol) en DMF (2.5 mL) se agregó con agitación HOBt (0.17 g, 1.27 mmol) seguido por hidrocloreuro de exo- nortropinol (0.21 g, 1.27 mmol) , DIPEA (0.45 g, 3.48 mmol) . Luego se agregó EDCI.HCl y se agitó a temperatura ambiente durante 12 horas. Luego el solvente se evaporó y el
10 residuo se diluyó con agua (5 mL) y se extrajo con CH₂Cl₂. La fase orgánica se lavó con solución de salmuera, se seco (Na₂SO₄) y el solvente se evaporó. El residuo se purificó mediante HPLC preparativa lo cual proporcionó 0.26 g (67%) de 3- [5- (3- hidrox- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- propionitrilo . MS- ESI *m/z* 325 (M +1)

15

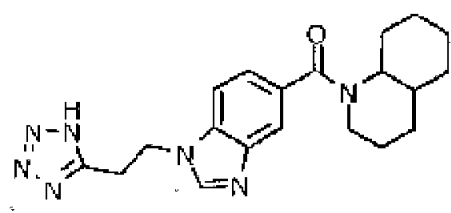
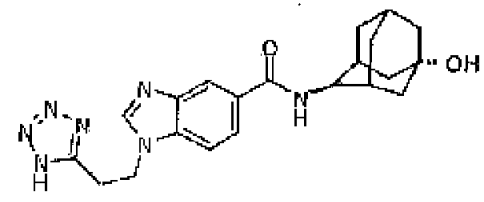
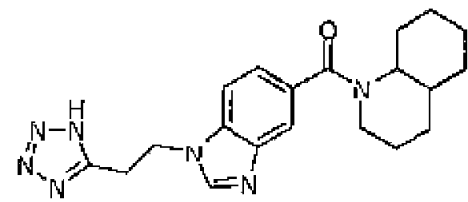
Paso F:

3- hidrox- 8- aza- biciclo[3.2.1]oct- 8- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il}- metanona:

A una solución de 3- [5- (3- hidrox- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol-
20 1- il]- propionitrilo (250 mg, 0.7 mmol) en DMF (5 mL) se agregó azida sódica (184 mg, 2.83 mmol) y cloruro de amonio (152 mg, 2.83 mmol) y se calentó a 100°C durante 12 horas. El solvente se evaporó completamente; se agregó metanol (20 mL) y se filtró. El filtrado se concentró y el residuo se purificó mediante HPLC preparativa para proporcionar 36 mg (13%) de
25 3- hidrox- 8- aza- biciclo[3.2.1]oct- 8- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il}- metanona: MS- ESI *m/z* 368 (M+1) ; ¹H NMR (300 MHz, DMSO- D6) δ 1.3- 2.0 (m, 8H) , 3.15 (s, 1H) , 3.5 (t, 2H) , 3.15 (s, 1H) , 3.5 (t, 2H) , 3.9- 4.0 (m, 2H) , 4.6 (br, 1H) , 4.75 (t, 2H) , 7.4 (dd, 1H) , 7.6- 7
.7 (m, 2H) , 8.25 (s, 1H) .

Los siguientes compuestos se sintetizaron utilizando un método similar a aquellos
30 descritos en el ejemplo 11 anterior:

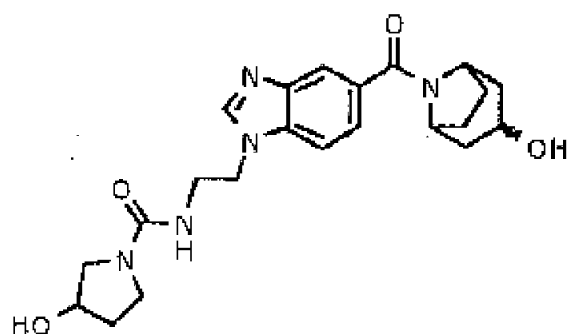
224

Ejemplo	Estructura	PM	Nombre IUPAC	MS-ESI m/z
12-1		379.41	(octahidro- quinolin- 1- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il}- metanona	380
12-2		407.48	(5- hidroxi- adamantan- 2- il) - amida del ácido trans- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico	355
12-3		477.48	(5- hidroxi- adamantan- 2- il) - amida del ácido cis- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico	438

Ejemplo 13

- 5 {2- [5- (3- hidroxi- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 3- hidroxi- pirrolidina- 1- carboxílico

2185



Paso A:

Éster metílico del ácido 4- fluoro- 3- nitro- benzoico:

A una solución del ácido 4- fluoro- 3- nitrobenzónico (16.0 g, 0.0864 mol) en DMF seco (100 mL) se agregó con agitación carbonato de potasio (59.0 g, 0.43 mol) seguido por yoduro de metilo (24.6 g, 0.173 mol) y la mezcla se agito durante 3 horas a temperatura ambiente. La mezcla de reacción se diluyo con agua helada (500 mL) , se extrajo con EtOAC (3 x 100 mL) y las fases orgánicas combinadas se lavaron con agua (3 x 100 mL) y solución saturada de salmuera (100 mL) . La fase orgánica se secó (Na₂SO₄) y el solvente se evaporó proporcionando 17.0 g (99%) de éster metílico del ácido 4- fluoro- 3- nitro- benzóico.

Paso B:

Éster metílico del ácido 4- (2- cloroetilamino) - 3- nitro- benzoico:

A una solución de éster metílico del ácido 4- fluoro- 3- nitro- benzoico (10.0 g, 0.0502 mol) en DMF seco (100 mL) se agregó con agitación carbonato de potasio (59.0 g, 0.43 mol) seguido por hidrocloreuro de 2- cloroetilamina (8.7 g, 0.075 mol) y la mezcla se agitó durante 15 horas a temperatura ambiente. La mezcla de reacción se diluyo con agua helada (500 mL) , se extrajo con EtOAC (3 x 100 mL) y el sólido precipitado se filtró, se lavó con agua y se secó al vacío para obtener un sólido amarillo (12.7 g, 98%) . MS- ESI m/z 259 (M+1) .

Paso C:

Éster metílico del ácido 3- amino- 4- (2- cloroetilamino) - benzoico:

A una solución de éster metílico del ácido 4- (2- cloroetilamino) - 3- nitro- benzoico (12.7 g, 0.0492 mol) en metanol (500 mL) se agregó 10% Pd/C (1.3 g) bajo una atmosfera N₂. La mezcla de reacción se hidrogenó en un aparato Parr a una presión de 3 kilogramos durante 2

horas. El catalizador se filtró sobre Celite y el filtrado se concentró proporcionando 11.0 g (98%) de éster metílico del ácido 4- (2- cloroetilamino) - benzoico como un sólido.

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Paso- D:

5 1- (2- cloroetil) - 1H- benzimidazol- 5- carboxílico:

A éster metílico del ácido 3- amino- 4- (2- cloroetilamino) - benzoico (11.0 g, 0.0482 mol) se agregó HCO₂H (30 mL) y se calentó a 100°C durante 1 hora. La reacción se enfrió a temperatura ambiente y se diluyó con agua helada (100 mL). El pH de la mezcla de reacción se ajustó a 7 con NaHCO₃ y el sólido precipitado se filtró, se lavó con agua y se secó al vacío para obtener un sólido verde claro (9.9 g, 86%) de 1- (2- cloroetil) - 1H- benzimidazol- 5- carboxílico. (MS- ESI m/z 239 (M+1)).

Paso E:

Éster metílico del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico

15 A una solución de éster metílico del ácido 1- (2- cloroetil) - 1H- benzimidazol- 5- carboxílico (9.9 g, 0.0416 mol) en DMSO seco (90 mL) se agregó con agitación NaN₃ (5.4 g, 0.0832 mol) y la mezcla se agitó durante 15 horas a 75°C. La mezcla de reacción se enfrió a temperatura ambiente y se diluyó con agua helada (500 mL) y el sólido precipitado se filtró, se lavó con agua y se secó al vacío proporcionando 9.3 g (91%) de éster metílico del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico MS- ESI m/z 264 (M+1); ¹H NMR (300 MHz, DMSO- D₆) δ 3.8 (t, 2H), 3.9 (s, 3H), 4.5 (t, 2H), 7.8 (d, 1H), 7.9 (dd, 1H), 8.25 (s, 1H), 8.4 (s, 1H).

Paso F:

Ácido 1- (2- azido- etil) - 1H- benzimidazol- 5- carboxílico:

25 A una solución de éster metílico del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico (5.0 g, 0.0204 mol) en THF/agua 1:1 (100 mL) se agregó con agitación LiOH (0.73 g, 0.0306 mol) y la mezcla se agitó durante 5 horas a temperatura ambiente. El solvente se evaporó y al residuo se le agregó agua helada (100 mL). El pH de la mezcla de reacción se ajustó a 5 con HCl 1N y la mezcla se extrajo con EtOAc (5x100 mL). Las fases orgánicas combinadas se lavaron con solución saturada de salmuera (100 mL), se secaron (Na₂SO₄) y el solvente se evaporó proporcionando 4.2 g (89%) de ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico como

un sólido de color ceniza. MS- ESI m/z 232 (M+1); ¹H NMR (300 MHz, DMSO- D6) δ 3.8 (t, 2H), 4.5 (t, 2H), 7.8 (d, 1H), 7.9 (d, 1H), 8.25 (s, 1H), 8.4 (s, 1H).

Paso G:

- 5 [1- (2- azidoetil) - 1H- benzimidazol- 5- il]- (3- hidroxi- 8- azabicyclo[3.2.1]oct- 8- ol) metanona:
A una solución de ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico (0.82 g, 0.00357 mol) en DMF seco (8.0 mL) se agregó con agitación HOBt (0.578 g, 0.00428 mol), DIPEA (1.9 mL, 0.0107 mol), 8- azabicyclo[3.2.1]octan- 3- ol (0.5 g, 0.00393 mol) y la mezcla se enfrió a 0°C. A la mezcla resultante se agregó EDCI (0.82 g, 0.00428 mol) y se agitó durante 15 horas a
10 temperatura ambiente. Luego la mezcla de reacción se diluyó con agua helada (100 mL), se extrajo con EtOAc (3x50 mL) y las fases orgánicas combinadas se lavaron con agua (3x50 mL) y solución saturada de salmuera (50 mL). La fase orgánica se secó (Na₂SO₄) y el solvente se evaporó proporcionando (1.1 g, 98%) de [1- (2- azidoetil) - 1H- benzimidazol- 5- il]- (3- hidroxi- 8- azabicyclo[3.2.1]oct- 8- il) metanona. MS- ESI m/z 341 (M+1).

15

Paso H:

[1- (2- amino- etil) - 1H- benzimidazol- 5- il]- (3- hidroxi- 8- aza- bicyclo[3.2.1]oct- 8- il) metanona:

- A una solución de [1- (2- azidoetil) - 1H- benzimidazol- 5- il]- (3- hidroxi- 8- aza- bicyclo[3.2.1]oct- 8- il) metanona (1.1 g, 0.0035 mol) en metanol (15 mL) se agregó 10% Pd/C (0.17) y la mezcla se hidrógeno a 3 kg de presión durante 1 hora. El catalizador se filtro sobre Celite y el filtrado se concentro para proporcionar [1- (2- amino- etil) - 1H- benzimidazol- 5- il]- (3- hidroxi- 8- aza- bicyclo[3.2.1]oct- 8- il) metanona (0.87 g, 86%). MS- ESI m/z 315 (M+1).

