



Industria y Comercio

SUPERINTENDENCIA

P. C. T.

Delegatura de propiedad Industrial

División de Nuevas Creaciones

04056454

SOLICITUD

PATENTE DE INVENCION

21 EXPEDIENTE No.

04056454

54

TÍTULO *Diceto piperacinas sustituidas como Antagonistas de Oxitocina*

51 CLASIFICACIÓN INTERNACIONAL

71

SOLICITANTE *Glaxo Group Limited*

DOMICILIO

*Glaxo Wellcome House, Berkeley Avenue,
Greenford, Middlesex UB6 0BB. OND Reino Unido*

74

APODERADO *Carlos R Olarte*

22

BOGOTÁ, D. C., *junio 17.-2004*

OLARTE RAISBECK


Industria y Comercio
 SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
 Radicación : 04036454 00000000 : Folios: 252
 Fecha (AMD): 2004-06-17 09:40:33
 Trámite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
 Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

SOLICITUD DE:

1



Patente de Invención.



Patente de Modelo de Utilidad.



Capítulo I.



Capítulo II.

2

**SOLICITANTE
 (71)**
Nombre: GLAXO GROUP LIMITED.Dirección: Glaxo Wellcome House, Berkeley
 Avenue, Greenford, Middlesex UB6 0NN GB.Nacionalidad o Domicilio: BRITANICALugar de Constitución: INGLATERRA
 AMERICA

Teléfono: _____ Fax: _____

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C.C. ☐ NIT ☐C.E. ☐ Otro ☐

Cual _____

Número _____

3

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Número 79.782.747 Btá
 TP 74.295

4

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PCT (86)Solicitud Internacional No. PCT/EP02/14823 Fecha Diciembre 20, 2002Publicación Internacional No. WO 03/053443 Fecha Julio 3, 2003

6

**Título (54) DICETOPIPERACINAS SUSTITUIDAS COMO ANTAGONISTAS DE
 OXITOCINA.**

7

Clasificación Internacional (51) A61K 31/495.

8

Prioridad

SI



NO



(33) País de Origen

GB

(32) Fecha

Diciembre 21, 2001

(31) Número de Solicitud

0130677.8

9

Comprobante de pago No. 46,365 Fecha Junio 9, 2004

10

ANEXOS

☒

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

☐

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

☒

Poderes, si fuere el caso.

☐

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

☐

Declaraciones.

☒

Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos).

☒

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

☒

Copia del examen preliminar Internacional efectuado por la Autoridad Internacional de Examen Preliminar (IPEA).

☐

Traducción del examen preliminar Internacional efectuado por la IPEA.

☐

De ser el caso, copia del contrato de acceso.

☐

De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.

☐

De ser el caso, certificado de depósito del material biológico.

☐

Arte final 12 x 12.

☐

De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.

☐

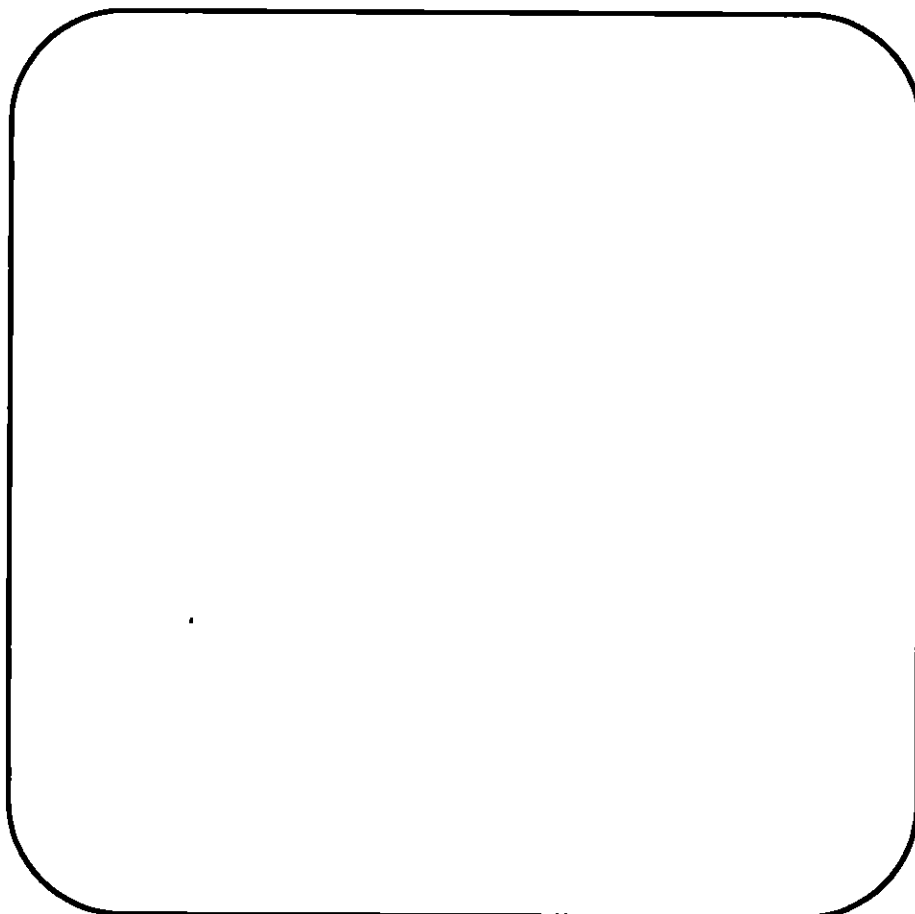
De ser el caso, modificaciones efectuadas a la solicitud Internacional.

☒

Otros. Búsqueda Internacional

11

FIGURA CARACTERÍSTICA:



12

Solicito la concesión de la patente,

NOMBRE: CARLOS R. OLARTE

FIRMA: [Signature]

C.C. 79.782.747 Btá T.P. 74.295

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5

NIT : 800176089-2

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04036454 00000000 Folios: 252
Fecha (REC): 2004-06-17 09:48:33
Tramite : 011 PCT-PATENT 379 FASE NAC: 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

RECIBO OFICIAL DE CAJA : 04 - 46,365
FECHA : JUNIO 9 DE 2004

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
LUZ MARINA BULLA	CONSIGNACION	BANCO POPULAR	030-00110-6	27514619	09/06/2004	6,461,000.00

***** CONCEPTO *****

CANT. CONTABILISTICO	CONCEPTO	TOTAL CONCEPTO
1 50005-01-01 SOLICITUDES	110 PTC SOLICITUD DE PATENTE DE INVEN	422,000.00
	TOTAL :	9 422,000.00

SON: CUATROCIENTOS VEINTIDOS MIL PESOS

RESPONSABLE : 

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

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

PODER DE REPRESENTACION

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

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

APOSTILLA

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

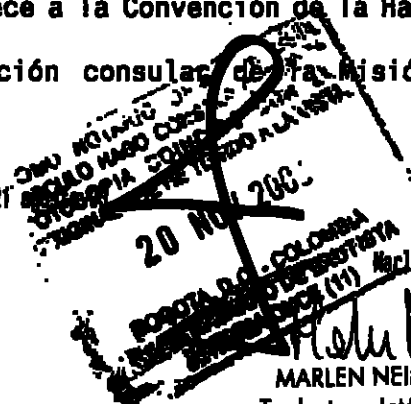
1. País: Reino Unido de Gran Bretaña e Irlanda del Norte
- Este documento Público
2. ha sido firmado por James Kerr Milligan
3. Quien ejerce funciones de Notario público
4. Lleva el sello del Notario público

CERTIFICADO

5. En Londres
6. El 14 agosto 2003
7. Por el Secretario de Estado Principal de su Majestad para Asuntos exteriores y de la Mancomunidad
8. No. G229474
9. Gran Sello de la Oficina de Asuntos exteriores y de la Mancomunidad
10. Firma legible de J. Garbrah- Por el Secretario de Estado

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

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



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

7

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

C E R T I F I C O:

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

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

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

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

[Handwritten signature]

JAMES KERR MILLIGAN
Notario Público de Londres, Inglaterra



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

UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND

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

This public document / Le présent acte public

2. Has been signed by **James Kerr Milligan**
a été signé par

3. Acting in the capacity of **Notary Public**
agissant en qualité de

4. Bears the seal/stamp of **The Said Notary Public**
est revêtu du sceau/timbre de

5. at London/à Londres
6. the/le **14 August 2003**

7. by Her Majesty's Principal Secretary of State for Foreign and Commonwealth Affairs /
par le Secrétaire d'Etat Principal de Sa Majesté aux Affaires Etrangères et du Commonwealth.

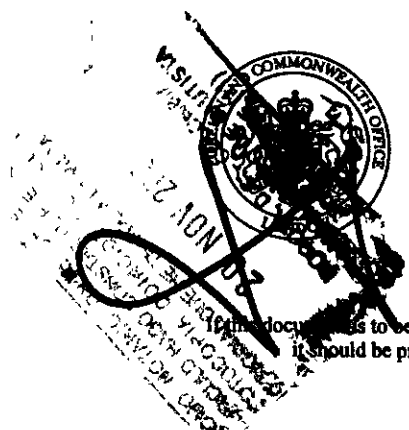
8. Number/sous No **G229474**

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



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

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



OLARTE RAISBECK

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Power of Attorney

The undersigned,

domiciled in

Glaxo Wellcome House, Berkeley Avenue, Greenford, Middlesex UB6 0NN, GB

by means of these presents hereby grants to **Carlos R. Olarte, J. Ian Raisbeck and Ana María Frieri** full and sufficient Power of Attorney to file, prosecute, obtain, defend and enforce any and all of the company's Patents, Utility Models and Industrial Designs in the Republic of Colombia, to which end it empowers them to take all steps necessary before any administrative or judicial authority of any class for the objects stated, to file petitions, appeals, replies and oppositions, pay taxes and annuities, request testimonies, receive documents and securities, abandon applications and collect refunds. Sufficient power is hereby granted to receive notifications on behalf of the Company, to confer powers on those who are to represent the company judicially and extrajudicially, to answer in court in the matter of all claims and demands that may be presented in connection with the objects stated, giving them likewise power to substitute these presents and revoke such substitutions.

Poder

El suscrito,

Glaxo Group Limited

domiciliado en

por medio del presente otorga a **Carlos R. Olarte, J. Ian Raisbeck y Ana María Frieri** poder especial, amplio y suficiente para

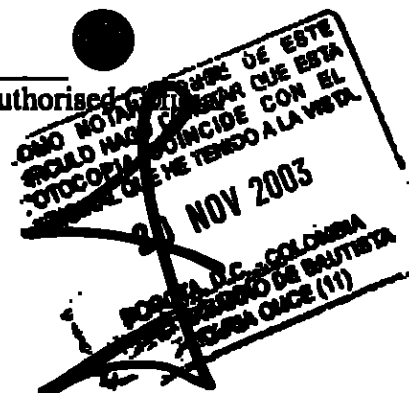
presentar, tramitar, obtener, defender y hacer respetar todas y cualquiera de Patentes, Modelos de Utilidad y Diseños Industriales de la compañía en la República de Colombia, a cuyo efecto los faculta para dar todos los pasos necesarios ante cualquier autoridad administrativa o judicial de cualquier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

Signature/Firma: _____

Peter John GIDDINGS as Attorney and Authorised _____

Date/Fecha: 13 August 2003

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



9

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(81) Designated States (national): AE, AG, AL, AM, AT, AU,
AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,
CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH,
GM, HR, HU, ID, IL, IN, IS, JP, KR, KG, KP, KZ, LC,
LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW,
MX, MZ, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE,
SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US,
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(84) Designated States (regional): ARIPO patent (GI, GM,
KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW),
Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),
European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE,
ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, SK,
TR), OAPI patent (BF, BI, CF, CG, CI, CM, GA, GN, GQ,
GW, ML, MR, NE, SN, TD, TG).

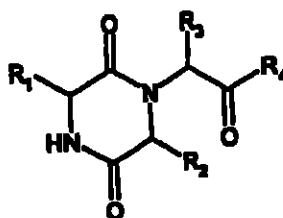
Published:

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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.

WO 03/053443 A1

(54) Title: SUBSTITUTED DIKETOPIPERAZINES AS OXYTOCIN ANTAGONISTS



(I)

(57) Abstract: A method of treating or preventing diseases or conditions
mediated through the action of oxytocin which comprises administering to
a mammal in need thereof of an effective amount of a compound of the for-
mula (I) and/or a physiologically acceptable derivative thereof, wherein the
substituents have the meaning given in the description. Disclosed are also
novel compounds of formula (I) and processes for their preparation.

SUBSTITUTED DIKETOPIPERAZINES AS OXYTOCIN ANTAGONISTS

5 This invention relates to the use of a class of diketopiperazine derivatives as potent and selective antagonists of oxytocin, to novel compounds within that class and to processes for their preparation.

10 USP5817751 describes combinatorial and solid phase methods for the synthesis of diverse diketopiperazine derivatives and the use of these methods to create libraries of diverse diketopiperazine derivatives.

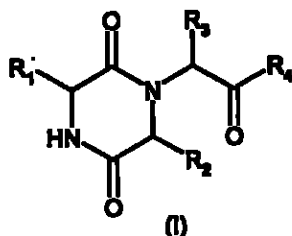
WO99/47549 describes diketopiperazine derivatives including 3-benzyl-2,5 diketopiperazine derivatives as inhibitors of fructose 1,6-bisphosphate (FBPase).
15 WO99/38844 describes a method for preparing N-[aliphatic or aromatic) carbonyl]-2-aminoacetamide compounds and their cyclisation to give inter alia diketopiperazine derivatives.

WO99/37304 describes oxaheterocyclyl compounds including oxapiperazinyll compounds that are inhibitors of Factor Xa.

20 The hormone oxytocin is potent contractor of the uterus and is used for the induction or augmentation of labour. Also the density of uterine oxytocin receptors increases significantly by >100 fold during pregnancy and peaks in labour (pre-term and term). Pre-term births/labour (between 24 and 37 weeks) causes about 60% of infant
25 mortality/morbidity and thus a compound which inhibits the uterine actions of oxytocin e.g. oxytocin antagonists, should be useful for the prevention or control of pre-term labour.

30 We have found a class of diketopiperazine derivatives which exhibit a particularly useful level of activity as selective antagonists at the oxytocin receptor.

The present invention thus a method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in
35 need thereof of an effective amount of a compound of the formula (I)



and/or a physiologically acceptable derivative thereof, wherein:

R₁ represents aryl (C₁₋₄) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;

- 5 R₂ represents C₁₋₆alkyl (optionally substituted by a C₁₋₃alkoxy, C₁₋₂alkithio, di(C₁₋₃alkyl) amino or a C₃₋₆ cycloalkyl group) or C₃₋₆cycloalkyl, or 5-6 membered heterocyclic group containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;

- 10 R₃ represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene;

R₄ represents OH or OC₁₋₄ alkyl (optionally substituted with C₁₋₄alkylcarbonyloxy) or NR₅R₆;

- 15 R₅ represents hydrogen, C₁₋₆alkyl (optionally substituted with C₁₋₄alkoxy) or C₃₋₇cycloalkyl;

R₆ represents hydrogen, C₁₋₄alkoxy, C₃₋₇cycloalkyl, C₁₋₄alkyl [optionally substituted with one or more groups selected from, carboxyl, C₁₋₄alkylsulphonyl, or C₁₋₄alkoxycarbonyl], C₂₋₄alkyl [optionally substituted with one or more groups selected from halogen, hydroxy,

- 20 C₁₋₄alkoxy or NR₇R₈ wherein R₇ and R₈ independently represent hydrogen or C₁₋₄alkyl or together with the nitrogen atom to which they are attached to form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from

- 25 C₁₋₃alkyl, hydroxy, C₁₋₃alkoxy (optionally substituted by C₃₋₆cycloalkyl or optionally substituted phenyl), C₃₋₆cycloalkyl or NR₉R₁₀ wherein R₉ and R₁₀ each independently represent a group selected from C₁₋₃alkyl (optionally substituted by C₃₋₆cycloalkyl or optionally substituted phenyl) or C₃₋₆cycloalkyl)] or R₆ represents a phenyl or benzyl

- group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C₃₋₇cycloalkyl or

- 30 the group CH₂CONR₉R₁₀ wherein R₉ represents hydrogen or C₁₋₄alkyl, R₁₀ represents hydrogen, C₁₋₄alkyl optionally substituted by a 5 or 6 membered heteroaryl group or R₉, R₁₀ and the nitrogen atom to which they are attached together form a 5 or 6 membered

- 35 saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a C₁₋₄alkyl or C₁₋₄alkanoyl group; or R₅ and R₆ together with the nitrogen atom to which they are attached form a 3 to 7

- membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g. SO₂ and the additional nitrogen atom either carries a

- 40 hydrogen atom or a C₁₋₄alkyl or a C₁₋₄alkanoyl group or a C₁₋₄alkylsulphonyl group or a C₁₋₃alkoxyC₂₋₄alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from C₁₋₃alkyl, hydroxy, oxo, C₃₋₆cycloalkyl or NR₉R₁₀]

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wherein R₆ and R₇ each independently represent a group selected from C₁₋₃alkyl (optionally substituted by C₃₋₆cycloalkyl or optionally substituted phenyl) or C₃₋₆cycloalkyl].

- 5 The invention also provides novel compounds of formula (I). A particularly useful class of novel compounds of formula (I) are those wherein R₁ is 2-indanyl optionally substituted by hydroxyl and more particularly a 2-indanyl group and R₂, R₃ and R₄ have the meanings defined above and/or physiologically acceptable derivatives thereof. A further useful class of novel compounds of formula (I) are those wherein R₁ is a 2-phenethyl and R₂, R₃ and R₄ have the meanings defined above and/or physiologically acceptable derivatives thereof.

- 15 The compounds of formula (I) contain at least three centers of asymmetry, namely the carbon atoms carrying the substituents R₁, R₂ and R₃ respectively and it is to be understood that formula (I) includes all possible stereoisomers and mixtures thereof. The substituent R₃ may exist in more than one tautomeric form and it is to be all understood that formula (I) includes all possible tautomeric forms and mixtures thereof.

- 20 The compounds of formula (I) wherein at least one of the groups R₁, R₂, R₃ or R₄ contains a basic or acidic grouping may form salts with physiologically acceptable acids or bases and reference to compounds of formula (I) herein includes such salts.

- 25 As used herein, the terms "physiologically acceptable derivative" or "pharmaceutically acceptable derivative", mean any pharmaceutically acceptable salt, solvate, or prodrug e.g. ester or carbamate, or salt or solvate of such a prodrug, of a compound of formula (I), which upon administration to the recipient is capable of providing (directly or indirectly) a compound of formula (I), or an active metabolite or residue thereof. Preferred pharmaceutically acceptable derivatives are salts and solvates.

- 30 As used herein, the term "prodrug" means a compound which is converted within the body, e.g. by hydrolysis in the blood, into its active form that has medical effects. Pharmaceutically acceptable prodrugs are described in T. Higuchi and V. Stella, Prodrugs as Novel Delivery Systems, Vol. 14 of the A.C.S. Symposium Series, and in Edward B. Roche, ed., Bioreversible Carriers in Drug Design, American Pharmaceutical Association and Pergamon Press, 1987, both of which are incorporated herein by reference. Esters may be active in their own right and /or be hydrolysable under *in vivo* conditions in the human body. Suitable pharmaceutically acceptable *in vivo* hydrolysable ester groups include those which break down readily in the human body to leave the parent acid or its salt. Examples of such esters include alkyl and 1-(acetoxy)ethyl esters.

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The term alkyl as a group or part of a group refers to a straight or branched alkyl group e.g. methyl, ethyl, propyl, isopropyl, n-butyl, 1-methylpropyl, 2-methylpropyl, t-butyl, pentyl or hexyl.

- 5 The term C₃₋₆ cycloalkyl as a group or part of a group includes cyclopropyl, cyclobutyl, cyclopentyl and cyclohexyl groups. The term C₃₋₇cycloalkyl also includes cycloheptyl.

The term halogen refers to fluorine, chlorine, bromine or iodine.

- 10 Unless otherwise specified the term optionally substituted phenyl refers to a phenyl group which may be substituted by 1 to 3 substituents which may be the same or different and selected from halogen, hydroxy, C₁₋₄alkyl (optionally substituted by 1-3 halogen atoms or NR_aR_b [wherein R_a is hydrogen or C₁₋₄ alkyl, R_b is hydrogen, C₁₋₄ alkyl, or R_a and R_b together with the nitrogen atom to which they are attached to form a 5 to 7 membered
- 15 ring, which ring is saturated and may contain an additional heteroatom selected from nitrogen, oxygen or sulphur]), C₁₋₄ alkylsulphonyl, carboxyl, C₁₋₄ alkoxy, carbonyl, di(C₁₋₄alkyl)aminocarbonyloxy, C₁₋₄alkoxy (optionally substituted by 1-3 halogen atoms, amino, C₁₋₄ alkylamino or di-(C₁₋₄alkyl) amino), phenyl (optionally substituted by halogen or alkylaminosulphonyl), C₁₋₄alkoxy, NR_aR_b [wherein R_a is hydrogen or C₁₋₄ alkyl, R_b is hydrogen, C₁₋₄ alkyl, C₁₋₄ alkanoyl or C₁₋₄ alkylsulphonyl or R_a and R_b together with the nitrogen atom to which they are attached to form a 5 to 7 membered
- 20 ring, which ring is saturated and may be substituted by hydroxyl or 1 or 2 C₁₋₄alkyl groups or may be spiro-fused to a dioxalane ring or may contain an additional heteroatom selected from nitrogen, oxygen or sulphur and may be substituted by 1 or 2 C₁₋₄alkyl groups, or which ring is unsaturated and contains 1-3 additional nitrogen atoms], a 5 or 6 membered heteroaryl group, an optionally N-substituted aminocarbonyl or aminosulphonyl group (wherein the substituents may be 1 or 2 C₁₋₄ alkyl groups) or a dihydroxyboryl group).
- 25 The term 5 membered heteroaryl refers to a 5 membered ring which contains a heteroatom selected from oxygen, sulphur or nitrogen and which may also contain from 1 to 3 additional nitrogen atoms and which groups may be substituted by 1 or more groups selected from halogen, trifluoromethyl, C₁₋₄ alkyl, cycloalkyl, heteroaryl, saturated heterocyclic, or phenyl groups. Examples of such 5 membered heteroaryl groups include
- 30 furanyl, thienyl, pyrrolyl, oxazolyl, isoxazolyl, thiazolyl, imidazolyl, pyrazolyl, oxadiazolyl, thiadiazolyl, triazolyl or tetrazolyl and these heterocycles may be substituted as described above.
- 35 The term 6-membered heteroaryl group refers to a 6-membered unsaturated ring which contains from 1 to 3 nitrogen atoms and which may be substituted by 1 to 3 C₁₋₄ alkyl groups, or trifluoromethyl, or alkoxy groups. Examples of such groups include pyridyl, methylpyridyl, trifluoromethylpyridyl, pyrimidinyl and triazinyl.
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When R_3 is a 5 or 6 membered heteroaryl group this is linked to the rest of the molecule via a carbon atom in the ring.

- 5 When R_3 is a fused bicyclic carbocyclic ring system this may be for example a naphthyl, tetrahydronaphthyl, indanyl or indenyl group.

- 10 When R_3 is a fused bicyclic system containing up to 3 heteroatoms which may be the same or different, this is conveniently a 6,5 or 6,6 ring system wherein the heterocycle may be partially saturated or together with the benzene ring to which it is fused to form a heteroaryl group and the heterocycle may be substituted by 1 or 2 groups selected from C_{1-4} alkyl or halogen or haloalkyl and or may contain a carbonyl group. The said R_3 group may be linked to the rest of the molecule via a carbon atom in the benzene ring or a carbon atom in the heterocyclic group.

- 15 When R_3 is a fused 6,6 heteroaryl group the hetero ring contains from 1 to 3 nitrogen atoms and examples of such heteroaryl groups include quinoliny, isoquinoliny, phthalaziny, cinnoliny, quinazoliny, quinoxaliny, 1,2,3 benzotriazinyl or 1,2,4 benzotriazinyl.

- 20 When R_3 is a 6,5 bicyclic heteroaryl group the 5 membered heterocycle contains a hetero atom selected from O, S or N and may in addition also contain a further 1 or 2 nitrogen atoms and the heterocyclic ring may also be substituted by 1 or 2 C_{1-4} alkyl or halogen or haloalkyl and or may contain a carbonyl group. Examples of such 6, 5 bicyclic heteroaryl groups include benzofuranyl, benzothienyl, indolyl, benzo-oxadiazolyl, 25 benzothiadiazolyl, benzo-oxazolyl, benzothiazolyl, benzoisothiazolyl, benzoisoxazolyl, benzimidazolyl, indazolyl or benzotriazolyl and these groups may be substituted as described above.

- 30 When R_3 is a 6,6 or 6,5 bicyclic heterocyclic group and the heterocycle is partially saturated, this may contain 1 or 2 heteroatoms selected from O, S or N. Examples of such groups include indoliny, isoindoliny, dihydrobenzofuranyl, dihydrobenzothienyl, 1,3-benzodioxolyl, benzopyrrolyl, 1,3-benzodithiolyl, 1,4-benzodioxanyl, phthalyl, thiophthalyl, chromanyl or chromenyl and the groups may be substituted by one or more 35 halogen or C_{1-4} alkyl groups, haloalkyl, or may contain a carbonyl group.

- When R_3 is a fused bicyclic heteroaryl linked via the benzene ring therein then suitable examples of such a group include 6-quinoliny, 4-isoindoliny, 4-(N-methyl-isoindoliny, benzimidazolyl, benzothiazolyl, benzofuranyl, benzothienyl, benzimidazolyl 40 benzoxazolyl, 2 methyl-benzo-oxazolyl, benzothiadiazolyl, benzotriazolyl and 1-methyl benzotriazolyl.

When R_3 is a fused bicyclic heteroaryl group linked via the heteroaryl ring this may be for example a 2-benzofuranyl, 2-benzothienyl or 2-N-methylindolyl group.

When R_3 is a 6,6 or 6,5 heterocyclic group wherein the heterocycle is partially saturated this is conveniently linked via the benzene ring therein and suitable examples include
 5 dihydrobenzofuran, dihydrobenzopyrrole, 1,3-benzodioxolyl, 2,2-difluoro-1,3-benzodioxolyl, and 1,4-benzodioxanyl.

When R_3 is a substituted phenyl group the said group conveniently carries from 1 to 3
 10 substituents which may be the same or different selected from fluorine, chlorine, bromine C_{1-3} alkyl(methyl), C_{1-3} haloalkyl (trifluoromethyl), C_{1-3} alkoxy (methoxy, ethoxy), haloalkoxy (trifluoromethoxy), aminoethoxy e.g. dimethylaminoethoxy, C_{1-3} alkoxycarbonyl, carboxy, hydroxy, phenyl or phenyl (substituted by halogen or alkylaminosulphonyl), NR_4R_5 [wherein R_4 is hydrogen or C_{1-3} alkyl and R_5 is C_{1-3} alkyl, C_{1-4} alkanoyl, C_{1-4} alkylsulphonyl, C_{1-3} alkylaminocarbonyl] or NR_4R_5 represents a
 15 pyrrolidino or piperidino ring, which ring may be substituted by a C_{1-3} alkyl, hydroxyl or a 2,2-1,3-dioxolane group or NR_4R_5 represents a morpholino or a piperazino group which groups may be substituted by 1 or 2 C_{1-3} alkyl groups or NR_4R_5 represents a 5 or 6 membered heteroaryl group containing from 1 to 4 nitrogen atoms (such as a 1-imidazolyl, 1,2-pyrazolyl, 1,2,3-triazolyl or 1,2,4-triazolyl substituent), C_{1-3} alkylsulphonyl, C_{1-3} alkylaminocarbonyl, C_{1-3} alkylaminosulphonyl, dihydroxyboryl or a
 20 5 or 6 membered atom heteroaryl group containing from 1 to 4 nitrogen atoms and which is linked to the phenyl group via a carbon atom in the heteroaryl group (for example pyridyl, pyrazolyl, imidazolyl or tetrazol-5-yl, which heteroaryl groups may be substituted by 1 or more C_{1-4} alkyl groups.

25 Examples of suitable R_3 groups wherein R_3 is optionally substituted phenyl include phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2-fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butylloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4-aminocarbonylphenyl, 4-methylaminosulphonylphenyl,
 40 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridyl)phenyl, 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-

(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, 4-(1-3,5-di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4-t-butylthiazolyl)phenyl, 4-(5-2-t-butyltetrazolyl)phenyl, 4-(4-spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl or 3-(dihydroxyboryl)phenyl.

When R₃ is a 5 or 6 membered heteroaryl group suitable examples of such groups include 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-fluoro-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 2,3-dimethyl-5-thienyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-hydroxy-3-pyridyl, 6-methoxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, 4-oxazolyl, 4-thiazolyl, 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 4-isoxazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2-(4-morpholino)-5-thiazolyl or 2-(4-methyl-1-piperazino)-5-thiazolyl.

When R₃ is an optionally substituted fused bicyclic ring system examples of suitable groups include 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-indol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

When the group R₁ is a 5-7 membered cycloalkyl group which is fused to an optionally substituted benzene ring the optional substituents may be from 1 to 3 groups which may be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

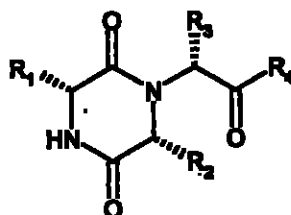
When the group R_1 is aralkyl the aryl moiety is phenyl optionally substituted by 1 to 3 groups which may be the same or different and selected from halogen, alkyl, alkoxy, hydroxy, trifluoromethyl, nitro, carboxyl, alkoxycarbonyl or carboxamido.

- 5 Examples of suitable R_1 groups include phenethyl or indanyl optionally substituted by hydroxyl e.g. 2-indanyl, 1-hydroxy-2-indanyl, 5-hydroxy-2-indanyl. Examples of suitable R_2 groups include C_{3-4} alkyl e.g. isopropyl, 1-methylpropyl or 2-methylpropyl, C_{3-6} cycloalkyl e.g. cyclopentyl.
- 10 Conveniently R_4 is hydroxy, C_{1-4} alkoxy e.g. methoxy, propoxy, t-butoxy, 1-acetyloxyethoxy or NR_5R_6 .

A preferred class of compounds of formula (I) are those wherein R_4 represents hydroxy or the group NR_5R_6 or more preferably NR_5R_6 .

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A further preferred class of compounds is represented by formula (1a)



(1a)

wherein the groups R_1 , R_2 , R_3 and R_4 have the meanings defined for formula (I)

- 20 Conveniently R_1 is a group selected from 2-phenethyl or 2-indanyl optionally substituted by hydroxyl and more particularly 2-indanyl. Conveniently R_2 is a group selected from isopropyl, 1-methylpropyl, 2-methylpropyl or cyclopentyl and more preferably R_2 is a group selected from 1-methylpropyl, or 2-methylpropyl.
- 25 Conveniently R_3 is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2-fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4-methoxyphenyl, 2-fluoro-4-hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butyloxycarbonylmethyloxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphenyl, 3-chloro-4-trifluoromethoxyphenyl, 2,3-difluoro-4-methylphenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-
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- methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4-aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, 4-(1-3,5-di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4-t-butylthiazolyl)phenyl, 4-(5-2-t-butyltetrazolyl)phenyl, 4-(4-spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-indol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.
- Conveniently the group R_5 is hydrogen, C_{1-4} alkyl e.g. methyl or C_{1-4} alkoxy C_{2-4} alkyl e.g. 2-methoxyethyl and R_6 is a group selected from hydrogen, C_{1-4} alkoxy e.g. methoxy, C_{1-4} alkyl e.g. methyl, n-propyl, isopropyl or t-butyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C_{1-4} alkyl substituted by alkoxycarbonyl or carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g. methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzoyloxyphenyl, dimethoxybenzyl, optionally substituted heteroarylmethyl e.g. 2-pyridylmethyl, 3-

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pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl e.g. 2-1,3-thiazolyl, alkyl substituted by NR_7R_8 [wherein NR_7R_8 form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino, N-methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

10 A preferred class of compounds of the invention are those of formula (1a) wherein R_1 is 2-indanyl, R_2 is a group selected from 1-methylpropyl or 2-methylpropyl and R_4 is hydroxy and/or more particularly the group NR_5R_6 .

15 A further preferred class of compounds of the invention are those of formula (1a) wherein R_3 is a group selected from hydrogen, C_{1-4} alkyl e.g. methyl or C_{1-4} alkoxy C_{2-4} alkyl e.g. 2-methoxyethyl and R_6 is a group selected from hydrogen, C_{1-4} alkoxy e.g. methoxy, C_{1-4} alkyl e.g. methyl, n-propyl, isopropyl or t-butyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms e.g. 2,2,2-trifluoroethyl or 2-fluoroethyl, C_{1-4} alkyl substituted by alkoxycarbonyl or carboxyl e.g. methoxycarbonylmethyl or carboxymethyl, alkyl substituted by alkoxy e.g. methoxyethyl, 2,2-dimethoxyethyl, alkyl substituted by hydroxy e.g. hydroxyethyl or alkyl substituted by dialkylamino e.g. dimethylaminoethyl, 2-benzyloxyphenyl, dimethoxybenzyl, optionally substituted heteroaryl methyl e.g. 2-pyridylmethyl, 3-pyridylmethyl, 4-pyridylmethyl, 3-methylimidazolylmethyl, heteroaryl such as thiazolyl e.g. 2-1,3-thiazolyl, alkyl substituted by NR_7R_8 [wherein NR_7R_8 form a 6-membered heterocyclic ring (e.g. piperidinoethyl or morpholinoethyl)], cycloalkyl e.g. cyclopropyl or cyclohexyl, or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring e.g. N-methylpiperazino, N-methanesulphonylpiperazino, N-2-methoxyethylpiperazino, thiomorpholino or the sulphoxide or sulphone thereof.

A yet further preferred class of compounds of the invention are those of formula (1a) wherein R_3 is a group selected from phenyl, halophenyl such as 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl 2,3,4-trifluorophenyl 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethyloxyphenyl, 3-fluoro-4-t-butylloxycarbonylmethyloxyphenyl, 3-fluoro-4-

- dimethylaminocarbonyloxyphenyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4-aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5-2-t-butyltetrazolyl)phenyl, 4-(4 spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-indol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

Particular preferred compounds of the invention include:

- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

- (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-morpholinamide
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- 5 (2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-
- 10 (4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
 (2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- 15 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-
- 20 1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
 (3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- 25 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-
- 30 dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- 35 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
 (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
 methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-
- 40 dioxopiperazin-1-yl]ethanoate
 propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

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- 1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- 5 (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione.
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione.
- 10 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.
- 15 (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide.
- 20 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione.
- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
- 25 (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
- (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- 30 (2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- 35 (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.
- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide.
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(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione.

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide.

5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide.

(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione.

10 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide.

(2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.

15 The ability of the compounds of formula (I) to inhibit the actions of oxytocin may be determined using a variety of conventional procedures.

20 Thus, compounds of formula (I) have a high affinity for the oxytocin receptors on the uterus of rats and humans and this may be determined using conventional procedure. For example the affinity for the oxytocin receptors on the rat uterus may be determined by the procedure of Pettibone et al, Drug Development Research 30, 129-142 (1993). The compounds of the invention also exhibit high affinity at the human recombinant oxytocin receptor in CHO cells and this may be conveniently demonstrated using the procedure described by Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p1301-1305.

25 The compounds of the invention are therefore useful in the treatment or prevention of diseases and/or conditions mediated through the action of oxytocin. Examples of such diseases and/or conditions include pre-term labour, dysmenorrhea and endometriosis.

30 The compounds may also be useful to delay labour prior to elective caesarean section or transfer of the patient to a tertiary care centre. The compounds of the invention may also be useful for improving fertility rates in animals, e.g. farm animals.

35 The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salts for use in therapy and in particular use as medicine for antagonising the effects of oxytocin upon the oxytocin receptor.

40 The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt thereof for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

24

According to a further aspect, the invention also provides for a method for antagonising the effects of oxytocin upon the oxytocin receptor, comprising administering to a patient in need thereof an antagonistic amount of a compound of formula (I) and/or a physiologically acceptable salt thereof.

5

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylactics as well as the treatment of established diseases or symptoms.

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It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.

15

Thus for parenteral administration a daily dose will typically be in the range 2 to 50mg, preferably 5 to 25mg per day. For oral administration a daily dose will typically be within the range 10 to 800mg, e.g. 20 to 150 mg per day.

20

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

25

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

30

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or non-toxic metabolically labile esters thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

35

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant or rectal administration.

40

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, acacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for

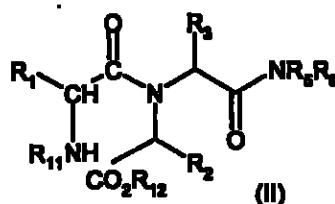
example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or ethyl alcohol; solubilizers such as surfactants for example polysorbates or other agents such as cyclodextrins; and preservatives, for example, methyl or propyl p-hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

The compositions according to the invention may contain between 0.1-99% of the active ingredient, conveniently from 30-95% for tablets and capsules and 3-50% for liquid preparations.

Compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by cyclisation of the compound of formula (II)



26-

wherein R_1 , R_2 and R_3 have the meanings defined in formula (I) R_{11} is hydrogen and R_{12} is a C_{1-3} alkyl group(e.g. methyl) in a suitable solvent such as an alkanol e.g. methanol and/or 2,2,2-trifluoroethanol, dioxan or a mixture thereof or a halohydrocarbon e.g. dichloromethane.

5

The compound of formula (II) wherein R_{11} is hydrogen is conveniently prepared in-situ by treating a compound of formula (II) wherein R_{11} is an acid labile nitrogen protecting group and R_{12} is hydrogen or C_{1-3} alkyl, with an acid in a suitable solvent followed by treatment with a hydrohalic acid and methanol if R_{12} in the starting material is hydrogen, and then addition of a suitable base e.g. triethylamine or by treating a compound of

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formula (II) wherein R_{11} is an hydrogenolysable nitrogen protecting group and R_{12} is C_{1-3} alkyl in a suitable solvent such as methanol or 2,2,2-trifluoroethanol with hydrogen in the presence of a suitable catalyst e.g. palladium on carbon.

15

Examples of suitable nitrogen protecting groups R_{11} include alkoxycarbonyl e.g. t-butyloxycarbonyl or an optionally substituted benzyloxycarbonyl group.

When R_{12} is C_{1-3} alkyl this is conveniently ethyl or more particularly methyl.

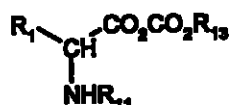
Examples of a suitable acids include mineral acids such as hydrohalic acids e.g.

hydrochloric acid or organic acids such as trifluoroacetic acid. The reaction is

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conveniently carried out in a solvent such as 1,4-dioxan or an alkanol e.g. methanol or a mixture thereof, or halohydrocarbon e.g. dichloromethane.

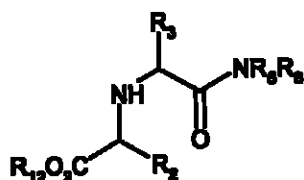
The compounds of formula (II) may be prepared by reaction of the mixed anhydride (III)



(III)

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wherein R_1 and R_{11} have the meanings defined above and wherein R_{13} is a C_{1-6} straight or branched chain alkyl, optionally substituted phenyl or benzyl group, with the amine (IV)

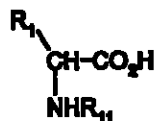


(IV)

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wherein R_2 , R_3 , R_4 and R_5 have the meanings defined above, and R_{12} is hydrogen.