25 Paso I:

{2- [5- (3- hidroxi- 8- azabicyclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido 3- hidroxipirrolidina- 1- carboxílico:

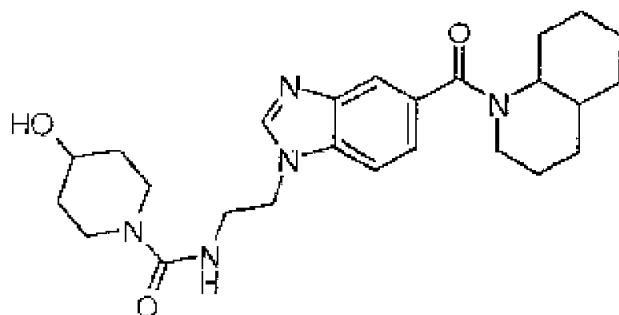
A) cloruro de 3- hidroxipirrolidina- 1- carbonilo:

A una solución de pirrolidin-3-ol (0.083 g, 0.955 mmol) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 1.91 mmol) y se enfrió a 0°C. A la mezcla resultante se agregó trifosgeno (0.127 g, 0.429 mmol) y la mezcla se agitó durante 2 horas a temperatura ambiente.

B) A una solución de [1-(2-aminoetil)-1H-benzimidazol-5-il]-(3-hidroxi-8-azabicyclo[3.2.1]oct-8-il) metanona (0.25 g, 0.79 mmol) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 1.91 mmol) a 0°C. A esta mezcla de reacción se agregó lentamente el compuesto A y se agitó durante 3 días a temperatura ambiente. El solvente se evaporó y el residuo se purificó mediante HPLC preparativa para proporcionar 175 mg (54%) de {2-[5-(3-hidroxi-8-azabicyclo[3.2.1]octano-8-carbonil)-benzimidazol-1-il]-etil}amida del ácido 3-hidroxipirrolidina-1-carboxílico MS-ESI m/z 428 (M+1); ^1H -NNR (300 MHz, CD_3OD) δ 1.5 (t, 1H), 4.1.9 (m, 6H), 2.1 (m, 3H), 3.2 (m, 2H), 3.5 (t, 2H), 4.2 (m, 2H), 4.4 (m, 1H), 4.5 (t, 2H), 4.8 (s, 1H), 7.45 (dd, 1H), 7.7 (d, 1H), 7.8 (s, 1H), 8.25 (s, 1H).

15 Ejemplo 14

{2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 4-
hidroxi- piperidina- 1- carboxílico



Los pasos A- F son similares a aquellos utilizados en el ejemplo 13 anterior.

Paso G:

[1-(2-azidoetil)-1H-benzimidazol-5-il]-(octahidroquinolin-1-il) metanona:

25 A una solución de ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico (1 g, 0.00433 mol) en DMF seco (7.0 mL) se agregó con agitación HOBt (0.00649 mol) , DIPEA (2.25 mL, 0.0129 mol) , dècahidroquinolina (0.902 g, 0.00649 mol) a 0°C. A la mezcla resultante se agregó EDCI

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(1.24 g, 0.00649 mol) y se agitó durante 15 horas a temperatura ambiente. La mezcla de reacción se diluyó con agua helada (100 mL) y se extrajo con EtOAc (3x50 mL). Las fases orgánicas combinadas se lavaron con agua, se secaron (Na₂SO₄) y el solvente se evaporó para proporcionar [1- (2- azidoetil) - 1H- benzimidazol- 5- il]- (octahidroquinolin- 1- il) metanona (1.5 g, 98%).

Paso H:

[1- (2- aminoetil) - 1H- benzimidazol- 5- il]- (octahidroquinolin- 1- il) metanona:

A una solución de [1- (2- azidoetil) - 1H- benzimidazol- 5- il]- (octahidroquinolin- 1- il) metanona (1.8 g, 0.0051 mol) en metanol (10 mL) se agregó 10% Pd/C (0.2 g). La mezcla de reacción se hidrogenó a 3 kg de presión durante 2 horas. El catalizador se filtró sobre Celite y el filtrado se concentró para proporcionar [1- (2- aminoetil) - 1H- benzimidazol- 5- il]- (octahidroquinolin- 1- il) metanona (1.5g, 90%).

Paso I:

{2- [5- (octahidroquinolina- 1- carbonil) benzimidazol- 1- il]etil}amida del ácido 4- hidroxipiperidina- 1- carboxílico:

A) cloruro de 4- hidroxipiperidina- 1- carbonilo:

A una solución de piperidina- 4- ol (0.074 g, 0.73 mmol) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 1.91 mmol) a 0°C. A la mezcla resultante se agregó trifosgeno (0.076 g, 2.1 mmol) y se agitó durante 2 horas a temperatura ambiente.

B) A una solución de [1- (2- aminoetil) - 1H- benzimidazol- 5- il]- (octahidroquinolin- 1- il) metanona (0.2 g, 0.613 mmol) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 1.91 mmol) a 0°C. A esta mezcla de reacción se agregó lentamente el compuesto A y se agitó durante 2 horas a temperatura ambiente. El solvente se evaporó y el residuo se purificó mediante HPLC preparativa proporcionando los isómeros cis y trans de {2- [5- (octahidroquinolina- 1- carbonil) benzimidazol- 1- il]etil}amida del ácido 4- hidroxipiperidina- 1- carboxílico.

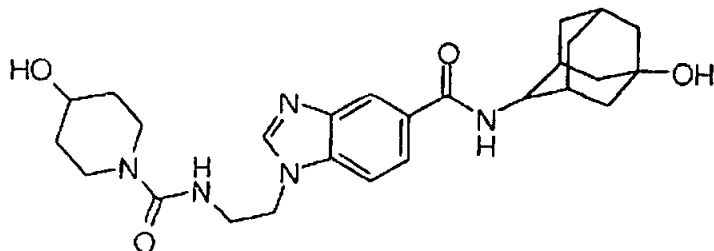
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Isómero I (12 mg) : MS- ESI m/z 454 (M+1) ; ^1H - NMR (300 MHz, CD_3OD) δ 1.30- 1.80 (m, 13H) , 2.0 (m, 3H) , 2.9 (m, 2H) , 3.2 (m, 2H) , 3.55 (t, 2H) , 3.7 (m, 3H) , 4.5 (t, 2H) , 7.35 (d, 1H) , 7.7 (m, 2H) , 8.25 (s, 1H) HPLC (VERYPOL.M) : tr = 7.73 min (95%) .

5 Isómero II (8 mg) : MS- ESI m/z 454 (M+1) ; ^1H - NMR (300 MHz, CD_3OD) δ 1.2 (m, 3H) , 1.4 (m, 8H) , 1.7 (m, 6H) , 3.0 (m, 2H) , 3.6 (t, 2H) , 3.7 (m, 3H) , 4.4 (t, 2H) , 7.4 (dd, 1H) , 7.65 (d, 1H) , 7.7 (s, 1H) , 8.3 (s, 1H) . HPLC (VERYPOL.M) : tr = 7.86 min (94%) .

Ejemplo 15

10 (5- hidroxí- adamanantan- 2- il) - amida del ácido 1- {2- [(4- hidroxí- piperidina- 1- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico



Los pasos A- F son similares a aquellos utilizados en el ejemplo 14 anterior

15 Paso G:

(5- hidroxíadamantan- 2- il) - amida del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico:

A una solución de ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico (0.65 gm 0.0028 mol) en DMF seco (5.0 mL) se agregó con agitación HOBt (0.46 g, 0.0034 mol) , DIPEA (2.5 mL, 0.014 mol) , 4- aminoadamantan- 1- ol (0.685 g, 0.0034 mol) a 0°C. A la mezcla resultante se agregó EDCI (0.65 g, 0.0034 mol) y se agitó durante 15 horas a temperatura ambiente. La mezcla de reacción se diluyó con agua helada (100 mL) y se extrajo con EtOAc (3x50 mL) y las fases orgánicas combinadas se lavaron con agua, se secaron (Na_2SO_4) y el solvente se evaporó proporcionando (1.0 g, 93.5%) de (5- hidroxíadamantan- 2- il) - amida del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico. NS- ESI m/z 381 (M+1) .

Paso H:

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(5- hidroxí- adamantán- 2- il)]- amida del ácido 1- [(2- aminoetil) - 1H- benzimidazol- 5- carboxílico:

A una solución (5- hidroxíadamantán- 2- il) - amida del ácido 1- (2- azidoetil) - 1H- benzimidazol- 5- carboxílico (1.0 g, 0.00263 mol) en metanol (20 mL) se agregó 10% Pd/C (200 mg) . La mezcla de reacción se hidrogenó a 3 kg de presión durante 1 hora.. El catalizador se filtró sobre Celite y el filtrado se concentró para proporcionar (5- hidroxí- adamantán- 2- il)]- amida del ácido 1- [(2- aminoetil) - 1H- benzimidazol- 5- carboxílico (0.7 g, 75%) :

Paso I:

10 (5- hidroxí- adamantán- 2- il)]- amida del ácido 1- [2- {(4- hidroxípiperidina- 1- carbonil) - amino]- etil} - 1H- benzimidazol- 5- carboxílico:

A una solución de (5- hidroxíadamantán- 2- il) - amida del ácido 1- (2- aminoetil) - 1H- benzimidazol- 5- carboxílico (0.35 g, 0.988 mol) en THF seco (5 mL) se agregó DIPEA (0.3 ml, 1.91 mmol) a 0°C. A esta mezcla de reacción se agregó lentamente cloruro de 4- hidroxípiperidina- 1- carbonilo y se agitó durante 2 horas a temperatura ambiente. Los solventes se evaporaron y el residuo se purificó mediante HPLC preparativa isómeros cis y trans de (5- hidroxí- adamantán- 2- il)]- amida del ácido 1- [2- {(4- hidroxípiperidina- 1- carbonil) - amino]- etil} - 1H- benzimidazol- 5- carboxílico.

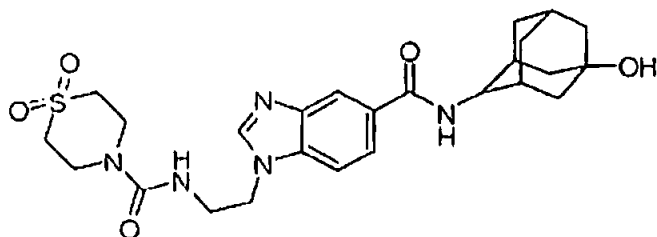
20 Isómero I (0.008 g) : MS- ESI m/z 482 (M+1) ; ¹H - NMR (300 MHz, CD₃OD) δ 1.4 (m, 3H) , 1.6 (d, 3H) , 1.8 (m, 9H) , 2.0 (d, 2H) , 2.2 (s, 1H) , 2.4 (s, 2H) , 2.9 (m, 2H) , 3.5- 3.8 (m, 5H) , 4.0 (s, 1H) , 4.5 (t, 2H) , 7.65 (d, 1H) , 7.8 (d, 1H) , 7.95 (d, 1H) , 8.15 (s, 1H) , 8.25 (s, 1H) . HPLC (VERYPOL.M) : tr = 6.59 min (95%) .

25 Isómero II (0.022 g) : MS- ESI m/z 482 (M+1) ; ¹H - NMR (300 MHz, CD₃OD) δ 1.4 (m, 3H) , 1.5 (d, 2H) , 1.8 (m, 5H) , 1.9 (d, 2H) , 2.1 (d, 2H) , 2.2 (brs, 1H) , 4.23 (d, 2H) , 2.9 (m, 2H) , 3.55 (t, 2H) , 3.7 (m, 3H) , 4.1 (s, 1H) , 4.4 (t, 2H) , 4.6 (s, 1H) , 7.65 (d, 1H) , 7.8 (dd, 1H) , 8.15 (d, 1H) , 8.25 (s, 1H) . HPLC (VERYPOL.M) : tr = 6.12 min (98%) .