The reaction is preferably carried out in an aprotic solvent such as an ether e.g. tetrahydrofuran or a tertiary amide such as N, N-dimethylformamide or a mixture thereof. The compounds of formula (III) may be prepared by treating the N-protected amino acid (V)



(V)

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wherein R_1 and R_{11} have the meanings defined above with the corresponding haloformate (VI; $R_{13}CO_2X$ wherein R_{13} has the meaning defined in formula (III) and X is halogen e.g. chlorine, or bromine) in the presence of a suitable tertiary organic amine e.g. N-methylmorpholine and in an aprotic solvent e.g. an ether such as tetrahydrofuran or a hydrocarbon e.g. toluene.

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The amine (IV) wherein R_5 is hydrogen may be prepared treating the amino acid (VII)



(VII)

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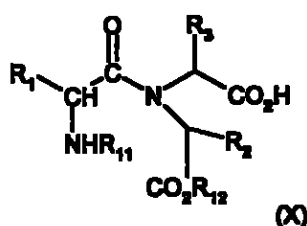
wherein R_2 has the meanings defined above and R_{12} is hydrogen with the aldehyde (VIII; R_3CHO wherein R_3 has the meaning defined in formula (I)) in a suitable solvent such as an alcohol e.g. methanol followed by reaction with the isonitrile (IX; $R_6N=C$ wherein R_6 has the meanings defined in formula I other than hydrogen). Alternatively, the compounds of formula (II) wherein R_1 , R_2 and R_3 have the meanings given in formula (I) and R_{11} is a nitrogen protecting group and R_{13} is a carboxyl protecting group may be prepared by reacting the amino acid derivative (VII) wherein R_2 has the meaning given in formula (I) and R_{12} is a carboxyl protecting group with the aldehyde (VIII) wherein R_3 has the meaning given in formula (I) in a solvent such as an alcohol e.g. methanol or 2,2,2-trifluoroethanol followed by the sequential addition of the amino acid (V) wherein R_1 has the meanings given in formula (I) and R_{11} is a carboxyl protecting group and the isonitrile (IX) wherein R_6 has the meanings given in formula (I).

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Compounds of formula (II) wherein R_{12} is a C_{1-3} alkyl group may also be prepared by reacting the carboxylic acid (X) or an activated derivative thereof

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wherein R_1 , R_2 , R_3 and R_{11} have the meanings defined above and R_{12} is a C_{1-3} alkyl group, with the amine NHR_5R_6 wherein R_5 and R_6 have the meanings defined in formula (I).

- 5 Examples of a suitable activated derivative of the carboxylic acid (X) include those commonly used in peptide synthesis e.g. that derived from reaction of benzotriazol-1-yloxytri-pyrrolidinophosphonium hexafluorophosphate in the presence of a suitable amine such as diisopropylethylamine.
- 10 The carboxylic acid (X) may be prepared from the corresponding compound of formula (II) wherein R_3 represents hydrogen and R_6 represents the 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with aqueous acetone.
- 15 Compounds of formula (I) wherein R_6 represents 2-hydroxyphenyl are conveniently prepared by catalytic hydrogenolysis (e.g. Pd/H_2) of the corresponding compound wherein R_6 is a 2-benzyloxyphenyl group.
- 20 In a further aspect of the invention compounds of formula (I) as defined above may be converted into other compounds of formula (I). Thus compounds of formula (I) wherein R_4 is hydroxyl may be prepared from a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen R_6 is 2-hydroxyphenyl by reaction with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent
- 25 reaction of the product thus formed with aqueous acetone.

Compounds of formula (I) wherein R_5 is hydrogen and R_6 is 2-hydroxyphenyl may be from the corresponding compound of formula (I) wherein R_6 is a 2-benzyloxyphenyl group by hydrogenolysis using hydrogen and a palladium catalyst.

- 30 Compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by reaction of the compound of formula (I) wherein R_4 is hydroxyl or an activated derivative thereof with the amino NHR_5R_6 wherein R_5 and R_6 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine
- 35 such as NHR_5R_6 .

- Thus the amides may be prepared by treating the compound of formula (I) wherein R_4 is hydroxyl with an activating agent such as BOP (benzotriazol-1-yloxy-tris(dimethylamino)phosphonium hexafluorophosphate), TBTU (2-(1H-benzotriazol-1-yl)-1,1,3,3-tetramethyluronium tetrafluoroborate), BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride) or oxalyl chloride in an aprotic solvent such as dichloromethane optionally in the presence of a tertiary amine such as triethylamine and subsequent reaction of the product thus formed with the amine NHR_5R_6 .
- Alternatively compounds of formula (I) wherein R_4 is the group NR_5R_6 may be prepared by reacting a compound of formula (I) wherein R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent such as dichloromethane and subsequent reaction of the product thus formed with the amine NHR_5R_6 .
- Compounds of formula (I) wherein R_4 is OC_{1-4} alkyl (optionally substituted with C_{1-4} alkylcarbonyloxy) may be prepared by reacting the corresponding carboxylic acid (R_4 is OH) or an activated derivative thereof with the appropriate alcohol (R_4OH) or alkyl halide (R_4 halide) under standard conditions for preparing such esters. Suitable activated derivatives include the acid halides, mixed anhydrides, those formed with coupling reagents commonly used in peptide synthesis e.g. carbonyldiimidazole and base salts of the acid e.g. alkali metal salts.
- Compounds of formula (IV) may be converted into other compounds of formula (IV) using standard procedures. Thus compound of formula (IV) wherein R_5 is hydrogen and R_6 is 2-benzyloxyphenyl may be converted into other compounds of formula (IV) wherein R_5 and R_6 have other meanings as defined in formula (I) using the same procedures as described above for carrying out analogous reactions on compounds of formula (I).
- Compounds of formula (I) wherein the stereochemistry of any of the substituents R_1 , R_2 and R_3 is as shown in formula (1a) may be prepared starting from the corresponding single isomers of the intermediates (III), (IV) and (VII) and/or the various isomeric mixtures may be separated by conventional procedures.
- The intermediates (V), (VI), (VII), (VIII) and (IX) are either known compounds may be prepared by analogous methods to those known for preparing structurally related compounds.
- Compounds of formula group (I) wherein R_4 is OH may be prepared by cyclisation of a corresponding compound of formula (II) under the conditions described above for preparing compounds of formula (I).

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Physiologically acceptable salts of a compound of formula (I) wherein R_4 is OH or one of the groups R_1 , R_2 , R_3 or NR_4R_5 has a basic or acidic centre may be prepared by treating the said base or acid with the required physiologically acceptable acid or base and this reaction is conveniently carried out in a solvent for the said compound of formula (I).

- 5 Physiologically acceptable derivatives of a compound of formula (I) may be prepared from the appropriate intermediate corresponding to formula (II) using the process described above for preparing compounds of formula (I) or directly from the compounds of formula (I) by conventional procedures for preparing such derivatives. Thus metabolically labile esters may be prepared by esterification of the free carboxyl or
- 10 hydroxyl group using standard esterification techniques.

The following examples are illustrative, but not limiting of the embodiments of the present invention.

15 General purification and analytical methods

- Analytical HPLC was conducted on a Supelcosil LCABZ+PLUS column (3.3 cm x 4.6 mm ID), eluting with 0.1% HCO_2H and 0.01 M ammonium acetate in water (solvent A), and 0.05% HCO_2H 5% water in acetonitrile (solvent B), using the following elution gradient 0-0.7 minutes 0%B, 0.7-4.2 minutes 0%-100%B, 4.2-5.3 minutes 100%B, 5.3-5.5 minutes 0%B at a flow rate of 3 ml/minute. The mass spectra (MS) were recorded on a Fisons VG Platform spectrometer using electrospray positive [(ES+ve to give MH^+ and $M(NH_4)^+$ molecular ions] or electrospray negative [(ES-ve to give $(M-H)^-$ molecular ion] modes on a Micromass series 2 or a Waters ZQ mass spectrometer. 1H NMR spectra were recorded using a Bruker DPX 400MHz spectrometer using tetramethylsilane as the external standard. BiotageTM chromatography refers to purification carried out using equipment sold by Dyax Corporation (either the Flash 40i or Flash 150i) and cartridges pre-packed with KPSil. Mass directed autoprep refers to methods where the material was purified by high performance liquid chromatography on a HPLCABZ+ 5 μ m column (5cmx10mm i.d.) with 0.1% HCO_2H in water and 95% MeCN, 5% water (0.5% HCO_2H)
- 20 25 30 utilising gradient elution at a flow rate of 8ml minutes⁻¹. The Gilson 202-fraction collector was triggered by a VG Platform Mass Spectrometer on detecting the mass of interest.

- Hydrophobic frits refer to filtration tubes sold by Whatman. SPE (solid phase extraction) refers to the use of cartridges sold by International Sorbent Technology Ltd. TLC (thin layer chromatography) refers to the use of TLC plates sold by Merck coated with silica gel 60 F₂₅₄. OasisTM refers to Waters[®] OasisTM HLB Extraction Cartridges, sold by Waters Corporation[®].

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Method 1

Example 1

5 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

To a solution of (D)-leucine methyl ester hydrochloride (300mg) in methanol (4ml) was added triethylamine (230 μ l) and 4-fluorobenzaldehyde (177 μ l). The mixture was stirred for 2.5 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (481mg) and isopropylisocyanide (225 μ l) were sequentially added. After stirring for 16hr, the solvent was removed *in vacuo* and the residue was dissolved in chloroform. This solution was washed with a saturated aqueous sodium carbonate solution (x2), aqueous citric acid (0.5M, x2) and brine (x1), dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in dichloromethane (2ml) and trifluoroacetic acid (5ml) and stirred for 3 hours at ambient temperature. After this time, the solvent was removed *in vacuo* and the residue co-evaporation with toluene (x3) and cyclohexane/ ether (1:1, x2). The residue was treated with a solution of triethylamine in dioxane (2% solution, 10ml) and was left to stir overnight. After this time, the dioxane was removed *in vacuo* and the residue was dissolved in ethyl acetate. The solution was washed with citric acid solution (0.5M, x2), saturated aqueous sodium bicarbonate solution (x1) and brine (x1). The liquors were then dried over magnesium sulphate and *in vacuo* and were then co-evaporated with cyclohexane: ether (1:1, x2). This crude material was purified by BiotageTM (90g, silica) eluting with toluene: ethyl acetate: cyclohexane (5: 3: 2) with 5% triethylamine to give (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide (149mg)

HPLC Rt = 3.42 minutes; m/z [M+H]⁺ = 480.

¹H NMR (CDCl₃) δ 7.44 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H), 7.11 (t, 2H), 6.50 (d, 1H), 5.60 (d, 1H), 5.11 (s, 1H), 4.10 (m, 1H), 3.96 (m, 2H), 3.16 (dd, 1H), 3.07 (d, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 1.84 (m, 1H), 1.73 (m, 1H), 1.42 (m, 1H), 1.13 (d, 3H), 1.12 (d, 3H), 0.84 (d, 3H), 0.79 (d, 3H)

Similarly prepared

Example 2

35 (2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide

HPLC Rt = 3.27 minutes; m/z [M+H]⁺ = 575.

(CDCl₃) δ 7.3 (d, 2H), 7.2 (m, 2H), 7.15 (m, 2H), 6.9 (d, 2H), 6.1 (d, 1H), 5.5 (s, 1H), 5.15 (s, 1H), 3.95 (m, 2H), 3.9 (m, 1H), 3.6 (m, 2H), 3.15 (m, 1H), 3.1 (m, 2H), 3.0 (m, 2H), 2.9 (m, 1H), 2.75 (m, 1H), 2.0 (m, 2H), 1.75 (m, 1H), 1.65 (m, 3H), 1.45 (m, 1H), 1.3 (s, 9H), 0.8 (d, 3H), 0.7 (d, 3H).

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Example 3

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z [M+H]⁺ = 565

- 5 ¹H NMR (CDCl₃) δ 7.52 (t, 1H), 7.22-7.11 (m, 4H), 7.04 (br s, 1H), 6.66 (dd, 1H), 6.56 (dd, 1H), 5.07 (s, 1H), 4.19-4.08 (m, 2H), 3.98 (dd, 1H), 3.86-3.81 (4H, m), 3.21-2.91 (m, 8H), 2.80-2.73 (m, 1H), 1.96-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (d, 3H), 1.16 (d, 3H), 1.06 (d, 3H), 0.92 (t, 3H).

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Method 2**Example 4**

- 15 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

Methyl (2R)-2-[(1R,S)-2-[[2-(benzyloxy)phenyl]amino]-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino]-4-methylpentanoate

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- A mixture of 4-fluorobenzaldehyde (1.2g), (D)-leucine methyl ester hydrochloride (1.7g), triethylamine and methanol (56ml) was stirred at room temperature for 3 hours. 2-Benzyloxyphenylisocyanide (2.0g) and N-*tert*-butoxycarbonyl-(D)-indanyl glycine (2.77g) were then added sequentially. After 40 hours the reaction mixture was partitioned
25 between 2M hydrochloric acid and ethyl acetate. The separated organic layer was washed with a saturated aqueous sodium bicarbonate solution and brine, dried over magnesium sulphate and evaporated *in vacuo*. The resultant crude material was purified by column chromatography (eluting with 0.5% and 0.2% methanol/ dichloromethane) to afford
30 methyl (2R)-2-[(1R,S)-2-[[2-(benzyloxy)phenyl]amino]-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino)-4-methylpentanoate (4.3g)
HPLC Rt = 4.34 minutes, m/z [M+H]⁺ = 752

- 35 Methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-[(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-D-leucinate

- A mixture of methyl (2R)-2-[(1R,S)-2-[[2-(benzyloxy)phenyl]amino]-1-(4-fluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino)-4-methylpentanoate (560mg), palladium on carbon (70mg)
40 and ethanol (15ml) was stirred under an atmosphere of hydrogen for 5 hours. The mixture was filtered through Celite and the filtrate was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane

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(10% to 15%) to give methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-[(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-D-leucinate.

5 HPLC $R_t = 4.06$ minutes, m/z $[M+H]^+ = 662$

(2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid.

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Carbonyldiimidazole (558mg) was added to a solution of methyl N-[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]-N-[(1R,S)-1-(4-fluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-D-leucinate (2.0g) in dichloromethane (20ml) and the resultant mixture was stirred at room temperature for 24 hours. The reaction was then concentrated to dryness, dissolved in a mixture of acetone: water (60ml: 40ml) and stirred for 17 hours at room temperature. The solution was then partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The separated organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. Half of the material was taken to be used crude in further experiments. The second half was purified by Biotage™ (silica, 90g) eluting with methanol: dichloromethane: ammonia (1: 98.5: 0.5 to 2.5: 86.5: 1). Evaporation of the appropriate fractions gave (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid. (173mg).

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(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide

A solution of (2R)-{[(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl][(1R)-1-(methoxycarbonyl)-3-methylbutyl]amino}(4-fluorophenyl)ethanoic acid (73mg) in N,N-dimethylformamide (2ml) was sequentially treated with diisopropylethylamine (51μl), phosphorus¹ (1-hydroxy-1H-benzotriazolato-O)tri-1-pyrrolidinyl-(T-4)-hexafluorophosphate (80mg) and then after 2 minutes, 2,2,2-trifluoroethylamine (25μl). This reaction mixture was stirred for 2 hours before being partitioned between 2M aqueous hydrochloric acid and ethyl acetate. The organic layer was washed with saturated aqueous sodium bicarbonate solution and brine before being dried over magnesium sulphate and evaporated *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane and stirred for 7 hours at room temperature. The reagent was removed *in vacuo* and the residue partitioned between ethyl acetate and saturated aqueous sodium bicarbonate solution. The separated organic fraction was washed with brine before being dried over magnesium sulphate and evaporated *in vacuo*. The crude material was purified by column chromatography (silica) eluting with

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methanol: dichloromethane (1% to 3%) to furnish ((2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl]-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide (10mg)

HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 520

- 5 ¹H NMR (CDCl₃) δ 7.42 (m, 2H), 7.34 (d, 1H), 7.20-7.10 (m, 6H), 6.61 (t, 1H), 5.28 (s, 1H), 4.08-3.96 (m, 3H), 3.88 (m, 1H), 3.14 (dd, 1H), 3.02 (m, 2H), 2.95-2.77 (m, 2H), 1.88-1.70 (m, 2H), 1.40 (ddd, 1H), 0.85 (d, 3H), 0.79 (d, 3H).

The following compounds were prepared in a similar manner

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Example 5

((2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl]-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

HPLC Rt = 3.37 minutes, m/z [M+H]⁺ = 466

- 15 ¹H NMR (CDCl₃); δ 7.47-7.40 (m, 2H), 7.25-7.12 (m, 6H), 6.50 (d, 1H), 6.47 (s, 1H), 4.15 (dd, 1H), 3.98 (dd, 1H), 3.21-3.01 (m, 3H), 2.99 (s, 3H), 2.92-2.73 (m, 2H), 2.83 (m, 3H), 1.59-1.49 (m, 1H), 1.42 (dt, 1H), 0.66-0.57 (m, 1H), 0.62 (d, 3H), 0.40 (d, 3H).

Example 6

20 ((2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl]-2,5-dioxopiperazin-1-yl]-morpholinamide

HPLC Rt = 3.32 minutes, m/z [M+H]⁺ = 508

- 25 ¹H NMR (CDCl₃); δ 7.44-7.39 (m, 2H), 7.26-7.12 (m, 6H), 6.87 (d, 1H), 6.51 (s, 1H), 4.12 (dd, 1H), 4.00 (dd, 1H), 3.73-3.62 (m, 3H), 3.60-3.54 (m, 2H), 3.37 (m, 1H), 3.23 (m, 1H), 3.20-3.02 (m, 4H), 2.91-2.75 (m, 2H), 1.60-1.50 (m, 1H), 1.45 (dt, 1H), 0.63 (d, 3H), 0.62-0.55 (m, 1H), 0.42 (d, 3H).

The 2-fluoro-4-(morpholino)-benzaldehyde used in this synthesis was prepared by the following procedure.

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2-Fluoro-4-(morpholino)-benzonitrile

A solution of 2,4-difluorobenzonitrile (6.03g, 43.35mmol) and morpholine (8.3ml, 95.17mmol) in tetrahydrofuran (27ml) was stirred at room temperature for 24hr. The mixture was evaporated and the white solid purified by Biotage™ column (90g, silica) eluting with cyclohexane: ethyl acetate: (4: 1) to give 2-fluoro-4-(morpholino)-benzonitrile as a white solid (5.81g, 65%).

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HPLC Rt = 2.83 minutes; m/z [M+H]⁺ = 207.

2-Fluoro-4-(morpholino)-benzaldehyde

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To a solution of 2-fluoro-4-(morpholino)-benzonitrile (2.82g, 13.7mmol) in tetrahydrofuran (27ml) under a nitrogen atmosphere was added dropwise a 1.5 M solution of DIBAL-H in toluene (18.3ml, 27.3mmol) during 13minutes and the resulting mixture

stirred for 23.5hr at room temperature. The mixture was cooled to -50 °C and the excess DIBAL-H destroyed by careful addition of methanol (27ml). The mixture was then stirred at room temperature for 10 mins, saturated ammonium chloride (27ml) added and the resulting mixture stirred at room temperature for 40 mins., and then evaporated under reduced pressure to a yellow solid. This solid was partitioned between dichloromethane (120ml) and water (120ml) and solid potassium carbonate added until the aqueous phase was pH10. The phases were separated via a hydrophobic frit and the organic phase evaporated and the residue purified by a Biotage™ column (40g, silica) eluting with cyclohexane: ethyl acetate: (7:3) to give 2-fluoro-4-(morpholino)-benzaldehyde (1.96g, 68%) as a white solid.

HPLC Rt = 2.63 minutes; m/z [M+H]⁺ = 210.

Method 3

Example 7

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

Methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate

To a stirred suspension of (L)-Leucine (1.3g) in methanol (100ml) under a nitrogen atmosphere was added 2,4-difluorobenzaldehyde (1.42g). After stirring at ambient temperature for 3 days, the suspension was cooled to -30°C and a solution of isopropylisocyanide (0.691g) in methanol (5ml) was added. After 3 hours at -30°C the reaction was allowed to warm to room temperature and was stirred for a further 20 hours. The solvent was removed *in vacuo*, the residue purified using a Biotage™ column (40g, silica) eluting with cyclohexane: ethyl acetate (gradient from 8:1 to 1:1). The required fractions were combined and concentrated *in vacuo* to furnish methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.326g). ¹H NMR (CDCl₃) δ 7.32 (m, 1H), 6.88 (m, 1H), 6.82 (m, 1H), 6.78 (m, 1H), 4.42 (s, 1H), 4.07 (m, 1H), 3.69 (s, 3H), 3.18 (t, 1H), 1.66 (m, 1H), 1.49 (t, 2H), 1.18 (d, 3H), 1.15 (d, 3H), 0.88 (d, 3H), 0.77 (d, 3H)

N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucinate (1.32g) in methanol (15ml) was added a solution of lithium hydroxide (294mg) in water (15ml). The reaction was rapidly stirred for 1.5 hours and then evaporated *in vacuo*. The residue was dissolved in water and neutralised using 2N hydrochloric acid. The resulting solid was collected by filtration and dried *in vacuo*. The filtrate was applied to 4 Oasis cartridges (6g), which were eluted with water (x2) and methanol (x2). The required fractions were combined and concentrated *in vacuo* to afford

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N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (1.01g).

HPLC Rt = 2.51 minutes; m/z [M+H]⁺ = 343.

5 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (291mg) in dry tetrahydrofuran (5ml) under a nitrogen atmosphere at -20°C was added N-methylmorpholine (101mg) and a solution of isopropylchloroformate in toluene (1.0M, 1ml). After 10 minutes, a solution of N-[(1R)-1-(2,4-difluorophenyl)-2-(isopropylamino)-2-oxoethyl]-L-leucine (342mg) in N,N-dimethylformamide/
10 tetrahydrofuran (5ml/ 10ml) was added and the resultant mixture was stirred at room temperature for 4 hours. The solvent was then removed *in vacuo* and the residue was treated with 4N hydrochloric acid in dioxane (2ml). After 4 hours, methanol (5ml) was added to the reaction mixture and this was left to stand for 18 hours. The solvent was then
15 removed *in vacuo* and the residue was purified on an SPE cartridge (50g, silica) eluting with cyclohexane/ ethyl acetate (gradient from 4:1 to neat ethyl acetate), which furnished the two diastereomers as white solids (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide;
(0.137g)

20 HPLC Rt = 3.47 minutes, m/z [M+H]⁺ = 498

¹H NMR (CDCl₃) δ 7.68 (m, 1H), 7.21 (m, 2H), 7.17 (m, 2H), 6.95 (m, 1H), 6.89 (m, 1H), 6.79 (d, 1H), 5.91 (d, 1H), 5.33 (s, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.92 (dd, 1H), 3.16 (m, 1H), 3.05 (m, 2H), 2.90 (m, 1H), 2.78 (m, 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 1.17 (m, 6H), 0.88 (d, 3H), 0.82 (d, 3H)

25

Method 4

Example 8

30 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-([2-(benzyloxy)phenyl]amino)-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate

35 To a suspension of L-leucine (2.33g) in methanol (200ml) at -30°C under nitrogen was added a solution of 2,4-difluorobenzaldehyde (2.52g) in methanol (10ml) and a suspension of 2-benzyloxyphenylisocyanide (3.7g) in methanol (40ml). The reaction was stirred at -30°C for 2.5 hours and then allowed to warm to room temperature and stirred for a further 6 days. The solvent was removed *in vacuo* and the residue was passed
40 through a Biotage™ column (90g) eluting with cyclohexane: ethyl acetate (8:1 and 7:1) to afford after evaporation of the appropriate fractions methyl N-[(1R)-2-([2-

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(benzyloxy)phenyl]amino)-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (5.06g).
HPLC Rt=4.0 minutes, m/z [M-H]⁻ = 495

5 Methyl N-[(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate

A mixture of palladium on carbon (10%, 300mg), methyl N-[(1R)-2-[(2-(benzyloxy)phenyl]amino)-1-(2,4-difluorophenyl)-2-oxoethyl]-L-leucinate (2.88g) and ethyl acetate (30ml) was stirred under a hydrogen atmosphere for 3 hours. The reaction
10 was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-[(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (2.179g).
HPLC Rt=3.52 min, m/z [M-H]⁻ = 405

15 Methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

A solution of methyl N-[(1R)-1-(2,4-difluorophenyl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (203mg) and 1,1'-thiocarbonyldiimidazole (100mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (10ml) was added to the
20 reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide (TBTU, 321mg) and a solution of dimethylamine in tetrahydrofuran (0.5ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was
25 then passed down an SPE (5g, silica) eluting with a gradient (8:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg).
HPLC Rt = 3.16 minutes m/z [M+H]⁺ = 343

30 N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

To a solution of methyl N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (100mg) in methanol (3ml) was added a solution of lithium hydroxide (15.4mg) in water (1ml). After stirring vigorously for 4 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid.
35 This solution was applied to an OasisTM cartridge (6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg).
HPLC Rt = 2.23 minutes m/z [M+H]⁺ = 329

40 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

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To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (84mg) in dry tetrahydrofuran (6ml) at -20°C under a nitrogen atmosphere was added N-methylmorpholine (32μl) and a solution of isopropylchloroformate in toluene (1.0M, 290μl). After 10 minutes, a solution of N-[1-(2,4-difluorophenyl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (95mg) in tetrahydrofuran (10ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (5ml) was added and the reaction was left to stand for a further 18 hours. The solvent was then removed *in vacuo* and the residue was dissolved in dioxan (5ml) and to this was added triethylamine (0.5ml). After 1 hour, the solvent was removed and the residue was applied to an SPE (10g, silica). The product was eluted using methanol. A second SPE was used to further purify the material (2g, silica) using an ethyl acetate: methanol gradient (20:1 to 1:1) to afford (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (38mg).

HPLC Rt=3.5 minutes, m/z [M+H]⁺ = 484
¹H NMR (CDCl₃) δ 7.42 (m, 1H), 7.22 (m, 2H), 7.17 (m, 2H), 7.02-6.90 (m, 2H), 6.62 (s, 1H), 6.37 (m, 1H), 4.09 (m, 1H), 3.98 (dd, 1H), 3.20-3.02 (m, 3H), 2.99 (s, 3H), 2.87 (m, 1H), 2.85 (s, 3H), 2.74 (m, 1H), 1.55 (m, 2H), 0.70 (m, 1H), 0.67 (d, 3H), 0.41 (d, 3H)

Similarly prepared

Example 9

(2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt=3.41 minutes, m/z [M+H]⁺ = 496.
¹H NMR (CDCl₃) δ 7.67 (dt, 1H), 7.59 (1H, d), 7.21-7.11 (m, 4H), 6.99-6.92 (m, 1H), 6.92-6.84 (m, 1H), 6.35 (d, 1H), 5.43 (s, 1H), 3.99 (dd, 1H), 3.93 (dd, 1H), 3.17-2.71 (m, 6H), 1.88-1.70 (m, 2H), 1.48-1.38 (m, 1H), 0.86 (s, 3H), 0.81-0.74 (m, 5H), 0.51-0.45 (m, 2H).

Example 10

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide;

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

A mixture of 2,4-difluorobenzaldehyde (1.421g), (D)-leucine methyl ester hydrochloride (1.817g), triethylamine (1.391ml) and methanol (20ml) was stirred at room temperature for 16 hours. N-tert-butoxycarbonyl-(D)-indanylglycine (2.914g) and 2-benzyloxyphenylisocyanide (2.090g) were then added sequentially. After 24 hours the solvent was

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removed under reduced pressure and the reaction mixture was taken up in dichloromethane (ca. 20ml) and purified by Biotage™ flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:9 ethyl acetate:cyclohexane) to afford methyl (2R)-2-[[[(1R,S)-2-[[2-(benzyloxy)phenyl]amino]-1-(2,4-difluorophenyl)-2-oxoethyl][(2R)-2-[(tert-butoxycarbonyl)amino]-2-(2,3-dihydro-1H-inden-2-yl)ethanoyl]amino]-4-methylpentanoate (5.100g) (HPLC Rt = 4.40 minutes m/z [M+H]⁺ = 770). This was taken up in 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was left at room temperature for 3 hours. The solvent and hydrogen chloride were blown off using a stream of nitrogen overnight. The crude material was taken up in methanol (90ml) containing triethylamine (10ml). After 30 minutes, the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by Biotage™ flash column chromatography (2x90g silica cartridges on a Biotage Quad 3 system eluted with 1:2 ethyl acetate:cyclohexane) to yield (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g). HPLC Rt = 3.99 minutes, m/z [M+H]⁺ = 638

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (3.381g) was dissolved in ethyl acetate (200ml) and hydrogenated at atmospheric pressure over 10% palladium on carbon catalyst (0.980g of 10% Pd/C:water 1:1 w/w) at room temperature for five hours. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to give the (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide as a cream-coloured foam (2.650g).

HPLC Rt = 3.61 minutes, m/z [M-H]⁺ = 546 (no [M+H]⁺ visible)

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.650g) was stirred in dichloromethane (20ml) and carbonyldiimidazole (1.178g) was added. the mixture was left at room temperature for 16 hours then the solvent was removed under reduced pressure. The residue was then taken up in 1:1 acetone:water (v/v) (80ml) and left at room temperature for 30 minutes. The bulk of the acetone was then removed under reduced pressure and the residue was partitioned between dichloromethane and 0.5M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated

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under reduced pressure. The crude product was purified (BiotageTM flash chromatography column, 90g silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to afford (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid as a colourless solid 1.524g as a mixture of epimers.
HPLC Rt = 3.44 and 3.58 minutes, both m/z [M+H]⁺ = 457

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

The acid (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-ethanoic acid (0.747g) prepared as described above was dried over P₄O₁₀ in vacuo for five hours to give 0.724g drier material; this was dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, dissolved in anhydrous dichloromethane:acetonitrile (1:1 v/v, 6ml) and treated with triethylamine (0.223ml) and BOP-Cl (bis(2-oxo-3-oxazolidinyl)phosphinic chloride, 0.450g) and the mixture was sonicated for ca. 1 min to give a gelatinous mass. After 10 minutes at room temperature a solution of dimethylamine in tetrahydrofuran (10ml of 2M solution) was added to give a clear solution; this was left for 16 hours at room temperature. The solvents were removed under reduced pressure and the mixture was partitioned between dichloromethane and 0.1M hydrochloric acid. The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure. The crude product was purified by flash column chromatography (12g BiotageTM silica cartridge eluted with (i) 1:1 ethyl acetate:cyclohexane (ii) ethyl acetate (iii) ethyl acetate:methanol 9:1) to give the (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a colourless solid 0.285g.
HPLC Rt = 3.43 minutes, m/z [M+H]⁺ = 484
¹H NMR (CDCl₃) δ 7.47-7.40 (m, 1H), 7.24-7.11 (m, 4H), 7.01-6.91 (m, 3H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19-3.01 (m, 3H), 2.99 (s, 3H), 2.92-2.75 (m, 5H), 1.64-1.51 (m, 2H), 0.76-0.66 (m, 4H), 0.43 (d, 3H).

Method 5

Example 11

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

(2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid

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R-Indanylglycine (1.91g) was suspended in dioxane (10ml) and water (10ml). To this was added triethylamine (1.7ml) and N-(benzyloxycarbonyloxy)succinimide (2.54g) and the reaction mixture was stirred rapidly at room temperature for 2 days. The reaction mixture was poured into water (50ml) and extracted with chloroform (100ml). The organic phase was washed with 1N hydrochloric acid (50ml) and water (50ml). This was dried over magnesium sulphate and the solvent removed *in vacuo* to give (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (3.06g).
 HPLC Rt = 3.35 minutes; m/z [M+H]⁺ = 326.
¹H NMR (CDCl₃) δ 7.40-7.29 (m, 5H), 7.21-7.11 (m, 4H), 5.28 (d, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.14-2.79 (m, 5H).

(2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

To a solution of (D)-leucine methyl ester hydrochloride (1.45g) in methanol (10ml) was added triethylamine (1.12ml) and 2,4-difluorobenzaldehyde (0.875ml). The mixture was stirred for 3 days before (2R)-[(benzyloxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (2.6g) and 2-benzyloxyphenylisocyanide (1.76g) were sequentially added. The reaction mixture was left to stand for 24 hours. The solvent was removed *in vacuo* and the residue was separated between ethyl acetate (200ml) and water (200ml). The organic phase was washed with brine. To this solution was added palladium on carbon (2.0g) and acetic acid (10ml) and the reaction mixture was stirred under an atmosphere of hydrogen for 2 hours. The mixture was filtered through Celite and washed with water (3x100ml), saturated sodium bicarbonate solution, brine and dried over magnesium sulphate. The solvent was evaporated *in vacuo*. The crude product was purified by column chromatography (silica) eluting with ethyl acetate: cyclohexane (50% to 66%) to give (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (2.0g).
 HPLC Rt = 3.59 minutes; m/z [M+H]⁺ = 548.

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Carbonyldiimidazole (4.80g, 1.54 equiv.) was suspended in anhydrous dichloromethane (40ml) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (10.50g, pre-dried *in vacuo* over P₄O₁₀ for 24 hours) was then added with stirring and the resultant solution was stirred at room temperature for 6 hours. The resulting yellow solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (54ml, 5.6 equiv.) and the resulting mixture was stirred at room temperature for 16 hours. The solvents plus residual dimethylamine were removed under reduced pressure and the reaction mixture was taken up in

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dichloromethane (200mL) and washed with 1M hydrochloric acid (200mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to ca. 50mL. The crude product was applied to 4x90g silica Biotage™ columns on a Quad 3 system; each column being eluted with (i) 2:1v/v ethyl acetate:cyclohexane (12x50mL fractions), (ii) ethyl acetate (12x50mL fractions), (iii) 9:1v/v ethyl acetate:methanol to give (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (5.753g, 62%) as a colourless solid.

HPLC Rt = 3.41 minutes, m/z [M+H]⁺ = 484

¹H NMR (CDCl₃) δ 7.48–7.38 (m, 2H), 7.24–7.11 (m, 4H), 7.01–6.90 (m, 2H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19–3.01 (m, 3H), 2.99 (s, 3H), 2.92–2.75 (m, 5H), 1.64–1.51 (m, 2H), 0.76–0.66 (m, 4H), 0.43 (d, 3H).

Similarly prepared:

Example 12

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide colourless solid, 41%

HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 470

Example 13

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide colourless solid, 36%

HPLC Rt = 3.3 minutes, m/z [M+H]⁺ = 456

Example 14

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 61%

HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 526

Example 15

(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 45%

45%

HPLC Rt = 3.2 minutes, m/z [M+H]⁺ = 512

(azetidin-3-ol prepared by the method of S S Chatterjee and D J Trigg; J Chem. Soc. Chem. Comm. (2) 93 (1968))

Example 16

(3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione colourless solid, 46%

HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 496

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Example 17

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide colourless solid, 59%

5 HPLC Rt = 3.3 minutes, m/z [M+H]⁺ = 514

Example 18

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide colourless solid,

10 22%

HPLC Rt = 3.2 minutes, m/z [M+H]⁺ = 576

Example 19

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide colourless solid, 11%

15 HPLC Rt = 3.5 minutes, m/z [M+H]⁺ = 552

(2,2,2-trifluoroethylmethylamine hydrochloride was prepared by the method of E R Bissell and M Finger, J. Org. Chem. 24 1256-1259 (1959))

Example 20

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide tan foam, 19%

HPLC Rt = 3.5 minutes, m/z [M+H]⁺ = 561

Example 21

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide

HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 500

Example 22

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid

Carbonyldiimidazole (1.42g, 1.6 equiv.) was suspended in anhydrous dichloromethane (10mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-

35 dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (3.00g) was then added and the resultant solution was stirred at room temperature for 16 hours. The resulting yellow solution was then evaporated under reduced pressure and the residue was treated with a 1:1(v/v) mixture of water and acetone (10 mL). The mixture was stirred for 2

40 hours, then the acetone was removed under reduced pressure and the residue was partitioned between dichloromethane and 0.1M HCl aq. The organic phase was separated using a hydrophobic frit then evaporated to low volume and purified by chromatography

on a Biotage Quad 3 system (90g silica column) eluted with 1:1(v/v) ethyl acetate:cyclohexane, then ethyl acetate, then 1:1 (v/v) ethyl acetate:methanol to give a mixture of diastereomers (2.61g). These were separated on a chiral reverse-phase column (Chiralcel OD, eluted with 15% propan-2-ol/heptane containing 0.1%TFA) to give:

- 5 (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid (1.60g)
HPLC Rt = 3.4 minutes, m/z [M+H]⁺ = 457

Example 23

- 10 methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

Carbonyldiimidazole (0.324g, 1.6 equiv.) was suspended in anhydrous dichloromethane (4mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-

- 15 dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (0.800g) was then added with stirring and the resultant solution was left at room temperature for 16 hours. The mixture was then treated with methanol (10mL) and left at room temperature overnight. The solvents were removed under reduced pressure and the residue was purified by preparative plate chromatography on silica (20x20cm plates x4 eluted with 1:3 ethyl acetate:cyclohexane x5) to give methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate (0.453g, 66%)
20 HPLC Rt = 3.42 minutes, m/z [M+H]⁺ = 471

Similarly prepared:

25

Example 24

propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

HPLC Rt = 3.71 minutes, m/z [M+H]⁺ = 499

30

Example 25

1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate

- (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid (example 22) (0.130g) was stirred in anhydrous DMF (1mL) and anhydrous potassium carbonate (0.020g, 0.5 eq.) was added. The mixture was stirred at room temperature for 1 hour then cooled to -10°C (ice-salt bath). The heterogeneous mixture was treated with 1-bromoethyl acetate (0.120mL, excess) and stirred for 3.5 hours keeping the bath temperature between -10 and -5°C. It was then
35 partitioned between DCM and 1M HCl aq. (20 mL each). The organic phase was separated (hydrophobic frit) and evaporated under reduced pressure to give a purple gum; this was purified by SPB cartridge (5g, silica eluted with (i) cyclohexane x2, (ii) DCM x2,
40

45

(iii) diethyl ether x2, (iv) ethyl acetate x2, (v) methanol x2 to give 1-(acetyloxy)ethyl (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide (0.081g) as a yellow foam.
HPLC Rt = 3.5 minutes, m/z [M+H]⁺ = 543

5

Similarly prepared:

In the table below, Examples 26, 54-55, 66-104, 107-117, 124-131 were prepared via method 1. The t-butyl ester Example 39 was prepared via perchloric acid-catalysed transesterification of the corresponding acid (Example 22) with t-butyl acetate by the procedure of T Kolasa and M J Miller; Journal of Organic Chemistry (1990), 55(6), 1711-21. Other Examples in the table below were prepared via method 5.