30 Ejemplo 16

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(5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(1,1- díoxo- tiomorfolina- 4- carbonil) - amino]- etil} - 1H- benzoimidazol- 5- carboxílico



Los pasos A- F son similares a aquellos utilizados en el ejemplo 15 anterior.

5 Paso I:

A) cloruro de 1,1- díoxo- tiomorfolina- 4- carbonilo:

A una solución de 1,1- dióxido de tiomorfolina (0.181 g, 0.00105) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 0.00191 mol) a 0°C. A esta mezcla resultante se agregó trifosgeno (0.11 g, 0.00037 mol) y la mezcla se agitó durante 2 horas a temperatura ambiente.

- 10 B) A una solución (5- hidroxí- adamantán- 2- il) - amida del ácido 1- (2- aminoetil) - 1H- benzimidazol- 5- carboxílico (0.25 g, 0.706 mmol) en THF seco (5 mL) se agregó DIPEA (0.3 mL, 1.91 mmol) a 0°C. A esta mezcla de reacción se agregó lentamente el compuesto A y se agito durante 2 horas a temperatura ambiente. Los solventes se evaporaron y el residuo se purificó mediante HPLC preparativa proporcionando isómeros cis y trans de (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(1,1- díoxo- tiomorfolina- 4- carbonil) - amino]- etil}- 1H- benzoimidazol- 5- carboxílico
- 15

Isómero I (15 mg) : MS- ESI m/z 516 (M+1) ; ¹H - NMR (300 MHz, CD3OD) δ 1.5 (d, 2H) , 1.8 (d, 4H) , 1.9 (d, 2H) , 2.1 (m, 3H) , 2.3 (s, 2H) , 2.7 (t, 4H) , 3.6 (t, 2H) , 4.1 (s, 1H) , 4.5 (t, 2H) , 7.6 (d, 1H) , 7.8 (d, 1H) , 8.2 (s, 1H) , 8.35 (s, 1H) . HPLC (VERYPOL.M) : tr = 6.54 min (98%) .

20

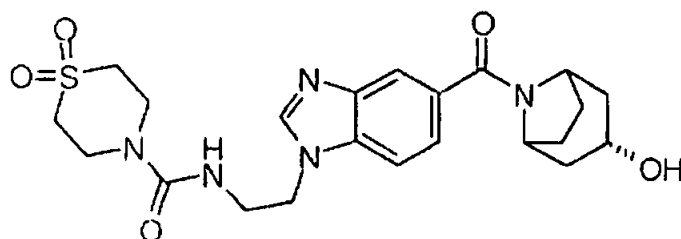
Isómero II (15 mg) : MS- ESI m/z 516 (M+1) ; ¹H - NMR (300 MHz, CD3OD) δ 1.5 (d, 2H) , 1.8 (d, 4H) , 1.9 (d, 2H) , 2.1 (m, 3H) , 2.3 (s, 2H) , 2.7 (t, 4H) , 3.6 (t, 2H) , 4.1 (s, 1H) , 4.5 (t, 2H) , 7.6 (d, 1H) , 7.8 (d, 1H) , 8.2 (s, 1H) , 8.35 (s, 1H) . HPLC (VERYPOL.M) : tr = 6.84 min (94%) .

25

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Ejemplo 17

{2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico



5 Los pasos A- F son similares a aquellos utilizados en el ejemplo 16 anterior.

Paso I:

A una solución de [1- (2- aminoetil) - 1H- benzimidazol- 5- il]- (3- hidroxí- 8- azabicyclo[3.2.1]oct- 8- il) - metanona (0.2 g, 0.636 mmol) en THF seco (5 mL) se agregó

10 DIPEA (0.3 mL, 1.91 mmol) a 0°C. A esta mezcla de reacción se agregó lentamente cloruro de 1,1- dioxo- tiomorfolina- 4- carbonilo y se agitó durante 2 horas a temperatura ambiente. Los solventes se evaporaron y el residuo se purificó mediante HPLC preparativa para proporcionar {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico (0.007 g, 2.3%) MS- ESI m/z 476 (M+1); ¹H - NMR (300 MHz, CD₃OD) δ 1.5 (t, 1H) , 1.8 (d, 4H) , 2.1 (brs, 3H) , 2.8 (s, 4H) , 3.6 (t, 2H) , 3.8 (s, 4H) , 4.2 (m, 2H) , 4.5 (t, 2H) , 4.7 (s, 1H) , 7.5 (d, 1H) , 7.7 (d, 1H) , 7.85 (s, 1H) , 8.3 (s, 1H) . HPLC (VERYPOL.M) : tr = 6.24 min (97%) .

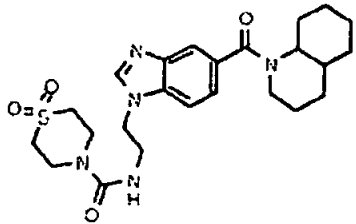
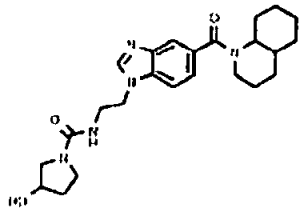
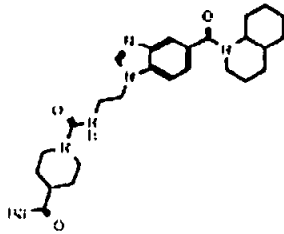
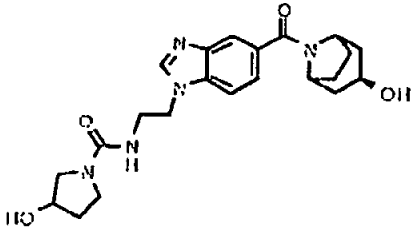
20 Los siguientes compuestos se sintetizaron utilizando un método similar a aquellos descritos en los ejemplos 13 y 17 anteriores:

Ejemplo	Estructura	PM	Nombre IUPAC	MS-ESI m/z

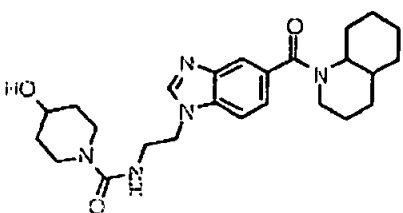
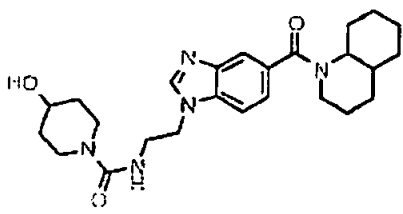
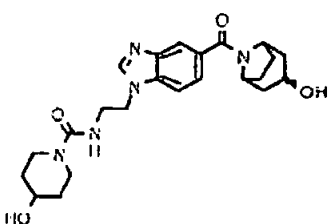
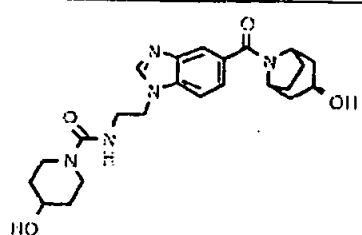
254

17-1		467.57	(5- hidroxí- adamantan-2- il) - amida del ácido cis- 1- [2- (morfolina- 4- carbonil) - amino]- etil}- 1H- benzo- imidazol- 5- carboxílico	458
17-2		467.57	(5- hidroxí- adamantan-2- il) - amida del ácido trans- 1- [2- (morfolina- 4- carbonil) - amino]- etil}- 1H- benzo- imidazol- 5- carboxílico	458
17-3		439.56	{2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido cis- morfolina- 4- carboxílico.	440
17-4		439.56	{2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido trans- morfolina- 4- carboxílico	440
17-5		427.51	{2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido	428

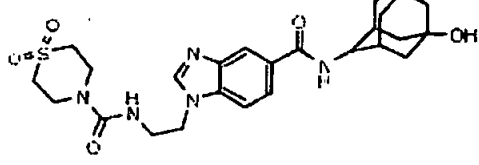
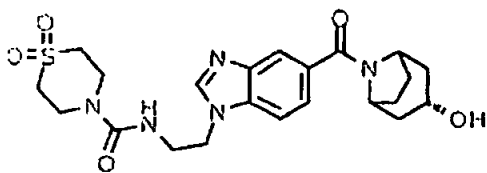
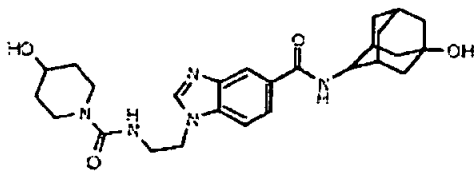
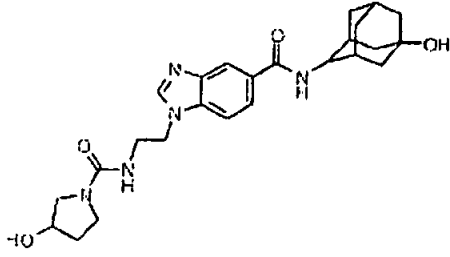
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			morfolina- 4- carboxílico	
17- 6		487.63	{2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido 1,1- díoxo- tiomorfolina- 4- carboxílico	488
17- 7		439.56	{2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]etil}- amida del ácido 3- hidroxí- pirrolidina- 1- carboxílico	440
17- 8		481.60	Ácido 1- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico	482
17- 9		427.51	{2- [5- (3- hidroxí- 8- aza- bíciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 3- hidroxí- pirrolidina- 1- carboxílico	428

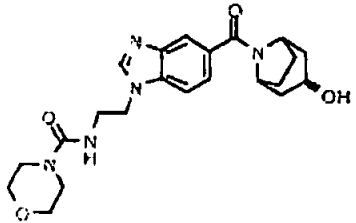
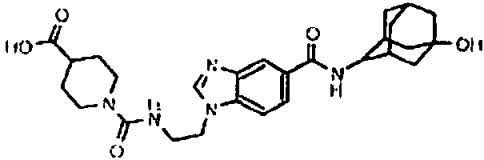
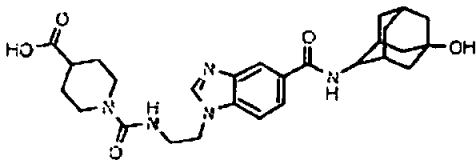
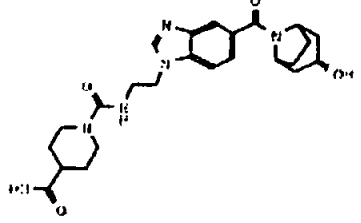
796

17- 10		453.59	{2- [5- (octahidro-quinolina- 1- carbonil) -benzoimidazol- 1- il]-etil}- amida del ácido cis- 4- hidroxipiperidina- 1- carboxílico	454
17- 11		453.59	{2- [5- (octahidro-quinolina- 1- carbonil) -benzoimidazol- 1- il]-etil}- amida del ácido trans- 4- hidroxipiperidina- 1- carboxílico	454
17- 12		441.53	{2- [5- (3- hidroxibiciclo[3.2.1]octano- 8- carbonil) -benzoimidazol- 1- il]-etil}- amida del ácido endo- 4- hidroxipiperidina- 1- carboxílico	442
17- 13		441.53	{2- [5- (3- hidroxibiciclo[3.2.1]octano- 8- carbonil) -benzoimidazol- 1- il]-etil}- amida del ácido exo- 4- hidroxipiperidina- 1-	442

957

			carboxílico	
17- 14		515.64	(5- hidroxí- adamantan-2- il) - amida del ácido 1-{2- [8,1,1- dioxo- tiomorfolina- 4- carbonil) - amino]- etil }- 1H- benzoimidazol- 5- carboxílico	516
17- 15		475.57	{2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]- octano- 8- carbonil- benzo- imidazol- il]- etil}- amida del ácido 1,12- dioxo- tiomorfolina- 4- carboxílico	476
17- 16		481.60	(5- hidroxí- adamantan-2- il) - amida del ácido 1- {2- [(4- hidroxí- piperidina- 1- carbonil) - amino]- etil}- 1H- benzoimidazol- 5- carboxílico	482
17- 17		467.57	(5- hidroxí- adamantan-2- il) - amida del ácido 1- {2- [(3- hidroxí- pirrolidina- 1- carbonil) - amino]- etil}- 1H- benzoimidazol- 5- carboxílico	468

958

17-18		427.51	{2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido morfolino- 4- carboxílico	428
17-19		509.61	ácido cis- 1- {2- [5- (5- hidroxí- adamantan- 2- ilcarbamoil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico	510
17-20		509.61	ácido trans- 1- {2- [5- (5- hidroxí- adamantan- 2- ilcarbamoil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico	510
17-21		469.55	ácido 1- {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil- carbamoil}- piperidina- 4- carboxílico	470

MÉTODOS FARMACOLOGICOS

Ensayo de enzimas 11 β HSD1

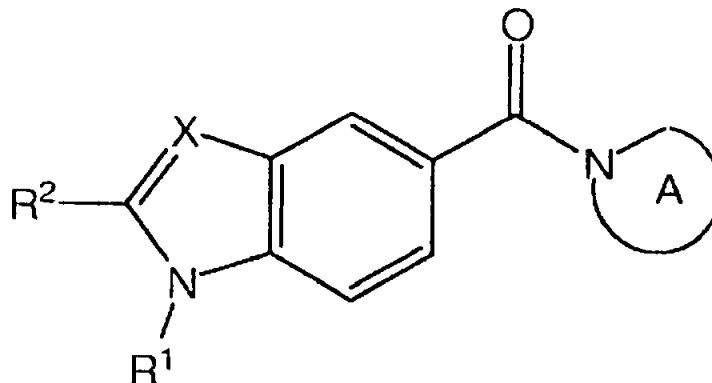
Se compraron perlas de ensayo de proximidad de centelleo (SPA) recubiertas con ^3H -cortisona e Ig anti- conejo en Amersham Pharmacia Biotech, β - NADPH de Sigma y anticuerpos anti- cortisol de conejo de Fitzgerald. Un extracto de levadura transformada con 11 β HSD1 (Hule, FEBS Lett, 441, 25 (1998)) se utilizó como la fuente de enzima. Los compuestos de prueba se disolvieron en DMSO (10 mM) . Todas las diluciones se realizaron en un amortiguador conteniendo 50 mM de TRIS- HCl (Sigma Chemical Co) , 4mM EDTA (Sigma Chemical Co) , BSA al 0.1%, Tween- 20 al 0.01% (Sigma Chemical Co) y bacitracin al 0.005% (Novo Nordisk A/S) , pH=7.4. Placas optiplate de 96 pozos fueron suministradas por Packard. La cantidad de ^3H - cortisol ligado a las perlas SPA se midió sobre TopCount NXT, Packard.

Métodos

Se agregó a los pozos h- 11 β HSD1, 120 nM ^3H - cortisona, 4 mM β - NADPH, anticuerpo (1:200) , diluciones seriales de compuesto de prueba y partículas SPA (2 mg/pozo) . La reacción se inició mezclando los diferentes componentes y se dejó avanzar bajo agitación durante 60 minutos a 30°C. La reacción se detuvo mediante la adición de exceso de 10 veces de un buffer de detención que contiene carbenoxolona 500 uM y 1 cortisona 1 uM. Los datos se analizaron utilizando software GraphPad Prism.

REIVINDICACIONES

1. Un compuesto de la fórmula I:

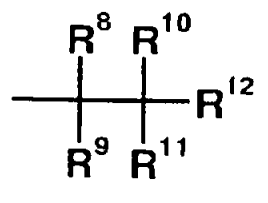


5 en donde:

X es seleccionada de CR5 y nitrógeno;

10 R1 es seleccionado de H y C1- C6alquilo- R6, en donde el grupo alquilo es sustituido con 0- 3 R7;

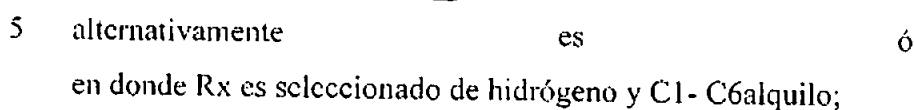
R2 es seleccionado de hidrógeno, halo, C1- C6alquilo, y -C(=O) R13;



alternativamente, R1 y R2 son, independientemente,

15 El anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

Vol.



R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;
R6 es seleccionado de ciano, arilo, hetero, - oxoC1- C6alquil- S(=O) R13, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) R13, - N(R18) C(=O) - C3- C10cicloalquilo, - N(R18) C(=O) - heterocicloalquilo de 3- 10 miembros, en donde los grupos cicloalquilo, heterocicloalquilo, arilo, y hetero son sustituidos con 0- 3 R16;

20 R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1-
C6alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1-
C6alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

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donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

5 Alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

10 Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

20 R13 es seleccionado de OH, C1- 6alquilo, C1- C6alquiloxilo, C1- C8alquiloxiC1- C4alquileno, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

R15 y R16 son independientemente seleccionados de H, C1- C6alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

25 R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C8alquilo, C1- C8alquiloxilo, y ariloxilo;

R18 y R19 son independientemente seleccionados de H, C1- C8alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C8alquileno, y hetarilC1- C8alquileno, en donde los grupos alquilo/alquileno, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

30 Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta

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del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquileo, hetarilC1- C6alquileo, hidroxilo, oxo, C1- C6alquiloxilo, arilC1- C6alquiloxilo, hetarilC1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilo, C1- C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1- C6carbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquiloxilo, NR21R22, metilendioxo, dihalometilendioxo, trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C8alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

n es seleccionado de 0, 1, y 2;

Y es seleccionado de O y S;

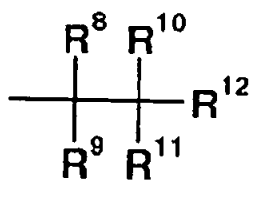
o una sal del mismo con un ácido o base farmacéuticamente aceptable o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

2. Un compuesto según la reivindicación 1 en donde:

X se selecciona de CR5 y nitrógeno;

R1 se selecciona de C1- C6alquil- R6, en donde el grupo alquilo es sustituido con 0- 3 R7;

R2 se selecciona de hidrógeno, halo, C1- C6alquilo, y -C(=O) R13;

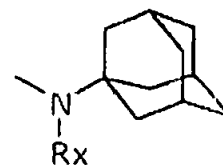
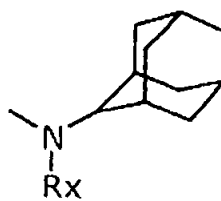
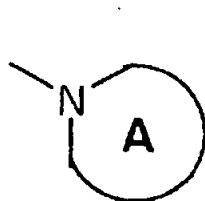


Alternativamente, R1 y R2 son, independientemente,

El Anillo A es un anillo bicíclico o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno y azufre;

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El Anillo A es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquileo, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquileo es sustituido con 0- 3 R14;

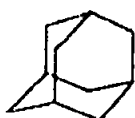


alternativamente

es

ó

en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquileo, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquileo es sustituido con 0- 3 R14;

R5 es seleccionado de hidrógeno, C1- C6alquilo, - C(=O) R13, y ciano;

R6 es seleccionado de ciano, arilo, hetarilo, - oxoC1- C6alquil- S(=O) R13, - C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19, - C(=NR15) NR15, - N(R18) C(=O) R13, - N(R18) C(=O) - C3- C10cicloalquilo, - N(R18) C(=O) - heticicloalquilo de 3- 10 miembros, en donde los grupos cicloalquilo, heticicloalquilo, arilo, y hetarilo son sustituidos con 0- 3 R16;

R7 es seleccionado de C1- C6alquilo, halo, hidroxilo, oxo y ciano;

R8, R9, R10 y R11 son cada uno independientemente seleccionados de hidrógeno, C1- C6alquilo, F, trihalometilo, trihalometoxilo, hidroxilo, y C1- C6alquiloxilo, en donde el C1- C6alquilo y C1- C6alquiloxilo son sustituidos con 0- 3 R17;

Alternativamente, R8 y R9 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos

de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados del halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

20

5 Alternativamente, R10 y R11 junto con el átomo de carbono al cual están fijados forman un anillo saturado o parcialmente saturado que consta del átomo de carbono mostrado, 2- 5 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo o hetarilC1- C6alquiloxilo;

10 Alternativamente, R8 y R10 junto con los dos átomos de carbono a los cuales están fijados forman un anillo saturado o parcialmente saturado que consta de los dos átomos de carbono y 1- 4 átomos de carbono adicionales, y 0- 2 heteroátomos seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 grupos seleccionados de halo, trihalometilo, C1- C6alquilo, arilo, hetarilo, arilC1- C6alquileno, hetarilC1- C6alquileno, hidroxilo, oxo, C1- C6alquiloxilo, ariloxilo, arilC1- C6alquiloxilo, y hetarilC1- C6alquiloxilo;

R12 es seleccionado de H, OH, NR18R19, C3- C10cicloalquilo, hetcicloalquilo de 3- 10 miembros, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, y -C(=NR15) NR16; en donde los grupos cicloalquilo y hetcicloalquilo son sustituidos con 0- 3 R17;

20 R13 es seleccionado de OH, C1- 6alquilo, C1- C6alquiloxilo, C1- C8alquiloxiC1- C4alquileno, arilo, hetarilo, ariloxilo, hetariloxilo, y NR18R19;

R14 es seleccionado de halo, hidroxilo, oxo, y ciano;

25 R15 y R16 son independientemente seleccionados de H, C1- C6alquilo, cicloalquilo de 3- 10 miembros, halo, OH, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, arilo, y hetarilo, en donde los grupos alquilo y cicloalquilo son sustituidos con 0- 3 R20;

R17 es seleccionado de halo, OH, oxo, nitro, ciano, - C(=O) R13, - S(=O) nR13, S(=O) nNR18R19, - N(R18) S(=O) nR13, NR18R19, C1- C8alquilo, C1- C8alquiloxilo, y ariloxilo;

30 R18 y R19 son independientemente seleccionados de H, C1- C8alquilo, C1- C8alquiloxilo, arilo, hetarilo, arilC1- C8alquileno, y hetarilC1- C8alquileno, en donde los grupos alquilo/alquileno, arilo, y hetarilo son independientemente sustituidos por 0- 3 R20;