10

Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
26		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
27		537.5	3.4	538	536	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2,2,2-trifluoroethyl)ethanamide
28		543.6	3.2	544	542	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2,2-dimethoxyethyl)ethanamide
29		513.6	3.3	513	511	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-methoxyethyl)ethanamide
30		527.6	3.4	528	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-methoxyethyl)-N-methylethanamide

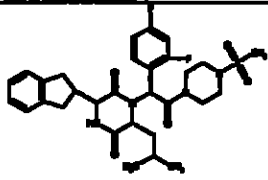
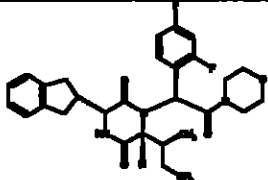
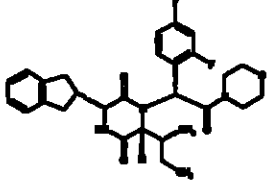
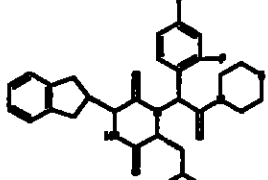
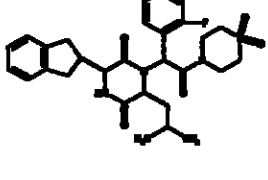
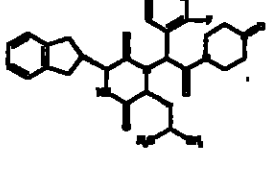
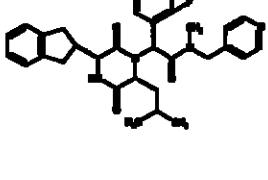
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31		571.7	3.3	572	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-bis(2-methoxyethyl)ethanamide
32		528.6	2.7	529	none	(2R)-2-(2,4-difluorophenyl)-N-[2-(dimethylamino)ethyl]-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N-methylethanamide
33		654.7	2.7	541	539	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-[2-(dimethylamino)ethyl]-N-methylethanamide trifluoroacetate
34		511.6	3.6	512	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-N-methylethanamide
35		471.6	3.2	472	470	(2R)-2-(2,4-difluorophenyl)-2-[(2R,5R)-2-isobutyl-3,6-dioxo-5-(2-phenylethyl)piperazin-1-yl]-N,N-dimethylethanamide
36		497.6	3.5	498	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-4-methyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
37		554.7	2.7	555	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-4-[2-(dimethylamino)ethyl]-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

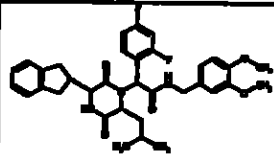
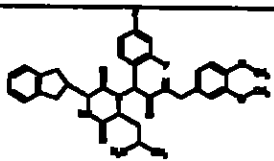
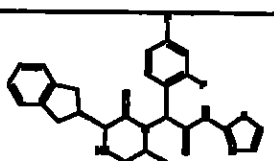
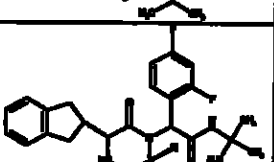
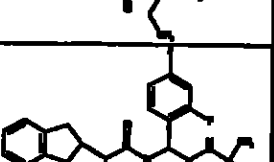
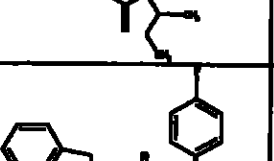
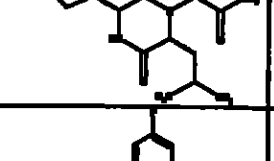
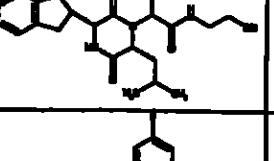
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38		527.6	3.3	528	526	[(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl](methylamino)acetic acid
39		512.6	3.7	513	511	tert-butyl (2R)-2-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
40		583.7	3.6	584	none	tert-butyl [(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoyl](methylamino)acetate
41		525.6	3.3	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-methoxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
42		509.6	3.5	510	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-pyrrolidin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
43		561.1	2.7	525	none	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-piperazin-1-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione hydrochloride
43a		652.7	2.7	539	583(M+45)	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(4-methylpiperazin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione trifluoroacetate

48

44		602.7	3.3	603	601	(3R,6R)-1-((1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
45		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
46		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
47		541.7	3.6	542	540	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-oxo-2-thiomorpholin-4-ylethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
48		573.7	3.3	574	572	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1,1-dioxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
49		557.7	3.1	558	556	(3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(1-oxidothiomorpholin-4-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
50		560.6	3	561	none	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-4-ylmethyl)ethanamide

49

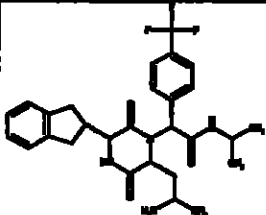
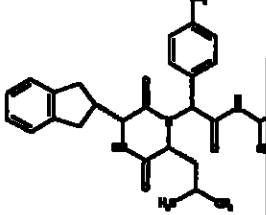
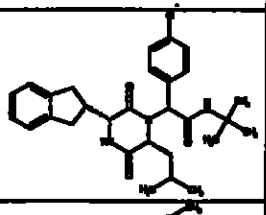
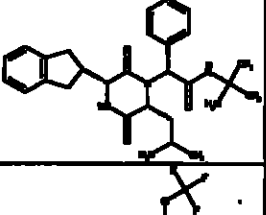
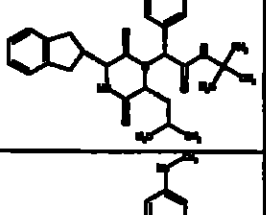
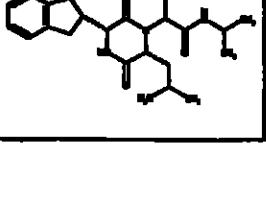
51		605.7	3.5	606	604	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
52		605.7	3.5	606	604	(2S)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(3,4-dimethoxybenzyl)ethanamide
53		538.6	3.4	539	537	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(1,3-thiazol-2-yl)ethanamide
54		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
55		511.6	3.6	512	510	(2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
56		437.5	3.3	438	436	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide
57		481.6	3	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-hydroxyethyl)ethanamide
58		509.6	3.4	510	508	[(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)]

50

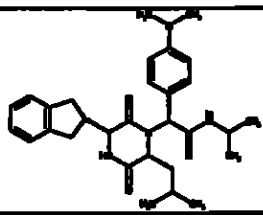
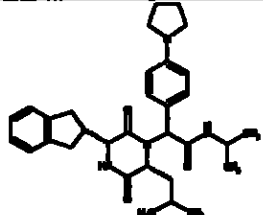
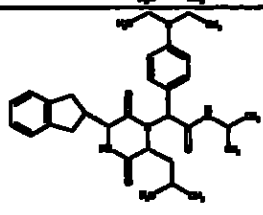
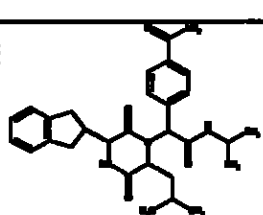
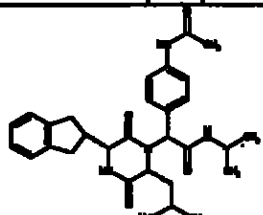
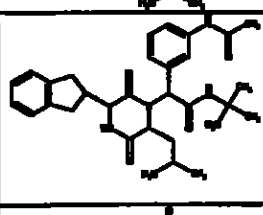
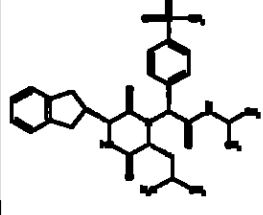
						fluorophenyl)ethanoyl](methyl)amino]acetic acid
59		509.6	3.4	510	508	methyl {[[(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanoyl]amino}acetate
60		564.7	2.6	565	563	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(4-fluorophenyl)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
61		534.7	2.6	535	533	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(4-fluorophenyl)-2-(4-methyl-1,4-diazepan-1-yl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
62		548.7	2.6	549	547	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-2-[4-(dimethylamino)piperidin-1-yl]-1-(4-fluorophenyl)-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
63		550.7	2.7	551	549	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-morpholin-4-ylethyl)ethanamide
64		548.7	2.8	549	547	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2-piperidin-1-ylethyl)ethanamide
65		619.7	3.9	620	618	(2R)-N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)ethanamide

Similarly prepared:

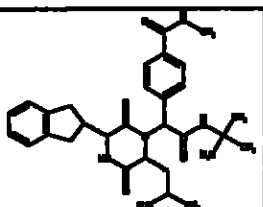
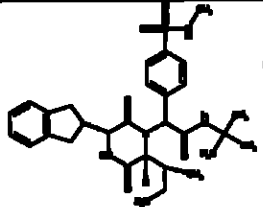
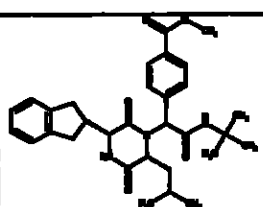
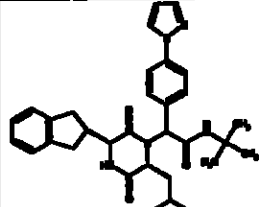
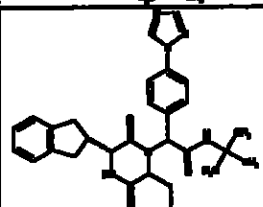
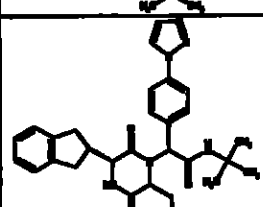
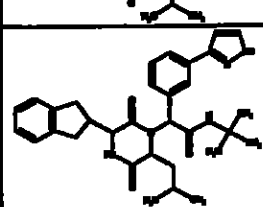
51

Eg No.	Regno	Mwt	Rt /min	+ve ion	-ve ion	name
66		529.6	3.8	530	528	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(trifluoromethyl)phenyl]ethanamide
67		475.6	3.6	476	474	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-methylphenyl)ethanamide
68		510.1	3.8	510	508	(2R)-N-(tert-butyl)-2-(4-chlorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
69		505.7	3.5	506	504	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-methoxyphenyl)ethanamide
70		559.7	3.8	560	558	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(trifluoromethoxy)phenyl]ethanamide
71		490.6	3.4	491	489	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylamino)phenyl]ethanamide

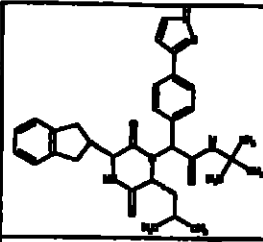
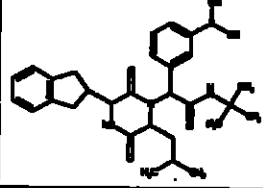
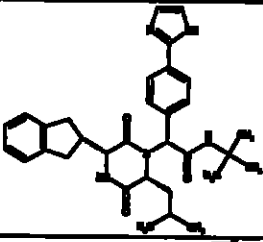
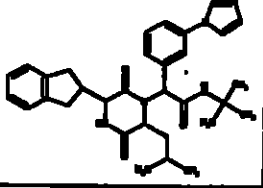
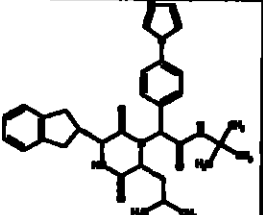
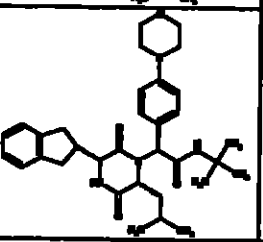
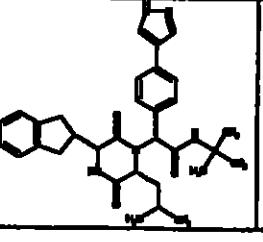
52

72		504.7	3.6	505	503	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)phenyl]-N-isopropylethanamide
73		530.7	3.7	553(M+Na)	529	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(4-pyrrolidin-1-ylphenyl)ethanamide
74		532.7	3.7	533	531	(2R)-2-[4-(diethylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
75		504.6	3.1	505	503	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]benzamide
76		518.6	3.0	519	517	(2R)-2-[4-(acetylamino)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
77		532.7	3.2	533	531	(2R)-2-[3-(acetylamino)phenyl]-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
78		539.7	3.3	540	538	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[4-(methylsulfonyl)phenyl]ethanamide

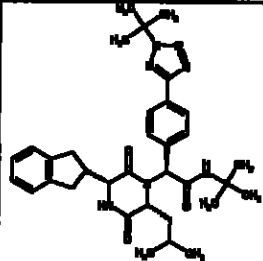
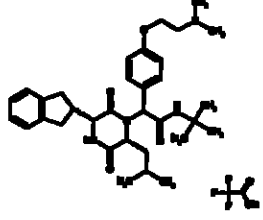
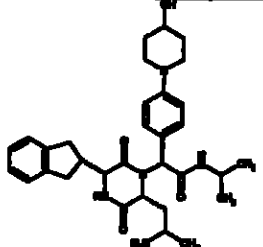
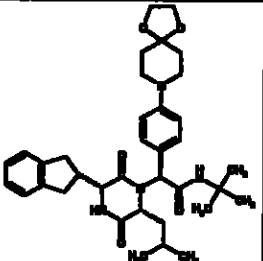
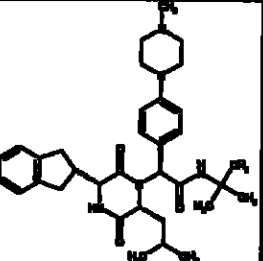
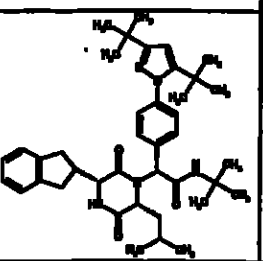
53

79		532.7	3.3	533	531	4-((1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl)-N-methylbenzamide
80		568.7	3.4	569	567	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-[4-[(methylamino)sulfonyl]phenyl]ethanamide
81		533.7	3.6	532	534	methyl 4-[(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl]benzoate
82		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-1-yl)phenyl]ethanamide
83		542.8	3.3	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,4-triazol-1-yl)phenyl]ethanamide
84		542.8	3.2	543	541	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-1,2,3-triazol-1-yl)phenyl]ethanamide
85		541.7	3.5	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-pyrazol-3-yl)phenyl]ethanamide

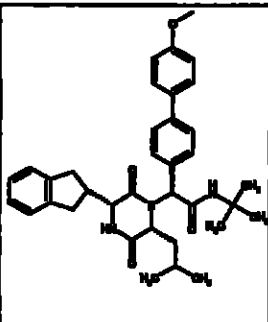
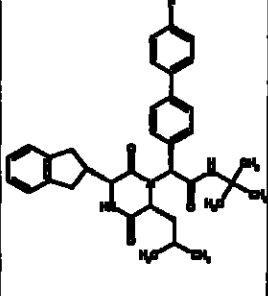
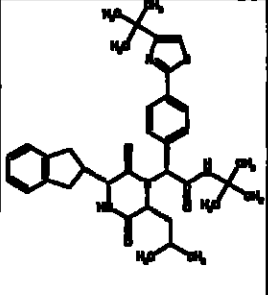
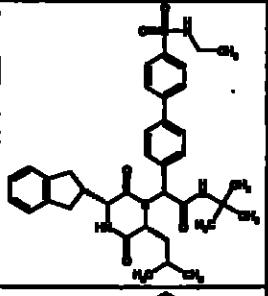
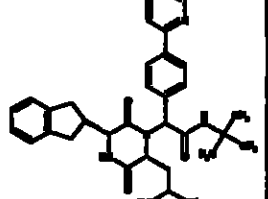
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86		541.8	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-3-yl)phenyl]ethanamide
87		519.4	3.4	520	518	3-[(1R)-2-(tert-butylamino)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-oxoethyl]phenylboronic acid
88		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-2-yl)phenyl]ethanamide
89		541.7	3.1	542.0	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[3-(1H-imidazol-1-yl)phenyl]ethanamide
90		541.7	3.0	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-imidazol-1-yl)phenyl]ethanamide
91		560.8	3.4	561	559	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-morpholin-4-ylphenyl)ethanamide
92		541.7	3.3	542	540	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1H-pyrazol-4-yl)phenyl]ethanamide

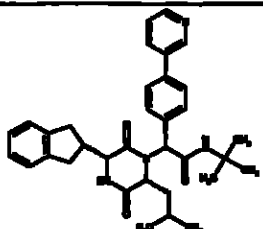
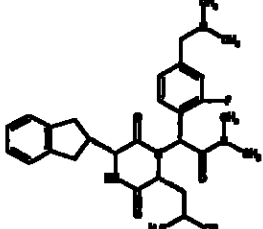
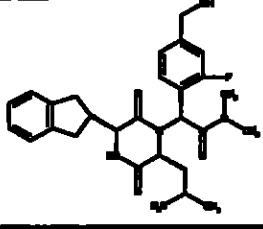
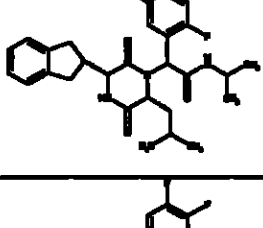
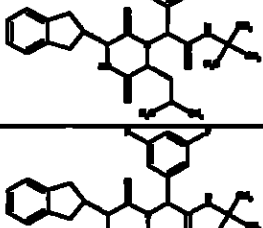
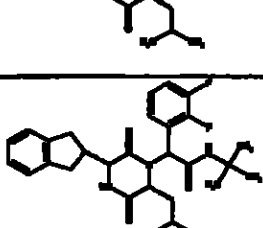
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93		599.8	3.9	600	598	(2R)-N-(tert-butyl)-2-[4-(2-tert-butyl-2H-tetrazol-5-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
94		562.7	2.9	563	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-[2-(dimethylamino)ethoxy]phenyl]ethanamide trifluoroacetate
95		560.8	3.0	561	559	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
96		616.9	3.5	617	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(1,4-dioxo-8-azaspiro[4.5]dec-8-yl)phenyl]ethanamide
97		573.8	2.9	574	none	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-methylpiperazin-1-yl)phenyl]ethanamide
98		654.0	4.1	654	652	(2R)-N-(tert-butyl)-2-[4-(3,5-ditert-butyl-1H-pyrazol-1-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

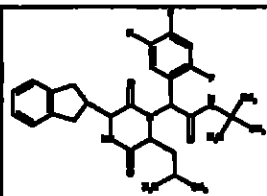
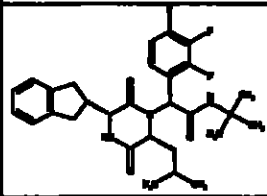
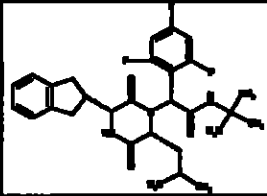
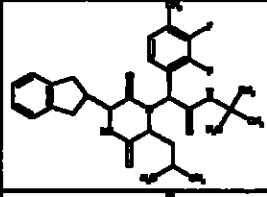
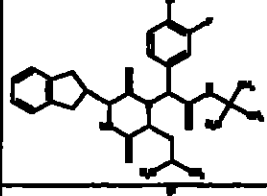
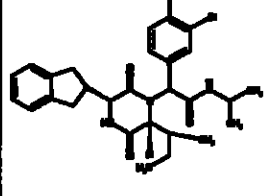
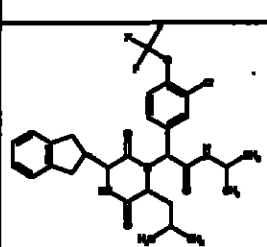
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99		581.7	4.0	582	580	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-methoxy-1,1'-biphenyl-4-yl)ethanamide
100		569.8	3.9	none	568	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4'-fluoro-1,1'-biphenyl-4-yl)ethanamide
101		614.8	4.3	615	613	(2R)-N-(tert-butyl)-2-[4-(4-tert-butyl-1,3-thiazol-2-yl)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
102		658.9	3.6	659	657	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4'-[(ethylamino)sulfonyl]-1,1'-biphenyl-4-yl]ethanamide
103		552.8	3.6	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-2-ylphenyl)ethanamide

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104		552.8	3.3	553	551	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-pyridin-3-ylphenyl)ethanamide
105		522.7	2.4	523	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-{4-[(dimethylamino)methyl]-2-fluorophenyl}-N,N-dimethylethanamide
106		495.6	2.9	496	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(hydroxymethyl)phenyl]-N,N-dimethylethanamide
107			3.4	498	496	(2R)-2-(2,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
108			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
109			3.6	512	510	(2R)-N-(tert-butyl)-2-(3,5-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
110			3.6	512	510	(2R)-N-(tert-butyl)-2-(2,3-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

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111			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,5-trifluorophenyl)ethanamide
112			3.7	530	528	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,3,4-trifluorophenyl)ethanamide
113			3.6	530	528	(2S)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2,4,6-trifluorophenyl)ethanamide
114			3.8	526	524	(2R)-N-(tert-butyl)-2-(2,3-difluoro-4-methylphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
115			3.8	528	526	(2R)-N-(tert-butyl)-2-(4-chloro-3-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
116			3.7	530	528	(2R)-2-(3,4-dichlorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
117			3.7	580	578	(2R)-2-[3-chloro-4-(trifluoromethoxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

118			3.0	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-hydroxyphenyl)-N,N-dimethylethanamide
119			3.3	496	494	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isopropyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-methoxyphenyl)-N-isopropylethanamide
120			3.6	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-methoxyphenyl)ethanamide
121			3.1	540	538	{4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetic acid
122			3.6	596	594	tert-butyl {4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenoxy}acetate
123			3.3	553	none	4-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(dimethylamino)-2-oxoethyl]-2-fluorophenyl dimethylcarbamate
124			3.5	none	552	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4,5-dimethoxyphenyl)ethanamide

125			3.7	524	522	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluoro-3-methoxyphenyl)ethanamide
126			3.8	none	570/572	(2R)-2-(4-bromo-2-fluorophenyl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
127			3.5	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(dimethylamino)-3-fluorophenyl]-N-isopropylethanamide
128			3.7	540	538	(2R)-N-(tert-butyl)-2-(3-chloro-4-methoxyphenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
129			3.3	565	563	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide
130			3.2	579	577	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-(4-hydroxypiperidin-1-yl)phenyl]-N-isopropylethanamide
131			3.3	587	585	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[2-fluoro-4-[(methylsulfonyl)amino]phenyl]ethanamide

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5 Hydroxylated metabolites of (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide were prepared as follows:

10 2 litres of growing cell cultures of *Streptomyces rimosus* BS33 was used to biotransform GW796679x. 500mg of GW796679X was added after 3 days growth and the broth harvested after another 5 days incubation. At harvest, 2 litres of methanol was added, then the cells removed by centrifugation. Methanol was removed from the supernatant by evaporation. The compounds were then extracted with ethyl acetate, evaporated to dryness, and purified by preparative HPLC to give examples 132,133,134 and 135.

132		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-((2S)-5-hydroxy-2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
133		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-((2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
134		485.5	2.9	486	484	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-((2R)-1-hydroxy-2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
135		485.5	3.1	486	530(M+45)	(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(hydroxymethyl)ethanamide

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Example 136
(2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

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Benzofuran-5-carboxaldehyde (215 mg, 1.47 mmol) and D-leucine t-butyl ester hydrochloride (329 mg, 1.47 mmol) were dissolved in methanol (1.5ml) and triethylamine (0.205 ml, 1.47 mmol) added. The mixture, a pale yellow solution, was left to stand at room temperature overnight (23.5 hours). Then Boc-D-indanylglycine (429 mg, 1.47 mmol) was added followed by isopropylisocyanide (0.138 ml, 1.51 mmol). The mixture, a yellow solution, was left to stand at room temperature overnight (23.5 hours) before the solvent was evaporated under reduced pressure to leave a yellow gum. The gum was dissolved in 4M hydrogen chloride in dioxan (3 ml, 12 mmol) and left to stand at room temperature for 7.5 hours before it was evaporated under reduced pressure to leave an orange / brown gum. The gum was dissolved in methanol (2 ml) and 4M hydrogen chloride in dioxan (1 ml, 4 mmol) added. The mixture was left to stand at room temperature for 5.5 hours before the solvent was removed by evaporation under reduced pressure. The residue was dissolved in dichloromethane (4ml) and triethylamine (0.5 ml, excess) added. The mixture was stirred at room temperature overnight (18.3 hours) before the solvent was removed by evaporation under reduced pressure. The residue was loaded in dichloromethane onto a SPE column (10g silica, Mega Bond Elut cartridge, pre-eluted with cyclohexane). The column was eluted stepwise (40 – 45 ml each step) with 100% chloroform, 3 : 1 cyclohexane : diethyl ether, 1 : 1 cyclohexane : diethyl ether, 1 : 3 cyclohexane : diethyl ether, 100% diethyl ether, 1 : 1 cyclohexane : ethyl acetate, 1 : 2 cyclohexane : ethyl acetate and 100% ethyl acetate. The 1 : 3 cyclohexane : diethyl ether to 1 : 2 cyclohexane : ethyl acetate fractions inclusive were combined to give a pale yellow solid (336 mg). The solid was loaded in dichloromethane onto 6 preparative chromatography plates (silica gel 60 plates, 20 x 20 cm²). The plates were eluted four times with 30 : 1 dichloromethane : isopropanol. The required band was extracted with 9 : 1 ethyl acetate : methanol to give (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide as a white solid (141mg, 0.28 mmol)

HPLC Rt = 3.46 minutes; m/z [M+H]⁺ = 502.

¹H NMR δ 7.95 (d, 1H), 7.73 (d, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.37 (dd, 1H), 7.16 (m, 4H), 6.79 (d, 1H), 5.79 (d, 1H), 5.37 (s, 1H), 4.11 (m, 1H), 4.03 (br dd, 1H), 3.99 (dd, 1H), 3.16-2.97 (m, 3H), 2.95-2.78 (m, 2H), 1.79 (m, 1H), 1.69 (m, 1H), 1.33 (m, 1H), 1.09 (t, 6H), 0.78 (d, 3H), 0.67 (d, 3H).

Similarly prepared

Example 137

(2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.50 minutes; m/z [M+H]⁺ = 534.

¹H NMR δ 8.66 (d, 1H), 7.82 (d, 1H), 7.67 (dd, 1H), 7.20 (m, 4H), 6.72 (br d, 1H), 6.13 (s, 1H), 5.19 (s, 1H), 4.06 (br dd, 1H), 4.00 (dd, 1H), 3.18 (m, 1H), 3.07 (m, 2H), 2.92

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(m, 1H), 2.81 (m, 1H), 1.86(m, 1H), 1.80 (m, 1H), 1.54 (m, 1H), 1.36 (s, 9H), 0.85 (d, 3H), 0.78 (d, 3H).

Example 138

5 (2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

HPLC Rt = 3.34 minutes; m/z [M+H]⁺ = 504.

¹H NMR δ 7.81 (br s, 1H), 7.18 (m, 5H), 6.79 (d, 1H), 6.44 (br d, 1H), 5.50 (d, 1H), 5.06 (s, 1H), 4.61 (t, 2H), 4.08 (m, 1H), 3.96 (m, 2H), 3.22 (t, 2H), 3.15 (m, 1H), 3.07 (d, 2H),
10 2.90 (m, 1H), 2.79 (dd, 1H), 1.82(m, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.12 (dd, 6H), 0.83 (d, 3H), 0.77 (d, 3H).

Example 139

15 (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.

HPLC Rt = 3.48; m/z [M+H]⁺ = 520

¹H NMR (CDCl₃) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.97 (d, 1H), 6.88 (dd, 1H), 6.82 (d, 1H), 6.58 (m, 1H), 6.06 (m, 2H), 5.64 (s, 1H), 5.02 (m, 1H), 3.95 (m, 2H), 3.16 (m, 1H), 3.07 (m, 2H), 2.89 (m, 1H), 2.77 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.32 (s, 9H), 0.83 (d, 3H), 0.79 (d, 3H)

Example 140

25 (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

Methyl N-[(1R)-2-{[2-(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate

30 To a suspension of L-leucine (2.62g) in methanol (250ml) at -30°C under nitrogen was added a solution of benzofuran-5-carbaldehyde (2.92g) in methanol (15ml) and a suspension of 2-benzyloxyphenylisonitrile (4.19g) in methanol (15ml). The reaction was stirred at -30°C for 2 hours and then allowed to warm to room temperature and stirred for a further 3 days. The solvent was removed *in vacuo* and the residue was passed through a BiotageTM column (3x90g) eluting with cyclohexane: ethyl acetate (5:1) to afford after
35 evaporation of the appropriate fractions methyl N-[(1R)-2-{[2(benzyloxy)phenyl]amino}-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.11g).

HPLC Rt=3.97 minutes, m/z [M+H]⁺ = 499

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Methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate

- 5 A mixture of palladium on carbon (10%, 500mg), methyl N-[(1R)-2-[(2-(benzyloxy)phenyl)amino]-1-(benzofuran-5-yl)-2-oxoethyl]-L-leucinate (5.1g) and ethyl acetate (60ml) was stirred under a hydrogen atmosphere for 5 hours. The reaction was then filtered through Celite and the filter pad was washed with further portions of ethyl acetate. The combined organic fractions were evaporated to give methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (3.429g).
10 HPLC Rt=3.49 min, m/z [M+H]⁺ = 411

Methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate

- 15 A solution of methyl N-[(1R)-1-(benzofuran-5-yl)-2-[(2-hydroxyphenyl)amino]-2-oxoethyl]-L-leucinate (410mg) and 1,1'-thiocarbonyldiimidazole (196mg) in dichloromethane (5ml) was left to stand for 18 hours. Water (20ml) was added to the reaction mixture and this was then stirred rapidly for 30 minutes. After this, 1H-Benzotriazolium, 1-[bis(dimethylamino)methylene]-, tetrafluoroborate(1-), 3-oxide
20 (TBTU, 710mg) and a solution of dimethylamine in tetrahydrofuran (3ml of 2M solution) were added. The reaction mixture was stirred for a further 18 hours and was then passed down an SPE (5g, silica) eluting with a gradient (3:1 to 1:2 cyclohexane: ethyl acetate). The required fractions were combined and evaporated to furnish methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (140mg).
25 HPLC Rt = 2.70 minutes m/z [M+H]⁺ = 347

N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine

- To a solution of methyl N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucinate (520mg) in methanol (5ml) was added a solution of lithium hydroxide (91mg) in water (3ml). After stirring vigorously for 24 hours the solvent was removed *in vacuo*. The residue was diluted with water (10ml) then neutralised with 2N hydrochloric acid. This solution was applied to an OasisTM cartridge (2x6g) and eluted with water (x2) and methanol (x2). The required fractions were combined and evaporated to afford N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg).
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35 HPLC Rt = 2.27 minutes m/z [M+H]⁺ = 333

(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

- 40 To a solution of (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (419mg) in dry tetrahydrofuran (5ml) at -20°C under a nitrogen atmosphere was

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added N-methylmorpholine (158 μ l) and a solution of isopropylchloroformate in toluene (1.0M, 1.44ml). After 10 minutes, a solution of N-[1-(benzofuran-5-yl)-2-(dimethylamino)-2-oxoethyl]-L-leucine (478mg) in dimethylformamide (5ml) was added and the reaction was allowed to warm to room temperature. After 20 hours, the solvent was removed *in vacuo* and the residue was dissolved in 4N hydrochloric acid in dioxan (4ml). After 4 hours methanol (13ml) was added and the reaction was left to stand for a further 18 hours. The solvent was then removed *in vacuo* and the residue was separated between dichloromethane and saturated sodium bicarbonate solution. The organic phase was evaporated *in vacuo* and the residue was applied to an SPE (10g, silica). The product was eluted using an ethyl acetate: methanol gradient (3:1 to 1:3) to afford (2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide (51mg).

HPLC Rt=3.36 minutes, m/z [M+H]⁺ = 488

¹H NMR (D₆-DMSO) δ 8.47 (d, 1H), 8.07 (d, 1H), 7.71 (m, 1H), 7.69 (d, 1H), 7.38 (dd, 1H), 7.21 (m, 2H), 7.12 (m, 2H), 7.03 (m, 1H), 6.47 (s, 1H), 3.88 (m, 1H), 3.69 (dd, 1H), 3.07-2.67 (m, 5H), 2.87 (s, 3H), 2.77 (s, 3H), 1.40-1.70 (m, 2H), 0.46 (m, 1H), 0.42 (d, 3H), 0.02 (d, 3H)

Example 141

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

(2RS)-2-(2-methyl-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

A mixture of 2-methyl-5-formylbenzofuran (1.26g), (D)-leucine methyl ester hydrochloride (1.57g), triethylamine (1.2ml) and methanol (20ml) was stirred at room temperature for 6 hours and then left to stand for 19 hours. N-benzylcarbonyl-(D)-indanylglycine (2.80g) and 2-benzyloxy-phenylisocyanide (1.89g) were then added sequentially and the mixture stirred for 2 days. The reaction mixture was concentrated under reduced pressure and diluted with ethyl acetate. This was washed with 1N hydrochloric acid, saturated sodium bicarbonate solution and brine. The organic phase was dried over MgSO₄ and concentrated *in vacuo*. The residue was diluted with ethyl acetate (100ml) and acetic acid (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (1.5g). After 4 hours the catalyst was removed by filtration through a pad of celite and washed with dichloromethane/methanol (500ml of 1:1 v/v). The filtrate and washings were combined, evaporated under reduced pressure. The residue was separated between ethyl acetate and water. The organic phase was washed with water, saturated sodium bicarbonate solution and brine. The organic phase was dried over MgSO₄ and evaporated under reduced pressure. The residue was applied to a silica cartridge (100g) and eluted with cyclohexane/ethyl acetate (500ml of 3:1, 2:1, 1:1 v/v) and ethyl acetate (500ml). The required fractions were combined and evaporated

in vacuo to give (2RS)-2-(2-methylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (1.58g). HPLC Rt = 3.60 minutes; m/z [M+H]⁺ = 566.

5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

Carbonyldiimidazole (92mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (5mL) and the suspension was left at room temperature for 15 minutes. (2RS)-2-(2-methylbenzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.06mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to a silica cartridge (10g). This was eluted with cyclohexane (100ml), cyclohexane/ethyl acetate (100ml of 2:1, 3:2, 1:1, 2:3 and 1:2 v/v), ethyl acetate (200ml) and ethyl acetate/methanol (100ml of 19:1 v/v). The required fractions were combined and evaporated *in vacuo* to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide as an off-white solid (88mg).

HPLC Rt = 3.40 minutes; m/z [M+H]⁺ = 502.

25 ¹H NMR (CDCl₃) δ 7.52 (d, 1H), 7.43 (d, 1H), 7.27-7.13 (m, 5H), 6.54 (s, 1H), 6.38 (m, 1H), 6.31 (d, 1H), 4.24 (m, 1H), 3.99 (dd, 1H), 3.22-3.05 (m, 3H), 2.99 (s, 3H), 2.86 (m, 1H), 2.82 (s, 3H), 2.75 (m, 1H), 2.48 (m, 3H), 1.45 (m, 1H), 1.36 (m, 1H), 0.57 (m, 1H), 0.51 (d, 3H), 0.19 (d, 3H).

30 Similarly prepared: -

Example 142

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide

35 HPLC Rt = 3.40 minutes; m/z [M+H]⁺ = 516.

¹H NMR (CDCl₃) δ 7.57 (m, 1H), 7.41 (d, 1H), 7.28-7.11 (m, 5H), 6.61 (m, 1H), 6.37 (m, 1H), 5.49 (d, 1H), 5.23 (s, 1H), 4.11 (m, 1H), 4.02-3.93 (m, 2H), 3.19-3.05 (m, 3H), 2.92 (m, 1H), 2.77 (m, 1H), 2.48 (m, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.38 (m, 1H), 1.10 (m, 6H), 0.78 (d, 3H), 0.69 (d, 3H).

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Example 143**(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazin-2,5-dione**HPLC Rt = 3.38 minutes; m/z [M+H]⁺ = 544.

- 5 ¹H NMR (CDCl₃) δ 7.51 (d, 1H), 7.45 (d, 1H), 7.26-7.14 (m, 5H), 6.57 (s, 1H), 6.39 (m, 1H), 6.34 (m, 1H), 4.20 (m, 1H), 3.99 (m, 1H), 3.73-3.33 (6H), 3.22-3.03 (m, 5H), 2.88 (m, 1H), 2.75 (m, 1H), 2.49 (m, 3H), 1.45 (m, 1H), 1.37 (m, 1H), 0.54 (m, 1H), 0.51 (d, 3H), 0.20 (d, 3H).

Example 144**(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide**HPLC Rt = 3.39 minutes; m/z [M+H]⁺ = 505.

- 15 ¹H NMR (CDCl₃) δ 7.56 (d, 1H), 7.45 (d, 1H), 7.32 (dd, 1H), 7.23 (m, 2H), 7.16 (m, 2H), 6.55 (s, 1H), 6.23 (d, 1H), 5.89 (d, 1H), 4.22 (m, 1H), 3.99 (dd, 1H), 3.21-3.04 (m, 3H), 3.00 (s, 3H), 2.87 (m, 1H), 2.84 (s, 3H), 2.75 (m, 1H), 1.47 (m, 1H), 1.38 (m, 1H), 0.58-0.49 (m, 4H), 0.22 (d, 3H).

5-Bromo-2-fluoro-1-benzofuran

- 20 5-Bromobenzofuran-2-carboxylic acid (4.68g) was suspended in carbon tetrachloride (150ml) and water (50ml). To this was added sodium bicarbonate (3.36g), followed by Selectfluor (7.1g) and the reaction mixture was stirred rapidly for 20 hours. The reaction mixture was diluted with dichloromethane and 2N sodium hydroxide solution. The organic phase was separated, washed with brine and dried over anhydrous MgSO₄. The solvent was evaporated under reduced pressure at room temperature. The residue was applied to a silica cartridge (20g) and eluted with diethyl ether. This gave 5-bromo-2-fluoro-1-benzofuran (1.4g).

¹H NMR (CDCl₃) δ 7.61 (d, 1H), 7.36 (dd, 1H), 7.26 (d, 1H), 5.84 (dd, 1H).**2-Fluoro-5-formyl-1-benzofuran**

- 30 A slurry of magnesium powder (219mg) and iodine (cat) in dry tetrahydrofuran (3ml) was heated at 50°C under nitrogen for 20 minutes. 5-Bromo-2-fluoro-1-benzofuran (1.4g) was dissolved in dry tetrahydrofuran (6ml). A 1ml portion of the solution was added to the slurry at 50°C without stirring. After 30 minutes the rest of the solution was added slowly and the reaction was heated at reflux for 3 hours. The reaction was cooled in an ice/water bath and dimethylformamide (1ml) was added dropwise maintaining the temperature below 10°C. After 1 hour a mixture of 2N hydrochloric acid (12.5ml) and brine (12.5ml) was added. The reaction mixture was extracted using ethyl acetate (3x25ml). The combined organics were washed with brine and dried over anhydrous magnesium sulphate. The solvent was removed in vacuo and the residue applied to a silica cartridge (50g). This was eluted with cyclohexane, cyclohexane/ethyl acetate (6:1, 5:1 v/v). This gave 2-fluoro-5-formyl-1-benzofuran (376mg).

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¹H NMR (CDCl₃) δ 10.05 (s, 1H), 8.04 (m, 1H), 7.83 (dd, 1H), 7.54 (d, 1H), 6.01 (dd, 1H).

Example 145

5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide

HPLC Rt = 3.42 minutes; m/z [M+H]⁺ = 520.

¹H NMR (CDCl₃) δ 7.61 (d, 1H), 7.42 (d, 1H), 7.31 (dd, 1H), 7.21 (m, 2H), 7.16 (m, 2H), 6.70 (d, 1H), 5.89 (d, 1H), 5.57 (d, 1H), 5.18 (s, 1H), 4.11 (m, 1H), 3.98 (m, 2H), 3.16 (m, 1H), 3.08 (m, 2H), 2.91 (m, 1H), 2.78 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.41 (m, 1H), 1.12 (d, 3H), 1.10 (d, 3H), 0.81 (d, 3H), 0.72 (d, 3H).

Example 146

15 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione

HPLC Rt = 3.35 minutes; m/z [M+H]⁺ = 548.

¹H NMR (CDCl₃) δ 7.55 (d, 1H), 7.47 (d, 1H), 7.31 (dd, 1H), 7.27-7.14 (m, 4H), 6.58 (s, 1H), 6.38 (d, 1H), 5.91 (d, 1H), 4.19 (m, 1H), 4.00 (dd, 1H), 3.73-3.50 (m, 5H), 3.39 (m, 1H), 3.23-3.04 (m, 5H), 2.87 (m, 1H), 2.76 (m, 1H), 1.47 (m, 1H), 1.40 (m, 1H), 0.53 (d, 3H), 0.51 (m, 1H), 0.24 (d, 3H).

Example 147

25 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide

HPLC Rt = 3.38 minutes; m/z [M+H]⁺ = 487.

¹H NMR (CDCl₃) δ 9.03 (s, 1H), 7.66 (d, 1H), 7.49 (d, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 7.18-7.10 (m, 4H), 7.02 (m, 1H), 6.57 (s, 1H), 6.55 (m, 1H), 4.29 (m, 1H), 4.00 (dd, 1H), 3.22-3.03 (m, 3H), 3.00 (s, 3H), 2.92-2.73 (m, 5H), 1.40 (m, 1H), 1.33 (m, 1H), 0.57 (m, 1H), 0.45 (d, 3H), 0.06 (d, 3H).

Example 148

35 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-methyl-N-[2-(methylsulphonyl)ethyl]ethanamide

HPLC Rt = 3.20 minutes; m/z [M+H]⁺ = 579.

¹H NMR (CDCl₃) δ 9.62 (s, 1H), 7.64 (d, 1H), 7.41 (d, 1H), 7.30 (m, 1H), 7.26-7.10 (m, 6H), 6.51 (m, 1H), 6.48 (s, 1H), 4.18 (m, 1H), 4.05-3.90 (m, 2H), 3.68-3.50 (m, 2H), 3.28-3.01 (m, 4H), 2.96-2.69 (m, 8H), 1.41 (m, 2H), 0.65 (m, 1H), 0.47 (d, 3H), -0.10 (d, 3H).

Example 149

40 (2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

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(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide

- 5 A mixture of 5-formylbenzothiophene (2.0g), (D)-leucine methyl ester hydrochloride (2.24g), triethylamine (1.72ml) and methanol (20ml) was stirred at room temperature for 24 hours. N-*tert*-butoxycarbonyl-(D)-indanylglycine (3.59g) and 2-benzyloxy-phenylisocyanide (2.58g) were then added sequentially and the mixture stirred for 4 days. Then the solvent was removed under reduced pressure. The residue was taken up in
10 dichloromethane (20ml) and 4M hydrogen chloride in 1,4-dioxane (20ml) and the mixture was stirred at room temperature for 2 hours. The solvent and hydrogen chloride were evaporated under reduced pressure. The crude material was dissolved in dichloromethane (30ml) and triethylamine (10ml) added. The mixture was stirred for 18
15 hours before the dichloromethane and excess of triethylamine were removed under reduced pressure. The crude product was dissolved in dichloromethane (100ml) and washed with 1N hydrochloric acid (2x100ml) and brine. The organic phase was dried over MgSO₄ and evaporated *in vacuo* to yield (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide as a brown foam (7.5g).
20 HPLC Rt = 3.88 minutes, m/z [M+H]⁺ = 658.

(2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide

- 25 (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-benzyloxyphenyl)ethanamide (1.0g) was dissolved in dichloromethane (5ml) and to this was added dropwise a 1.0M solution of BBr₃ in dichloromethane (2.0ml). The reaction mixture was stirred at room temperature for 2
30 hours. To the reaction mixture was added 1N hydrochloric acid (30ml) and dichloromethane (20ml). The phases were separated and the organic phase was washed with 1N hydrochloric acid (30ml) and brine (30ml). The organic phase was dried over MgSO₄ and evaporated *in vacuo*. The residue was purified by BiotageTM flash column chromatography, eluting with 3:2 ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-
35 hydroxyphenyl)ethanamide (210mg).

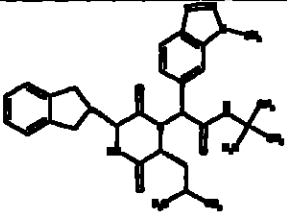
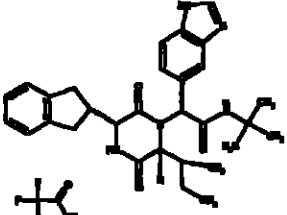
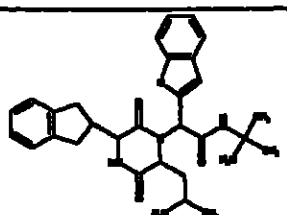
HPLC Rt = 3.55 minutes, m/z [M+H]⁺ = 568.

- 40 (2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide

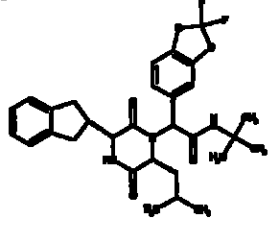
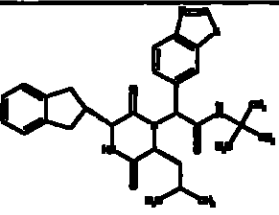
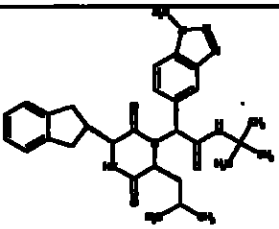
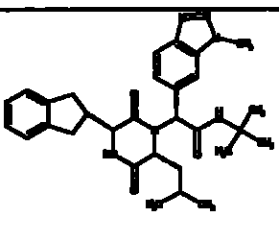
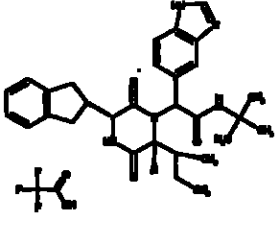
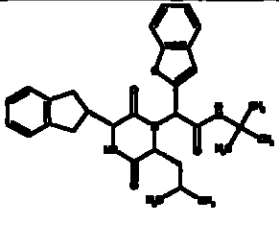
70

Carbonyldiimidazole (100mg) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. 2RS)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)ethanamide (200mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (1.0mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was evaporated under reduced pressure. The crude product was purified by silica column chromatography eluting with 1:1v/v ethyl acetate:cyclohexane. The required fractions were combined and evaporated *in vacuo* to give (2R)-2-(benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide as a white solid (90mg).
HPLC Rt = 3.35 minutes, m/z [M+H]⁺ = 504.
¹H NMR (CDCl₃) δ 7.94 (d, 1H), 7.89 (m, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.41 (m, 1H), 7.35 (d, 1H), 7.23 (m, 1H), 7.13 (m, 3H), 6.63 (s, 1H), 4.25 (m, 1H), 4.02 (dd, 1H), 3.23-3.04 (m, 3H), 3.01 (s, 3H), 2.93-2.77 (m, 5H), 1.50-1.32 (m, 2H), 0.52 (m, 1H), 0.49 (d, 3H), 0.12 (d, 3H).

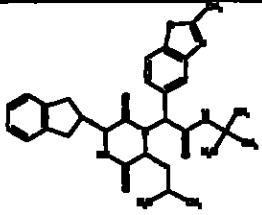
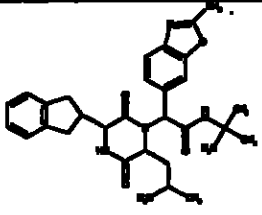
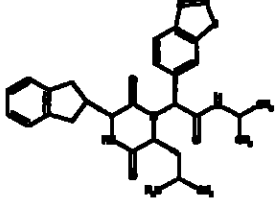
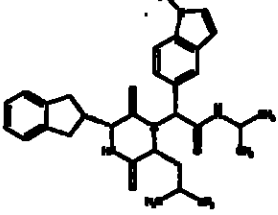
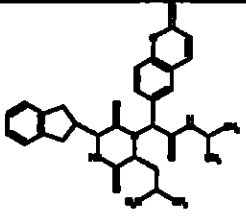
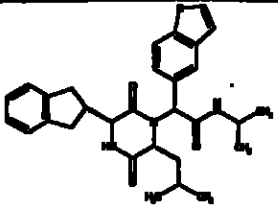
Compounds 150-169 and 174-175 were prepared via method 1. Compound 170 was prepared via method 2. Compounds 171, 172 and 173 were prepared via method 5.

No.	Regno	MWt	Rt/min	MH +	MH -	Name
150		517.7	3.62	518	516	(2R)-N-(tert-butyl)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
151		516.6	3.12	517	515	2-(1H-1,2,3-benzotriazol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]acetamide
152		533.7	3.42	534		(2R)-N-(tert-butyl)-2-(2,3-dihydro-1,4-benzodioxin-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

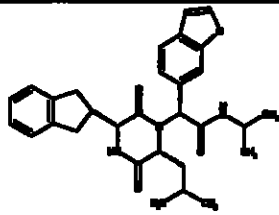
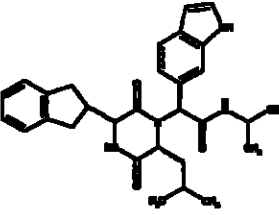
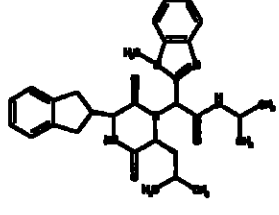
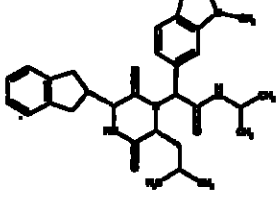
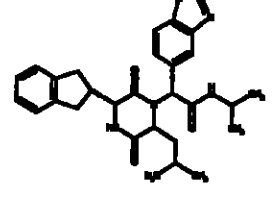
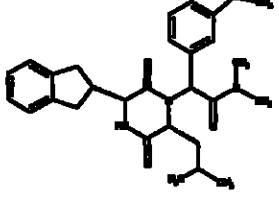
71

153		555.6	3.71	556	554	(2R)-N-(tert-butyl)-2-(2,2-difluoro-1,3-benzodioxol-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
154		532.7	3.32	533	531	(2R)-2-(1,3-benzothiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
155		530.7	3.18	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-5-yl)ethanamide
156		530.7	3.22	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1-methyl-1H-1,2,3-benzotriazol-6-yl)ethanamide
157		629.7	3.06		514	(2R)-2-(1H-benzimidazol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide trifluoroacetate
158		515.7	3.72	516	514	(2R)-2-(1-benzofuran-2-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide

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159		530.7	3.3	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-5-yl)ethanamide
160		530.7	3.35	531	529	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-methyl-1,3-benzoxazol-6-yl)ethanamide
161		519.7	3.37	520	518	(2R)-2-(1,2,3-benzothiadiazol-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
162		514.7	3.41	515		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-indol-5-yl)ethanamide
163		529.6				(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-oxo-2H-chromen-6-yl)ethanamide
164		517.7	3.53	518	516	(2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide

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165		501.6	3.42	502	500	(2R)-2-(1-benzofuran-6-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
166		500.6	3.35	501	499	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N-isopropylethanamide
167		515.7	4.88	516	514	2R-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-2-yl)acetamide
168		515.7	4.32	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-6-yl)ethanamide
169		515.7	2.65	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-benzimidazol-5-yl)ethanamide
170		502.6	3.35	503	501	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(3-methyl-1,2-benzisoxazol-5-yl)ethanamide

171		486.6	3.07	487	485	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-5-yl)-N,N-dimethylethanamide
172		487.6	2.94	488		(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-5-yl)-N,N-dimethylethanamide
173		487.6	2.99	488	486	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indazol-6-yl)-N,N-dimethylethanamide
174		511.7	3.56	512		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-naphthyl)acetamide
175		512.7	3.19	513		(2R,S)-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-quinolin-6-ylacetamide

Example 176

5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

To a solution of 5-trifluoromethyl-furan-2-carbaldehyde (140mg)[prepared as in ref. Chem. Heterocycl. Compd. 13, 1977, 1280-1282 by R.V.Grigorash, V.V.Lyalin, L.A.Alekseeva and L.M.Yagupol'skii: 5-Trifluoromethylfuran Derivatives] in methanol

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(1.1ml) was added triethylamine (118 μ l) and (D)-leucine t-butyl ester hydrochloride (190mg). The mixture was left to stand for 16.33 hours before (2R)-[(tert-butoxycarbonyl)amino](2,3-dihydro-1H-inden-2-yl)ethanoic acid (246mg) and isopropylisocyanide (77.4 μ l) were sequentially added. The mixture, a yellow solution, was left to stand for 24 hours before the solvent was removed *in vacuo*. The residue was dissolved in 4M hydrogen chloride in dioxane (3ml) and left to stand for 6.75 hours at ambient temperature. After this time, the solvent was removed *in vacuo*. The residue was dissolved in methanol (4ml) and treated with a solution of 4M hydrogen chloride in dioxane (0.2ml) and was left to stand overnight. After this time, the solvent was removed *in vacuo*. The residue was stirred in dioxane (9.5ml) containing triethylamine (0.5ml) and dichloromethane (5ml) for 4.75 hours. Then the mixture was evaporated *in vacuo* to leave a light brown solid. This crude material was purified by SPE column (10g, silica Mega Bond ElutTM) eluting stepwise with 100% chloroform, 4:1 cyclohexane : diethyl ether, 3:1 cyclohexane : diethyl ether, 2:1 cyclohexane : diethyl ether, 1:1 cyclohexane : diethyl ether, 1:2 cyclohexane : diethyl ether, 1:3 cyclohexane : diethyl ether, 100% diethyl ether, 1:1 ethyl acetate : cyclohexane, 2:1 ethyl acetate : cyclohexane, 3:1 ethyl acetate : cyclohexane, 100% ethyl acetate. The 1:2 cyclohexane : diethyl ether to 2:1 ethyl acetate : cyclohexane fractions inclusive were combined to give an orange gum (215mg). The gum was purified further, to separate the isomers, by preparative plate chromatography. Whatman PK6F silicagel 60 plates 20 x 20 cm², eluted in 1:1 ethyl acetate : cyclohexane six times and extracted with 9:1 ethyl acetate : methanol to give (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide (64mg).
HPLC Rt = 3.59 minutes; m/z [M+H]⁺ = 520.

¹H NMR (CDCl₃) δ 7.88 (d, 1H), 7.16 (m, 4H), 6.85 (d, 1H), 6.74 (d, 1H), 6.30 (d, 1H), 5.73 (s, 1H), 4.19 (dd, 1H), 4.08 (m, 1H), 3.97 (dd, 1H), 3.14 (m, 2H), 3.01 (m, 1H), 2.84 (m, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.15 (d, 6H), 1.11 (m, 1H), 0.82 (dd, 6H).

Similarly prepared

Example 177

(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide

By the procedure of Example 176 but using 5-methyl-thiophene-2-carbaldehyde

HPLC Rt = 3.46 minutes; m/z [M+H]⁺ = 482.

¹H NMR (CDCl₃) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.94 (d, 1H), 6.67 (d, 1H), 6.63 (d, 1H), 5.73 (d, 1H), 4.94 (s, 1H), 4.07 (m, 1H), 3.93 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.93 (m, 1H), 2.77 (m, 1H), 2.47 (s, 3H), 1.96 (m, 1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.17 (d, 3H), 1.12 (d, 3H), 0.94 (d, 3H), 0.92 (d, 3H)

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Example 178

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

- 5 N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide
 A mixture of 5-trifluoromethyl-furan-2-carbaldehyde (351mg), (D)-leucine methyl ester hydrochloride (389mg), triethylamine (0.298ml) and methanol (2.2ml) was stirred at room temperature for 4 hours and then left to stand for 19 hours. N-*tert*-butoxycarbonyl-
 10 (D)-indanylglycine (623mg) and 2-benzyloxy-phenylisocyanide (448mg) were then added sequentially and the mixture stirred for 7 hours before being left to stand at room temperature for 41 hours. Then the solvent was removed under reduced pressure to leave an orange / brown syrup. This was taken up in 4M hydrogen chloride in 1,4-dioxane (2.8ml) and the mixture was stirred at room temperature for 2 hours. The solvent and hydrogen chloride were evaporated under reduced pressure. The crude material was
 15 dissolved in methanol (5ml) and triethylamine (0.54ml) added. The mixture was stirred for 18 hours before the methanol and excess of triethylamine were removed under reduced pressure. The crude product was purified by BiotageTM flash column chromatography (40g silica cartridge eluted with 1:5 ethyl acetate:cyclohexane (600ml), 1:3 ethyl acetate:cyclohexane (400ml) and 1:2 ethyl acetate:cyclohexane (450ml)) to
 20 yield N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide as an orange solid (472mg).
 25 HPLC Rt = 4.04 minutes, m/z [M+H]⁺ = 660.

2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide

- 30 N-[2-(benzyloxy)phenyl]-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[5-(trifluoromethyl)-2-furyl]acetamide (469mg) was dissolved in ethyl acetate (10ml) and hydrogenated at atmospheric pressure over 10% palladium on activated carbon (100mg). After 4 hours the catalyst was removed by filtration through glass fibre filters and washed with ethyl acetate. The filtrate and washings were
 35 combined, evaporated under reduced pressure and dried *in vacuo* at room temperature to leave a yellow / brown solid (400mg). The solid was dried over P₂O₅ overnight to give 2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-[5-(trifluoromethyl)-2-furyl]acetamide (365mg).
 HPLC Rt = 3.64 minutes, m/z [M+H]⁺ = 570.
 40

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide

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Carbonyldiimidazole (78mg, 1.6 equiv.) was suspended in anhydrous dichloromethane (1mL) and the suspension was left at room temperature for 15 minutes. (R)-N-(2-Hydroxy-phenyl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(5-trifluoromethyl-furan-2-yl)-acetamide (172mg) was then added and the mixture was stirred at room temperature for 5 hours 20 minutes. The resulting brown solution was then treated with a 2.0M solution of dimethylamine in tetrahydrofuran (0.9mL, 6 equiv.) and the resulting mixture was stirred for 30 minutes and then left to stand at room temperature for 18 hours 15 minutes. The reaction mixture was diluted with dichloromethane (2mL) and washed with 1M hydrochloric acid (2mL). The organic phase was separated using a hydrophobic frit and was evaporated under reduced pressure to leave a brown gum. The crude product was applied to 3 preparative chromatography plates, which were eluted with 1:1v/v ethyl acetate:cyclohexane. The required band was extracted with ethyl acetate to give the (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide as a pale yellow solid (87mg).
HPLC Rt = 3.51 minutes, m/z [M+H]⁺ = 506.
¹H NMR (CDCl₃) δ 7.19 (m, 5H), 6.86 (dd, 1H), 6.64 (d, 1H), 6.61 (s, 1H), 4.25 (m, 1H), 3.97 (dd, 1H), 3.20-3.02 (m, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 2.88 (m, 1H), 2.80 (m, 1H), 1.70 (m, 1H), 1.67 (m, 1H), 0.74 (d, 3H), 0.70 (m, 1H), 0.63 (d, 3H).

Example 179

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

By the procedure of Example 178, using (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

HPLC: Rt = 2.88 minutes ; m/z (M+H)⁺ = 453

(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide

A mixture of 2-methyl-oxazole-4-carbaldehyde⁽¹⁾ (340mg), (D)-leucine methyl ester hydrochloride (568mg), triethylamine (0.435ml) and anhydrous methanol (20ml) was stirred at room temperature for 18 hours. N-benzyloxycarbonyl-(D)-indanylglycine (1.015g) and 2-benzyloxy-phenylisocyanide (648mg) were then added sequentially and the mixture stirred for 12 days before being left to stand at room temperature for 10 days. The solvent was removed under reduced pressure to leave a dark orange gum which was dissolved in ethyl acetate (150mL) and washed with 2M hydrochloric acid (100mL), saturated sodium bicarbonate solution (100mL) and saturated sodium chloride solution (50mL) then dried over anhydrous magnesium sulphate and concentrated under reduced pressure to a volume of 5mL. This crude solution was diluted with ethanol (80mL)

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- containing acetic acid (1.6mL) and added under vacuum to 10% palladium on carbon (50% water, 425mg). The resulting suspension was stirred under an atmosphere of hydrogen for 20 hours, filtered (celite filteraid) washed with ethanol (50mL) and the filtrate added under vacuum to a second quantity of 10% palladium on carbon (50% water, 670mg). The suspension was stirred under an atmosphere of hydrogen for 2 hours, the hydrogenation apparatus was then evacuated and refilled with hydrogen and the suspension stirred for a further 20 hours. The suspension was filtered (celite filteraid) washed with ethanol (200mL) and the combined filtrates concentrated under reduced pressure. The residue was partitioned between saturated sodium bicarbonate solution (100mL) and dichloromethane (60mL), then the organic layer dried (hydrophobic frit) and the solvent removed under reduced pressure. Purification by Biotage flash chromatography (40g silica) eluting with ethyl acetate : cyclohexane (3:1, 300mL) ethyl acetate (300mL) then ethyl acetate : methanol (20:1, 600mL) gave (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyphenyl)-2-(2-methyl-1,3-oxazol-4-yl)ethanamide as a brown foam (197mg).
HPLC : Rt = 3.28 minutes ; m/z (M+H)⁺ = 517
Ref (1) CAS 113732-84-6

Example 180

- (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
By the procedure of Example 179, using morpholine
HPLC: Rt = 2.89 minutes ; m/z (M+H)⁺ = 495

Example 181

- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
By the procedure of Example 180, using 5-methyl-thiophene-2-carbaldehyde
HPLC Rt = 3.25 minutes; m/z M⁺ = 468.

Example 182

- (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
By the procedure of Example 178, using 3-fluoro-5-methyl-thiophene-2-carbaldehyde
HPLC: Rt = 3.20 minutes ; m/z M⁺ = 486

2-(3-Bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane

- 3-Bromo-5-methyl-2-thiophenecarbaldehyde (1.00g) was dissolved in dry 1,4-dioxane (8ml). Molecular sieves (4 Angstrom, 2g), 1,3-propanediol (9ml), p-toluene sulphonic acid (362mg) were added and the mixture was stirred under a nitrogen atmosphere, at room temperature, over night. Molecular sieves were removed by filtration and the filtrate evaporated. The residue was taken up with ethyl acetate and washed with

saturated solution of sodium carbonate. The aqueous was extracted with more ethyl acetate and the combined layers washed with brine, dried over magnesium sulphate, filtrated and concentrated to a yellow oil (1g).

- 5 Purification was performed by filtration on a SPE cartridge (Silica-10g) using dichloromethane as eluent. The solution was eventually concentrated to yield 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane as a yellow solid (1.18g).
¹H-NMR (CDCl₃, 400MHz): 6.60ppm (s, 1H); 5.72ppm (s, 1H); 4.23ppm (m, 2H); 3.98ppm (m, 2H); 2.44ppm (d, 3H); 2.22ppm (m, 1H); 1.42ppm (m, 1H).

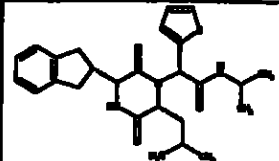
10

3-Fluoro-5-methyl-thiophene-2-carbaldehyde

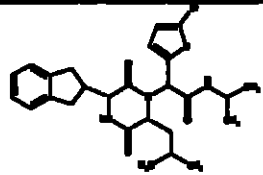
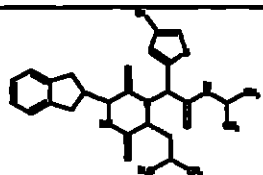
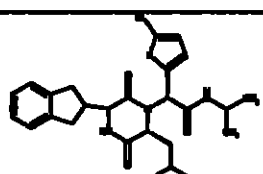
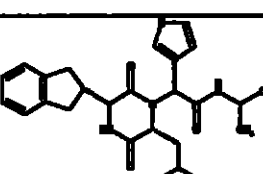
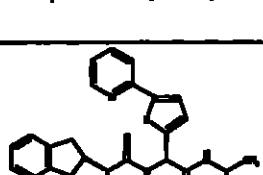
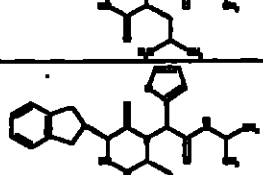
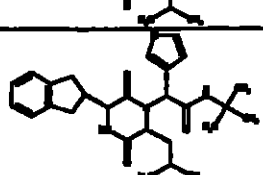
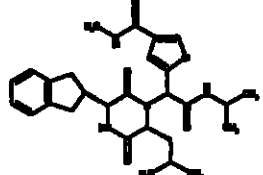
- To a solution of 2-(3-bromo-5-methyl-thiophen-2-yl)-[1,3]dioxane (1.16g) in dry tetrahydrofuran (10ml), under a nitrogen atmosphere, at -78 °C, 1.6M *n*-butyl lithium in hexane (3.30ml) was added dropwise. After 15 minutes stirring, N-fluoro-benzene-sulfonyl-imide (1.66g) was added portionwise. The solution was stirred at -78 °C for further 10 minutes, allowed to warm to room temperature and then stirred for a further 60 minutes. The reaction was quenched with water (5ml), diluted with diethyl ether (20ml) and washed with 1N sodium hydroxide (30ml). The aqueous was extracted with diethyl ether again (2x10ml), the combined organic layers were dried over magnesium sulphate, filtrated and evaporated. The residue was redissolved in 1,4-dioxane (15ml) and water (10), p-toluene sulphonic acid (837mg) was added and the solution was stirred at room temperature, over night. Neutralised with a saturated solution of sodium bicarbonate (10ml), then extracted with ether twice. The organic was dried over magnesium sulphate and evaporated at reduced pressure (200mbar). The residual dioxane was removed by distillation at reduced pressure, the residue further purified by flash chromatography (petroleum ether / dichloromethane 55/45), giving 3-fluoro-5-methyl-thiophene-2-carbaldehyde as a colourless oil (366mg), approximately 70% pure.
¹H-NMR (CDCl₃, 400MHz): δ 9.93ppm (s, 1H); 6.62ppm (s, 1H); 2.52ppm (m, 3H).

- 30 Similarly prepared:

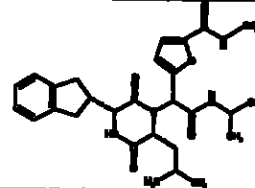
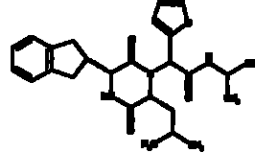
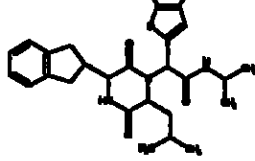
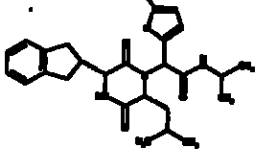
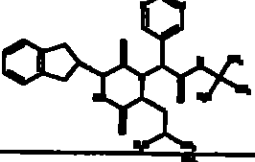
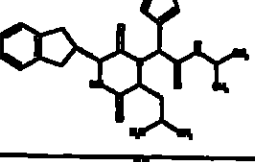
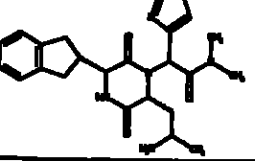
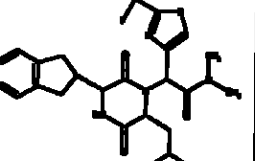
Compounds 183 -206,213,215,218,222-225 were prepared via method 1. Compounds 207,208,216, were prepared via method 2. Compounds 209-212, 214,217,219-221 and 226 were prepared via method 5.

Eg No.	Structure	MWt	Rt /min	+ve ion	-ve ion	name
183		467.7	3.4	468	466	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-2-ylethanamide

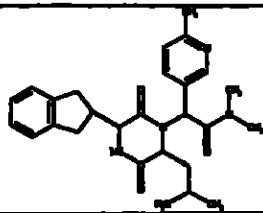
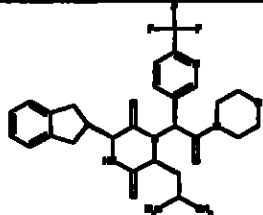
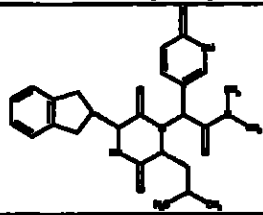
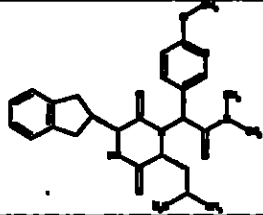
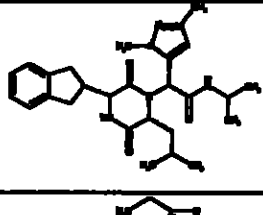
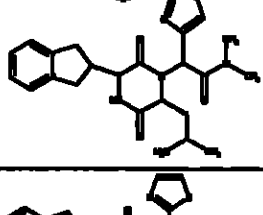
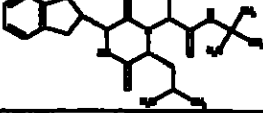
80

184		546.6	3.6	546/5 48	546/5 44	(2S)-2-(5-bromothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
185		546.6	3.6	546/5 48	544/5 46	(2S)-2-(4-bromothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
186		502.1	3.6	501-3	499- 501	(2S)-2-(5-chlorothiophen-2-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
187		467.7	3.3	468	466	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-thien-3-ylethanamide
188		544.8	3.4	545	543	(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-pyridin-2-ylthien-2-yl)ethanamide
189		451.6	3.3	452	450	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-furyl)-N-isopropylethanamide
190		465.7	3.4	466	464	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-furyl)ethanamide
200		508.7	2.9	509	507	5-[1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-3-furamide

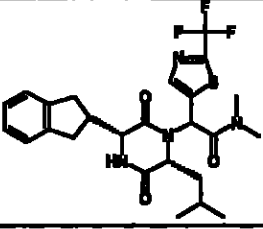
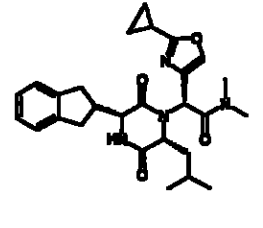
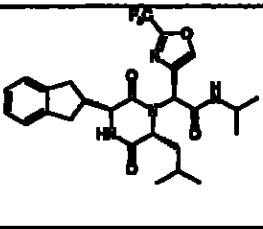
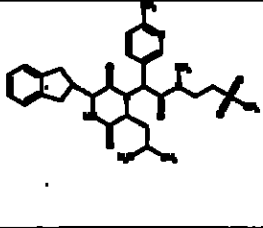
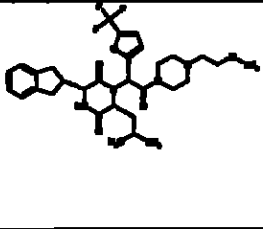
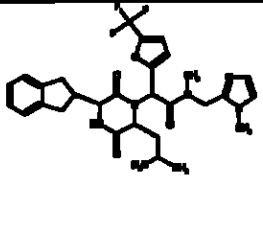
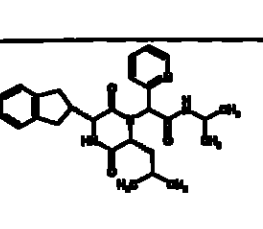
81

201		508.7	3	509	507	5-[(1R)-1-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(isopropylamino)-2-oxoethyl]-N-methyl-2-furamide
202		530.5	3.5	529/531	527/529	(2R)-2-(5-bromo-2-furyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide
203		479.7	3.5	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4,5-dimethyl-2-furyl)-N-isopropylethanamide
204		465.7	3.4	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methyl-2-furyl)ethanamide
205		477.6	3.3	478	476	(2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-pyrimidin-5-ylethanamide
206		465.7	2.9	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(1-methyl-1H-pyrazol-4-yl)ethanamide
207		468.7	3	469	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-thiazol-4-yl)ethanamide
208		522.6	3.4	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-4-yl]ethanamide

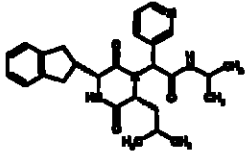
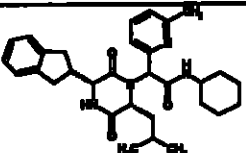
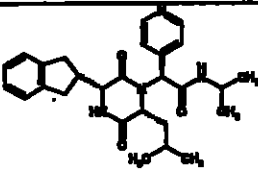
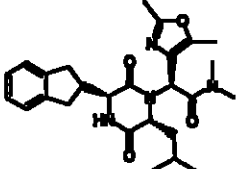
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209		462.7	3.1	463	none	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-methylpyridin-3-yl)ethanamide
210		558.7	3.3	559	557	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-2-morpholin-4-yl-2-oxo-1-[6-(trifluoromethyl)pyridin-3-yl]ethyl]piperazine-2,5-dione
211		464.6	2.7	465	463	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(6-oxo-1,6-dihydropyridin-3-yl)ethanamide
212		478.6	3.04	479.23	477.26	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(6-methoxypyridin-3-yl)-N,N-dimethylethanamide
213		479.6	3.03	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-dimethyl-1H-pyrazol-5-yl)-N-isopropylethanamide
214		466.56	3.1	467	-	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-ethyl-1,3-oxazol-4-yl)-N,N-dimethylethanamide
215		482.6	3.58	483	481	N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1,3-thiazol-2-yl)acetamide

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216		522.6	3.46	523	521	2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[2-(trifluoromethyl)-1,3-thiazol-5-yl]acetamide
217		478.6	3.07	479	477	(2R)-2-(2-cyclopropyl-1,3-oxazol-4-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
218		520.5	3.47	521	519	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[2-(trifluoromethyl)-1,3-oxazol-4-yl]ethanamide
219		554.7	2.8	555	553	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-2-(6-methylpyridin-3-yl)-N-[2-(methylsulfonyl)ethyl]ethanamide
220		604.7	2.7	605	603	(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-2-[4-(2-methoxyethyl)piperazin-1-yl]-2-oxo-1-[5-(trifluoromethyl)-2-furyl]ethyl]piperazine-2,5-dione
221		585.6	2.8	586	584	(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[(1-methyl-1H-imidazol-2-yl)methyl]-2-[5-(trifluoromethyl)-2-furyl]ethanamide
222		462.6	3.29	463	461	2-[(3R,6R)-3-Inden-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl]-N-isopropyl-2-pyridin-2-yl-acetamide

81

223		462.6	3.09	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-3-yl-acetamide
224		516.7	3.41	517	515	N-Cyclohexyl-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-2-(6-methyl-pyridin-2-yl)-acetamide
225		462.6	2.93	463	461	2-((3R,6R)-3-Indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N-isopropyl-2-pyridin-4-yl-acetamide
226		466.6	3.06	467	-	(R)-2-(2,5-Dimethyl-oxazol-4-yl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperazin-1-yl)-N,N-dimethylacetamide

Example 227

(3R,6R)-1-[[(1R)-1-(2,4-Difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

- 5 The azetidinol (Example 15) (57 mg) in anhydrous dichloromethane (2 mL) was stirred at -5°C and diethylaminosulfur trifluoride (50 µL, excess) was added in one portion. The mixture was left at room temperature overnight and saturated aqueous sodium hydrogen carbonate (3 mL) was added. The mixture was diluted with dichloromethane (10 mL)
- 10 and the organic phase was separated using a hydrophobic frit and blown down with nitrogen. The crude reaction mixture was purified using the mass-directed autoprep system to give (3R,6R)-1-[[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione (26 mg) as a white solid.
- 15 HPLC Rt = 3.34 minutes, m/z [M+H]⁺ = 514

65

Pharmacy Examples

Tablets

- 5

a)

Compound of the invention

Lactose

Microcrystalline Cellulose

Cross-linked polyvinylpyrrolidone

Magnesium Stearate

Compression weight

50.0mg

70.0mg

70.0mg

8.0mg

2.0mg

200.0mg
- 10

The compound of the invention, microcrystalline cellulose, lactose and cross-linked polyvinylpyrrolidone are sieved through a 500 micron sieve and blended in a suitable mixer. The magnesium stearate is sieved through a 250 micron sieve and blended with the active blend. The blend is compressed into tablets using suitable punches.
- 15

b)

Compound of the invention

Lactose

Pregelatinised Starch

Cross-linked polyvinylpyrrolidone

Magnesium Stearate

Compression weight

50.0mg

120.0mg

20.0mg

8.0mg

2.0mg

200.0mg
- 20

The compound of the invention, lactose and pregelatinised starch are blended together and granulated with water. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granule. The resultant blend is compressed using suitable tablet punches.

Capsules

- 25

a)

Compound of the invention

Lactose

Magnesium Stearate

Fill weight

50.0mg

148.0mg

2.0mg

200.0mg
- 30

The compound of the invention and pregelatinised starch are screened through a 500 micron mesh sieve, blended together and lubricated with magnesium stearate, (meshed through a 250 micron sieve). The blend is filled into hard gelatine capsules of a suitable size.
- 35

b)

Compound of the invention

Lactose

Polyvinylpyrrolidone

Cross-linked polyvinylpyrrolidone

50.0mg

132.0mg

8.0mg

8.0mg

46

Magnesium Stearate	2.0mg
Fill weight	200.0mg

5 The compound of the invention and lactose are blended together and granulated with a solution of polyvinylpyrrolidone. The wet mass is dried and milled. The magnesium stearate and cross-linked polyvinylpyrrolidone are screened through a 250 micron sieve and blended with the granules. The resultant blend is filled into hard gelatine capsules of a suitable size.

10 Injection Formulation

	% w/v
Compound of the invention	0.10
Water for injections B.P. to	100.00

15 Sodium chloride may be added to adjust the tonicity of the solution and the pH may be adjusted to that of maximum stability and/or to facilitate solution of the compound of the invention using dilute acid or alkali or by the addition of suitable buffer salts. Solubilisers, such as cosolvents, may also be added to facilitate solution of the compound of the invention. Antioxidants and metal chelating salts may also be included. The solution is clarified, made up to final volume with water and the pH remeasured and adjusted if necessary, to provide 1mg/ml of the compound of formula (I).

25 The solution may be packaged for injection, for example by filling and sealing in ampoules, vials or syringes. The ampoules, vials or syringes may be aseptically filled (e.g. the solution may be sterilised by filtration and filled into sterile ampoules under aseptic conditions) and/or terminally sterilised (e.g. by heating in an autoclave using one of the acceptable cycles). The solution may be packed under an inert atmosphere of nitrogen.

 Preferably the solution is filled into ampoules, sealed by fusion of the glass and terminally sterilised.

30 Further sterile formulations are prepared in a similar manner containing 0.05, 0.20 and 0.5% w/v of the compound of the invention, so as to provide respectively 0.5, 2 and 5mg/ml of the compound of the invention.

35 Measurement of Oxytocin Antagonist Activity

 Assay Buffer used throughout the assay: 50mM HEPES, 10mM MgCl₂, 0.125mg/ml BSA, pH adjusted to 7.4 with KOH.

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hOT-CHO membranes were prepared at a concentration of 0.3mg protein/ml in assay buffer. Test compounds were initially dissolved in DMSO (to 10mM) and diluted in DMSO (Beckman Biomek FX). 1µl of compound was transferred to black 384 assay plates (NUNC) using a Biomek FX. 20µl of 1nM Bodipy TMR Oxytocin (Perkin Elmer) in assay buffer was added to all wells (Labystems Multidrop) then 20µl membrane added to all wells (Multidrop). Plates were incubated at room temp for 60 min.

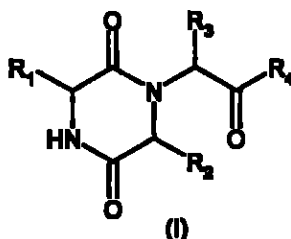
Polarisation was read on LJI Analyst ($\lambda_{Ex}=535nm$, $\lambda_{Em}=580nm$, $\lambda_{Dichroic}=555nm$). Data were fitted to a 4 parameter logistic equation. An estimated K_i was calculated as $IC_{50/5}$.