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Alternativamente, R18 y R19, junto con el átomo de nitrógeno al cual están fijados forman un anillo monocíclico, bicíclico, o tricíclico saturado o parcialmente saturado que consta del nitrógeno mostrado, 4- 10 átomos de carbono, y 0- 2 heteroátomos adicionales seleccionados de nitrógeno, oxígeno, y azufre, en donde este anillo es sustituido con 0- 3 C1- C8 alquilo, arilo, hetarilo, arilC1- C6alquileo, hetarilC1- C6alquileo, hidroxilo, oxo, C1- C6alquilo, arilC1- C6alquilo, hetarilC1- C6alquilo, C1- C6alquilo, C1- C6alquilcarbonilo, arilcarbonilo, hetarilcarbonilo, arilC1- C6carbonilo, hetarilC1- C6alquilcarbonilo, C1- C6alquilcarboxilo, arilcarboxilo, hetarilcarboxilo, arilC1- C6alquil- carboxilo, y hetarilC1- C6alquilcarboxilo;

R20 es seleccionado de H, OH, oxo, halo, ciano, nitro, C1- C6alquilo, C1- C6alquilo, NR21R22, metilendio, dihalometilendio, trihalometilo, y trihalometiloxilo;

R21 y R22 son independientemente seleccionados de H, C1- C8alquilo, y arilC1- C6alquilo;

R23 es seleccionado de H y C1- C6alquilo;

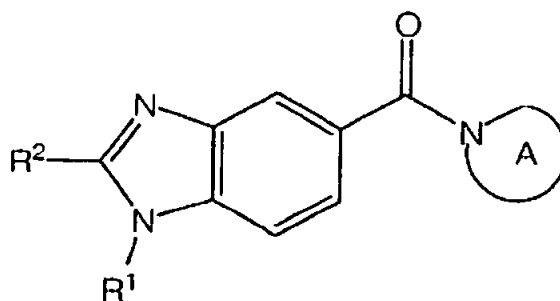
n es seleccionado de 0, 1, y 2;

Y es seleccionado de O y S;

siempre que cuando X es CR5, entonces R6 es -C(=O) R13 en donde R13 es OH;

o una sal del mismo con un ácido o base farmacéuticamente aceptable o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

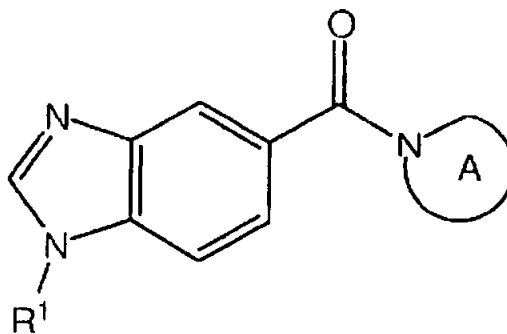
3. Un compuesto según la Reivindicación 1, en donde el compuesto es de la formula IA:



IA.

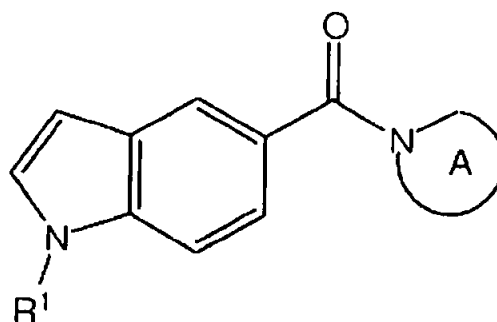
4. El compuesto de la Reivindicación 1, en donde el compuesto es de la formula IB:

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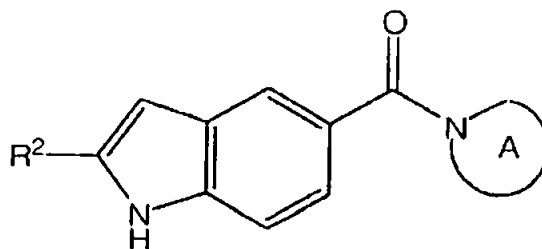
IB.

5. El compuesto según la Reivindicación 1, en donde el compuesto es de la formula IC:



IC.

6. El compuesto según la Reivindicación 1, en donde el compuesto es de la formula ID:



ID.

7. El compuesto según la Reivindicación 1, en donde R6 se selecciona de -C(=O) R13, - S(=O) nR13, - S(=O) nR18R19, - N(R18) S(=O) nR13, - N(R23) C(=Y) NR18R19 o -C(=NR15) NR15.

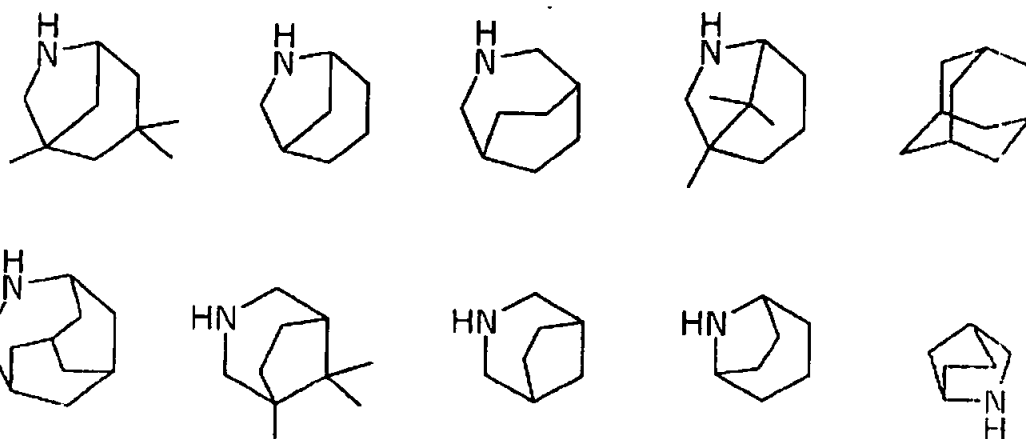
8. El compuesto según la reivindicación 1, en donde R6 es seleccionado de -C(=O) R13, - S(=O) nR13, - S(=O) nNR18R19, o -N(R23) C(=Y) NR18R19.

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9. El compuesto según la Reivindicación 1, en donde R6 se selecciona de - N(R23) C(=Y) NR18R19.

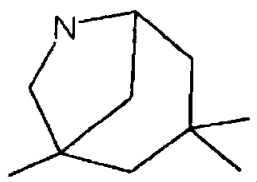
5 10. El compuesto según la Reivindicación 1, en donde Y es oxígeno (O) .

11. El compuesto según la reivindicación 1, en donde el Anillo A se selecciona de:

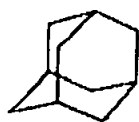


10 El Anillo A se sustituye con 0- 2 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, oxo, ciano, COOH, - CONR18R19, - S(=O) nR13, - S(=O) nNR18R19 y C1- C6alquiloxilo.

12. El compuesto según la reivindicación 11, en donde el Anillo A es

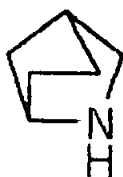


15 13. El compuesto según la reivindicación 11, en donde el Anillo A es

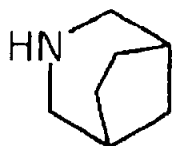


14. El compuesto según la reivindicación 11, en donde el Anillo A es

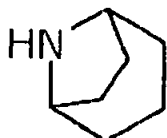
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15. El compuesto según la reivindicación 11, en donde el Anillo A es

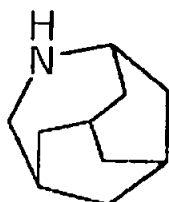


16. El compuesto según la reivindicación 11, en donde el Anillo A es

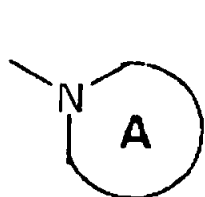


5

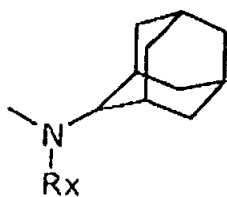
17. El compuesto según la reivindicación 11, en donde el Anillo A es



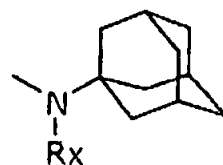
18. El compuesto según la reivindicación 1, en donde



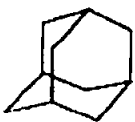
es



ó



10 en donde Rx es seleccionado de hidrógeno y C1- C6alquilo;



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es sustituido con 0- 3 grupos seleccionados de C1- C8alquilo, halo, hidroxilo, - COOH, - CONR¹⁸R¹⁹, - S(=O) nR¹³, - S(=O) nNR¹⁸R¹⁹ oxo, ciano, C1- C6alquiloxilo, C1- C6alquiloxiC1- C6alquilenos, y C1- C6alquilcarbonilo, en donde cada grupo alquilo/alquilenos es sustituido con 0- 3 R¹⁴;

5

19. Un compuesto seleccionado del grupo:

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido furan- 2- carboxílico

10

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}amida del ácido 1- acetil- piperidina- 4- carboxílico

2- metoxi- N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- acetamida

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- isonicotinamida

15

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- acetamida

Éster tert- butílico del ácido {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}carbámico

20

{2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido isoxazole- 5- carboxílico

N- {2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzoimidazol- 1- il]- etil}- benzamida

Éster etílico del ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

25

Ácido 3- [2- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - benzimidazol- 1- il]- propiónico

Éster etílico del ácido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]- ciclopropanocarboxílico

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- Acido 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- benzimidazol- 2- il]-
ciclopropanocarboxílico
- Éster etílico del ácido 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
benzimidazol- 1- il]- propiónico
- 5 Éster etílico del ácido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
1H- benzimidazol- 2- il]- ciclopropanocarboxílico
- Ácido de 3- [2- metil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) -
benzimidazol- 1- il]- propiónico
- Acido 2- [1- etil- 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H-
10 benzimidazol- 2- il]- ciclopropanocarboxílico
- Éster etílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1-
il]- propiónico
- Acido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propiónico
- Éster tert- butílico del ácido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
15 1- il]- acético
- Acido [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- acético
- 1- morfolin- 4- il- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propan- 1- ona
- 1- morfolin- 4- il- 2- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
20 etanona
- Éster etílico del ácido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6-
carbonil) - indol- 1- il]- propiónico
- Acido 2,2- dimetil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propiónico
- 25 Éster metílico del ácido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil)
- indol- 1- il]- propiónico
- Éster metílico del ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol-
1- il]- butírico
- Acido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- butírico
- 30 Acido 2- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]-
propiónico

- Ácido 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- Éster metílico del ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- 5 Ácido 4- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- ilmetil]- benzoico
- Éster etílico del ácido 3- [5- (4- aza- tricyclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- Ácido 3- [5- (4- aza- tricyclo[4.3.1.1^{*}3,8^{*}]undecano- 4- carbonil) - indol- 1- il]- propiónico
- 10 Éster etílico de ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- Ácido 5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - 1H- indol- 2- carboxílico
- N- metoxi- N- metil- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- 15 N- etoxi- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- N- hidroxí- 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- {1- [2- (2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 20 {1- [2- (3- ciclopropil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- {1- [2- (3- metil- [1,2,4]oxadiazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 25 N- (1H- tetrazol- 5- il) - 3- [5- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]octano- 6- carbonil) - indol- 1- il]- propionamida
- {1- [2- (2- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- {1- [2- (1- metil- 2H- tetrazol- 5- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza- biciclo[3.2.1]oct- 6- il) metanona
- 30 biciclo[3.2.1]oct- 6- il) metanona

{1- [2- (5- metil- [1,2,4]oxadiazol- 3- il) - etil]- 1H- indol- 5- il}- (1,3,3- trimetil- 6- aza-
biciclo[3.2.1]oct- 6- il) metanona

o una sal del mismo con un ácido o base farmacéuticamente aceptable, o cualquier
isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma
5 tautomérica.