In the above test compounds of the invention in general have a pK_i value within the range of 7 to 11. Thus the compounds of examples 1 to 227 have a pK_i within the range 8.5 to 10.8.

The compounds of the invention are essentially non toxic at therapeutically active doses. Thus compound of the example 10 has been administered to rats at doses of up to 300mg/kg p.o for 4 days. and no adverse toxicological effects were observed.

Claims

1. A method of treating or preventing diseases or conditions mediated through the action of oxytocin which comprises administering to a mammal in need thereof of an effective amount of a compound of the formula (I)



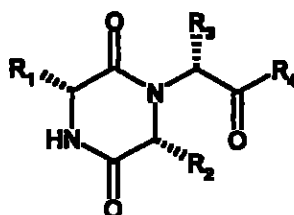
and/or a physiologically acceptable derivative thereof, wherein:

- 10 R_1 represents aryl (C_{1-4}) alkyl or a 5-7 membered cycloalkyl group optionally substituted with one or more hydroxyl groups which is fused to an optionally substituted benzene ring;
- R_2 represents C_{1-6} alkyl (optionally substituted by a C_{1-2} alkoxy, C_{1-2} alkylthio, di(C_{1-2} alkyl) amino or a C_{3-6} cycloalkyl group) or C_{3-6} cycloalkyl, or 5-6 membered heterocyclic group
- 15 containing a single hetero atom selected from O, S or N, which nitrogen atom carries a hydrogen atom or a methyl or ethyl group;
- R_3 represents optionally substituted phenyl, a 5 or 6 membered hetero aryl group or a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused
- 20 rings is benzene;
- R_4 represents OH or OC_{1-4} alkyl (optionally substituted with C_{1-4} alkylcarbonyloxy) or NR_5R_6 ;
- R_5 represents hydrogen, C_{1-6} alkyl (optionally substituted with C_{1-4} alkoxy) or C_{3-7} cycloalkyl;
- 25 R_6 represents hydrogen, methyl, C_{1-4} alkoxy, C_{3-7} cycloalkyl, C_{2-4} alkyl [optionally substituted with one or more groups selected from: carboxyl, C_{1-4} alkylsulphonyl, or C_{1-4} alkoxycarbonyl], C_{2-4} alkyl [optionally substituted with one or more groups selected from halogen, hydroxy, C_{1-4} alkoxy or NR_7R_8 wherein R_7 and R_8 independently represent hydrogen or C_{1-4} alkyl or together with the nitrogen atom to which they are attached to
- 30 form a 3-7 membered saturated heterocyclic ring which may contain an additional heteroatom selected from O, S or N (and which heterocyclic group may be substituted by 1 to 3 groups selected from C_{1-3} alkyl, hydroxy, C_{1-3} alkoxy (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl), C_{3-6} cycloalkyl or NR_9R_{10} wherein R_9 and R_{10} each independently represent a group selected from C_{1-3} alkyl (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl) or C_{3-6} cycloalkyl]] or R_6 represents a
- 35 phenyl or benzyl group (optionally substituted by one or more methoxy or benzyloxy groups) or an optionally substituted heteroarylmethyl group or a heteroaryl group or C_{3-7}

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cycloalkyl or the group $\text{CH}_2\text{CONR}_9\text{R}_{10}$ wherein R_9 represents hydrogen or C_{1-4} alkyl, R_{10} represents hydrogen, C_{1-4} alkyl optionally substituted by a 5 or 6 membered heteroaryl group or $\text{R}_9, \text{R}_{10}$ and the nitrogen atom to which they are attached together form a 5 or 6 membered saturated heterocyclic ring and wherein the 6 membered heterocyclic group may contain an additional heteroatom selected from oxygen, sulphur or nitrogen and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4} alkyl or C_{1-4} alkanoyl group; or R_5 and R_6 together with the nitrogen atom to which they are attached form a 3 to 7 membered saturated heterocyclic ring which heterocycle may contain an additional heteroatom selected from oxygen, sulphur and nitrogen and wherein the sulphur atom may be in an oxidised form e.g. SO_2 and the additional nitrogen atom either carries a hydrogen atom or a C_{1-4} alkyl or a C_{1-4} alkanoyl group or a C_{1-4} alkylsulphonyl group or a C_{1-3} alkoxy C_{2-4} alkyl [and which heterocyclic groups may be substituted by one or more halogen atoms or a group selected from C_{1-3} alkyl, hydroxy, oxo, C_{3-6} cycloalkyl or NR_eR_f wherein R_e and R_f each independently represent a group selected from C_{1-3} alkyl (optionally substituted by C_{3-6} cycloalkyl or optionally substituted phenyl) or C_{3-6} cycloalkyl.].

2. A compound of formula (1) as defined in claim 1 wherein R_1 is a 2-indanyl group and R_2, R_3 and R_4 have the meanings defined in claim 1.
3. A compound of formula (1) as defined in claim 1 or claim 2 wherein R_4 is hydroxy or the group NR_5R_6 .
4. A compound of formula (1) as defined in claim in any of claims 1 to 3 wherein the compounds have the stereochemistry as defined in formula (1a).



(1a)

wherein the groups $\text{R}_1, \text{R}_2, \text{R}_3$ and R_4 have the meanings defined for formula (I).

5. A compound of formula (1) as defined in claim in any of claims 1 to 4 wherein R_2 is a group selected from 1-methylpropyl or 2-methylpropyl.
6. A compound of formula (1) as defined in claim in any of claims 1 to 5 wherein R_3 is an optionally substituted phenyl group.

aD

7. A compound of formula (1) as defined in claim in any of claims 1 to 6 wherein R_3 is a 5 or 6 membered hetero aryl group.
8. A compound of formula (1) as defined in claim in any of claims 1 to 7 wherein R_3 is a fused bicyclic ring system containing 9-10 ring members which may be a carbocyclic group or it may contain up to 3 heteroatoms selected from O, S or N and one of the fused rings is benzene.
9. A compound of formula (1) as defined in claim in any of claims 1 to 8 wherein R_3 is a group selected from phenyl, 2-fluorophenyl, 3-fluorophenyl, 4-fluorophenyl, 4-chlorophenyl, 3-chlorophenyl, 2-chlorophenyl, 4-bromophenyl, 2,3-difluorophenyl, 3,4-difluorophenyl, 2,4-difluorophenyl, 3,5-difluorophenyl, 2,5-difluorophenyl, 2-chloro-4-fluorophenyl, 2,4-dichlorophenyl, 3,4-dichlorophenyl, 2 fluoro-4-bromophenyl, 4-chloro-3-fluorophenyl, 2,3,4-trifluorophenyl, 2,4,5-trifluorophenyl or 2,4,6-trifluorophenyl, 2-fluoro-4,5-dimethoxyphenyl, 3-fluoro-4-methoxyphenyl, 4-fluoro-3-methoxyphenyl, 2-fluoro-4 methoxyphenyl, 2- fluoro-4 hydroxyphenyl, 2-fluoro-4-dimethylaminomethylphenyl, 2-fluoro-4-hydroxymethylphenyl, 3-fluoro-4-(4-morpholino)phenyl, 3-fluoro-4-carboxymethylphenoxyphenyl, 3-fluoro-4-t-butylloxycarbonylmethylphenoxyphenyl, 3-fluoro-4-dimethylaminocarbonyloxyphe-
 20 nyl, 3-chloro-4 trifluoromethoxyphenyl, 2,3-difluoro-4-methyl-phenyl, 4-trifluoromethoxyphenyl, 4-trifluoromethylphenyl, 4-hydroxyphenyl, 4-methoxyphenyl, 4-methoxycarbonylphenyl, 3-methoxycarbonylphenyl, 4-methylsulphonylphenyl, 4-methylaminocarbonylphenyl, 4- aminocarbonylphenyl, 4-methylaminosulphonylphenyl, 3-(3-pyrazolyl)phenyl, 4-(3-pyrazolyl)phenyl, 4-(4-pyrazolyl)phenyl, 4-(3-pyridyl)phenyl, 4-(2-pyridylphenyl), 4-(2-imidazolyl)phenyl, 3-(2-imidazolyl)phenyl, 4-(1-t-butyl-tetrazol-5-yl)phenyl, 4-methylaminophenyl, 4-dimethylaminophenyl, 4-diethylaminophenyl, 4-acetylaminophenyl, 3-acetylaminophenyl, 4-hydroxy-3-acetylaminophenyl, 4-methylsulphonylaminophenyl, 4-N-methylpiperazinophenyl, 4-N-pyrrolidinophenyl, 2-fluoro-4-(4-morpholino)phenyl, 4-(4-morpholino)phenyl, 4-(4-hydroxypiperidino)phenyl, 2-fluoro-4-(4-hydroxypiperidino)phenyl, 3-(1-pyrazolyl)phenyl, 4-(1-pyrazolyl)phenyl, , 4-(1-3,5 di-t-butylpyrazolyl)phenyl, 3-(1-imidazolyl)phenyl, 4-(1-imidazolyl)phenyl, 4-(1-1,2,4-triazolyl)phenyl, 4-(1-1,2,3-triazolyl)phenyl, 4-(2-4,-t-butylthiazolyl)phenyl, 4-(5- 2-t-butyltetrazolyl)phenyl, 4-(4-spiro-1,3-dioxolanyl)piperidinophenyl, 4-(4-fluorophenyl)phenyl, 4-(4-ethylaminosulphonylphenyl)phenyl, 4-dimethylaminoethoxyphenyl, 3-(dihydroxyboryl)phenyl, 2-furanyl, 3-thienyl, 3-furanyl, 2-thienyl, 4-bromo-2-thienyl, 5-bromo-2-thienyl, 5-chloro-2-thienyl, 3-fluoro-5-methyl-2-thienyl, 5-methyl-2-thienyl, 5-methyl-2-furanyl, 5-bromo-2-furanyl, 4,5-dimethyl-2-furanyl, 5-trifluoromethyl-2-furanyl, 2-furanyl-4-carboxylic acid methylamide, 2-furanyl-5-carboxylic acid methylamide, 2-pyridyl, 6-methyl-2-pyridyl, 6-methyl-3-pyridyl, 6-methoxy-3-pyridyl, 6-hydroxy-3-pyridyl, 6-trifluoromethyl-3-pyridyl, 3-pyridyl, 4-pyridyl, 3,5-pyrimidinyl, 2-thiazolyl, , 2-methyl-4-oxazolyl, 2-ethyl-4-oxazolyl, 2-cyclopropyl-4-oxazolyl, 2-

a1

trifluoromethyl-4-oxazolyl, 2,5-dimethyl-4-oxazolyl, 4-thiazolyl, 2-methyl-4-thiazolyl, 2-trifluoromethyl-4-thiazolyl, 2-trifluoromethyl-5-thiazolyl, 1-methyl-4-pyrazolyl, 1,3-dimethyl-5-pyrazolyl, 5-(2-pyridyl)-2-thienyl, 2,3-dihydro-1-benzofuran-5-yl, 1,3-benzodioxol-5-yl, 1H-1,2,3-benzotriazol-5-yl, 2,3-dihydro-1,4-benzodioxin-6-yl, 2,2-difluoro-1,3-benzodioxol-5-yl, 1,3-benzothiazol-6-yl, 1-methyl-1H-1,2,3-benzotriazol-5-yl, 1-methyl-1H-1,2,3-benzotriazol-6-yl, 1,2,3-benzothiadiazol-6-yl, 2-methyl-1,3-benzoxazol-5-yl, 2-methyl-1,3-benzoxazol-6-yl, 1-benzofuran-5-yl, 1-methyl-1H-indol-5-yl, 1-benzothien-5-yl, 1-benzofuran-6-yl, 1H-indol-6-yl, 1-methyl-1H-benzimidazol-6-yl, 1-methyl-1H-benzimidazol-5-yl, 3-methyl-1,2-benzoisoxazol-5-yl, 2-fluoro-1-benzofuran-5-yl, 1H-indol-5-yl, 2-methyl-1H-benzofuran-5-yl, 1H-indazol-5-yl, 1H-indazol-6-yl, 1-benzofuran-2-yl or 1-methyl-1H-benzimidazol-2-yl.

10. A compound of formula (1) as defined in claim in any of claims 1 to 9 wherein R_3 is a group selected from hydrogen, C_{1-4} alkyl, C_{1-4} alkoxy C_{2-4} alkyl and R_6 is a group selected from hydrogen, C_{1-4} alkoxy, C_{1-4} alkyl, C_{1-4} alkyl substituted by 1 to 3 halogen atoms, C_{1-4} alkyl substituted by alkoxycarbonyl or carboxyl, alkyl substituted by alkoxy, alkyl substituted by hydroxy, alkyl substituted by dialkylamino, 2-benzyloxypheyl, dimethoxybenzyl, optionally substituted heteroaryl, heteroaryl, alkyl substituted by NR_7R_8 wherein NR_7R_8 form a 6-membered heterocyclic ring, cycloalkyl, or NR_5R_6 represents, azetidino, 3-hydroxyazetidino, 3-methoxyazetidino, pyrrolidino, piperidino, 4-dimethylaminopiperidino, 4-methyl 1,4-diazepan-1-yl, morpholino, an optionally substituted piperazino ring, thiomorpholino or the sulfoxide or sulphone thereof.

11. A compound selected from:-

(2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-morpholinamide
 (2R)-2-(4-fluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
 (2R)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-[4-(4-hydroxypiperidin-1-yl)phenyl]ethanamide.
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-4-morpholin-4-ylphenyl)-N-isopropylethanamide.
 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(4-fluorophenyl)-N-(2,2,2-trifluoroethyl)ethanamide.
 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.

- (2R)-N-cyclopropyl-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methylethanamide
- 5 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-hydroxyazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- 10 (3R,6R)-1-[(1R)-2-azetidin-1-yl-1-(2,4-difluorophenyl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-(2-hydroxyethyl)-N-methylethanamide
- 15 (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-[2-(methylsulfonyl)ethyl]ethanamide
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(2,2,2-trifluoroethyl)ethanamide
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methyl-N-(pyridin-2-ylmethyl)ethanamide
- 20 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-[4-(methylsulfonyl)piperazin-1-yl]-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione
- (2R)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-methoxy-N-methylethanamide
- 25 (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoic acid
- methyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- propyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- 30 1-(acetyloxy)ethyl (2R)-(2,4-difluorophenyl)[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanoate
- (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- 35 (2R)-N-(tert-butyl)-2-(2,4-difluorophenyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]-2,5-dioxopiperazin-1-yl]ethanamide
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1S)-1-methylpropyl]piperazine-2,5-dione
- (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-morpholin-4-yl-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-[(1R)-1-methylpropyl]piperazine-2,5-dione
- 40 (3R,6R)-1-[(1R)-1-(2,4-difluorophenyl)-2-(3-fluoroazetidin-1-yl)-2-oxoethyl]-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutylpiperazine-2,5-dione

B

- (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(5-methylthien-2-yl)ethanamide
- 5 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-[5-(trifluoromethyl)-2-furyl]ethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1,3-oxazol-4-yl)ethanamide
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1,3-oxazol-4-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
- 10 (2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(5-methylthien-2-yl)ethanamide
(2S)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(3-fluoro-5-methylthien-2-yl)-N,N-dimethylethanamide
- 15 (2R)-2-(1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
(2R)-2-(1,2,3-benzothiadiazol-6-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(2,3-dihydro-1-benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropylethanamide.
- 20 (2R)-2-(1,3-benzodioxol-5-yl)-N-(tert-butyl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]ethanamide.
(2R)-2-(benzofuran-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide.
- 25 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N-isopropyl-2-(2-methyl-1-benzofuran-5-yl)ethanamide
(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-1-[(1R)-1-(2-methyl-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]piperazine-2,5-dione
- 30 (2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimethylethanamide
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(2-fluoro-1-benzofuran-5-yl)-N-isopropylethanamide
- 35 (3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-yl)-2-morpholin-4-yl-2-oxoethyl]-6-isobutylpiperazine-2,5-dione
(2R)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-2-(1H-indol-6-yl)-N,N-dimethylethanamide
(2R)-2-(1-benzothien-5-yl)-2-[(3R,6R)-3-(2,3-dihydro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperazin-1-yl]-N,N-dimethylethanamide
- 40

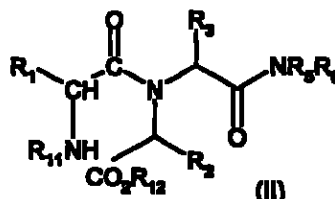
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12. A pharmaceutical composition comprising a compound of formula (I) as defined in claim 1 or claim 2 together with one or more pharmaceutically acceptable carriers.

13. The use of compound of formula (I) as defined in claim 1 for the manufacture of a medicament for antagonising the effects of oxytocin on the oxytocin receptor.

14. A process for the preparation of compounds of formula (I) wherein R_4 is the group NR_5R_6 which comprises:

(a) cyclisation of the compound of formula (II)



wherein R_1 , R_2 and R_3 have the meanings defined in formula (I) R_{11} is hydrogen and R_{12} is a C_{1-3} alkyl group in a suitable solvent or

(b) reacting a compound of formula (I) wherein R_4 is hydroxyl or an activated derivative thereof with the amine NHR_5R_6 wherein R_5 and R_6 have the meaning defined in formula (I) under the standard condition for preparing amides from a carboxylic acid and an amine.

(c) reacting a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with amine NHR_5R_6

15. A process for preparing compounds of formula (I) wherein R_4 is hydroxyl by reacting a compound of formula (I) wherein R_4 is the group NR_5R_6 and R_5 is hydrogen and R_6 is 2-hydroxyphenyl with carbonyldiimidazole or thiocarbonyldiimidazole in a suitable solvent and subsequent reaction of the product thus formed with aqueous acetone.

DICETOPIPERACINAS SUSTITUIDAS COM ANTAGONISTAS DE
OXITOCINA

MEMORIA DESCRIPTIVA

5

Esta invención se relaciona con el uso de una clase de derivados de dicetopiperacina como antagonistas potentes y selectivos de la oxitocina, con compuestos novedosos dentro de esa clase y con procedimientos para su preparación.

10

La USP5817751 describe los métodos para la fase combinada y sólida para la síntesis de diversos derivados de dicetopiperacina y el uso de estos métodos para crear bibliotecas de diversos derivados de dicetopiperacina.

15

La WO99/47549 describe los derivados de piperacina que incluyen derivados de 3-bencil-2,5-piperacina como inhibidores del 1,6-bisfosfato de fructosa (FBPasa). La WO99/38844 describe un método para preparar los compuestos de N-[alifático o aromático]carbonil]-2-aminoacetamida y su ciclización para proporcionar inter alia derivados de dicetopiperacina.

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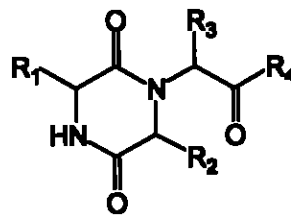
La WO99/37304 describe compuestos de oxaheterociclilo que incluyen compuestos de oxapiperacinilo que son inhibidores del Factor Xa.

La hormona oxitocina es un potente contractor del útero y es utilizado en la inducción o aumento del trabajo de parto. También la densidad

de los receptores de la oxitocina uterina se incrementa de manera significativa por >100 veces durante el embarazo y llega a un máximo en el trabajo de parto (a pretérmino y a término). Los nacimientos/trabajos de parto a pretérmino (entre 24 y 37 semanas) causan aproximadamente 60% de la mortalidad/morbididad infantil, y así, un compuesto el cual inhiba las acciones uterinas de la oxitocina, por ejemplo, antagonistas de oxitocina, sería útil para la prevención o control del trabajo de parto a pretérmino.

Hemos encontrado una clase de derivados de dicetopiperacina, los cuales exhiben un nivel de actividad particularmente útil como antagonistas selectivos al receptor de oxitocina.

La presente invención, es por lo tanto, un método para tratar o prevenir enfermedades o condiciones mediadas a través de la acción de la oxitocina, el cual comprende administrar a un mamífero en necesidad del mismo una cantidad efectiva de un compuesto de la fórmula (I)



(I)

y/o un derivado fisiológicamente aceptable del mismo, en donde:

R_1 representa arilalquilo de (C₁₋₄) o un grupo cicloalquilo de 5-7 miembros sustituido opcionalmente con uno o más grupos hidroxilo, el cual está fusionado a un anillo de benceno sustituido opcionalmente;

R₂ representa alquilo de C₁₋₆ (sustituido opcionalmente por un grupo alcoxi de C₁₋₂, alquitio de C₁₋₂, di(alquil de C₁₋₂)amino o un cicloalquilo de C₃₋₆) o cicloalquilo de C₃₋₆, o un grupo heterocíclico de 5-6 miembros que contiene un solo heteroátomo seleccionado de O, S o N, átomo de nitrógeno el cual porta un átomo de hidrógeno o un grupo metilo o etilo;

R₃ representa fenilo sustituido opcionalmente, un grupo heteroarilo de 5 ó 6 miembros o un sistema anular bicíclico fusionado, que contiene 9-10 miembros en el anillo, el cual puede ser un grupo carbocíclico o éste puede contener hasta 3 heteroátomos seleccionados de O, S o N, y uno de los anillos fusionados es benceno;

R₄ representa OH u O-alquilo de C₁₋₄ (sustituido opcionalmente con alquilcarbonilo de C₁₋₄) o NR₅R₆;

R₅ representa hidrógeno, alquilo de C₁₋₆ (sustituido opcionalmente con alcoxi de C₁₋₄) o cicloalquilo de C₃₋₇;

R₆ representa hidrógeno, alcoxi de C₁₋₄, cicloalquilo de C₃₋₇, alquilo de C₁₋₄ [sustituido opcionalmente con uno o más grupos seleccionados de carboxilo, alquilsulfonilo de C₁₋₄ o alcoxicarbonilo de C₁₋₄], alquilo de C₂₋₄ [sustituido opcionalmente con uno o más grupos seleccionados de halógeno, hidroxi, alcoxi de C₁₋₄ o NR₇R₈, en donde R₇ y R₈ de manera independiente representan hidrógeno o alquilo de C₁₋₄, o junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico saturado de 3-7 miembros, el cual puede contener un heteroátomo adicional seleccionado de O, S o N (y grupo heterocíclico el cual puede estar sustituido por 1 a 3 grupos

AB

seleccionados de alquilo de C_{1-3} , hidroxilo, alcoxi de C_{1-3} (sustituido opcionalmente por cicloalquilo de C_{3-6} o fenilo sustituido opcionalmente), cicloalquilo de C_{3-6} o NR_cR_d , en donde R_c y R_d , cada uno de manera independiente, representa un grupo seleccionado de alquilo de C_{1-3} (sustituido

5 opcionalmente por cicloalquilo de C_{3-6} o fenilo sustituido opcionalmente) o cicloalquilo de C_{3-6}], o R_6 representa un grupo fenilo o bencilo (sustituido opcionalmente por uno o más grupos metoxi o benciloxi), o un grupo heteroarilmetilo sustituido opcionalmente o un grupo heteroarilo o cicloalquilo de C_{3-7} o el grupo $CH_2CONR_9R_{10}$, en donde R_9 representa hidrógeno o alquilo

10 de C_{1-4} , R_{10} representa hidrógeno, alquilo de C_{1-4} sustituido opcionalmente por un grupo heteroarilo de 5 ó 6 miembros, o R_9 , R_{10} y el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico saturado de 5 ó 6 miembros y en donde el grupo heterocíclico de 6 miembros puede contener un heteroátomo adicional seleccionado de oxígeno, azufre o nitrógeno y el átomo

15 de nitrógeno adicional porta un átomo de hidrógeno o un grupo alquilo de C_{1-4} o alcanilo de C_{1-4} ; o R_5 y R_6 junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico saturado de 3 a 7 miembros, heterociclo el cual puede contener un heteroátomo adicional seleccionado de oxígeno, azufre y nitrógeno, y en donde el átomo de azufre puede estar en una forma

20 oxidada, por ejemplo, SO_2 y el átomo de nitrógeno adicional porta un átomo de hidrógeno o un grupo alquilo de C_{1-4} o alcanilo de C_{1-4} , o un grupo alquilsulfonilo de C_{1-4} o un alcoxi de C_{1-3} alquilo de C_{2-4} [y grupos heterocíclicos los cuales pueden estar sustituidos por uno o más átomos de

qd

halógeno o un grupo seleccionado de alquilo de C₁₋₃, hidroxilo, oxo, cicloalquilo de C₃₋₆ o NR_eR_f, en donde R_e y R_f, cada uno de manera independiente representa un grupo seleccionado de alquilo de C₁₋₃ (sustituido opcionalmente por cicloalquilo de C₃₋₆ o fenilo sustituido opcionalmente), o cicloalquilo de C₃₋₆].

5 La invención también proporciona compuestos novedosos de fórmula (I). Una clase particularmente útil de compuestos novedosos de fórmula (I), son aquéllos en donde R₁ es 2-indanilo sustituido opcionalmente por hidroxilo, y de manera más particular un grupo 2-indanilo y R₂, R₃ y R₄ tienen los significados definidos anteriormente y/o los derivados
10 fisiológicamente aceptables de los mismos. Una clase útil adicional de compuestos novedosos de fórmula (I) son aquéllos en donde R₁ es 2-fenetilo y R₂, R₃ y R₄ tienen los significados definidos anteriormente y/o los derivados fisiológicamente aceptables de los mismos.

 Los compuestos de fórmula (I) contienen al menos tres centros
15 de asimetría, a saber, los átomos de carbono que portan los sustituyentes R₁, R₂ y R₃, respectivamente, y deberá entenderse que la fórmula (I) incluye todos los posibles estereoisómeros y mezclas de los mismos. El sustituyente R₃ pueden existir en más de una forma tautomérica y deberá entenderse que la fórmula (I) incluye todas las posibles formas tautoméricas y mezclas de los
20 mismos.

 Los compuestos de fórmula (I), en donde al menos uno de los grupos R₁, R₂, R₃ o R₄ contiene un agrupamiento básico o ácido pueden

formar sales con ácidos o bases fisiológicamente aceptables y la referencia a los compuestos de fórmula (I) aquí incluyen tales sales.

Como se utilizan aquí, los términos "derivado fisiológicamente aceptable" o "derivado farmacéuticamente aceptable", significan cualquier sal, solvato, o profármaco farmacéuticamente aceptable, por ejemplo, éster o carbamato, o sal o solvato de tal profármaco, de un compuesto de fórmula (I), el cual, una vez administrado al recipiente, es capaz de proporcionar (directa o indirectamente) un compuesto de fórmula (I), o un metabolito activo o residuo del mismo. Los derivados farmacéuticamente aceptables preferidos son sales y solvatos.

Como se utiliza aquí, el término "profármaco" significa un compuesto el cual es convertido dentro del cuerpo, por ejemplo, mediante hidrólisis en la sangre, en su forma activa que tiene efectos médicos. Los profármacos farmacéuticamente aceptables se describen en T. Higuchi y V. Stella, *Prodrugs as Novel Delivery Systems*, Vol. 14 de la Serie del Simposio de la A. C. S., y en Edward B. Roche, ed., *Bioreversible Carriers in Drug Design*, American Pharmaceutical Association y Pergamon Press, 1987, ambas de las cuales se incorporan aquí como referencia. Los ésteres pueden ser activos por derecho propio y/o ser hidrolizables bajo condiciones *in vivo* en el cuerpo humano. Los grupos éster hidrolizables *in vivo* farmacéuticamente aceptables adecuados, incluyen aquéllos que se fragmentan fácilmente en el cuerpo humano para dejar el ácido original o su sal. Los ejemplos de tales ésteres incluyen ésteres de alquilo y de 1-(acetiloxi)etilo.

El término alquilo como un grupo o parte de un grupo, se refiere a un grupo alquilo lineal o ramificado, por ejemplo, metilo, etilo, propilo, isopropilo, n-butilo, 1-metilpropilo, 2-metilpropilo, t-butilo, pentilo o hexilo.

El término cicloalquilo de C_{3-6} como un grupo o parte de un grupo, incluye grupos ciclopropilo, ciclobutilo, ciclopentilo y ciclohexilo. El término cicloalquilo de C_{3-7} también incluye cicloheptilo.

El término halógeno, se refiere a flúor, cloro, bromo o yodo.

A menos que se especifique de otra manera, el término fenilo sustituido opcionalmente se refiere a un grupo fenilo el cual puede estar sustituido por 1 a 3 sustituyentes, los cuales pueden ser los mismos o diferentes y se seleccionan de halógeno, hidroxilo, alquilo de C_{1-4} (sustituido opcionalmente por 1-3 átomos de halógeno o NR_gR_h [en donde R_g es hidrógeno o alquilo de C_{1-4} , R_h es hidrógeno, alquilo de C_{1-4} , o R_g y R_h junto con el átomo de nitrógeno al cual están unidos para formar un anillo de 5 a 7 miembros, anillo el cual está saturado y puede contener un heteroátomo adicional seleccionado de nitrógeno, oxígeno o azufre]), alquilsulfonilo de C_{1-4} , carboxilo, alcóxicarbonilo de C_{1-4} , di(alquilo de C_{1-4})aminocarbonilo, alcoxido de C_{1-4} (sustituido opcionalmente por 1-3 átomos de halógeno, amino, alquilamino de C_{1-4} o di-(alquil de C_{1-4})amino), fenilo (sustituido opcionalmente por halógeno o alquilaminosulfonilo), alcoxido de C_{1-4} , NR_aR_b [en donde R_a es hidrógeno o alquilo de C_{1-4} , R_b es hidrógeno, alquilo de C_{1-4} , alcanilo de C_{1-4} o alquilsulfonilo de C_{1-4} o R_a y R_b junto con el átomo de nitrógeno al cual están unidos para formar un anillo de 5 a 7 miembros, anillo el cual está saturado y

puede estar sustituido por grupos hidroxilo o 1 ó 2 alquilo de C₁₋₄ o puede ser un espiro fusionado a un anillo de dioxalano o puede contener un heteroátomo adicional, seleccionado de nitrógeno, oxígeno o azufre, y puede estar sustituido por 1 ó 2 grupos alquilo de C₁₋₄, o anillo el cual no está saturado y
5 contiene 1-3 átomos de nitrógeno adicionales], un grupo heteroarilo de 5 ó 6 miembros, un grupo aminocarbonilo o aminosulfonilo N sustituido opcionalmente (en donde los sustituyentes pueden ser 1 ó 2 grupos alquilo de C₁₋₄) o un grupo dihidroxiborilo).

El término heteroarilo de 5 miembros se refiere a un anillo de 5
10 miembros, el cual contiene un heteroátomo seleccionado de oxígeno, azufre o nitrógeno, y el cual también puede contener de 1 a 3 átomos de nitrógeno adicionales y grupos los cuales pueden estar sustituidos por 1 o más grupos seleccionados de grupos halógeno, trifluorometilo, alquilo de C₁₋₄, cicloalquilo, heteroarilo, heterocíclico saturado, o fenilo. Los ejemplos de tales grupos
15 heteroarilo de 5 miembros incluyen furanilo, tienilo, pirrolilo, oxazolilo, isoxazolilo, tiazolilo, imidazolilo, pirazolilo, oxadiazolilo, tiadiazolilo, triazolilo o tetrazolilo y estos heterociclos pueden estar sustituidos como se describió anteriormente.

El término grupo heteroarilo de 6 miembros se refiere a un anillo
20 no saturado de 6 miembros, el cual contiene de 1 a 3 átomos de nitrógeno y el cual puede estar sustituido por 1 a 3 grupos alquilo de C₁₋₄, o trifluorometilo o grupos alcoxi. Los ejemplos de tales grupos incluyen piridilo, metilpiridilo, trifluorometilpiridilo, pirimidinilo y triacinilo.

Cuando R_3 es un grupo heteroarilo de 5 ó 6 miembros, éste está enlazado al resto de la molécula vía un átomo de carbono en el anillo.

Cuando R_3 es un sistema anular bicíclico fusionado, éste puede ser, por ejemplo, un grupo naftilo, tetrahidronaftilo, indanilo o indenilo.

- 5 Cuando R_3 es un sistema bicíclico fusionado que contiene hasta 3 heteroátomos, que pueden ser los mismos o diferentes, éste es convenientemente un sistema anular 6,5 ó 6,6, en donde el heterociclo puede estar parcialmente saturado o junto con el anillo de benceno al cual está fusionado para formar un grupo heteroarilo, y el heterociclo puede estar
- 10 sustituido por 1 ó 2 grupos seleccionados de alquilo de C_{1-4} o halógeno o haloalquilo y/o puede contener un grupo carbonilo. El grupo R_3 puede estar enlazado al resto de la molécula vía un átomo de carbono en el anillo de benceno o un átomo de carbono en el grupo heterocíclico.

- Cuando R_3 es un grupo heteroarilo 6,6 fusionado, el heteroanillo
- 15 contiene de 1 a 3 átomos de nitrógeno y los ejemplos de tales grupos heteroarilo incluyen quinolinilo, isoquinolinilo, ftalacinilo, cinolinilo, quinazolinilo, quinoxalinilo, 1,2,3-benzotriacinilo o 1,2,4-benzotriacinilo.

- Cuando R_3 es un grupo heteroarilo bicíclico 6,5, el heterociclo de 5 miembros contiene un heteroátomo seleccionado de O, S o N, y puede
- 20 además, también contener 1 ó 2 átomos de nitrógeno adicionales, y el anillo heterocíclico también puede estar sustituido por 1 ó 2 alquilo de C_{1-4} o halógeno o haloalquilo y, o puede contener un grupo carbonilo. Los ejemplos de tales grupos heteroarilo bicíclicos 6,5 incluyen benzofuranilo, benzotienilo,

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indolilo, benzo-oxadiazolilo, benzotiadiazolilo, benzo-oxazolilo, benzotiazolilo, benzoisotiazolilo, benzoisoxazolilo, bencimidazolilo, indazolilo o benzotriazolilo y estos grupos pueden estar sustituidos como se describió anteriormente.

Cuando R_3 es un grupo heterocíclico bicíclico 6,6 ó 6,5, y el
5 heterociclo está parcialmente saturado, éste puede contener 1 ó 2 heteroátomos seleccionados de O, S o N. Los ejemplos de tales grupos incluyen indolinilo, isoindolinilo, dihidrobenzofuranilo, dihidrobenzotienilo, 1,3-benzodioxolilo, benzopirrolilo, 1,3-benzoditiolilo, 1,4-benzodioxanilo, ftalilo, tioftalilo, cromanilo o cromenilo y los grupos pueden estar sustituidos por uno
10 o más grupos halógeno o alquilo de C_{1-4} , haloalquilo, o pueden contener un grupo carbonilo.

Cuando R_3 es un heteroarilo bicíclico fusionado enlazado vía el anillo de benceno en él, entonces los ejemplos adecuados de tal grupo incluyen 6-quinolinilo, 4-isoindolinilo, 4-(N-metil-isoindolinilo, bencimidazolilo,
15 benzotiazolilo, benzofuranilo, benzotienilo, bencimidazolilo, benzoxazolilo, 2-metil-benzo-oxazolilo, benzotiadiazolilo, benzotriazolilo y 1-metil benzotriazolilo.

Cuando R_3 es un grupo heteroarilo bicíclico fusionado enlazado vía el anillo de heteroarilo, éste puede ser, por ejemplo un grupo 2-
20 benzofuranilo, 2-benzotienilo o 2-N-metilindolilo. Cuando R_3 es un grupo heterocíclico 6,6 ó 6,5, en donde el heterociclo está parcialmente saturado, éste está enlazado convenientemente vía el anillo de benceno en él y los

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ejemplos adecuados incluyen dihidrobenzofurano, dihidrobenzopirrol, 1,3-benzodioxolilo, 2,2-difluoro-1,3-benzodioxolilo y 1,4-benzodioxanilo.

Cuando R_3 es un grupo fenilo sustituido, el grupo porta de manera conveniente de 1 a 3 sustituyentes, los cuales pueden ser los mismos o diferentes, seleccionados de flúor, cloro, bromo o alquilo de C_{1-3} (metilo), haloalquilo de C_{1-3} (trifluorometilo), alcoxi de C_{1-3} (metoxi, etoxi), haloalcoxi (trifluorometoxi), aminoetoxi, por ejemplo dimetilaminoetoxi, alcóxicarbonilo de C_{1-3} , carboxi, hidroxilo, fenilo o fenilo (sustituido por halógeno o alquilaminosulfonilo), NR_aR_b [en donde R_a es hidrógeno o alquilo de C_{1-2} y R_b es alquilo de C_{1-2} , alcanilo de C_{1-4} , alquilsulfonilo de C_{1-4} , alquilaminocarbonilo de C_{1-3}] o NR_aR_b representa un anillo de pirrolidino o piperidino, anillo el cual puede estar sustituido por un grupo alquilo de C_{1-2} , hidroxilo o 2,2-1,3-dioxolano, o NR_aR_b representa un grupo morfolino o piperacino, grupos los cuales pueden estar sustituidos por 1 ó 2 grupos alquilo de C_{1-2} o NR_aR_b representa un grupo heteroarilo de 5 ó 6 miembros que contiene de 1 a 4 átomos de nitrógeno (tales como sustituyentes 1-imidazolilo, 1,2-pirazolilo, 1,2,3-triazolilo o 1,2,4-triazolilo), alquilsulfonilo de C_{1-3} , alquilaminocarbonilo de C_{1-3} , alquilaminosulfonilo de C_{1-3} , dihidroxiborilo o un grupo de átomos de heteroarilo de 5 ó 6 miembros que contiene de 1 a 4 átomos de nitrógeno, y el cual está enlazado al grupo fenilo vía un átomo de carbono en el grupo heteroarilo (por ejemplo, piridilo, pirazolilo, imidazolilo o tetrazol-5-ilo, grupos heteroarilo los cuales pueden estar sustituidos por 1 o más grupos alquilo de C_{1-4}).

Los ejemplos de grupos R_3 adecuados, en donde R_3 es fenilo sustituido opcionalmente, incluyen fenilo, halofenilo tales como 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 4-clorofenilo, 3-clorofenilo, 2-clorofenilo, 4-bromofenilo, 2,3-difluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 3,5-difluorofenilo, 2,5-difluorofenilo, 2-cloro-4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 2-fluoro-4-bromofenilo, 4-cloro-3-fluorofenilo, 2,3,4-trifluorofenilo, 2,4,5-trifluorofenilo o 2,4,6-trifluorofenilo, 2-fluoro-4,5-dimetoxifenilo, 3-fluoro-4-metoxifenilo, 4-fluoro-3-metoxifenilo, 2-fluoro-4-metoxifenilo, 2-fluoro-4-hidroxifenilo, 2-fluoro-4-dimetilaminometilfenilo, 2-fluoro-4-hidroximetilfenilo, 3-fluoro-4-(4-morfolino)fenilo, 3-fluoro-4-carboximetiloxifenilo, 3-fluoro-4-t-butiloxycarbonilmetiloxifenilo, 3-fluoro-4-dimetilaminocarboniloxifenilo, 3-cloro-4-trifluorometoxifenilo, 2,3-difluoro-4-metil-fenilo, 4-trifluorometoxifenilo, 4-trifluorometilfenilo, 4-hidroxifenilo, 4-metoxifenilo, 4-metoxicarbonilfenilo, 3-metoxicarbonilfenilo, 4-metilsulfonilfenilo, 4-metilaminocarbonilfenilo, 4-aminocarbonilfenilo, 4-metilaminosulfonilfenilo, 3-(3-pirazolil)fenilo, 4-(3-pirazolil)fenilo, 4-(4-pirazolil)fenilo, 4-(3-piridil)fenilo, 4-(2-piridilfenilo), 4-(2-imidazolil)fenilo, 3-(2-imidazolil)fenilo, 4-(1-t-butil-tetrazol-5-il)fenilo, 4-metilaminofenilo, 4-dimetilaminofenilo, 4-dietilaminofenilo, 4-acetilaminofenilo, 3-acetilaminofenilo, 4-hidroxi-3-acetilaminofenilo, 4-metilsulfonilaminofenilo, 4-N-metilpiperacinafenilo, 4-N-pirrolidinafenilo, 2-fluoro-4-(4-morfolino)fenilo, 4-(4-morfolino)fenilo, 4-(4-hidroxipiperidino)fenilo, 2-fluoro-4-(4-hidroxipiperidino)fenilo, 3-(1-pirazolil)fenilo, 4-(1-pirazolil)fenilo, 4-(1-3,5-di-t-butilpirazolil)fenilo, 3-(1-imidazolil)fenilo, 4-(1-imidazolil)fenilo, 4-(1-1,2,4-

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triazolil)fenilo, 4-(1-1,2,3-triazolil)fenilo, 4-(2-4-t-butiltiazolil)fenilo, 4-(5-2-t-butiltetrazolil)fenilo, 4-(4-espiro-1,3-dioxolanil)piperidinofenilo, 4-(4-fluorofenil)fenilo, 4-(4-etilaminosulfonilfenil)fenilo, 4-dimetilaminoetoxifenilo o 3-(dihidroxiboril)fenilo.

- 5 Cuando R_3 es un grupo heteroarilo de 5 ó 6 miembros, los ejemplos adecuados de tales grupos incluyen 2-furanilo, 3-tienilo, 3-furanilo, 2-tienilo, 4-bromo-2-tienilo, 5-bromo-2-tienilo, 5-cloro-2-tienilo, 3-fluoro-5-metil-2-tienilo, 5-fluoro-2-tienilo, 5-metil-2-tienilo, 5-metil-2-furanilo, 5-bromo-2-furanilo, 4,5-dimetil-2-furanilo, 2,3-dimetil-5-tienilo, 5-trifluorometil-2-furanilo, metilamida
- 10 del ácido 2-furanil-4-carboxílico, metilamida del ácido 2-furanil-5-carboxílico, 2-piridilo, 6-metil-2-piridilo, 6-metil-3-piridilo, 6-hidroxi-3-piridilo, 6-metoxi-3-piridilo, 6-trifluorometil-3-piridilo, 3-piridilo, 4-piridilo, 3,5-pirimidinilo, 2-tiazolilo, 4-oxazolilo, 4-tiazolilo, 2-metil-4-oxazolilo, 2-etil-4-oxazolilo, 2-ciclopropil-4-oxazolilo, 2-trifluorometil-4-oxazolilo, 2,5-dimetil-4-oxazolilo, 4-tiazolilo, 2-metil-
- 15 4-tiazolilo, 2-trifluorometil-4-tiazolilo, 2-trifluorometil-5-tiazolilo, 4-isoxazolilo, 1-metil-4-pirazolilo, 1,3-dimetil-5-pirazolilo, 5-(2-piridil)-2-tienilo, 2-(4-morfolino)-5-tiazolilo o 2-(4-metil-1-piperacino)-5-tiazolilo.

- Cuando R_3 es un sistema anular bicíclico fusionado sustituido opcionalmente, los ejemplos de los grupos adecuados incluyen 2,3-dihidro-1-
- 20 benzofuran-5-ilo, 1,3-benzodioxol-5-ilo, 1H-1,2,3-benzotriazol-5-ilo, 2,3-dihidro-1,4-benzodioxin-6-ilo, 2,2-difluoro-1,3-benzodioxol-5-ilo, 1,3-benzotiazol-6-ilo, 1-metil-1H-1,2,3-benzotriazol-5-ilo, 1-metil-1H-1,2,3-benzotriazol-6-ilo, 1,2,3-benzotiadiazol-6-ilo, 2-metil-1,3-benzoxazol-5-ilo, 2-

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metil-1,3-benzoxazol-6-ilo, 1-benzofuran-5-ilo, 1-metil-1H-indol-5-ilo, 1-benzotien-5-ilo, 1-benzofuran-6-ilo, 1H-indol-6-ilo, 1-metil-1H-bencimidazol-6-ilo, 1-metil-1H-bencimidazol-5-ilo, 3-metil-1,2-benzoisoxazol-5-ilo, 2-fluoro-1-benzofuran-5-ilo, 1H-indol-5-ilo, 2-metil-1H-benzofuran-5-ilo, 1H-indazol-5-ilo, 5 1H-indazol-6-ilo, 1-benzofuran-2-ilo o 1-metil-1H-bencimidazol-2-ilo.

Cuando el grupo R_1 es un grupo cicloalquilo de 5-7 miembros, el cual está fusionado a un anillo de benceno sustituido opcionalmente, los sustituyentes opcionales pueden ser de 1 a 3 grupos los cuales pueden ser los mismos o diferentes y se seleccionan de halógeno, alquilo, alcoxi, hidroxilo, 10 trifluorometilo, nitro, carboxilo, alcoxycarbonilo o carboxamido.

Cuando el grupo R_1 es aralquilo, la porción arilo es fenilo sustituido opcionalmente por 1 a 3 grupos, los cuales pueden ser los mismos o diferentes y se seleccionan de halógeno, alquilo, alcoxi, hidroxilo, trifluorometilo, nitro, carboxilo, alcoxycarbonilo o carboxamido.

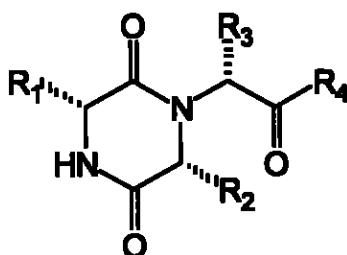
15 Los ejemplos de grupos R_1 adecuados, incluyen fenetilo o indanilo sustituido opcionalmente por hidroxilo, por ejemplo, 2-indanilo, 1-hidroxilo-2-indanilo, 5-hidroxilo-2-indanilo. Los ejemplos de grupos R_2 adecuados incluyen alquilo de C_{3-4} , por ejemplo, isopropilo, 1-metilpropilo o 2-metilpropilo, cicloalquilo de C_{3-6} , por ejemplo, ciclopentilo.

20 De manera conveniente, R_4 es hidroxilo, alcoxi de C_{1-4} , por ejemplo, metoxi, propoxi, t-butoxi, 1-acetiloxi etoxi o NR_5R_6 .

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Una clase preferida de compuestos de fórmula (I), son aquéllos en donde R_4 representa hidroxilo o el grupo NR_5R_6 , o de manera más preferida NR_5R_6 .

Una clase preferida adicional de compuestos, está representada
5 por la fórmula (1a)



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(1a)

en donde los grupos R_1 , R_2 , R_3 y R_4 tienen los significados definidos para la fórmula (I). De manera conveniente, R_1 es un grupo seleccionado de 2-fenetilo o 2-indanilo sustituido opcionalmente por hidroxilo, y de manera más particular 2-indanilo. De manera conveniente, R_2 es un grupo seleccionado de
15 isopropilo, 1-metilpropilo, 2-metilpropilo o ciclopentilo, y de manera más preferida R_2 es un grupo seleccionado de 1-metilpropilo o 2-metilpropilo.

De manera conveniente R_3 es un grupo seleccionado de fenilo, halofenilo tal como 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 4-clorofenilo, 3-
20 clorofenilo, 2-clorofenilo, 4-bromofenilo, 2,3-difluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 3,5-difluorofenilo, 2,5-difluorofenilo, 2-cloro-4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 2-fluoro-4-bromofenilo, 4-cloro-3-fluorofenilo, 2,3,4-trifluorofenilo, 2,4,5-trifluorofenilo o 2,4,6-trifluorofenilo, 2-

- fluoro-4,5-dimetoxifenilo, 3-fluoro-4-metoxifenilo, 4-fluoro-3-metoxifenilo, 2-fluoro-4-metoxifenilo, 2-fluoro-4-idroksifenilo, 2-fluoro-4-dimetilaminometilfenilo, 2-fluoro-4-idroksimetilfenilo, 3-fluoro-4-(4-morfolino)fenilo, 3-fluoro-4-karboximetiloksifenilo, 3-fluoro-4-t-butiloksikarbonilmetiloksifenilo, 3-fluoro-4-dimetilaminokarboniloksifenilo, 3-kloro-4-trifluorometoksisfenilo, 2,3-difluoro-4-metil-fenilo, 4-trifluorometoksisfenilo, 4-trifluorometilfenilo, 4-idroksifenilo, 4-metoksisfenilo, 4-metoksikarbonilfenilo, 3-metoksikarbonilfenilo, 4-metilsulfonilfenilo, 4-metilaminokarbonilfenilo, 4-aminokarbonilfenilo, 4-metilaminosulfonilfenilo, 3-(3-pirazolil)fenilo, 4-(3-pirazolil)fenilo, 4-(4-pirazolil)fenilo, 4-(3-piridil)fenilo, 4-(2-piridilfenilo), 4-(2-imidazolil)fenilo, 3-(2-imidazolil)fenilo, 4-(1-t-butil-tetrazol-5-il)fenilo, 4-metilaminofenilo, 4-dimetilaminofenilo, 4-dietilaminofenilo, 4-acetilaminofenilo, 3-acetilaminofenilo, 4-idroksi-3-acetilaminofenilo, 4-metilsulfonilaminofenilo, 4-N-metilpiperacinafenilo, 4-N-pirrolidinafenilo, 2-fluoro-4-(4-morfolino)fenilo, 4-(4-morfolino)fenilo, 4-(4-idroksipiperidino)fenilo, 2-fluoro-4-(4-idroksipiperidino)fenilo, 3-(1-pirazolil)fenilo, 4-(1-pirazolil)fenilo, 4-(1-3,5-di-t-butilpirazolil)fenilo, 3-(1-imidazolil)fenilo, 4-(1-imidazolil)fenilo, 4-(1-1,2,4-triazolil)fenilo, 4-(1-1,2,3-triazolil)fenilo, 4-(2-4-t-butiltiazolil)fenilo, 4-(5-2-t-butiltetrazolil)fenilo, 4-(4-espiro-1,3-dioxolanil)piperidinafenilo, 4-(4-fluorofenil)fenilo, 4-(4-etilaminosulfonilfenil)fenilo, 4-dimetilaminoetoksifenilo, 3-(dihidroksiboril)fenilo, 2-furanilo, 3-tienilo, 3-furanilo, 2-tienilo, 4-bromo-2-tienilo, 5-bromo-2-tienilo, 5-kloro-2-tienilo, 3-fluoro-5-metil-2-tienilo, 5-metil-2-tienilo, 5-metil-2-furanilo, 5-bromo-2-furanilo, 4,5-dimetil-2-furanilo, 5-trifluorometil-2-

furanilo, metilamida del ácido 2-furanil-4-carboxílico, metilamida del ácido 2-furanil-5-carboxílico, 2-piridilo, 6-metil-2-piridilo, 6-metil-3-piridilo, 6-metoxi-3-piridilo, 6-hidroxi-3-piridilo, 6-trifluorometil-3-piridilo, 3-piridilo, 4-piridilo, 3,5-pirimidinilo, 2-tiazolilo, 2-metil-4-oxazolilo, 2-etil-4-oxazolilo, 2-ciclopropil-4-oxazolilo, 2-trifluorometil-4-oxazolilo, 2,5-dimetil-4-oxazolilo, 4-tiazolilo, 2-metil-4-tiazolilo, 2-trifluorometil-4-tiazolilo, 2-trifluorometil-5-tiazolilo, 1-metil-4-pirazolilo, 1,3-dimetil-5-pirazolilo, 5-(2-piridil)-2-tienilo, 2,3-dihidro-1-benzofuran-5-ilo, 1,3-benzodioxol-5-ilo, 1H-1,2,3-benzotriazol-5-ilo, 2,3-dihidro-1,4-benzodioxin-6-ilo, 2,2-difluoro-1,3-benzodioxol-5-ilo, 1,3-benzotiazol-6-ilo, 1-metil-1H-1,2,3-benzotriazol-5-ilo, 1-metil-1H-1,2,3-benzotriazol-6-ilo, 1,2,3-benzotiadiazol-6-ilo, 2-metil-1,3-benzoxazol-5-ilo, 2-metil-1,3-benzoxazol-6-ilo, 1-benzofuran-5-ilo, 1-metil-1H-indol-5-ilo, 1-benzotien-5-ilo, 1-benzofuran-6-ilo, 1H-indol-6-ilo, 1-metil-1H-bencimidazol-6-ilo, 1-metil-1H-bencimidazol-5-ilo, 3-metil-1,2-benzoisoxazol-5-ilo, 2-fluoro-1-benzofuran-5-ilo, 1H-indol-5-ilo, 2-metil-1H-benzofuran-5-ilo, 1H-indazol-5-ilo, 1H-indazol-6-ilo, 1-benzofuran-2-ilo o 1-metil-1H-bencimidazol-2-ilo.

De manera conveniente, el grupo R_5 es hidrógeno, alquilo de C_{1-4} , por ejemplo metilo o alcoxi de C_{1-4} alquilo de C_{2-4} , por ejemplo 2-metoxietilo y R_6 es un grupo seleccionado de hidrógeno, alcoxi de C_{1-4} , por ejemplo, metoxi, alquilo de C_{1-4} , por ejemplo metilo, n-propilo, isopropilo o t-butilo, alquilo de C_{1-4} sustituido por 1 a 3 átomos de halógeno, por ejemplo 2,2,2-trifluoroetilo o 2-fluoroetilo, alquilo de C_{1-4} sustituido por alcóxicarbonilo o carboxilo, por ejemplo, metoxycarbonilmetilo o carboximetilo, alquilo sustituido

por alcoxi, por ejemplo, metoxietilo, 2,2-dimetoxietilo, alquilo sustituido por hidroxilo, por ejemplo, hidroxietilo o alquilo sustituido por dialquilamino, por ejemplo, dimetilaminoetilo, 2-benciloxifenilo, dimetoxibencilo, heteroarilmetilo sustituido opcionalmente, por ejemplo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 3-metilimidazolilmetilo, heteroarilo tal como tiazolilo, por ejemplo 2-1,3-tiazolilo, alquilo sustituido por NR_7R_8 [en donde NR_7R_8 forman un anillo heterocíclico de 6 miembros (por ejemplo piperidinoetilo o morfolinoetilo)], cicloalquilo, por ejemplo, ciclopropilo o ciclohexilo, o NR_5R_6 representa, acetidino, 3-hidroxiacetidino, 3-metoxiacetidino, pirrolidino, piperidino, 4-dimetilaminopiperidino, 4-metil-1,4-diazepan-1-ilo, morfolino, un anillo de piperacino sustituido opcionalmente, por ejemplo, N-metilpiperacino, N-metansulfonilpiperacino, N-2-metoxietilpiperacino, tiomorfolino o el sulfóxido o sulfona de los mismos.

Una clase preferida de compuestos de la invención son aquéllos de fórmula (1a), en donde R_1 es 2-indanilo, R_2 es un grupo seleccionado de 1-metilpropilo o 2-metilpropilo y R_4 es hidroxilo y/o más particularmente el grupo NR_5R_6 .

Una clase preferida de compuestos de la invención adicional, es aquélla de fórmula (1a), en donde R_5 es un grupo seleccionado de hidrógeno, alquilo de C_{1-4} , por ejemplo, metilo o alcoxi de C_{1-4} alquilo de C_{2-4} , por ejemplo, 2-metoxietilo y R_6 es un grupo seleccionado de hidrógeno, alcoxi de C_{1-4} , por ejemplo, metoxi, alquilo de C_{1-4} , por ejemplo, metilo, n-propilo, isopropilo o t-butilo, alquilo de C_{1-4} sustituido por 1 a 3 átomos de halógeno, por ejemplo,

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2,2,2-trifluoroetilo o 2-fluoroetilo, alquilo de C₁₋₄ sustituido por alcóxicarbonilo o carboxilo, por ejemplo, metoxycarbonilmetilo o carboximetilo, alquilo sustituido por alcoxi, por ejemplo, metoxietilo, 2,2-dimetoxietilo, alquilo sustituido por hidroxilo, por ejemplo, hidroxietilo o alquilo sustituido por dialquilamino, por ejemplo, dimetilaminoetilo, 2-benciloxifenilo, dimetoxibencilo, heteroarilmetilo sustituido opcionalmente, por ejemplo, 2-piridilmetilo, 3-piridilmetilo, 4-piridilmetilo, 3-metilimidazolilmetilo, heteroarilo tal como tiazolilo, por ejemplo, 2-1,3-tiazolilo, alquilo sustituido por NR₇R₈ [en donde NR₇R₈ forma un anillo heterocíclico de 6 miembros (por ejemplo, piperidinoetilo o morfolinoetilo)], cicloalquilo, por ejemplo, ciclopropilo o ciclohexilo, o NR₅R₆ representa, acetidino, 3-hidroxiacetidino, 3-metoxiacetidino, pirrolidino, piperidino, 4-dimetilaminopiperidino, 4-metil-1,4-diazepan-1-ilo, morfolino, un anillo de piperacino sustituido opcionalmente, por ejemplo, N-metilpiperacino, N-metansulfonilpiperacino, N-2-metoxietilpiperacino, tiomorfolino o el sulfóxido o sulfona de los mismos.

Una clase preferida de compuestos de la invención adicional, son aquéllos de fórmula (1a), en donde R₃ es un grupo seleccionado de fenilo, halofenilo, tal, como 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 4-clorofenilo, 3-clorofenilo, 2-clorofenilo, 4-bromofenilo, 2,3-difluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 3,5-difluorofenilo, 2,5-difluorofenilo, 2-cloro-4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 2-fluoro-4-bromofenilo, 4-cloro-3-fluorofenilo, 2,3,4-trifluorofenilo, 2,4,5-trifluorofenilo o 2,4,6-trifluorofenilo, 2-fluoro-4,5-dimetoxifenilo, 3-fluoro-4-metoxifenilo, 4-fluoro-3-metoxifenilo, 2-

- fluoro-4-metoxifenilo, 2-fluoro-4-hidroxifenilo, 2-fluoro-4-dimetilaminometilfenilo, 2-fluoro-4-hidroximetilfenilo, 3-fluoro-4-(4-morfolino)fenilo, 3-fluoro-4-carboximetiloxifenilo, 3-fluoro-4-t-butiloxycarbonilmetiloxifenilo, 3-fluoro-4-dimetilaminocarboniloxifenilo, 3-cloro-4-trifluorometoxifenilo, 2,3-difluoro-4-metil-fenilo, 4-trifluorometoxifenilo, 4-trifluorometilfenilo, 4-hidroxifenilo, 4-metoxifenilo, 4-metoxycarbonilfenilo, 3-metoxycarbonilfenilo, 4-metilsulfonilfenilo, 4-metilaminocarbonilfenilo, 4-aminocarbonilfenilo, 4-metilaminosulfonilfenilo, 3-(3-pirazolil)fenilo, 4-(3-pirazolil)fenilo, 4-(4-pirazolil)fenilo, 4-(3-piridil)fenilo, 4-(2-piridil)fenilo, 4-(2-imidazolil)fenilo, 3-(2-imidazolil)fenilo, 4-(1-t-butyl-tetrazol-5-il)fenilo, 4-metilaminofenilo, 4-dimetilaminofenilo, 4-dietilaminofenilo, 4-acetilaminofenilo, 3-acetilaminofenilo, 4-hidroxi-3-acetilaminofenilo, 4-metilsulfonilaminofenilo, 4-N-metilpiperacinafenilo, 4-N-pirrolidinafenilo, 2-fluoro-4-(4-morfolino)fenilo, 4-(4-morfolino)fenilo, 4-(4-hidroxipiperidino)fenilo, 2-fluoro-4-(4-hidroxipiperidino)fenilo, 3-(1-pirazolil)fenilo, 4-(1-pirazolil)fenilo, 4-(1-3,5-di-t-butilpirazolil)fenilo, 3-(1-imidazolil)fenilo, 4-(1-imidazolil)fenilo, 4-(1-1,2,4-triazolil)fenilo, 4-(1-1,2,3-triazolil)fenilo, 4-(2-4-t-butiltiazolil)fenilo, 4-(5-2-t-butiltetrazolil)fenilo, 4-(4-espiro-1,3-dioxolanil)piperidinafenilo, 4-(4-fluorofenil)fenilo, 4-(4-etilaminosulfonilfenil)fenilo, 4-dimetilaminoetoxifenilo, 3-(dihidroxiboril)fenilo, 2-furanilo, 3-tienilo, 3-furanilo, 2-tienilo, 4-bromo-2-tienilo, 5-bromo-2-tienilo, 5-cloro-2-tienilo, 3-fluoro-5-metil-2-tienilo, 5-metil-2-tienilo, 5-metil-2-furanilo, 5-bromo-2-furanilo, 4,5-dimetil-2-furanilo, 5-trifluorometil-2-furanilo, metilamida del ácido 2-furanil-4-carboxílico, metilamida del ácido 2-

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furanil-5-carboxílico, 2-piridilo, 6-metil-2-piridilo, 6-metil-3-piridilo, 6-metoxi-3-
 piridilo, 6-hidroxil-3-piridilo, 6-trifluorometil-3-piridilo, 3-piridilo, 4-piridilo, 3,5-
 pirimidinilo, 2-tiazolilo, 2-metil-4-oxazolilo, 2-etil-4-oxazolilo, 2-ciclopropil-4-
 oxazolilo, 2-trifluorometil-4-oxazolilo, 2,5-dimetil-4-oxazolilo, 4-tiazolilo, 2-metil-
 5 4-tiazolilo, 2-trifluorometil-4-tiazolilo, 2-trifluorometil-5-tiazolilo, 1-metil-4-
 pirazolilo, 1,3-dimetil-5-pirazolilo, 5-(2-piridil)-2-tienilo, 2,3-dihidro-1-
 benzofuran-5-ilo, 1,3-benzodioxol-5-ilo, 1H-1,2,3-benzotriazol-5-ilo, 2,3-
 dihidro-1,4-benzodioxin-6-ilo, 2,2-difluoro-1,3-benzodioxol-5-ilo, 1,3-
 benzotiazol-6-ilo, 1-metil-1H-1,2,3-benzotriazol-5-ilo, 1-metil-1H-1,2,3-
 10 benzotriazol-6-ilo, 1,2,3-benzotiadiazol-6-ilo, 2-metil-1,3-benzoxazol-5-ilo, 2-
 metil-1,3-benzoxazol-6-ilo, 1-benzofuran-5-ilo, 1-metil-1H-indol-5-ilo, 1-
 benzotien-5-ilo, 1-benzofuran-6-ilo, 1H-indol-6-ilo, 1-metil-1H-bencimidazol-6-
 ilo, 1-metil-1H-bencimidazol-5-ilo, 3-metil-1,2-benzoisoxazol-5-ilo, 2-fluoro-1-
 benzofuran-5-ilo, 1H-indol-5-ilo, 2-metil-1H-benzofuran-5-ilo, 1H-indazol-5-ilo,
 15 1H-indazol-6-ilo, 1-benzofuran-2-ilo o 1-metil-1H-bencimidazol-2-ilo.

Los compuestos particularmente preferidos de la invención incluyen:

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-
 6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida
 20 (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-
 isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida
 (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-
 isobutil-2,5-dioxopiperacin-1-il]-morfolinamida

(2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida.

(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(4-hidroxipiperidin-1-il)fenil]etanamida.

5 (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]-2-(2-fluoro-4-morfolin-4-ilfenil)-N-isopropiletanamida.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2,2,2-trifluoroetil)etanamida.

10 (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida.

(2R)-N-ciclopropil-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida.

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metiletanamida

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona

20 (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-hidroxiacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona

(3R,6R)-1-[(1R)-2-acetidin-1-il-1-(2,4-difluorofenil)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona

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- (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxietil)-N-metiletanamida
- (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-[2-(metilsulfonil)etil]etanamida
- 5 (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(2,2,2-trifluoroetil)etanamida
- (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(piridin-2-ilmetil)etanamida
- (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-[4-(metilsulfonil)piperacin-1-il]-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
- 10 (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metoxi-N-metiletanamida
- ácido (2R)-2-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanoico
- 15 etanoato de (2R)-2-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]metilo
- etanoato de (2R)-2-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]propilo
- etanoato de (2R)-2-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-1-(acetiloxi)etilo
- 20 (2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida

(2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida

(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-metilpropil]piperacin-2,5-diona.

5 (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]piperacin-2,5-diona.

(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-fluoroacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[5-(trifluorometil)-2-furil]etanamida.

(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(5-metiltien-2-il)etanamida.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[5-(trifluorometil)-2-furil]etanamida.

15 (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1,3-oxazol-4-il)etanamida.

(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-1-(2-metil-1,3-oxazol-4-il)-2-morfolin-4-il-2-oxoetil]piperacin-2,5-diona.

(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(5-metiltien-2-il)etanamida

20 (2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(3-fluoro-5-metiltien-2-il)-N,N-dimetiletanamida

(2R)-2-(1-benzofuran-5-il)-3-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida.

(2R)-2-(1,2,3-benzotiadiazol-6-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida.

5 (2R)-2-(2,3-dihidro-1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida.

(2R)-2-(1,3-benzodioxol-5-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida.

10 (2R)-2-(benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1-benzofuran-5-il)etanamida.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(2-metil-1-benzofuran-5-il)etanamida.

15 (3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-1-(2-metil-1-benzofuran-5-il)-2-morfolin-4-il-2-oxoetil]piperacin-2,5-diona.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-fluoro-1-benzofuran-5-il)-N,N-dimetiletanamida.

20 (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-fluoro-1-benzofuran-5-il)-N-isopropiletanamida.

(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-il)-2-morfolin-4-il-2-oxoetil]-6-isobutilpiperacin-2,5-diona.

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(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indol-6-il)-N,N-dimetiletanamida.

(2R)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida.

5 La capacidad de los compuestos de fórmula (I) para inhibir las acciones de la oxitocina, puede determinarse utilizando una variedad de procedimientos convencionales.

Así, los compuestos de fórmula (I) tienen una alta afinidad por los receptores de oxitocina en el útero de ratas y humanos, y esto puede
10 determinarse utilizando un procedimiento convencional. Por ejemplo, la afinidad por los receptores de oxitocina en el útero de la rata puede determinarse mediante el procedimiento de Pettibone et al, Drug Development Research 30.129-142 (1993). Los compuestos de la invención también exhiben alta afinidad en el receptor de la oxitocina recombinante humana en
15 las células de CHO y esto puede demostrarse convenientemente utilizando el procedimiento descrito por Wyatt et al. Bioorganic & Medicinal Chemistry Letters, 2001 (11) p 1301-1305.

Los compuestos de la invención, por lo tanto, son útiles en el tratamiento o la prevención de enfermedades y/o condiciones mediadas a
20 través de la acción de la oxitocina. Los ejemplos de tales enfermedades y/o condiciones incluyen trabajo de parte a pretérmino, dismenorrea y endometriosis.

Los compuestos también pueden ser útiles para retrasar el trabajo de parto antes de una sección cesárea opcional o la transferencia del paciente a un centro de cuidado superior. Los compuestos de la invención también pueden ser útiles para mejorar las proporciones de fertilidad en los animales, por ejemplo, animales de granja.

Por lo tanto, la invención proporciona el uso de un compuesto de fórmula (I) y/o sales fisiológicamente aceptables, para utilizarse en terapia y en uso particular como una medicina para antagonizar los efectos de la oxitocina con el receptor de la oxitocina.

La invención también proporciona el uso de un compuesto de fórmula (I) y/o una sal fisiológicamente aceptable del mismo para la manufactura de un medicamento para antagonizar los efectos de la oxitocina sobre el receptor de la oxitocina.

De acuerdo a un aspecto adicional, la invención también proporciona un método para antagonizar los efectos de la oxitocina sobre el receptor de la oxitocina, que comprende administrar a un paciente en necesidad del mismo una cantidad antagonista de un compuesto de fórmula (I) y/o una sal fisiológicamente aceptable del mismo.

Se apreciará por aquellos con experiencia en la técnica, que la referencia en la presente al tratamiento, se extiende a la profilaxis, así como al tratamiento de enfermedades o síntomas establecidos.

Se apreciará además, que la cantidad de un compuesto de la invención, requerida para utilizarse en el tratamiento, variará con la naturaleza

de la condición siendo tratada, la ruta de administración y la edad y la condición del paciente, y finalmente será a discreción del médico que atiende. En general, sin embargo, las dosis empleadas para el tratamiento de un humano adulto, estarán típicamente, en el intervalo de 2 a 800 mg por día, dependiendo de la ruta de administración.

Así, para la administración parenteral, una dosis diaria estar típicamente, en el intervalo de 2 a 50 mg, de manera preferida de 5 a 25 mg por día. Para la administración oral, una dosis diaria estará típicamente en el intervalo de 10 a 800 mg, por ejemplo de 20 a 150 mg por día.

10 La dosis deseada puede presentarse de manera conveniente en una sola dosis o como dosis divididas administradas a intervalos apropiados, por ejemplo, como dos, tres, cuatro o más subdosis por día.

Mientras que es posible que, para utilizarse en terapia, un compuesto de la invención pueda administrarse como el compuesto químico sin procesar, es preferible presentar el ingrediente activo como una formulación farmacéutica.

15 Por lo tanto, la invención proporciona además, una formulación farmacéutica que comprende un compuesto de fórmula (I) o una sal farmacéuticamente aceptable o ésteres lábiles metabólicamente no tóxicos del mismo, junto con uno o más portadores farmacéuticamente aceptables del mismo y, opcionalmente, otros ingredientes terapéuticos y/o profilácticos. Los portadores deben ser "aceptables" en el sentido que sean compatibles con

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otros ingredientes de la formulación y no dañinos para el receptor de los mismos.

Las composiciones de la invención incluyen aquéllas en una forma especialmente formulada para la administración oral, bucal, parenteral, por inhalación o insuflado, por implante o rectal.

Las tabletas y cápsulas para la administración oral pueden contener excipientes convencionales tales como agentes aglutinantes, por ejemplo, jarabe, acacia, gelatina, sorbitol, tragacanto, mucílago de almidón o polivinilpirrolidona; rellenos, por ejemplo, lactosa, azúcar, celulosa microcristalina, almidón de maíz, fosfato de calcio o sorbitol; lubricantes, por ejemplo, estearato de magnesio, ácido esteárico, talco, polietilenglicol o sílice; desintegrantes, por ejemplo, almidón de papa o glicolato almidón de sodio, o agentes humectantes tales como lauril sulfato de sodio. Las tabletas pueden recubrirse de acuerdo con métodos bien conocidos en la técnica. Las preparaciones orales líquidas pueden estar en la forma de, por ejemplo, suspensiones, soluciones, emulsiones acuosas u oleosas, jarabes o elixires o pueden presentarse como un producto seco para la constitución con agua u otro vehículo adecuado antes del uso. Tales preparaciones líquidas pueden contener aditivos convencionales tales como agentes de suspensión, por ejemplo, jarabe de sorbitol, metil celulosa, jarabe de glucosa/azúcar, gelatina, hidroxietilcelulosa, carboximetil celulosa, gel de estearato de aluminio o grasas comestibles hidrogenadas; agentes emulsificantes, por ejemplo, lecitina, monooleato de sorbitán o acacia; vehículos no acuosos (los cuales

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incluyen aceites comestibles), por ejemplo, aceite de almendra, aceite de coco fraccionado, ésteres oleosos, propilenglicol o alcohol etílico; solubilizantes tales como tensioactivos, por ejemplo polisorbato u otros agentes tales como ciclodextrinas; y preservativos, por ejemplo, p-hidroxibenzoatos de metilo o propilo o ácido ascórbico. Las composiciones también pueden formularse como supositorios, por ejemplo, que contienen bases convencionales para supositorio tales como manteca de cacao u otros glicéridos.

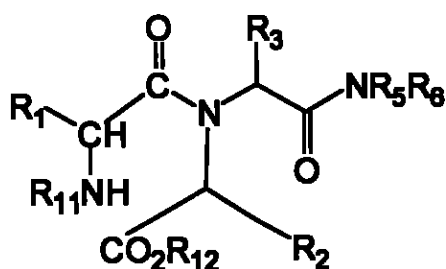
Para la administración bucal, la composición puede tomar la forma de tabletas o pastillas formuladas de manera convencional.

La composición de acuerdo con la invención puede formularse para la administración parenteral mediante inyección o infusión continua. Las formulaciones para inyección pueden presentarse en forma de dosificación unitaria en ampollas, o en recipientes de múltiples dosis con un preservativo agregado. Las composiciones pueden tomar formas tales como suspensiones, soluciones o emulsiones en vehículos oleosos o acuosos, y pueden contener agentes de formulación tales como agentes de suspensión, estabilizantes y/o de dispersión. De manera alterna, el ingrediente activo puede estar en forma de polvo para la constitución con un vehículo adecuado, por ejemplo, agua estéril, libre de pirógenos, antes del uso.

Las composiciones de acuerdo con la invención pueden contener entre 0.1-99% del ingrediente activo, de manera conveniente de 30-95% para tabletas y cápsulas, y 3-50% para preparaciones líquidas.

Los compuestos de fórmula (I), en donde R_4 es el grupo NR_5R_6 , puede prepararse mediante ciclización del compuesto de fórmula (II)

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(II)

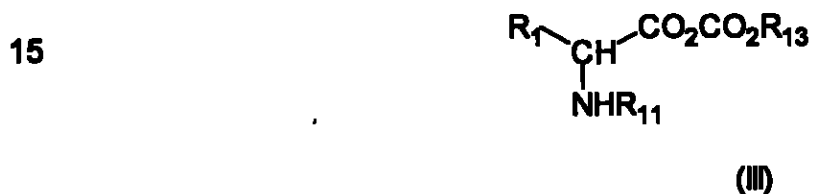
en donde R_1 , R_2 y R_3 tienen los significados definidos en la fórmula (I), R_{11} es hidrógeno y R_{12} es un grupo alquilo de C_{1-3} (por ejemplo metilo), en un solvente adecuado tal como un alcohol, por ejemplo, metanol y/o 2,2,2-trifluoroetanol, dioxano o una mezcla de los mismos o un hidrocarburo, por ejemplo, diclorometano.

El compuesto de fórmula (II), en donde R_{11} es hidrógeno es preparado de manera conveniente in situ tratando un compuesto de fórmula (II), en donde R_1 es un grupo protector lábil de nitrógeno ácido y R_{12} es hidrógeno o alquilo de C_{1-3} , con un ácido en un solvente adecuado, seguido por el tratamiento con un ácido hidrohálúrico y metanol si R_{12} en la materia prima es hidrógeno, y a continuación, la adición de una base adecuada, por ejemplo trietilamina o mediante el tratamiento de un compuesto de fórmula (II), en donde R_{11} es un grupo protector de nitrógeno hidrolizable y R_{12} es alquilo de C_{1-3} en un solvente adecuado tal como metanol o 2,2,2-trifluoroetanol con

hidrógeno en la presencia de un catalizador adecuado, por ejemplo, paladio o carbono.

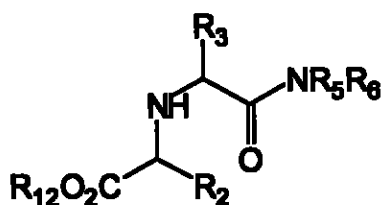
Los ejemplos de los grupos protectores de nitrógeno R_{11} adecuados, incluyen alcóxicarbonilo, por ejemplo t-butiloxicarbonilo o un grupo benciloxicarbonilo sustituido opcionalmente. Cuando R_{12} es alquilo de C_{1-3} , es de manera conveniente etilo o de manera más particular metilo. Los ejemplos de ácidos adecuados incluyen ácidos minerales, tales como ácidos hidrohalúricos, por ejemplo, ácido clorhídrico o ácidos orgánicos tales como ácido trifluoroacético. La reacción es llevada a cabo de manera conveniente en un solvente tal como 1,4-dioxano o un alcohol, por ejemplo, metanol o una mezcla de los mismos, o halohidrocarburo, por ejemplo, diclorometano.

Los compuestos de fórmula (II), pueden prepararse mediante la reacción del anhídrido mezclado (III)



en donde R_1 y R_{11} tienen los significados definidos anteriormente y en donde R_{13} es una cadena del alquilo de C_{1-6} lineal o ramificada, un grupo fenilo sustituido opcionalmente o bencilo, con la amina (IV)

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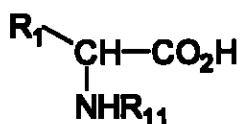
(IV)

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en donde R_2 , R_3 , R_5 y R_6 tienen los significados definidos anteriormente, y R_{12} es hidrógeno.

La reacción es, de manera preferida, llevada a cabo en un solvente aprótico tal como un éter, por ejemplo, tetrahidrofurano o una amida terciaria tal como N,N-dimetilformamida o una mezcla de los mismos. Los compuestos de fórmula (III) pueden prepararse mediante el tratamiento del aminoácido N protegido (V)

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(V)

en donde R_1 y R_{11} tienen los significados definidos anteriormente con el haloformiato correspondiente (VI; $\text{R}_{13}\text{CO}_2\text{X}$, en donde R_{13} tiene el significado definido en la fórmula (III), y X es halógeno, por ejemplo, cloro o bromo), en la presencia de una amina orgánica terciaria adecuada, por ejemplo N-metilmorfolina y un solvente aprótico, por ejemplo, un éter tal como tetrahidrofurano o un hidrocarbano, por ejemplo tolueno.

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La amina (IV), en donde R_5 es hidrógeno, puede prepararse tratando el aminoácido (VII)



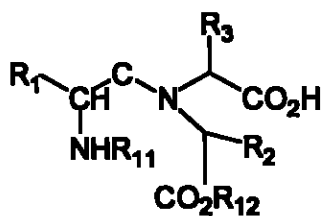
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(VII)

en donde R_2 tiene los significados definidos anteriormente y R_{12} es hidrógeno con el aldehído (VIII; R_3CHO , en donde R_3 tiene el significado definido en la fórmula (I)) en un solvente adecuado tal como un alcohol, por ejemplo, metanol, seguido por la reacción con el isonitrilo (IX; $R_6N = C$, en donde R_6 tiene los significados definidos en la fórmula I, diferente de hidrógeno). De manera alterna, los compuestos de fórmula (II), en donde R_1 , R_2 y R_3 tienen los significados proporcionados en la fórmula (I) y R_{11} es un grupo protector de nitrógeno y R_{13} es un grupo protector de carboxilo, pueden prepararse mediante la reacción del derivado de aminoácido (VII), en donde R_2 tiene el significado dado en la fórmula (I), y R_{12} es un grupo protector de carboxilo con el aldehído (VIII), en donde R_3 tiene el significado dado en la fórmula (I) en un solvente tal como un alcohol, por ejemplo, metanol o 2,2,2-trifluoroetanol seguido por una adición secuencial del aminoácido (V), en donde R_1 tiene los significados dados en la fórmula (I) y R_{11} es un grupo protector de carboxilo y el isonitrilo (IX), en donde R_6 tiene los significados proporcionados en la fórmula (I).

Los compuestos de la fórmula (II), en donde R_{12} es un grupo alquilo de C_{1-3} , también puede prepararse mediante la reacción del ácido carboxílico (X) o un derivado activado del mismo

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(X)

en donde R_1 , R_2 , R_3 y R_{11} tienen los significados definidos anteriormente y R_{12} es un grupo alquilo de C_{1-3} , con la amina NHR_5R_6 , en donde R_5 y R_6 tienen los significados definidos en la fórmula (I). Los ejemplos de un derivado activado adecuado del ácido carboxílico (X), incluyen aquéllos comúnmente utilizados en la síntesis peptídica, por ejemplo, aquél derivado de la reacción de hexafluorofosfato de benzotriazol-1-iloxitri-pirrolidinofosfonio en la presencia de una amina tal como disopropiletilamina.