20. Un compuesto seleccionado del grupo:

[1- (2- metanosulfonilmetoxi- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) -
metanona

10 (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonilmetoxi- etil) - 1H-
benzoimidazol- 5- il]- metanona

(5- hidroxí- adamantan- 2- il) - amida del ácido trans- 1- (2- metanosulfonil- metoxi- etil) - 1H-
benzoimidazol- 5- carboxílico

15 (5- hidroxí- adamantan- 2- il) - amida del ácido Cis- 1- (2- metanosulfonil- metoxi- etil) - 1H-
benzoimidazol- 5- carboxílico

(3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonilmetoxi- etil) - 1H-
benzoimidazol- 5- il]- metanona

(5- hidroxí- adamantan- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol-
5- carboxílico

20 (3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5-
il]- metanona

(3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - [1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5-
il]- metanona

[1- (2- metanosulfonil- etil) - 1H- benzoimidazol- 5- il]- (octahidro- quinolin- 1- il) - metanona

25 (5- hidroxí- adamantan- 2- il) - amida del ácido 1- (2- metanosulfonil- etil) - 1H- benzoimidazol-
5- carboxílico

(3- hidroxí- 8- aza- biciclo[3.2.1]oct- 8- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H-
benzoimidazol- 5- il]- metanona

30 (octahidro- quinolin- 1- il) - {1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- il]-
metanona

- (5- hidroxí- adamantán- 2- il) - amida del ácido trans- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico
- (5- hidroxí- adamantán- 2- il) - amida del ácido cis- 1- [2- (1H- tetrazol- 5- il) - etil]- 1H- benzoimidazol- 5- carboxílico
- 5 {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 3- hidroxí- pirrolidina- 1- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 4- hidroxí- piperidina- 1- carboxílico
- (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(4- hidroxí- piperidina- 1- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- 10 (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(1,1- dioxo- tiomorfolina- 4- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- 15 (5- hidroxí- adamantán- 2- il) - amida del ácido cis- 1- {2- [(morfolina- 4- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- (5- hidroxí- adamantán- 2- il) - amida del ácido Trans- 1- {2- [(morfolina- 4- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido cis- morfolina- 4- carboxílico
- 20 {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido trans- morfolina- 4- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido morfolina- 4- carboxílico
- 25 {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 3- hidroxí- pirrolidina- 1- carboxílico
- Ácido 1- {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}carbamoyl}- piperidina- 4- carboxílico
- 30

- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido 3- hidroxí- piperidina- 1- carboxílico
- {2- [5- (octahidro- quinolina- 1- carbonil) - benzo- imidazol- 1- il]- etil}- amida del ácido cis- 4- hidroxí- piperidina- 1- carboxílico
- 5 {2- [5- (octahidro- quinolina- 1- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido trans- 4- hidroxí- piperidina- 1- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido endo- 4- hidroxí- piperidina- 1- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido exo- 4- hidroxí- piperidina- 1- carboxílico
- 10 (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(1,1- dioxo- tiomorfolina- 4- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzo- imidazol- 1- il]- etil}- amida del ácido 1,1- dioxo- tiomorfolina- 4- carboxílico
- 15 (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(4- hidroxí- piperidina- 1- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- (5- hidroxí- adamantán- 2- il) - amida del ácido 1- {2- [(3- hidroxí- piperidina- 1- carbonil) - amino]etil}- 1H- benzoimidazol- 5- carboxílico
- {2- [5- (3- hidroxí- 8- aza- biciclo- [3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etil}- amida del ácido morfolina- 4- carboxílico
- 20 Ácido cis 1- {2- [5- (5- hidroxí- adamantán- 2- ilcarbamoil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico
- Ácido trans- 1- {2- [5- (5- hidroxí- adamantán- 2- ilcarbamoil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico
- 25 Ácido 1- {2- [5- (3- hidroxí- 8- aza- biciclo[3.2.1]octano- 8- carbonil) - benzoimidazol- 1- il]- etilcarbamoil}- piperidina- 4- carboxílico
- o una sal del mismo con un ácido o base farmacéuticamente aceptable, o cualquier isómero óptico o mezcla de isómeros ópticos, incluyendo una mezcla racémica, o cualquier forma tautomérica.

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21. Un compuesto según cualquiera de las reivindicaciones 1- 20, el cual es un agente útil para el tratamiento de condiciones, trastornos o enfermedades en donde una modulación o una inhibición de la actividad de 11β HSD1 es benéfica.

5 22. El compuesto según la reivindicación 21, en donde las condiciones, trastornos, y enfermedades están influenciadas por niveles glucocorticoides intracelulares.

10 23. El compuesto según la reivindicación 21, en donde las condiciones, trastornos, o enfermedades se seleccionan de síndrome metabólico, resistencia a insulina, dislipidemia, hipertensión, obesidad, diabetes tipo 2, intolerancia a la glucosa (IGT) , alteración de la glucosa en ayunas (IFG) , la progresión desde IGT a diabetes tipo 2, la progresión del síndrome metabólico a diabetes tipo 2, complicaciones diabéticas tardías, trastornos neurodegenerativos y psiquiátricos, y los efectos adversos de tratamiento o terapia con agonistas de receptores glucocorticoides.

15 24. Una composición farmacéutica que comprende, como un ingrediente activo, al menos un compuesto según cualquiera de las reivindicaciones 1- 20 junto con uno o más vehículos o excipientes farmacéuticamente aceptables.

20 25. La composición farmacéutica según la reivindicación 24 la cual es apropiada para administración oral, nasal, bucal transdérmica, pulmonar, o parenteral.

25 26. El uso de un compuesto según cualquiera de las reivindicaciones 1- 20 para la preparación de una composición farmacéutica para el tratamiento de condiciones, trastornos o enfermedades en donde una modulación o una inhibición de la actividad de 11β HSD1 es benéfica

30 27. El uso según la reivindicación 26, en donde las condiciones, trastornos, y enfermedades están influenciados por niveles glucocorticoides intracelulares.

From the INTERNATIONAL BUREAU

PCT

**NOTIFICATION OF THE RECORDING
OF A CHANGE**

(PCT Rule 92bis.1 and
Administrative Instructions, Section 422)

To:

TRANSTECH PHARMA
4170 Mendenhall Oaks Parkway
High Point, NC 27265
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)
20 March 2008 (20.03.2008)

Applicant's or agent's file reference
7227.204-WO

International application No.
PCT/EP2006/068017

IMPORTANT NOTIFICATION

International filing date (day/month/year)
01 November 2006 (01.11.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address
NOVO NORDISK A/S
Novo Allé
DK-2880 Bagsvaerd
Denmark

State of Nationality
DK

State of Residence
DK

Telephone No.
44 44 88 88

Facsimile No.
44 43 77 99

Teleprinter No.

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

Name and Address
TRANSTECH PHARMA
4170 Mendenhall Oaks Parkway
High Point, NC 27265
United States of America

State of Nationality
US

State of Residence
US

Telephone No.

Facsimile No.

Teleprinter No.

3. Further observations, if necessary:

Assignment. Please note that all future correspondence must be sent, until further notice, to the person identified in the addressee Box on top of the present notification.

4. A copy of this notification has been sent to:

☒ the receiving Office ☒ the designated Offices concerned
☐ the International Searching Authority ☐ the elected Offices concerned
☐ the International Preliminary Examining Authority ☐ other:

The International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland

Authorized officer

Muller Antonia

Facsimile No. +41 22 338 89 75

e-mail pt05.pct@wipo.int

Telephone No. +41 22 338 74 05

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter I of the Patent Cooperation Treaty)

(PCT Rule 44bis)

Applicant's or agent's file reference 7227.204-WO	FOR FURTHER ACTION See item 4 below	
International application No. PCT/EP2006/068017	International filing date (<i>day/month/year</i>) 01 November 2006 (01.11.2006)	Priority date (<i>day/month/year</i>) 01 November 2005 (01.11.2005)
International Patent Classification (8th edition unless older edition indicated) See relevant information in Form PCT/ISA/237		
Applicant TRANSTECH PHARMA		

- This international preliminary report on patentability (Chapter I) is issued by the International Bureau on behalf of the International Searching Authority under Rule 44 bis.1(a).
- This REPORT consists of a total of 8 sheets, including this cover sheet.

In the attached sheets, any reference to the written opinion of the International Searching Authority should be read as a reference to the international preliminary report on patentability (Chapter I) instead.
- This report contains indications relating to the following items:

☒ Box No. I	Basis of the report
☐ 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 Article 35(2) 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
- The International Bureau will communicate this report to designated Offices in accordance with Rules 44bis.3(c) and 93bis.1 but not, except where the applicant makes an express request under Article 23(2), before the expiration of 30 months from the priority date (Rule 44bis.2).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70 Form PCT/IB/373 (January 2004)	Date of issuance of this report 06 May 2008 (06.05.2008)
	Authorized officer Yolaine Cussac e-mail: pt05.pct@wipo.int

PATENT COOPERATION TREATY

290

From the
INTERNATIONAL SEARCHING AUTHORITY

To:

see form PCT/ISA/220

PCT

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/068017

International filing date (day/month/year)
01.11.2006

Priority date (day/month/year)
01.11.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4184 A61K31/404 A61P3/10

Applicant
NOVO NORDISK AS

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 usually 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:



European Patent Office
D-80298 Munich
Tel: +49 89 2399-0 Tx: 523856 epmu d
Fax: +49 89 2399-4465

Date of completion of
this opinion

see form
PCT/ISA/210

Authorized Officer

Friederich, Martin

Telephone No. +49 89 2399-7860



**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No.
PCT/EP2006/068017

Box No. 1 Basis of the 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
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) 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:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic 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/EP2006/068017

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

- ☐ the entire international application
- ☒ claims Nos. 30-33 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 30-33 relate to the following subject matter which does not require an international search (*specify*):
see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
 - ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
 - ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/068017

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

1. Statement

Novelty (N)

Yes: Claims 3,4,6,9,10,13-18,20
No: Claims 1,2,5,7,8,11,12,19,21-33

Inventive step (IS)

Yes: Claims
No: Claims 3,4,6,9,10,13-18,20

Industrial applicability (IA)

Yes: Claims 1-29
No: Claims

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No.

PCT/EP2006/068017

Re Item III

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

Claims 30-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

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

Reference is made to the following documents:

- D1: WO 2004/089470 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)
- D2: FOTSCH C ET AL: "11[beta]-Hydroxysteroid dehydrogenase-1 as a therapeutic target for metabolic diseases" EXPERT OPINION ON THERAPEUTIC PATENTS 2005 UNITED KINGDOM, vol. 15, no. 3, 2005, pages 289-303, XP002376609 ISSN: 1354-3776
- D3: WO 2004/089471 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)
- D4: WO 2004/089896 A (NOVO NORDISK A/S; GUNDERTOFTE, ANETTE; JOERGENSEN, ANKER STEEN; KAMPEN) 21 October 2004 (2004-10-21)

If not indicated otherwise, the relevant passages are those mentioned in the international search report.

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)

International application No.

PCT/EP2006/068017

Art. 33(2) The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of **claims 1, 2, 5, 7, 8, 11, 12, 19 and 21-33** does not appear to be new in the sense of Article 33(2) PCT.

D1 discloses substituted amides falling under the definition of present claim 1 and their use as 11-beta-HSD1 modulators.

The subject-matter of **claims 1, 2, 5, 7, 8, 11, 12, 19 and 21-33** is therefore not considered to be new (Article 33(2) PCT).

The subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** is considered to be new in the sense of Article 33(2) PCT since the structural variations delimit these claims from the prior art at hand.

Art. 33(3) The subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** is not considered to involve an inventive step in the sense of Article 33(3) PCT.

D1 discloses the use of substituted amides for the treatment of diabetes, from which the subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** differs in that similar compounds are used.

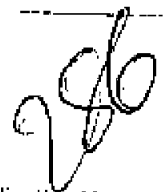
The problem to be solved by the present invention may therefore be regarded as how to provide a medicament for the treatment of diabetes.

Yet, structurally similar compounds having 11-beta-HSD1 modulating activity are known from the teaching of D2, D3 and D4.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of the remaining **claims 3, 4, 6, 9, 10, 13-18 and 20** the applicant's attention is drawn to the fact that there seems to be no

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)


International application No.

PCT/EP2006/068017

basis for inventive step within the present application as filed since no evidence can be found that the posed problem has been solved as it has not been shown that the compounds mentioned in **claims 3, 4, 6, 9, 10, 13-18 and 20** are effective in the treatment of diabetes.

It is therefore noted, that the solution proposed in **claims 3, 4, 6, 9, 10, 13-18 and 20** of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art. 33(4) The subject-matter of **claims 1-29** is considered to be industrially applicable in the sense of Art. 33(4) PCT.

For the assessment of the present **claims 30-33** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

gfh

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

To: NOVO NORDISK A/S Corporate Patents Novo Allé 2880 Bagsvaerd DENMARK		Notification of Transmittal of THE INTERNATIONAL SEARCH REPORT AND THE WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY, OR THE DECLARATION	
Reference: 0 3. DEC. 2007		(PCT Rule 44.1)	
Action: Form		Date of mailing (day/month/year) 30/11/2007	
Applicant's or agent's file reference 7227.204-WO		FOR FURTHER ACTION See paragraphs 1 and 4 below	
International application No. PCT/EP2006/068017		International filing date (day/month/year) 01/11/2006	
Applicant NOVO NORDISK A/S			

1. ☒ The applicant is hereby notified that the international search report and the written opinion of the International Searching Authority have been established and are transmitted herewith.

Filing of amendments and statement under Article 19:
 The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally two months from the date of transmittal of the International Search Report.

Where? Directly to the International Bureau of WIPO, 34 chemin des Colombettes
 1211 Geneva 20, Switzerland, Facsimile No.: (41-22) 338.82.70

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

2. ☐ The applicant is hereby notified that no international search report will be established and that the declaration under Article 17(2)(a) to that effect and the written opinion of the International Searching Authority are transmitted herewith.

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

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

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

4. **Reminders**

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

The applicant may submit comments on an informal basis on the written opinion of the International Searching Authority to the International Bureau. The International Bureau will send a copy of such comments to all designated Offices unless an international preliminary examination report has been or is to be established. These comments would also be made available to the public but not before the expiration of 30 months from the priority date.

Within **18 months** from the priority date, but only in respect of some designated Offices, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase **until 30 months** from the priority date (in some Offices even later); otherwise, the applicant must, **within 20 months** from the priority date, perform the prescribed acts for entry into the national phase before those designated Offices.

In respect of other designated Offices, the time limit of **30 months** (or later) will apply even if no demand is filed within 18 months.

See the Annex to Form PCT/IB/301 and, for details about the applicable time limits, Office by Office, see the *PCT Applicant's Guide*, Volume II, National Chapters and the WIPO Internet site.

Name and mailing address of the international Searching Authority  European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Authorized officer Christian Mihé
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NOTES TO FORM PCT/ISA/220

These Notes are intended to give the basic instructions concerning the filing of amendments under Article 19. The Notes are based on the requirements of the Patent Cooperation Treaty, the Regulations and the Administrative Instructions under that Treaty. In case of discrepancy between these Notes and those requirements, the latter are applicable. For more detailed information, see also the *PCT Applicant's Guide*, a publication of WIPO.

In these Notes, "Article", "Rule", and "Section" refer to the provisions of the PCT, the PCT Regulations and the PCT Administrative Instructions, respectively.

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

The applicant has, after having received the international search report and the written opinion of the International Searching Authority, one opportunity to amend the claims of the international application. It should however be emphasized that, since all parts of the international application (claims, description and drawings) may be amended during the international preliminary examination procedure, there is usually no need to file amendments of the claims under Article 19 except where, e.g. the applicant wants the latter to be published for the purposes of provisional protection or has another reason for amending the claims before international publication. Furthermore, it should be emphasized that provisional protection is available in some States only (see *PCT Applicant's Guide*, Volume I/A, Annexes B1 and B2).

The attention of the applicant is drawn to the fact that amendments to the claims under Article 19 are not allowed when the International Searching Authority has declared, under Article 17(2), that no international search report would be established (see *PCT Applicant's Guide*, Volume I/A, paragraph 296).

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 46.1).

Where not to file the amendments?

The amendments may only be filed with the International Bureau and not with the receiving Office or the International Searching Authority (Rule 46.2).

Where a demand for international preliminary examination has been/is filed, see below.

How?

Either by cancelling one or more entire claims, by adding one or more new claims or by amending the text of one or more of the claims as filed.

A replacement sheet must be submitted for each sheet of the claims which, on account of an amendment or amendments, differs from the sheet originally filed.

All the claims appearing on a replacement sheet must be numbered in Arabic numerals. Where a claim is cancelled, no renumbering of the other claims is required. In all cases where claims are renumbered, they must be renumbered consecutively (Section 205(b)).

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)).

The amendments must be submitted with a letter.

The letter will not be published with the international application and the amended claims. It should not be confused with the "Statement under Article 19(1)" (see below, under "Statement under Article 19(1)").

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 7227.204-WO	FOR FURTHER ACTION see Form PCT/ISA/220 as well as, where applicable, Item 5 below.	
International application No. PCT/EP2006/068017	International filing date (day/month/year) 01/11/2006	(Earliest) Priority Date (day/month/year) 01/11/2005
Applicant NOVO NORDISK A/S		

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 6 sheets.

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

1. Basis of the report

a. With regard to the language, the International search was carried out on the basis of:

- ☒ the International application in the language in which it was filed
☐ a translation of the International application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 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

A. CLASSIFICATION OF SUBJECT MATTER
 INV. A61K31/4184 A61K31/404 A61P3/10

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)
 A61K A61P

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

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

EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/089470 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21) examples on page 156-157	1-33
A	FOTSCH C ET AL: "11[beta]-Hydroxysteroid dehydrogenase-1 as a therapeutic target for metabolic diseases" EXPERT OPINION ON THERAPEUTIC PATENTS 2005 UNITED KINGDOM, vol. 15, no. 3, 2005, pages 289-303, XP002376609 ISSN: 1354-3776	

☒ 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
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *8* document member of the same patent family

Date of the actual completion of the international search

21 November 2007

Date of mailing of the international search report

30/11/2007

Name and mailing address of the ISA/

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

Authorized officer

Friederich, Martin

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim 1?
A	WO 2004/089471 A (NOVO NORDISK A/S; ANDERSEN, HENRIK; SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)	
A	WO 2004/089896 A (NOVO NORDISK A/S; GUNDERTOFT, ANETTE; JOERGENSEN, ANKER STEEN; KAMPEN) 21 October 2004 (2004-10-21)	

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 30-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

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

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/068017

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 2004089470	A	21-10-2004	WO 2004089896 A1	21-10-2004
			EP 1618090 A1	25-01-2006
			EP 1615698 A2	18-01-2006
			JP 2006522746 T	05-10-2006
			JP 2006522748 T	05-10-2006
WO 2004089471	A	21-10-2004	EP 1615697 A2	18-01-2006
			JP 2006522749 T	05-10-2006
WO 2004089896	A	21-10-2004	WO 2004089470 A2	21-10-2004
			EP 1618090 A1	25-01-2006
			EP 1615698 A2	18-01-2006
			JP 2006522746 T	05-10-2006
			JP 2006522748 T	05-10-2006

From the
INTERNATIONAL SEARCHING AUTHORITY

PCT

205

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/EP2006/068017

International filing date (day/month/year)
01.11.2006

Priority date (day/month/year)
01.11.2005

International Patent Classification (IPC) or both national classification and IPC
INV. A61K31/4184 A61K31/404 A61P3/10

Applicant
NOVO NORDISK AS

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 usually 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:



European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Date of completion of
this opinion

see form
PCT/ISA/210

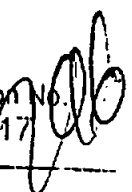
Authorized Officer

Friederich, Martin

Telephone No. +49 89 2399-7860



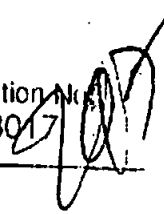
**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY**

International application No. 
PCT/EP2006/068017

Box No. I Basis of the 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
 - ☐ a translation of the international application into , which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) 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:
 - ☐ on paper
 - ☐ in electronic form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in electronic 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/EP2006/068017

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

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

- ☐ the entire international application
- ☒ claims Nos. 30-33 (with respect to industrial applicability)

because:

- ☒ the said international application, or the said claims Nos. 30-33 relate to the following subject matter which does not require an international search (*specify*):
- see separate sheet
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed (*specify*):
- ☐ no international search report has been established for the whole application or for said claims Nos.
- ☐ a meaningful opinion could not be formed without the sequence listing; the applicant did not, within the prescribed time limit:
- ☐ furnish a sequence listing on paper complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ furnish a sequence listing in electronic form complying with the standard provided for in Annex C of the Administrative Instructions, and such listing was not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ pay the required late furnishing fee for the furnishing of a sequence listing in response to an invitation under Rules 13ter.1(a) or (b).
- ☐ a meaningful opinion could not be formed without the tables related to the sequence listings; the applicant did not, within the prescribed time limit, furnish such tables in electronic form complying with the technical requirements provided for in Annex C-bis of the Administrative Instructions, and such tables were not available to the International Searching Authority in a form and manner acceptable to it.
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in electronic form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See Supplemental Box for further details

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY

International application No.
PCT/EP2006/068017

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

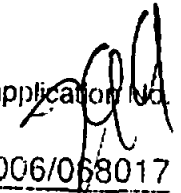
1. Statement

Novelty (N)	Yes: Claims	<u>3,4,6,9,10,13-18,20</u>
	No: Claims	<u>1,2,5,7,8,11,12,19,21-33</u>
Inventive step (IS)	Yes: Claims	
	No: Claims	<u>3,4,6,9,10,13-18,20</u>
Industrial applicability (IA)	Yes: Claims	<u>1-29</u>
	No: Claims	

2. Citations and explanations

see separate sheet

**WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING
AUTHORITY (SEPARATE SHEET)**

International application No. 

PCT/EP2006/068017

Re Item III

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

Claims 30-33 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

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

Reference is made to the following documents:

- D1: WO 2004/089470 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)
- D2: FOTSCH C ET AL: "11[beta]-Hydroxysteroid dehydrogenase-1 as a therapeutic target for metabolic diseases" EXPERT OPINION ON THERAPEUTIC PATENTS 2005 UNITED KINGDOM, vol. 15, no. 3, 2005, pages 289-303, XP002376609 ISSN: 1354-3776
- D3: WO 2004/089471 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)
- D4: WO 2004/089896 A (NOVO NORDISK A/S; GUNDERTOFT, ANETTE; JOERGENSEN, ANKER STEEN; KAMPEN) 21 October 2004 (2004-10-21)

If not indicated otherwise, the relevant passages are those mentioned in the International search report.