El ácido carboxílico (X) puede prepararse a partir del compuesto de fórmula (II) correspondiente, en donde R_5 representa hidrógeno y R_6 representa el 2-hidroxifenilo mediante la reacción con carbonildiimidazol o tiocarbonildiimidazol en un solvente adecuado tal como diclorometano y la subsiguiente reacción del producto así formado con acetona acuosa.

Los compuestos de fórmula (II), en donde R_6 representa 2-hidroxifenilo, son preparados de manera conveniente mediante hidrogenólisis

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catalítica (por ejemplo, Pd/H₂) del compuesto correspondiente, en donde R₆ es un grupo 2-beniloxifenilo.

En un aspecto adicional de la invención, los compuestos de fórmula (I) como se definieron anteriormente, pueden convertirse en otros compuestos de fórmula (I). Así, los compuestos de fórmula (I), en donde R₄ es hidroxilo, pueden prepararse a partir de un compuesto de fórmula (I), en donde R₄ es el grupo NR₅R₆ y R₅ es hidrógeno, R₆ es 2-hidroxifenilo mediante la reacción con carbonildimidazol o tiocarbonildimidazol en un solvente adecuado, tal como diclorometano y la reacción posterior el producto así formado con acetona acuosa.

Los compuestos de fórmula (I), en donde R₅ es hidrógeno y R₆ es 2-hidroxifenilo, pueden prepararse a partir del compuesto de fórmula (I) correspondiente, en donde R₆ es un grupo 2-beniloxifenilo, mediante la hidrogenólisis utilizando hidrógeno y un catalizador de paladio.

Los compuestos de fórmula (I), en donde R₄ es el grupo NR₅R₆, pueden prepararse mediante la reacción del compuesto de fórmula (I), en donde R₄ es hidroxilo o un derivado activado de los mismos con el amino NHR₅R₆, en donde R₅ y R₆ tienen los significados definidos en la fórmula (I) bajo las condiciones estándar para la preparación de amidas a partir de un ácido carboxílico y una amina tal como NHR₅R₆.

Así, las amidas pueden prepararse mediante el tratamiento del compuesto de fórmula (I), en donde R₄ es hidroxilo con un agente activante tal como BOP (hexafluorofosfato de benzotriazol-1-iloxi-

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tris(dimetilamino)fosfonio), TBTU (tetrafluoroborato de 2-(1H-benzotriazol-1-il)-1,1,3,3-tetrametiluronio), BOP-C1 (cloruro bis(2-oxo-3-oxazolidinil)fosfínico) o cloruro de oxalilo en un solvente aprótico, tal como diclorometano opcionalmente en la presencia de una amina terciaria tal como trietilamina y la

5 subsiguiente reacción del producto así formado con la amina NHR_5R_6 .

De manera alterna, los compuestos de fórmula (I), en donde R_4 es el grupo NR_5R_6 , pueden prepararse mediante la reacción de un compuesto de fórmula (I), en donde R_5 es hidrógeno y R_6 es 2-hidroxifenilo con carbonildiimidazol o tiocarbonildiimidazol en un solvente adecuado tal como

10 diclorometano y subsiguiente reacción del producto así formado con la amina NHR_5R_6 .

Los compuestos de fórmula (I), en donde R_4 es Oalquilo de C_{1-4} (sustituido opcionalmente con alquilcarboniloxi de C_{1-4}), pueden prepararse mediante la reacción del ácido carboxílico correspondiente (R_4 es OH) o un

15 derivado activado de los mismos con el alcohol apropiado (R_4OH) o haluro de alquilo (haluro R_4) bajo condiciones estándar para la preparación de tales ésteres. Los derivados activados adecuados incluyen los haluros ácidos, anhídridos mezclados, aquéllos formados con reactivos de acoplamiento utilizados comúnmente en la síntesis peptídica, por ejemplo,

20 carbonildiimidazol y sales básicas del ácido, por ejemplo, sales de metales alcalinos.

Los compuestos de fórmula (IV), pueden convertirse en otros compuestos de fórmula (IV), utilizando los procedimientos estándar. Así, el

compuesto de fórmula (IV), en donde R_5 es hidrógeno y R_6 es 2-benciloxifenilo, pueden convertirse en otros compuestos de fórmula (IV), en donde R_5 y R_6 tienen otros significados como se define en la fórmula (I), utilizando los mismos procedimientos como se describió anteriormente para

5 llevar a cabo las reacciones análogas en los compuestos de fórmula (I).

Los compuestos de fórmula (I), en donde la estereoquímica de cualquiera de los sustituyentes R_1 , R_2 y R_3 es como se muestra en la fórmula (1a), pueden prepararse a partir de los isómeros únicos correspondientes de los intermediarios (III), (IV) y (VII) y/o las varias mezclas isoméricas pueden

10 ser separadas mediante procedimientos convencionales.

Los intermediarios (V), (VI), (VII), (VIII) y (IX) son compuestos conocidos, que pueden prepararse mediante métodos análogos a aquéllos conocidos para la preparación de los compuestos estructuralmente relacionados.

15 Los compuestos del grupo de la fórmula (I), en donde R_4 es OH, pueden prepararse mediante la ciclización de un compuesto correspondiente de fórmula (II) bajo las condiciones descritas anteriormente para la preparación de los compuestos de fórmula (I).

Las sales fisiológicamente aceptables de un compuesto de

20 fórmula (I), en donde R_4 es OH o uno de los grupos R_1 , R_2 , R_3 o NR_4R_5 tienen un centro ácido o básico que puede prepararse mediante el tratamiento de la base o ácido con el ácido o la base fisiológicamente aceptables requeridos, y esta reacción es de manera conveniente, llevada a cabo en un solvente para

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el compuesto de fórmula (I). Los derivados fisiológicamente aceptables de un compuesto de fórmula (I), pueden prepararse a partir de un intermediario apropiado correspondiente a la fórmula (II), utilizando el procedimiento descrito anteriormente para la preparación de compuestos de fórmula (I) o
5 directamente a partir de los compuestos de fórmula (I), mediante procedimientos convencionales para la preparación de tales derivados. Así, los ésteres metabólicamente lábiles pueden prepararse mediante la esterificación del grupo carboxilo o hidroxilo libre utilizando técnicas de esterificación estándar.

10 Los siguientes ejemplos son ilustrativos, pero no limitantes de las modalidades de la presente invención.

Métodos generales de purificación y analíticos

Se llevó a cabo la HPLC analítica en una columna
15 SupelcosilLCABZ+PLUS (3.3 cm x 4.6 mm DI), eluyendo con HCO₂H al 0.1% y acetato de amonio 0.01 M en agua (solvente A) y HCO₂H al 0.05% agua al 5% en acetonitrilo (solvente B), utilizando el siguiente gradiente de elución 0-0.7 minutos 0% de B, 0.7-4.2 minutos 0%-100% de B, 4.2-5.3 minutos 100% de B, 5.3-5.5 minutos 0% de B a una velocidad de flujo de 3 ml/minuto. El
20 espectro de masas (MS, por su siglas en inglés) se registró en un espectrómetro de Plataforma Fisons VG, utilizando los modos de electrorrocío positivo [(ES+ve para proporcionar iones moleculares MH⁺ y M(NH₄)⁺] o electrorrocío negativo [(ES-ve para proporcionar el ion molecular (M-H)] en un

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espectrómetro de masas Micromass serie 2 o Waters ZQ. El espectro de ^1H RMN se registró utilizando un espectrómetro Bruker DPX 400MHz utilizando tetrametilsilano como el estándar externo. La cromatografía Biotage™ se refiere a la purificación llevada a cabo utilizando el equipo vendido por Dyax Corporation (ya sea Flash 40i o Flash 150i) y cartuchos preempacados con KPSil. Autoprep dirigido por masa se refiere a los métodos en donde el material se purificó mediante cromatografía líquida de alto rendimiento en una columna HPLCABZ+ de $5\mu\text{m}$ (5 cm x 10 mm d. i.) con HCO_2H al 0.1% en agua y MeCN al 95%, 5% de agua (HCO_2H al 0.5%) utilizando una elusión de gradiente a una velocidad de flujo de 8 ml/minutes^{-1} . El recolector de las fracciones Gilson 202 se activó mediante un Espectrómetro de Masas de Plataforma VG para detectar la masa de interés.

Los vidrios porosos hidrofóbicos se refieren a los tubos de filtración vendidos por Whatman. SPE (Extracción en fase sólida) se refiere al uso de los cartuchos vendidos por International Sorbent Technology Ltd. TLC (cromatografía en capa fina) se refiere al uso de placas de TLC vendidas por Merck, recubiertas con gel de sílice 60 F₂₅₄. Oasis™ se refiere a los Cartuchos de Extracción HLB Waters® Oasis™, vendidos por Waters Corporation®.

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MET D 1**EJEMPLO 1****(2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-isopropiletanamida**

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A una solución de clorhidrato del éster metílico de (D)-leucina (300 mg) en metanol (4 ml), se agregó trietilamina (230 µl) y 4-fluorobenzaldehído (177 µl). La mezcla se agitó durante 2.5 horas antes de agregar secuencialmente ácido (2R)-[(ter-butoxicarbonil)amino](2,3-dihidro-10 1H-inden-2-il)etanoico (481 mg) e isocianuro de isopropilo (225 µl). Después de agitar durante 16 horas, el solvente se removió *in vacuo* y el residuo se disolvió en cloroformo. Esta solución se lavó con una solución acuosa saturada de carbonato de sodio (x2), ácido cítrico acuoso (0.5 M, x2) y salmuera (x1), se secó sobre sulfato de magnesio y se evaporó *in vacuo*. El 15 residuo se disolvió en diclorometano (2 ml) y ácido trifluoroacético (5 ml), y se agitó durante 3 horas a temperatura ambiente. Después de este tiempo, el solvente se removió *in vacuo* y el residuo se coevaporó con tolueno (x3) y ciclohexano/éter (1:1, x2). El residuo se trató con una solución de trietilamina en dioxano (solución al 2%, 10 ml) y se dejó agitar durante la noche. Después 20 de este tiempo, el dioxano se removió *in vacuo* y el residuo se disolvió en acetato de etilo. La solución se lavó con una solución de ácido cítrico (0.5 M, x2), solución de bicarbonato de sodio acuoso saturado (x1) y salmuera (x1). Los licores se secaron a continuación sobre sulfato de magnesio e *in vacuo*, y

a continuación fueron coevaporados con ciclohexano:éter (1:1, x2). Este material crudo se purificó mediante Biotage™ (90 g, sílice), eluyendo con tolueno:acetato de etilo:ciclohexano (5:3:2) con trietilamina al 5% para proporcionar la (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-

5 isobutil-2, 5-dioxopiperacin-1-il]-N-isopropiletanamida (149 mg).

HPLC Rt = 3.42 minutos; m/z [M+H]⁺ = 480.

¹H RMN (CDCl₃) δ 7.44 (m, 2H), 7.22 (m, 2H), 7.16 (m, 2H), 7.11 (t, 2H), 6.50 (d, 1H), 5.60 (d, 1H), 5.11 (s, 1H), 4.10 (m, 1H), 3.96 (m, 2H), 3.16 (dd, 1H), 3.07 (d, 1H), 2.91 (m, 1H), 2.77 (m, 1H), 1.84 (m, 1H), 1.73 (m, 10 1H), 1.42 (m, 1H), 1.13 (d, 3H), 1.12 (d, 3H), 0.84 (d, 3H), 0.79 (d, 3H).

Preparado de manera similar.

EJEMPLO 2

(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-
15 dioxopiperacin-1-il]-2-[4-(4-hidroxipiperidin-1-il)fenil]etanamida

HPLC Rt = 3.27 minutos; m/z [M+H]⁺ = 575.

(CDCl₃) δ 7.3 (d, 2H), 7.2 (m, 2H), 7.15 (m, 2H), 6.9 (d, 2H), 6.1 (d, 1H), 5.5 (s, 1H), 5.15 (s, 1H), 3.95 (m, 2H), 3.9 (m, 1H), 3.6 (m, 2H), 3.15 (m, 1H), 3.1 (m, 2H), 3.0 (m, 2H), 2.9 (m, 1H), 2.75 (m, 1H), 2.0 (m, 2H), 1.75 (m, 1H), 1.65 (m, 3H), 1.45 (m, 1H), 1.3 (s, 9H), 0.8 (d, 3H), 0.7 (d, 3H).
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EJEMPLO 3

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]-2-(2-fluoro-4-morfolin-4-ilfenil)-N-isopropiletanamida

5 HPLC Rt = 3.34 minutos; m/z [M+H]⁺ = 565

¹H RMN (CDCl₃) δ 7.52 (t, 1H), 7.22-7.11 (m, 4H), 7.04 (s amplio, 1H), 6.66 (dd, 1H), 6.56 (dd, 1H), 5.07 (s, 1H), 4.19-4.08 (m, 2H), 3.98 (dd, 1H), 3.86-3.81 (4H, m), 3.21-2.91 (m, 8H), 2.80-2.73 (m, 1H), 1.96-1.86 (m, 1H), 1.72-1.61 (m, 1H), 1.51-1.40 (m, 1H), 1.19 (d, 3H), 1.16 (d, 3H), 1.06 (d, 3H),
10 0.92 (t, 3H).

METODO 2**EJEMPLO 4**

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2,2,2-trifluoroetil)etanamida

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(2R)-2-[(1R,S)-2-[2-(bencilloxi)fenil]amino]-1-(4-fluorofenil)-2-oxoetil][(2R)-2-(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanol]amino)-4-metilpentanoato de metilo

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Una mezcla de 4-fluorobenzaldehído (1.2 g), clorhidrato del éster metílico de (D)-leucina (1.7 g), trietilamina y metanol (56 ml), se agitó a temperatura ambiente durante 3 horas. Se agregaron a continuación

secuencialmente isocianuro de 2-benciloxifenilo (2.0 g) y N-ter-butoxicarbonil-(D)-indanil glicina (2.77 g). Después de 40 horas, la mezcla de reacción se repartió entre ácido clorhídrico 2M y acetato de etilo. La capa orgánica separada se lavó con una solución de bicarbonato de sodio acuoso saturado y salmuera, se secó sobre sulfato de magnesio y se evaporó *in vacuo*. El material crudo resultante se purificó mediante cromatografía en columna (eluyendo con 0.5% y 0.2% de metanol/diclorometano), para proporcionar el (2R)-2-[(1R,S)-2-[[2-(benciloxi)fenil]amino]-1-(4-fluorofenil)-2-oxoetil][(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]amino]-4-metilpentanoato de metilo (4.3 g).

HPLC Rt = 4.34 minutos, m/z [M+H]⁺ = 752

N-[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]-N-[(1R,S)-1-(4-fluorofenil)-2-[(2-hidroxifenil)amino]-2-oxoetil]-D-leucinato de metilo

Una mezcla de (2R)-2-[(1R,S)-2-[[2-(benciloxi)fenil]amino]-1-(4-fluorofenil)-2-oxoetil][(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]amino]-4-metilpentanoato de metilo (560 mg), paladio sobre carbono (70 mg) y etanol (15 ml), se agitó bajo una atmósfera de hidrógeno durante 5 horas. La mezcla se filtró a través de Celite y el filtrado se evaporó *in vacuo*. El producto crudo se purificó mediante cromatografía en columna (sílice), eluyendo con acetato de etilo:ciclohexano (10% al 15%), para

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proporcionar el N-[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]-N-[(1R,S)-1-(4-fluorofenil)-2-[(2-hidroxifenil)amino]-2-oxoetil]-D-leucinato de metilo.

HPLC Rt = 4.06 minutos, m/z [M+H]⁺ = 662

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Acido (2R)-[[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]-N-[(1R,S)-1-(4-fluorofenil)-2-[(2-hidroxifenil)amino]-2-oxoetil]-D-leucinato de metilo]

- 10 Se agregó carbonildiimidazol (558 mg) a una solución de N-[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]-N-[(1R,S)-1-(4-fluorofenil)-2-[(2-hidroxifenil)amino]-2-oxoetil]-D-leucinato de metilo (2.0 g) en diclorometano (20 ml), y la mezcla resultante se agitó a temperatura ambiente durante 24 horas. A continuación, la reacción se
- 15 concentró hasta sequedad, se disolvió en una mezcla de acetona:agua (60 ml:40 ml), y se agitó durante 17 horas a temperatura ambiente. A continuación, la solución se repartió entre ácido clorhídrico acuoso 2M y acetato de etilo. La capa orgánica separada se lavó con una solución de bicarbonato de sodio acuoso saturado y salmuera antes de secarse sobre
- 20 sulfato de magnesio y evaporarse *in vacuo*. La mitad del material se tomó para utilizarse crudo en un experimento adicional. La segunda mitad se purificó mediante BiotageTM (sílice, 90 g) eluyendo con metanol:diclorometano:amoníaco (1:98.5:0.5 a 2.5:86.5:1). La evaporación de

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las fracciones apropiadas proporcionó el ácido (2R)-{[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil][(1R)-1-(metoxicarbonil)-3-metilbutil]amino}(4-fluorofenil)etanoico, (173 mg).

HPLC Rt = 3.91 minutos, m/z [M+H]⁺ = 571.

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(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperidin-1-il]-2-(4-fluorofenil)-N-(2,2,2-trifluoroetil)etanamida

Una solución del ácido (2R)-{[(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil][(1R)-1-(metoxicarbonil)-3-metilbutil]amino}(4-fluorofenil)etanoico (73 mg) en N,N-dimetilformamida (2 ml) se trató secuencialmente con diisopropiletilamina (51 µl), fósforo (1-hidroxi-1H-benzotriazolato-O)tri-1-pirrolidinil-(T-4)-hexafluorofosfato (80 mg) y a continuación después de 2 minutos, 2,2,2-trifluoroetilamina (25 µl). Esta mezcla de reacción se agitó durante 2 horas antes de ser repartida entre ácido clorhídrico acuoso 2M y acetato de etilo. La capa orgánica se lavó con solución acuosa saturada de bicarbonato de sodio y salmuera antes de ser secada sobre sulfato de magnesio y se evaporó *in vacuo*. El residuo se disolvió en cloruro de hidrógeno 4M en dioxano, y se agitó durante 7 horas a temperatura ambiente. El reactivo se removió *in vacuo* y el residuo se repartió entre acetato de etilo y solución de bicarbonato de sodio acuoso saturado. La fracción orgánica separada se lavó con salmuera antes de ser secada sobre sulfato de magnesio y se evaporó *in vacuo*. El material crudo se purificó

mediante cromatografía en columna (sílice) eluyendo con metanol:diclorometano (1% al 3%) para proporcionar la ((2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2,2, 2-trifluoroetil)etanamida (10 mg).

5 HPLC Rt = 3.4 minutos, m/z [M+H]⁺ = 520

¹H RMN (CDCl₃) δ 7.42 (m, 2H), 7.34 (d, 1H), 7.20-7.10 (m, 6H), 6.61 (t, 1H), 5.28 (s, 1H), 4.08-3.96 (m, 3H), 3.88 (m, 1H), 3.14 (dd, 1H), 3.02 (m, 2H), 2.95-2.77 (m, 2H), 1.88-1.70 (m, 2H), 1.40 (ddd, 1H), 0.85 (d, 3H), 0.79 (d, 3H).

10 Los siguientes compuestos se prepararon en una manera similar.

EJEMPLO 5

(2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida

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HPLC Rt = 3.37minutos, m/z [M+H]⁺ = 466

¹H RMN (CDCl₃); δ 7.47-7.40 (m, 2H), 7.25-7.12 (m, 6H), 6.50 (d, 1H), 6.47 (s, 1H), 4.15 (dd, 1H), 3.98 (dd, 1H), 3.21-3.01 (m, 3H), 2.99 (s, 3H), 2.92-2.73 (m, 2H), 2.83 (m, 3H), 1.59-1.49 (m, 1H), 1.42 (dt, 1H), 0.66-0.57 (m, 1H), 0.62 (d, 3H), 0.40 (d, 3H).

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EJEMPL 6**(2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-morfolinamida**

5 HPLC Rt = 3.32 minutos, m/z [M+H]⁺ = 508

¹H RMN (CDCl₃); δ 7.44-7.39 (m, 2H), 7.26-7.12 (m, 6H), 6.87 (d, 1H), 6.51 (s, 1H), 4.12 (dd, 1H), 4.00 (dd, 1H), 3.73-3.62 (m, 3H), 3.60-3.54 (m, 2H), 3.37 (m, 1H), 3.23 (m, 1H), 3.20-3.02 (m, 4H), 2.91-2.75 (m, 2H), 1.60-1.50 (m, 1H), 1.45 (dt, 1H), 0.63 (d, 3H), 0.62-0.55 (m, 1H), 0.42 (d, 3H).

10 El 2-fluoro-4-(morfolino)-benzaldehído utilizado en esta síntesis se preparó mediante el siguiente procedimiento.

2-Fluoro-4-(morfolino)-benzonitrilo

15 Una solución 2,4-difluorobenzonitrilo (6.03 g, 43.35 mmoles) y morfolina (8.3 ml, 95.17 mmoles) en tetrahidrofurano (27 ml), se agitó a temperatura ambiente durante 24 horas. La mezcla se evaporó y el sólido blanco se purificó mediante una columna BiotageTM (90 g, sílice), eluyendo con ciclohexano:acetato de etilo: (4:1), para proporcionar el 2-fluoro-4-

20 (morfolino)-benzonitrilo como un sólido blanco (5.81 g, 65%).

HPLC Rt = 2.83 minutos; m/z [M+H]⁺ = 207.

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2-Fluoro-4-(morfolino)-benzaldehído

A una solución de 2-fluoro-4-(morfolino)-benzonitrilo (2.82 g, 13.7 mmoles) en tetrahidrofurano (27 ml), bajo una atmósfera de nitrógeno, se
5 agregó gota a gota una solución 1.5 M de DIBAL-H en tolueno (18.3 ml, 27.3 mmoles) durante 13 minutos, y la mezcla resultante se agitó durante 23.5 horas a temperatura ambiente. La mezcla se enfrió a -50°C, y el exceso de DIBAL-H se eliminó mediante la adición cuidadosa de metanol (27 ml). La
mezcla se agitó a continuación a temperatura ambiente durante 10 minutos,
10 se agregó cloruro de amonio saturado (27 ml) y la mezcla resultante se agitó a temperatura ambiente durante 40 minutos, y a continuación se evaporó bajo presión reducida hasta un sólido amarillo. Este sólido se repartió entre diclorometano (120 ml) y agua (120 ml), se agregó carbonato de potasio sólido hasta que la fase acuosa tuvo pH 10. Las fases se separaron vía un
15 vidrio poroso hidrofóbico, y la fase orgánica se evaporó y el residuo se purificó mediante una columna Biotage™ (40 g, sílice), eluyendo con ciclohexano:acetato de etilo (7:3), para proporcionar el 2-fluoro-4-(morfolino)-benzaldehído (1.96 g, 68%) como un sólido blanco.

HPLC Rt = 2.63 minutos; m/z [M+H]⁺ = 210.

METODO 3**EJEMPLO 7**

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida

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N-[(R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucinato de metilo

A una suspensión agitada de (L)-leucina (1.3 g) en metanol (100 ml) bajo una atmósfera de nitrógeno, se agregó 2,4-difluorobenzaldehído (1.42 g). Después de agitar a temperatura ambiente durante 3 días, la suspensión se enfrió a -30°C, y se agregó una solución de isocianuro de isopropilo (0.691 g) en metanol (5 ml). Después de 3 horas a -30°C, la reacción se dejó calentar a temperatura ambiente y se agitó durante 20 horas adicionales. El solvente se removió *in vacuo*, el residuo se purificó utilizando una columna Biotage™ (40 g, sílice) eluyendo con ciclohexano:acetato de etilo (gradiente de 8:1 a 1:1). Las fracciones requeridas se combinaron y se concentraron *in vacuo* para proporcionar el N-[(1R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucinato de metilo (1.326 g).

¹H RMN (CDCl₃) δ 7.32 (m, 1H), 6.88 (m, 1H), 6.82 (m, 1H), 6.78 (m, 1H), 4.42 (s, 1H), 4.07 (m, 1H), 3.69 (s, 3H), 3.18 (t, 1H), 1.66 (m, 1H), 1.49 (t, 2H), 1.18 (d, 3H), 1.15 (d, 3H), 0.88 (d, 3H), 0.77 (d, 3H).

N-[(1R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucina

A una solución de N-[(1R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucinato de metilo (1.32 g) en metanol (15 ml), se agregó una
 5 solución de hidróxido de litio (294 mg) en agua (15 ml). La reacción se agitó rápidamente durante 1.5 horas y a continuación se evaporó *in vacuo*. El residuo se disolvió en agua y se neutralizó utilizando ácido clorhídrico 2N. El sólido resultante se recolectó mediante filtración y se seco *in vacuo*. El filtrado se aplicó a 4 cartuchos Oasis (6 g), los cuales se eluyeron con agua (x2), y
 10 metanol (x2). Las fracciones requeridas se combinaron y se concentraron *in vacuo* para proporcionar la N-[(1R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucina (1.01 g).

HPLC Rt = 2.51 minutos; m/z [M+H]⁺ = 343.

15 **(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-isopropil-etanamida**

A una solución de ácido (2R)-[(ter-butoxicarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (291 mg) en tetrahidrofurano seco (5 ml) bajo
 20 una atmósfera de nitrógeno a -20°C se agregó N-metilmorfolina (101 mg) y una solución de cloroformiato de isopropilo en tolueno (1.0 M, 1 ml). Después de 10 minutos, se agregó una solución de N-[(1R)-1-(2,4-difluorofenil)-2-(isopropilamino)-2-oxoetil]-L-leucina (342 mg) en N,N-

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dimetilformamida/tetrahidrofurano (5 ml/10 ml), y la mezcla resultante se agitó a temperatura ambiente durante 4 horas. El solvente se removió a continuación *in vacuo* y el residuo se trató con ácido clorhídrico 4N en dioxano (2 ml). Después de 4 horas, se agregó metanol (5 ml) a la mezcla de
 5 reacción, y ésta se dejó reposar durante 18 horas. El solvente se removió a continuación *in vacuo* y el residuo se purificó sobre un cartucho SPE (50 g, sílice), eluyendo con ciclohexano/acetato de etilo (gradiente de 4:1 a acetato de etilo puro), el cual proporcionó dos diastereómeros como sólidos blancos de (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-
 10 2,5-dioxo-piperacín-1-il]-N-isopropiletanamida; (0.137 g).

HPLC Rt = 3.47 minutos, m/z [M+H]⁺ = 498

¹H RMN (CDCl₃) δ 7.68 (m, 1H), 7.21 (m, 2H), 7.17 (m, 2H), 6.95 (m, 1H), 6.89 (m, 1H), 6.79 (d, 1H), 5.91 (d, 1H), 5.33 (s, 1H), 4.12 (m, 1H), 4.02 (m, 1H), 3.92 (dd, 1H), 3.16 (m, 1H), 3.05 (m, 2H), 2.90 (m, 1H), 2.78 (m,
 15 1H), 1.85 (m, 1H), 1.79 (m, 1H), 1.49 (m, 1H), 1.17 (m, 6H), 0.88 (d, 3H), 0.82 (d, 3H).

METODO 4

EJEMPLO 8

20 (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N,N-dimetiletanamida

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N-[(1R)-2-[[2-(benciloxi)fenil]amino]-1-(2,4-difluorofenil)-2-oxoetil]-L-leucinato de metilo

A una suspensión de L-leucina (2.33 g) en metanol (200 ml) a
5 -30°C bajo nitrógeno, se agregó una solución de 2,4-difluorobenzaldehído
(2.52 g) en metanol (10 ml) y una suspensión de 2-benciloxifenilisonitrilo (3.7
g) en metanol (40 ml). La reacción se agitó a -30°C durante 2.5 horas y a
continuación se dejó calentar a temperatura ambiente y se agitó durante 6
días adicionales. El solvente se removió *in vacuo* y el residuo se pasó a
10 través de una columna Biotage™ (90 g), eluyendo con ciclohexano:acetato de
etilo (8:1 y 7:1) para proporcionar después de la evaporación de las fracciones
apropiadas el N-[(1R)-2-[[2-(benciloxi)fenil]amino]-1-(2,4-difluorofenil)-2-
oxoetil]-L-leucinato de metilo (5.06 g).

HPLC Rt = 4.0 minutos, m/z [M-H]⁻ = 495

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N-[(1R)-1-(2,4-difluorofenil)-2-[[2-(2-hidroxifenil)amino]-2-oxoetil]-L-leucinato de metilo

Una mezcla de paladio sobre carbono (10%, 300 mg), N-[(1R)-2-
20 [[2-(benciloxi)fenil]amino]-1-(2,4-difluorofenil)-2-oxoetil]-L-leucinato de metilo
(2.88 g) y acetato de etilo (30 ml), se agitó bajo una atmósfera de hidrógeno
durante 3 horas. La reacción a continuación se filtró a través de Celite, y la
almohadilla de filtración se lavó con porciones adicionales de acetato de etilo.

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Las fracciones orgánicas combinadas se evaporaron para proporcionar el N-
{(1R)-1-(2,4-difluorofenil)-2-[(2-hidroxifenil)amino]-2-oxoetil}-L-leucinato de
metilo (2.179 g).

HPLC Rt = 3.52 minutos, m/z [M-H]⁻ = 405.

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N-[1-(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo

Una solución de N-[(1R)-1-(2,4-difluorofenil)-2-[(2-
hidroxifenil)amino]-2-oxoetil]-L-leucinato de metilo (203 mg) y 1,1'-
10 tiocarbonildiimidazol (100 mg) en diclorometano (5 ml), se dejó reposar
durante 18 horas. Se agregó agua (10 µl) a la mezcla de reacción, y ésta se
agitó a continuación rápidamente durante 30 minutos. Después de esto, se
agregaron 1H-Benzotriazolio, 1-[bis(dimetilamino)metileno]-,
tetrafluoroborato(1-), 3-óxido (TBTU, 321 mg), y una solución de dimetilamina
15 en tetrahidrofurano (0.5 ml de solución 2M). La mezcla de reacción se agitó
durante 18 horas adicionales y a continuación se pasó a través de SPE (5 g,
sílice) eluyendo con un gradiente (8:1 a 1:2 ciclohexano:acetato de etilo). Las
fracciones requeridas se combinaron y evaporaron para proporcionar el N-[1-
(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo (100 mg).

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HPLC Rt = 3.16 minutos m/z [M+H]⁺ = 343.

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N-[1-(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucina

A una solución de N-[1-(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo (100 mg) en metanol (3 ml), se agregó una
5 solución de hidróxido de litio (15.4 mg) en agua (1 ml). Después de agitar vigorosamente durante 4 horas, el solvente se removi6 *in vacuo*. El residuo se diluy6 con agua (10 ml), a continuación se neutraliz6 con ácido clorhídrico 2N. Esta solución se aplic6 en un cartucho Oasis™ (6 g), y se eluy6 con agua (x2) y metanol (x2). Las fracciones requeridas se combinaron y se evaporaron
10 para proporcionar la N-[1-(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucina (95 mg).

HPLC Rt = 2.23 minutos m/z [M+H]⁺ = 329.

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-**2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida**

A una solución de ácido (2R)-[(ter-butoxicarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (84 mg) en tetrahidrofurano seco (6 ml) a -20°C bajo una atm6sfera de nitr6geno, se agregó N-metilmorfolina (32 µl) y una
20 solución de cloroformiato de isopropilo en tolueno (1.0 M, 290 µl). Después de 10 minutos, se agregó una solución de N-[1-(2,4-difluorofenil)-2-(dimetilamino)-2-oxoetil]-L-leucina (95 mg) en tetrahidrofurano (10 ml), y la reacción se dej6 calentar a temperatura ambiente. Después de 20 horas, el

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solvente se removió *in vacuo* y el residuo se disolvió en ácido clorhídrico 4N en dioxano (4 ml). Después de 4 horas, se agregó metanol (5 ml) y la reacción se dejó reposar durante 18 horas adicionales. El solvente se removió a continuación *in vacuo*, y el residuo se disolvió en dioxano (5 ml) y a éste se agregó trietilamina (0.5 ml). Después de 1 hora, el solvente se removió y el residuo se aplicó a un SPE (10 g, sílice). El producto se eluyó utilizando metanol. Se utilizó un segundo SPE para purificar adicionalmente el material (2 g, sílice), utilizando un gradiente de acetato de etilo:metanol (20:1 a 1:1), para proporcionar la (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetiletanamida (38 mg).

HPLC Rt = 3.5 minutos, m/z [M+H]⁺ = 484

¹H RMN (CDCl₃) δ 7.42 (m, 1H), 7.22 (m, 2H), 7.17 (m, 2H), 7.02-6.90 (m, 2H), 6.62 (s, 1H), 6.37 (m, 1H), 4.09 (m, 1H), 3.98 (dd, 1H), 3.20-3.02 (m, 3H), 2.99 (s, 3H), 2.87 (m, 1H), 2.85 (s, 3H), 2.74 (m, 1H), 1.55 (m, 2H), 0.70 (m, 1H), 0.67 (d, 3H), 0.41 (d, 3H).

Preparado de manera similar.

EJEMPLO 9

(2R)-N-ciclopropil-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]etanamida

HPLC Rt = 3.41 minutos, m/z [M+H]⁺ = 496.

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^1H RMN (CDCl_3) δ 7.67 (dt, 1H), 7.59 (1H, d), 7.21-7.11 (m, 4H), 6.99-6.92 (m, 1H), 6.92-6.84 (m, 1H), 6.35 (d, 1H), 5.43 (s, 1H), 3.99 (dd, 1H), 3.93 (dd, 1H), 3.17-2.71 (m, 6H), 1.88-1.70 (m, 2H), 1.48-1.38 (m, 1H), 0.86 (s, 3H), 0.81-0.74 (m, 5H), 0.51-0.45 (m, 2H).

5

EJEMPLO 10

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetiletanamida

10 **(2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-benciloxifenil)etanamida**

Una mezcla de 2,4-difluorobenzaldehído (1.421 g), clorhidrato del éster metílico de (D)-leucina (1.817 g), trietilamina (1.391 ml) y metanol (20 ml), se agitó a temperatura ambiente durante 16 horas. A continuación se agregaron secuencialmente N-ter-butoxicarbonil-(D)-indanilglicina (2.914 g) y isocianuro de 2-benciloxi-fenilisocianuro (2.090 g). Después de 24 horas, el solvente se removió bajo presión reducida y la mezcla de reacción se tomó en diclorometano (ca. 20 ml), y se purificó mediante cromatografía en columna instantánea BiotageTM (cartuchos de 2x90 g de sílice en un sistema Biotage Quad 3 eluido con 1:9 de acetato de etilo:ciclohexano), para proporcionar el (2R)-2-[(1R,S)-2-[2-(benciloxi)fenil]amino]-1-(2,4-difluorofenil)-2-oxoetil][(2R)-2-[(ter-butoxicarbonil)amino]-2-(2,3-dihidro-1H-inden-2-il)etanoil]amino}-4-

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metilpentanoato de metilo (5.100 g) (HPLC Rt = 4.40 minutos m/z $[M+H]^+ = 770$). Este se tomó en cloruro de hidrógeno 4M en 1,4-dioxano (20 ml), y la mezcla se dejó a temperatura ambiente durante 3 horas. El solvente y el cloruro de hidrógeno se eliminaron utilizando una corriente de nitrógeno durante la noche. El material crudo se tomó en metanol (90 moles), que contiene trietilamina (10 ml). Después de 30 minutos, el metanol y el exceso de trietilamina se removieron bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna instantánea Biotage™ (cartuchos de 2x90g de sílice sobre un sistema Biotage Quad 3 eluido con 1:2 de acetato de etilo:ciclohexano) para proporcionar la (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-benciloxifenil)etanamida (3.381 g).

HPLC Rt = 3.99 minutos, m/z $[M+H]^+ = 638$.

15 (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida

Se disolvió (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-benciloxifenil)etanamida (3.381 g) en acetato de etilo (200 ml), y se hidrogenó a presión atmosférica sobre paladio al 10% en catalizador de carbono (0.980 g Pd/C al 10%:agua 1:1 peso/peso) a temperatura ambiente durante cinco horas. La mezcla de reacción se filtró a través de Celite, y el solvente se removió bajo presión

reducida para proporcionar la (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)-etanamida como una espuma color crema (2.650 g).

HPLC Rt = 3.61 minutos, m/z $[M-H]^+$ = 546 ($[M+H]^+$ no visible).

5

Acido (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-etanoico

Se agitó (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida (2.650 g) en diclorometano (20 ml) y se agregó carbonildiimidazol (1.178 g). La mezcla se dejó a temperatura ambiente durante 16 horas, a continuación el solvente se removió bajo presión reducida. El residuo se tomó a continuación en 1:1 acetona:agua (v/v) (80 ml), y se dejó a temperatura ambiente durante 30 minutos. El volumen de acetona se removió a continuación bajo presión reducida, y el residuo se repartió entre diclorometano y ácido clorhídrico 0.5 M. La fase orgánica se separó (vidrio poroso hidrofóbico), y se evaporó bajo presión reducida. El producto crudo se purificó (columna de cromatografía instantánea BiotageTM, cartuchos de 90 g de sílice eluidos con (i) 1:1 de acetato de etilo:ciclohexano, (ii) acetato de etilo, (iii) acetato de etilo:metanol 9:1), para proporcionar el ácido (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-etanoico como un sólido incoloro 1.524 g, como una mezcla de epímeros.

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HPLC Rt = 3.44 y 3.58 minutos, ambos m/z [M+H⁺] = 457.

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida

5

El ácido (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-etanoico (0.747 g), preparado como se describió anteriormente, se secó sobre P₄O₁₀ *in vacuo* durante cinco horas, para proporcionar 0.724 g de material seco; éste se disolvió en
10 diclorometano anhidro:acetonitrilo (1:1 v/v, 6 ml), y se trató con trietilamina (0.223 ml) y BOP-C1 (cloruro de bis(2-oxo-3-oxazolidinilo)fosfínico), se disolvió en diclorometano anhidro:acetonitrilo (1:1 v/v, 6 ml), y se trató con trietilamina (0.223 ml) y BOP-CL (cloruro de bis (2-oxo-3-oxazolidinilo)fosfínico, 0.450 g), y la mezcla se sometió a sonicación durante
15 ca. 1 minuto, para proporcionar una masa gelatinosa. Después de 10 minutos a temperatura ambiente, se agregó una solución de dimetilamina en tetrahydrofurano (10 ml de solución 2M), para proporcionar una solución clara; ésta se dejó durante 16 horas a temperatura ambiente. Los solventes se removieron bajo presión reducida y la mezcla se repartió entre diclorometano
20 y ácido clorhídrico 0.1M. La fase orgánica se separó (vidrio poroso hidrofóbico) y evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía instantánea en columna (cartucho de sílice de 12 g de Biotage™, eluido con (i) 1:1 de acetato de etilo:ciclohexano, (ii) acetato de

etilo, (iii) acetato de etilo:metanol 9:1), para proporcionar la (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida como un sólido incoloro 0.285 g.

HPLC Rt = 3.43 minutos, m/z [M+H]⁺ = 484

5 ¹H RMN (CDCl₃) δ 7.47-7.40 (m, 1H), 7.24-7.11 (m, 4H), 7.01-6.91 (m, 3H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19-3.01 (m, 3H), 2.99 (3,3H), 2.92-2.75 (m, 5H), 1.64-1.51 (m, 2H), 0.76-0.68 (m, 4H), 0.43 (d, 3H).