Art. 33(2) The present application does not meet the requirements of Article 33(2) PCT, because the subject-matter of **claims 1, 2, 5, 7, 8, 11, 12, 19 and 21-33** does not appear to be new in the sense of Article 33(2) PCT.

D1 discloses substituted amides falling under the definition of present claim 1 and their use as 11-beta-HSD1 modulators.

The subject-matter of **claims 1, 2, 5, 7, 8, 11, 12, 19 and 21-33** is therefore not considered to be new (Article 33(2) PCT).

The subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** is considered to be new in the sense of Article 33(2) PCT since the structural variations delimit these claims from the prior art at hand.

Art. 33(3) The subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** is not considered to involve an inventive step in the sense of Article 33(3) PCT.

D1 discloses the use of substituted amides for the treatment of diabetes, from which the subject-matter of **claims 3, 4, 6, 9, 10, 13-18 and 20** differs in that similar compounds are used.

The problem to be solved by the present invention may therefore be regarded as how to provide a medicament for the treatment of diabetes.

Yet, structurally similar compounds having 11-beta-HSD1 modulating activity are known from the teaching of D2, D3 and D4.

Taking into account the teaching of the cited prior art the following reasoning applies:

With respect to the subject-matter of the remaining **claims 3, 4, 6, 9, 10, 13-18 and 20** the applicant's attention is drawn to the fact that there seems to be no

basis for inventive step within the present application as filed since no evidence can be found that the posed problem has been solved as it has not been shown that the compounds mentioned in **claims 3, 4, 6, 9, 10, 13-18 and 20** are effective in the treatment of diabetes.

It is therefore noted, that the solution proposed in **claims 3, 4, 6, 9, 10, 13-18 and 20** of the present application is not considered to be inventive in the sense of Article 33(3) PCT.

Art. 33(4) The subject-matter of **claims 1-29** is considered to be industrially applicable in the sense of Art. 33(4) PCT.

For the assessment of the present **claims 30-33** on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Possible steps after receipt of the international search report (ISR) and written opinion of the International Searching Authority (WO-ISA)

General information	For all international applications filed on or after 01/01/2004 the competent ISA will establish an ISR. It is accompanied by the WO-ISA. Unlike the former written opinion of the IPEA (Rule 66.2 PCT), the WO-ISA is not meant to be responded to, but to be taken into consideration for further procedural steps. This document explains about the possibilities.
Amending claims under Art. 19 PCT	Within 2 months after the date of mailing of the ISR and the WO-ISA the applicant may file amended claims under Art. 19 PCT directly with the International Bureau of WIPO. The PCT reform of 2004 did not change this procedure. For further information please see Rule 46 PCT as well as form PCT/ISA/220 and the corresponding Notes to form PCT/ISA/220.
Filing a demand for international preliminary examination	In principle, the WO-ISA will be considered as the written opinion of the IPEA. This should, in many cases, make it unnecessary to file a demand for international preliminary examination. If the applicant nevertheless wishes to file a demand this must be done before expiry of 3 months after the date of mailing of the ISR/ WO-ISA or 22 months after priority date, whichever expires later (Rule 54bis PCT). Amendments under Art. 34 PCT can be filed with the IPEA as before, normally at the same time as filing the demand (Rule 66.1 (b) PCT). If a demand for international preliminary examination is filed and no comments/amendments have been received the WO-ISA will be transformed by the IPEA into an IPRP (International Preliminary Report on Patentability) which would merely reflect the content of the WO-ISA. The demand can still be withdrawn (Art. 37 PCT).
Filing informal comments	After receipt of the ISR/WO-ISA the applicant may file informal comments on the WO-ISA directly with the International Bureau of WIPO. These will be communicated to the designated Offices together with the IPRP (International Preliminary Report on Patentability) at 30 months from the priority date. Please also refer to the next box.
End of the international phase	At the end of the international phase the International Bureau of WIPO will transform the WO-ISA or, if a demand was filed, the written opinion of the IPEA into the IPRP, which will then be transmitted together with possible informal comments to the designated Offices. The IPRP replaces the former IPEA (international preliminary examination report).
Relevant PCT Rules and more information	Rule 43 PCT, Rule 43bis PCT, Rule 44 PCT, Rule 44bis PCT, PCT Newsletter 12/2003, OJ 11/2003, OJ 12/2003

Bitte beachten Sie, dass angeführte Nichtpatentliteratur (wie z. B. wissenschaftliche oder technische Dokumente) je nach geltendem Recht dem Urheberrechtsschutz und/oder anderen Schutzarten für schriftliche Werke unterliegen könnte. Die Vervielfältigung urheberrechtlich geschützter Texte, ihre Verwendung in anderen elektronischen oder gedruckten Publikationen und ihre Weitergabe an Dritte ist ohne ausdrückliche Zustimmung des Rechtsinhabers nicht gestattet.

Veuillez noter que les ouvrages de la littérature non-brevets qui sont cités, par exemple les documents scientifiques ou techniques, etc., peuvent être protégés par des droits d'auteur et/ou toute autre protection des écrits prévue par les législations applicables. Les textes ainsi protégés ne peuvent être reproduits ni utilisés dans d'autres publications électroniques ou imprimées, ni rediffusés sans l'autorisation expresse du titulaire du droit d'auteur.

Please be aware that cited works of non-patent literature such as scientific or technical documents or the like may be subject to copyright protection and/or any other protection of written works as appropriate based on applicable laws. Copyrighted texts may not be copied or used in other electronic or printed publications or re-distributed without the express permission of the copyright holder.

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

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
10 May 2007 (10.05.2007)

PCT

(10) International Publication Number
WO 2007/051811 A3

(51) International Patent Classification:
A61K 31/4184 (2006.01) A61P 3/10 (2006.01)
A61K 31/404 (2006.01)

(21) International Application Number:
PCT/EP2006/068017

(22) International Filing Date:
1 November 2006 (01.11.2006)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
05110226.7 1 November 2005 (01.11.2005) EP

(71) Applicant (for all designated States except US): NOVO
NORDISK A/S [DK/DK]; Novo Allé, DK-2880 Bagsværd
(DK).

(72) Inventors; and

(75) Inventors/Applicants (for US only): KILBURN, John,
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(DK). EBDROP, Søren [DK/DK]; Nymarksvej 11,
DK-4000 Roskilde (DK).

(74) Common Representative: NOVO NORDISK A/S; Cor-
porative Patents, Novo Allé, DK-2880 Bagsværd (DK).

(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, GI, GM, GT, HN, HR, HU, ID, IL, IN, IS,
JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS,
LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MY,
MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS,
RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN,
TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States (unless otherwise indicated, for every
kind of regional protection available): ARIPO (BW, GH,
GM, KE, 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, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT,
RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA,
GN, GQ, GW, ML, MR, NI, SN, TD, TG).

Published:

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

(88) Date of publication of the international search report:
24 January 2008

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: PHARMACEUTICAL USE OF SUBSTITUTED AMIDES

(57) Abstract: The use of substituted amides for modulating the activity of 11-hydroxysteroid dehydrogenase type 1 (11HSD1) and the use of these compounds as pharmaceutical compositions, are described. Also a novel class of substituted amides, their use in therapy, pharmaceutical compositions comprising the compounds, as well as their use in the manufacture of medicaments are described. The present compounds are modulators and more specifically inhibitors of the activity of 11HSD1 and may be useful in the treatment, prevention and/or prophylaxis of a range of medical disorders where a decreased intracellular concentration of active glucocorticoid is desirable.

WO 2007/051811 A3

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/068017

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61K31/4184 A61K31/404 A61P3/10

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)
A61K A61P

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

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)
EPO-Internal, WPI Data, PAJ, BIOSIS, EMBASE, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 2004/089470 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21) examples on, page 156-157	1-33
A	FOTSCH C ET AL: "11[beta]-Hydroxysteroid dehydrogenase-1 as a therapeutic target for metabolic diseases" EXPERT OPINION ON THERAPEUTIC PATENTS 2005 UNITED KINGDOM, vol. 15, no. 3, 2005, pages 289-303, XP002376609 ISSN: 1354-3776	

-/--

☒ 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
- *E* earlier document but published on or after the international filing date
- *I* document which may throw doubt on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

21 November 2007

Date of mailing of the international search report

30/11/2007

Name and mailing address of the ISA/

European Patent Office, P.O. 5318 Patentlaan 2
NL - 2200 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 05; epo nl,
Fax: (+31-70) 340-2016

Authorized officer

Friederich, Martin

INTERNATIONAL SEARCH REPORT

International application No
PCT/EP2006/068017

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2004/089471 A (NOVO NORDISK A/S; ANDERSEN, HENRIK, SUNE; KAMPEN, GITA, CAMILLA, TEJLG) 21 October 2004 (2004-10-21)	
A	WO 2004/089896 A (NOVO NORDISK A/S; GUNDERTOFT, ANETTE; JOERGENSEN, ANKER STEEN; KAMPEN) 21 October 2004 (2004-10-21)	

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP2006/068017

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

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

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- ☐ The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- ☐ No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.1

Although claims 30-33 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

Continuation of Box II.1

Claims Nos.: -

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

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

PCT/EP2006/068017

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 2004089470 A	21-10-2004	WO 2004089896 A1	21-10-2004
		EP 1618090 A1	25-01-2006
		EP 1615698 A2	18-01-2006
		JP 2006522746 T	05-10-2006
		JP 2006522748 T	05-10-2006
WO 2004089471 A	21-10-2004	EP 1615697 A2	18-01-2006
		JP 2006522749 T	05-10-2006
WO 2004089896 A	21-10-2004	WO 2004089470 A2	21-10-2004
		EP 1618090 A1	25-01-2006
		EP 1615698 A2	18-01-2006
		JP 2006522746 T	05-10-2006
		JP 2006522748 T	05-10-2006



No. 08-054219- -00000-0000

Fecha: 2008-05-28 16:17:08 Dep. 2020 NUECREACION
Ira. 11 PATENTEIYII Eje: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 309

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE
PCT

PATENTE DE INVENCION

MODELO DE UTILIDAD []

- ◆ Indicación de que se solicita la concesión de una patente.
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Descripción de la invención
- ◆ Dibujos de ser estos pertinentes
- ◆ Comprobante de pago de las tasas establecidas

COMPLETA []

INCOMPLETA []

DISEÑO INDUSTRIAL []

- ◆ Indicación de que se solicita el registro de Diseño Industrial
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Representación gráfica 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 un Esquema de Trazado
- ◆ Datos de identificación del solicitante o de la persona que presenta la solicitud
- ◆ Representación gráfica del esquema trazado
- ◆ Comprobante de pago de las tasas establecidas

COMPLETA []

INCOMPLETA []

Firma Responsable

Fecha

311

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Bogotá,
2020

Doctor(a)
OLARTE GARCIA CARLOS REINALDO
Apoderado(a) y/o Representante de
TRANSTECH PHARMA, INC

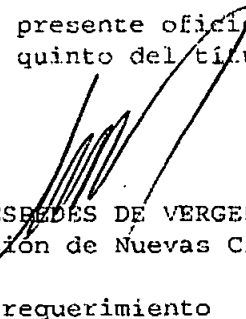
REFERENCIA	Radicación No.	8 54219
	Solicitud internacional	PCT/EP2006/068017
	Fecha inicio fase nacional	01/06/2008
	Trámite	11
	Evento	378
	Actuación	430
	Oficio No.	8125

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 CARMENZA CESEBEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

El anterior requerimiento fue notificado por fijación en lista de
fecha _____
adpall 20 JUN. 2008