10

METODO 5

EJEMPLO 11

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida

15 Acido (2R)-[(benciloxicarbonil)amino](2,3-dihidro-1H-inden-2-il)etanolico

Se suspendió R-indanilglicina (1.91 g) en dioxano (10 ml) y agua (10 ml). A esto se le agregó trietilamina (1.7 ml) y N-(benciloxicarbonilo)-succinimida (2.54 g), y la mezcla de reacción se agitó rápidamente a
20 temperatura ambiente durante 2 días. La mezcla de reacción se vertió en agua (50 ml), y se extrajo con cloroformo (100 ml). La fase orgánica se lavó con ácido clorhídrico 1N (50 ml) y agua (50 ml). Esta se secó sobre sulfato de

magnesio y el solvente se removió *in vacuo* para proporcionar el ácido (2R)-[(benciloxycarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (3.06 g).

HPLC Rt = 3.35 minutos; m/z [M+H]⁺ = 326.

¹H RMN (CDCl₃) δ 7.40-7.29 (m, 5H), 7.21-7.11 (m, 4H), 5.28 (d, 1H), 5.11 (s, 2H), 4.57 (m, 1H), 3.14-2.79 (m, 5H).

(2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)etanamida

- 10 A una solución de clorhidrato del éster metílico de (D)-leucina (1.45 g) en metanol (10 ml), se le agregó trietilamina (1.12 ml) y 2,4-difluorobenzaldehído (0.875 ml). La mezcla se agitó durante 3 días antes, se agregaron secuencialmente el ácido (2R)-[(benciloxycarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (2.6 g) e isocianuro de 2-benciloxifenilo (1.76 g).
- 15 La mezcla de reacción se dejó reposar durante 24 horas. El solvente se removió *in vacuo* y el residuo se separó entre acetato de etilo (200 ml) y agua (200 ml). La fase orgánica se lavó con salmuera. A esta solución se le agregó paladio sobre carbono (2.0 g) y ácido acético (10 ml), y la mezcla de reacción se agitó bajo una atmósfera de hidrógeno durante 2 horas. La
- 20 mezcla se filtró a través de Celite y se lavó con agua (3x100 ml), solución saturada de bicarbonato de sodio, salmuera y se secó sobre sulfato de magnesio. El solvente se evaporó *in vacuo*. El producto crudo se purificó mediante cromatografía en columna (sílice), eluyendo con acetato de

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etilo:ciclohexano (50% al 66%) para proporcionar la (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)etanamida (2.0 g).

HPLC Rt = 3.59 minutos; m/z [M+H]⁺ = 548.

5

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetiletanamida

Se suspendió carbonildiimidazol (4.80 g, 1.54 equivalentes) en
 10 diclorometano anhidro (40 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. La (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)etanamida (10.50 g, presecada in vacuo sobre P₄O₁₀ durante 24 horas) se
 agregó a continuación con agitación, y la solución resultante se agitó a
 15 temperatura ambiente durante 6 horas. La solución amarilla resultante se trató a continuación con solución 2.0 M de dimetilamina en tetrahidrofurano (54 mL, 5.6 equivalentes), y la mezcla resultante se agitó a temperatura ambiente durante 16 horas. Los solventes más la dimetilamina residual se
 removieron bajo presión reducida y la mezcla de reacción se tomó en
 20 diclorometano (200 mL), y se lavó con ácido clorhídrico 1M (200 mL). La fase orgánica se separó utilizando un vidrio poroso hidrofóbico, y se evaporó bajo presión reducida a ca. 50 mL. El producto crudo se aplicó a columnas de 4x90 g de sílice BiotageTM sobre un sistema Quad 3; cada columna se eluyó

con (i) 2:1 v/v de acetato de etilo:ciclohexano (fracciones de 12x50 mL), (ii) acetato de etilo (fracciones de 12x50 mL), (iii) 9:1 v/v acetato de etilo:metanol para proporcionar la (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida (5.753 g,

5 62%) como un sólido incoloro.

HPLC Rt = 3.41 minutos, m/z $[M+H]^+ = 484$

1H RMN ($CDCl_3$) δ 7.48-7.38 (m, 2H), 7.24-7.11 (m, 4H), 7.01-6.90 (m, 2H), 6.62 (s, 1H), 4.09 (dd, 1H), 3.98 (dd, 1H), 3.19-3.01 (m, 3H), 2.99 (3,3H), 2.92-2.75 (m, 5H), 1.64-1.51 (m, 2H), 0.76-0.66 (m, 4H), 0.43 (d, 10 3H).

Preparado de manera similar:

EJEMPLO 12

15 (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metiletanamida, sólido incoloro, 41%.

HPLC Rt = 3.4 minutos, m/z $[M+H]^+ = 470$

EJEMPLO 13

20

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida, sólido incoloro, 36%.

HPLC Rt = 3.3 minutos, m/z $[M+H]^+ = 456$.

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EJEMPL 14

(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacín-2,5-diona, sólido incoloro, 61%.

5 HPLC Rt = 3.4 minutos, m/z [M+H]⁺ = 526.

EJEMPLO 15

(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-hidroxiacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacín-2,5-diona, sólido incoloro, 45%.

HPLC Rt = 3.2 minutos, m/z [M+H]⁺ = 512.

(acetidin-3-ol preparado mediante el método de S. S. Chatterjee y D. J. Triggle; J Chem. Soc. Chem. Comm. (2) 93 (1968).

15

EJEMPLO 16

(3R,6R)-1-[(1R)-2-acetidin-1-il-1-(2,4-difluorofenil)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacín-2,5-diona, sólido incoloro, 46%.

20 HPLC Rt = 3.4 minutos, m/z [M+H]⁺ = 496.

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EJEMPLO 17

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxietil)-N-metiletanamida, sólido

5 incoloro, 59%.

HPLC Rt = 3.3 minutos, m/z [M+H]⁺ = 514.

EJEMPLO 18

10 **(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-[2-(metilsulfonil)etil]etanamida,**

sólido incoloro, 22%.

HPLC Rt = 3.2 minutos, m/z [M+H]⁺ = 576.

15

EJEMPLO 19

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(2,2,2-trifluoroetil)etanamida,

sólido incoloro, 11%.

20

HPLC Rt = 3.5 minutos, m/z [M+H]⁺ = 552.

(el cloruro de 2,2,2-trifluoroetilmetilamina se preparó mediante el método de E. R. Bissell y M. Finger; J. Org. Chem. 24 1256-1259 (1959)).

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EJEMPLO 20

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(piridin-2-ilmetil)etanamida,

5 espuma tostada, 19%.

HPLC Rt = 3.5 minutos, m/z [M+H]⁺ = 561.

EJEMPLO 21

(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-

10 **2,5-dioxopiperacin-1-il]-N-metoxi-N-metiletanamida**

HPLC Rt = 3.4 minutos, m/z [M+H]⁺ = 500.

EJEMPLO 22

15 **Acido (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-**
 isobutil-2,5-dioxopiperacin-1-il]etanoico

20 Se suspendió carbonildiimidazol (1.42 g, 1.6 equivalentes) en diclorometano anhidro (10 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. A continuación se agregó (2RS)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida (3.00 g), y la solución resultante se agitó a temperatura ambiente durante 16 horas. La solución amarilla

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resultante a continuación se evaporó bajo presión reducida y el residuo se trató con 1:1 (v/v) de mezcla de agua y acetona (10 mL). La mezcla se agitó durante 2 horas, a continuación la acetona se removió bajo presión reducida y el residuo se repartió entre diclorometano y HCl acuoso 0.1M. La fase orgánica se separó utilizando un vidrio poroso hidrofóbico, a continuación se evaporó a un volumen bajo y se purificó mediante cromatografía sobre un sistema Biotage Quad 3 (columna de 90 g de sílice) eluida con 1:1 (v/v) de acetato de etilo:ciclohexano, a continuación acetato de etilo, a continuación 1:1 (v/v) de acetato de etilo:metanol, para proporcionar una mezcla de diastereómeros (2.61 g). Estos se separaron sobre una columna quiral en fase inversa (Chiralcel OD, eluida con propan-2-ol al 15%/heptano que contiene 0.1% de TFA) para proporcionar: ácido (2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]etanoico (1.60 g).

HPLC Rt = 3.4 minutos, m/z [M+H]⁺ = 457.

EJEMPLO 23

(2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]etanoato de metilo

20

Se suspendió carbonildiimidazol (0.324 g, 1.6 equivalentes) en diclorometano anhidro (4 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. A continuación se agregó (2RS)-2-(2,4-difluorofenil)-2-

[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida (0.800 g) con agitación, y la solución resultante se dejó a temperatura ambiente durante 16 horas. La mezcla se trató a continuación con metanol (10 mL) y se dejó a temperatura ambiente durante la noche. Los

5 solventes se removieron bajo presión reducida y el residuo se purificó mediante cromatografía preparativa en placa sobre sílice (placas de 20x20 cm x4, eluida con 1:3 de acetato de etilo:ciclohexano x5), para proporcionar: (2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanoato de metilo (0.453 g, 66%).

10 HPLC Rt = 3.42 minutos, m/z [M+H]⁺ = 471.

Preparado de manera similar:

EJEMPLO 24

(2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-

15 dioxopiperacin-1-il]etanoato de propilo

HPLC Rt = 3.71 minutos, m/z [M+H]⁺ = 499.

EJEMPLO 25

20 (2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-

dioxopiperacin-1-il]etanoato de 1-(acetiloxi)etilo

JGH

Se agitó el ácido (2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanoico (ejemplo 22) (0.130 g) en DMF anhidro (1 mL) y se agregó carbonato de potasio anhidro (0.020 g, 0.5 equivalentes). La mezcla se agitó a temperatura ambiente durante 1 hora, a continuación se enfrió a -10°C (baño de hielo con sal). La mezcla heterogénea se trató con 1-bromoacetato de etilo (0.120 mL, exceso), y se agitó durante 3.5 horas manteniendo la temperatura del baño entre -10 y -5°C. Esta se repartió a continuación entre DCM y HCl acuoso 1M (20 mL de cada uno). La fase orgánica se separó (vidrio poroso hidrofóbico), y se evaporó bajo presión reducida para proporcionar una goma púrpura; ésta se purificó mediante un cartucho de SPE (5 g, sílice eluida con (i) ciclohexano x2, (ii) DCM x2, (iii) éter dietílico x2, (iv) acetato de etilo x2, (v) metanol x2, para proporcionar el (2R)-(2,4-difluorofenil)[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanoato de 1-(acetiloxi)etilo (0.081 g) como una espuma amarilla.

HPLC Rt = 3.5 minutos, m/z [M+H]⁺ = 543.

Preparado de manera similar:

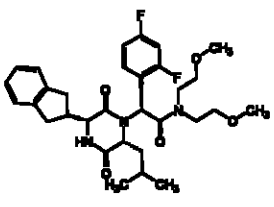
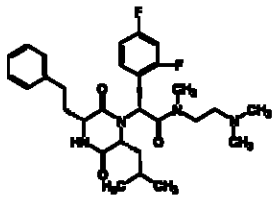
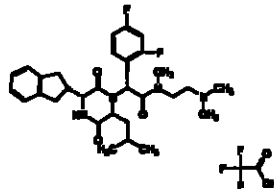
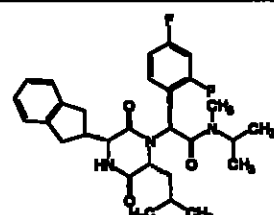
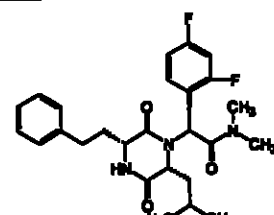
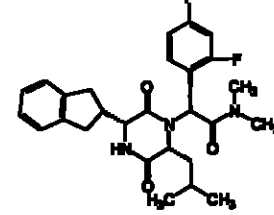
En el Cuadro siguiente, los Ejemplos 26, 54-55, 66-104, 107-117, 124-131 se prepararon vía el método 1. El éster t-butílico del Ejemplo 39 se preparó vía transesterificación catalizada con ácido perclórico del ácido correspondiente (Ejemplo 22) con acetato de t-butilo mediante el procedimiento de T. Kolasa y M. J. Miller; Journal of Organic Chemistry

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(1990), 55 (6), 1711-21. Otros Ejemplos en el Cuadro siguiente se prepararon
vía el método 5.

	Ej. No.	Regno	P.M.	Rt/ min	Ion +ve	Ion -ve	Nombre
5	26		511.6	3.6	512	510	(2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
10	27		537.5	3.4	538	536	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2,2,2-trifluoroetil)etanamida
15	28		543.6	3.2	544	542	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2,2-dimetoxietil)etanamida
	29		513.6	3.3	513	511	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-metoxietil)etanamida
20	30		527.6	3.4	528	ninguno	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-metoxietil)-N-metiletanamida

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5	31		571.7	3.3	572	ninguno	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-bis(2-metoxietil)-etanamida
	32		528.6	2.7	529	ninguno	(2R)-2-(2,4-difluorofenil)-N-[2-(dimetilamino)etil]-2-[(2R,5R)-2-isobutil-3,6-dioxo-5-(2-feniletil)]piperacin-1-il]-N-metiletanamida
	33		654.7	2.7	541	539	Trifluoroacetato de (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-[2-(dimetilamino)etil]-N-metiletanamida
	34		511.6	3.6	512	ninguno	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-N-metiletanamida
	35		471.6	3.2	472	470	(2R)-2-(2,4-difluorofenil)-2-[(2R,5R)-2-isobutil-3,6-dioxo-5-(2-feniletil)]piperacin-1-il]-N,N-dimetiletanamida
20	36		497.6	3.5	498	ninguno	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-4-metil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida

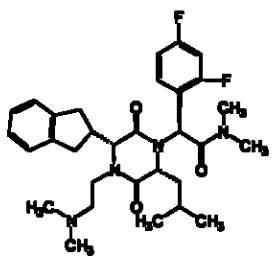
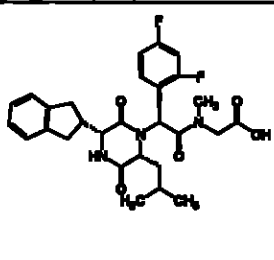
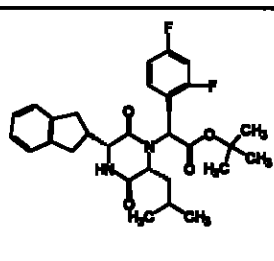
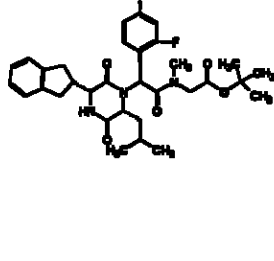
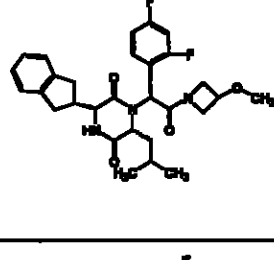
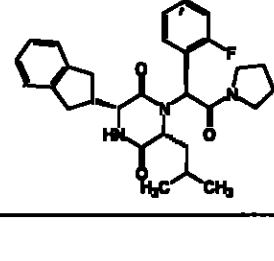
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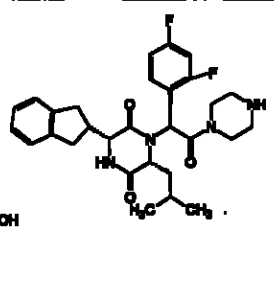
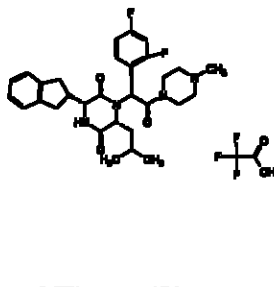
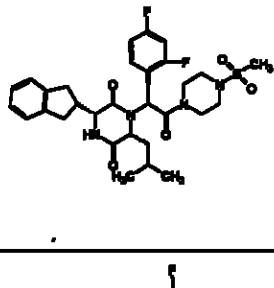
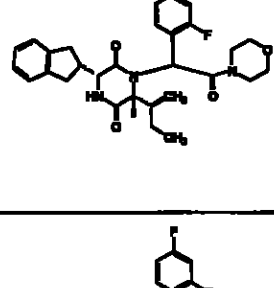
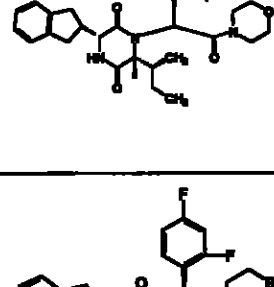
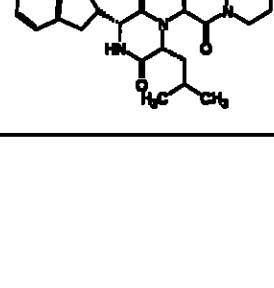
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37		554.7	2.7	555	ninguno	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-4-[2-(dimetilamino)etil]-6-isobutil-2,5-dioxopiperacin-1-il)-N,N-dimetiletanamida
38		527.6	3.3	528	526	ácido [((2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)etanol](metil)amino] acético
39		512.6	3.7	513	511	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)etanolato de ter-butilo
40		583.7	3.6	584	ninguno	[((2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)etanol](metil)amino] acetato de ter-butilo
41		525.6	3.3	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-metoxiacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
42		509.6	3.5	510	ninguno	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-oxo-2-pirrolidin-1-iletíl]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona

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5	43		561.1	2.7	525	ninguno	clorhidrato de la (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-oxo-piperacin-1-ilet]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
	43a		652.7	2.7	539	583 (M+45)	trifluoroacetato de la (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(4-metilpiperacin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
	44		602.7	3.3	603	601	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-[4-(metilsulfonil)piperacin-1-il]-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
	45		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-metilpropil]piperacin-2,5-diona
	46		525.6	3.2	526	524	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]piperacin-2,5-diona
20	47		541.7	3.6	542	540	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-oxo-2-tiomorfolin-4-ilet]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona

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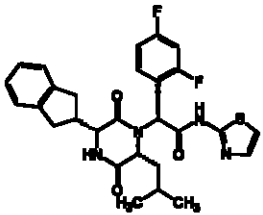
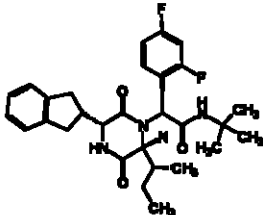
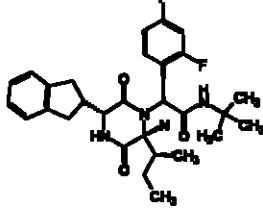
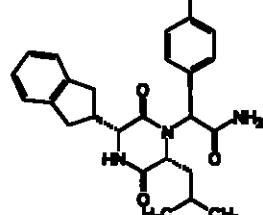
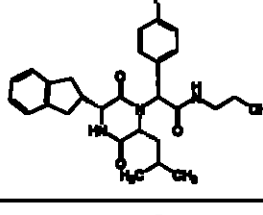
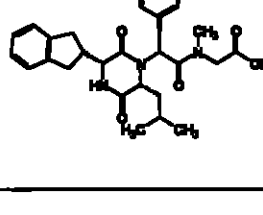
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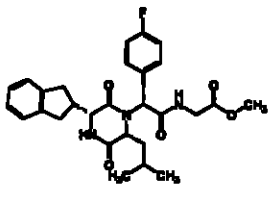
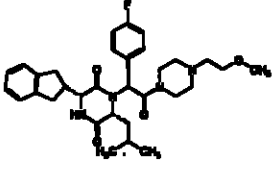
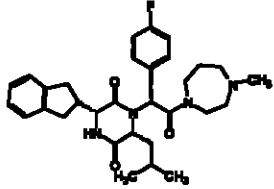
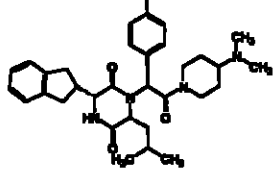
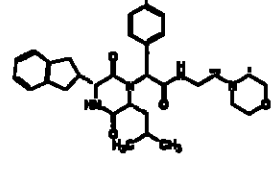
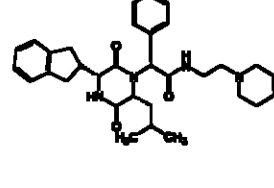
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48		573.7	3.3	574	572	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(1,1-dioxidotiormofolin-4-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
49		557.7	3.1	558	556	(3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(1-óxidotiormofolin-4-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona
50		560.6	3	561	Ninguno	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(piridin-4-ilmetil)etanamida
51		605.7	3.5	606	604	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(3,4-dimetoxibencil)-etanamida
52		605.7	3.5	606	604	(2S)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(3,4-dimetoxibencil)-etanamida

1-10

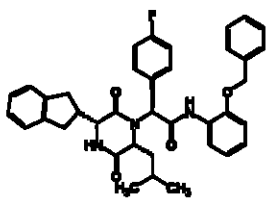
5	53		538.6	3.4	539	537	(2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(1,3-tiazol-2-il)etanamida
	54		511.6	3.6	512	510	(2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida
	55		511.6	3.6	512	510	(2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida
	56		437.5	3.3	438	436	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-etanamida
	57		481.6	3	482	480	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2-hidroxietil)etanamida
	58		509.6	3.4	510	508	ácido [(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)etanoil]-(metil)amino]acético
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15							
20							

fms

5	59		509.6	3.4	510	508	acetato de {[(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)etanoil]-amino} de metilo
	60		564.7	2.6	565	563	(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-[(1R)-1-(4-fluorofenil)-2-[4-(2-metoxietil)-piperacin-1-il]-2-oxoetil]-6-isobutilpiperacin-2,5-diona
	61		534.7	2.6	535	533	(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-[(1R)-1-(4-fluorofenil)-2-(4-metil-1,4-diazepan-1-il)-2-oxoetil]-6-isobutilpiperacin-2,5-diona
	62		548.7	2.6	549	547	(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-[(1R)-2-[4-(dimetilamino)-piperidin-1-il]-1-(4-fluorofenil)-2-oxoetil]-6-isobutilpiperacin-2,5-diona
	63		550.7	2.7	551	549	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2-morfolin-4-iletil)etanamida
20	64		548.7	2.8	549	547	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-(2-piperidin-1-iletil)etanamida

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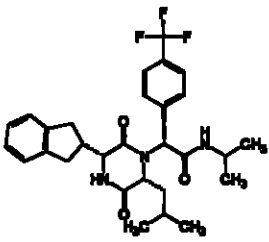
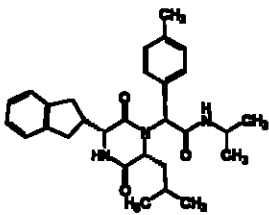
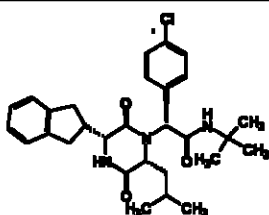
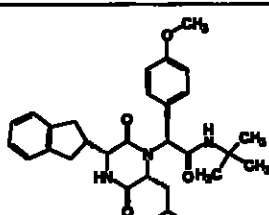
65		619.7	3.9	620	618	(2R)-N-[2-(benciloxi)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-etanamida
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Preparado de manera similar:

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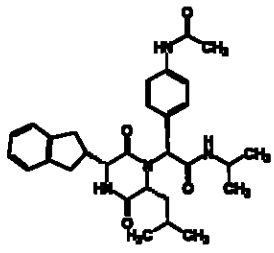
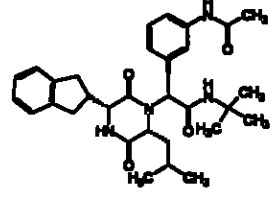
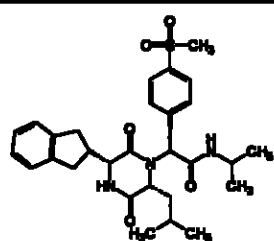
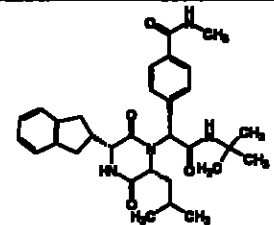
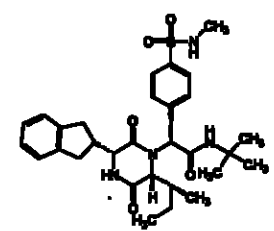
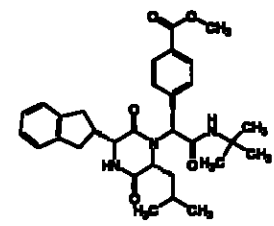
Ej. No.	Regno	P.M.	R/ min	Ion +ve	Ion -ve	Nombre
66		529.6	3.8	530	528	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[4-(trifluorometil)fenil]-etanamida
67		475.6	3.6	476	474	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(4-metilfenil)etanamida
68		510.1	3.8	510	508	(2R)-N-(ter-butil)-2-(4-clorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
69		505.7	3.5	506	504	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-metoxifenil)-etanamida

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5	70		559.7	3.8	560	558	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(trifluorometoxi)-fenil]etanamida
	71		490.6	3.4	491	489	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[4-(metilamino)fenil]-etanamida
	72		504.7	3.6	505	503	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(dimetilamino)fenil]-N-isopropiletanamida
10	73		530.7	3.7	555 (M+Na)	529	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(4-pirrolidin-1-ilfenil)-etanamida
	74		532.7	3.7	533	531	(2R)-2-[4-(dietilamino)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
20	75		504.6	3.1	505	503	4-[(1R)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(isopropilamino)-2-oxoetil]benzamida

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76		518.6	3.0	519	517	(2R)-2-[4-(acetilamino)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
77		532.7	3.2	533	531	(2R)-2-[3-(acetilamino)fenil]-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
78		539.7	3.3	540	538	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[4-(metilsulfonil)fenil]-etanamida
79		532.7	3.3	533	531	4-[(1R)-2-(ter-butilamino)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-oxoetil]-N-metilbenzamida
80		568.7	3.4	569	567	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]-2-[4-[(metilamino)sulfonil]fenil]etanamida
81		533.7	3.6	532	534	4-[(1R)-2-(ter-butilamino)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-oxoetil]benzoato de metilo

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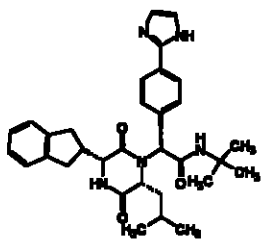
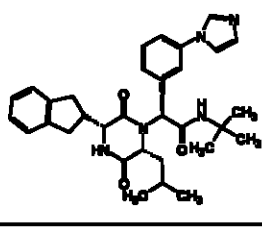
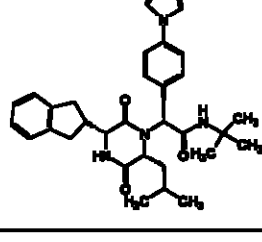
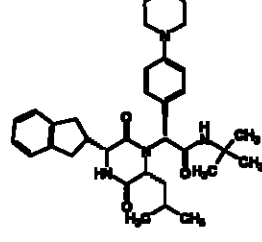
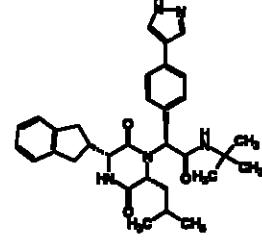
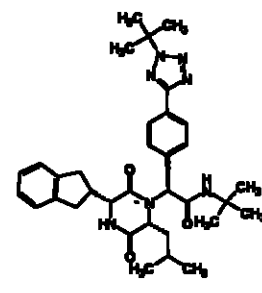
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82		541.8	3.3	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-pirazol-1-il)fenil]etanamida
83		542.8	3.3	543	541	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-1,2,4-triazol-1-il)fenil]etanamida
84		542.8	3.2	543	541	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-1,2,3-triazol-1-il)fenil]etanamida
85		541.7	3.5	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[3-(1H-pirazol-3-il)fenil]etanamida
86		541.8	3.3	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-pirazol-3-il)fenil]etanamida
87		519.4	3.4	520	518	ácido 3-((1R)-2-(ter-butilamino)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-oxoetil)fenilborónico

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5	88		541.7	3.0	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-imidazol-2-il)fenil]etanamida
	89		541.7	3.1	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[3-(1H-imidazol-1-il)fenil]etanamida
	90		541.7	3.0	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-imidazol-1-il)fenil]etanamida
	91		560.8	3.4	561	559	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-morfolin-4-ilfenil)etanamida
	92		541.7	3.3	542	540	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1H-pirazol-4-il)fenil]etanamida
20	93		599.8	3.9	600	598	(2R)-N-(ter-butyl)-2-[4-(2-ter-butil-2H-tetrazol-5-il)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

5	94		562.7	2.9	563	ninguno	trifluoroacetato de (2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-[2-(dimetilamino)etoxi]fenil]etanamida
	95		560.8	3.0	561	559	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(4-hidroxipiperidin-1-il)fenil]-N-isopropiletanamida
10	96		616.9	3.5	617	ninguno	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(1,4-dioxa-8-azaespiro[4.5]dec-8-il)fenil]etanamida
15	97		573.8	2.9	574	ninguno	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(4-metilpiperacin-1-il)fenil]etanamida
20	98		654.0	4.1	654	652	(2R)-N-(ter-butyl)-2-[4-(3,5-diter-butyl-1H-pirazol-1-il)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

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99		581.7	4.0	582	580	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4'-metoksi-1,1'-bifenil-4-il)etanamida
100		569.8	3.9	Ninguno	568	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4'-fluoro-1,1'-bifenil-4-il)etanamida
101		614.8	4.3	615	613	(2R)-N-(ter-butyl)-2-[4-(4-ter-butyl-1,3-tiazol-2-il)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
102		658.9	3.6	659	657	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4'-[(etilamino)sulfonyl]-1,1'-bifenil-4-il)etanamida
103		552.8	3.6	553	551	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-piridin-2-ilfenil)etanamida

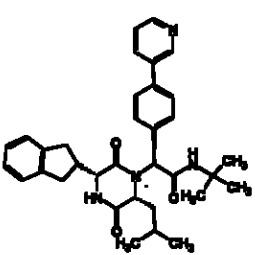
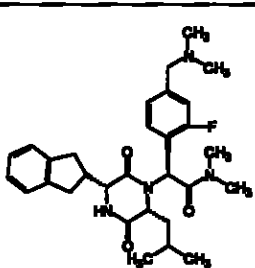
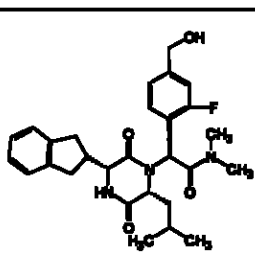
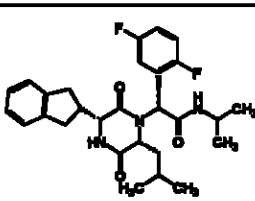
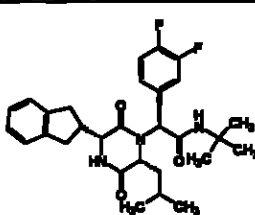
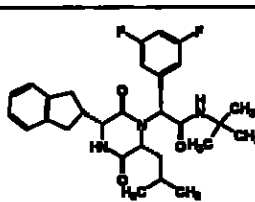
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104		552.8	3.3	553	551	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-piridin-3-ilfenil)etanamida
105		522.7	2.4	523	ninguno	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-[(dimetilamino)metil]-2-fluorofenil]-N,N-dimetiletanamida
106		495.6	2.9	496	ninguno	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[2-fluoro-4-(hidroximetil)fenil]-N,N-dimetiletanamida
107			3.4	498	496	(2R)-2-(2,5-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
108			3.6	512	510	(2R)-N-(ter-butil)-2-(3,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
109			3.6	512	510	(2R)-N-(ter-butil)-2-(3,5-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

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110			3.6	512	510	(2R)-N-(ter-butyl)-2-(2,3-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
111			3.7	530	528	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2,4,5-trifluorofenil)etanamida
112			3.7	530	528	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2,3,4-trifluorofenil)etanamida
113			3.6	530	528	(2S)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2,4,6-trifluorofenil)etanamida
114			3.8	526	524	(2R)-N-(ter-butyl)-2-(2,3-difluoro-4-metilfenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
115			3.8	526	526	(2R)-N-(ter-butyl)-2-(4-cloro-3-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

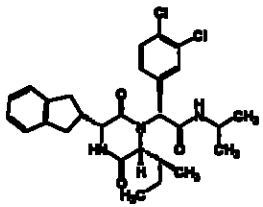
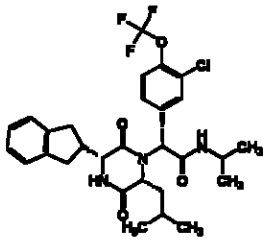
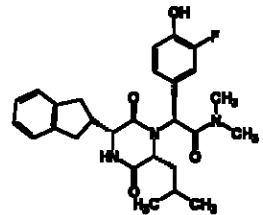
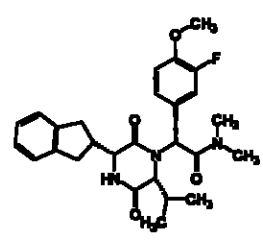
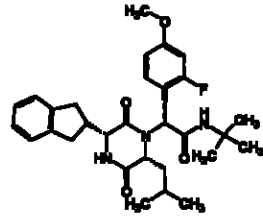
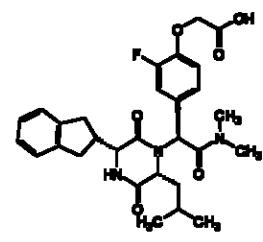
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116			3.7	530	528	(2R)-2-(3,4-diclorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-metilpropil]-2,5-dioxopiperacin-1-il)-N-isopropiletanamida
117			3.7	580	578	(2R)-2-[3-cloro-4-(trifluorometoxi)fenil]-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-N-isopropiletanamida
118			3.0	482	480	(2R)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-2-(3-fluoro-4-hidroxifenil)-N,N-dimetiletanamida
119			3.3	496	494	(2R)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isopropil-2,5-dioxopiperacin-1-il)-2-(3-fluoro-4-metoxifenil)-N-isopropiletanamida
120			3.6	524	522	(2R)-N-(ter-butil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-2-(2-fluoro-4-metoxifenil)etanamida
121			3.1	540	538	ácido {4-((1R)-1-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-2-(dimetilamino)-2-oxoetil)-2-fluorofenoxi}acético

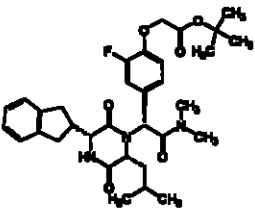
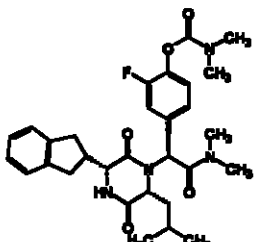
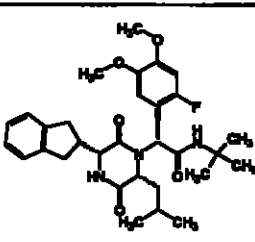
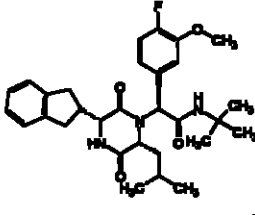
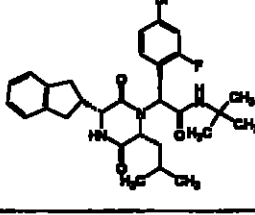
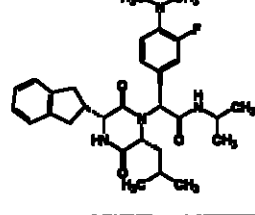
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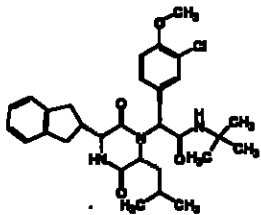
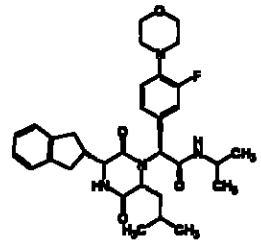
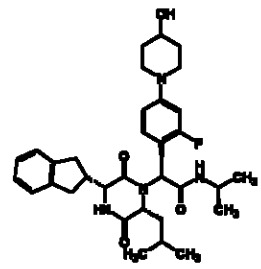
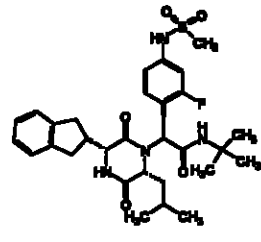
122			3.6	596	594	{4-[(1R)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(dimetilamino)-2-oxoetil]-2-fluorofenoxi}acetato de ter-butilo
123			3.3	553	ninguno	dimetilcarbarnato de 4-[(1R)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(dimetilamino)-2-oxoetil]-2-fluorofenilo
124			3.5	ninguno	552	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-fluoro-4,5-dimetoxifenil)etanamida
125			3.7	524	522	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluoro-3-metoxifenil)etanamida
126			3.8	ninguno	570/572	(2R)-2-(4-bromo-2-fluorofenil)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
127			3.5	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(dimetilamino)-3-fluorofenil]-N-isopropiletanamida

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128			3.7	540	538	(2R)-N-(ter-butil)-2-(3-cloro-4-metoxifenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
129			3.3	565	563	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(3-fluoro-4-morfolin-4-ilfenil)-N-isopropiletanamida
130			3.2	579	577	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[2-fluoro-4-(4-hidroxi piperidin-1-il)fenil]-N-isopropiletanamida
131			3.3	587	585	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[2-fluoro-4-[(metilsulfonil)amino]fenil]etanamida

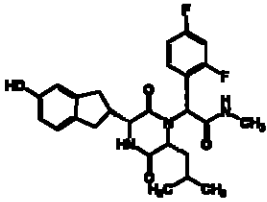
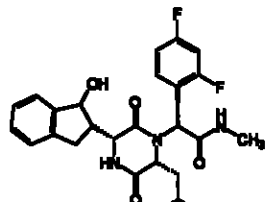
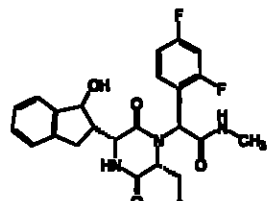
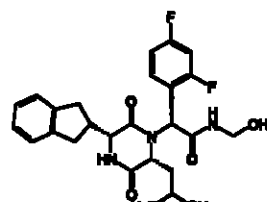
Los metabolitos hidroxilados de (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-
20 dimetiletanamida se prepararon como sigue:

2 litros de cultivos de células crecientes de *Streptomyces rimosus* BS33 se utilizaron para biotransformar GW796679x. Se agregaron 500 mg de GW796679X después de 3 días de crecimiento y el caldo se

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recolectó después de otros 5 días de incubación. Con la recolección, se agregaron 2 litros de metanol, a continuación las células se removieron por centrifugación. El metanol se removió del sobrenadante por evaporación. A continuación, los compuestos se extrajeron con acetato de etilo, se evaporaron hasta sequedad, y se purificaron mediante HPLC preparativa para proporcionar los ejemplos 132, 133, 134 y 135.

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132		485.5	2.9	486	484	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-((2S)-5-hidroxi-2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-N-metiletanamida
133		485.5	2.9	486	484	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-((2R)-1-hidroxi-2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-N-metiletanamida
134		485.5	2.9	486	484	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-((2R)-1-hidroxi-2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-N-metiletanamida
135		485.5	3.1	486	530 (M+45)	(2R)-2-(2,4-difluorofenil)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il)-N-(hidroximetil)etanamida

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EJEMPLO 136**(2R)-2-(1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-****isobutil-2,5-dioxopiperacina-1-il]-N-isopropiletanamida**

5 Se disolvió benzofuran-5-carboxaldehído (215 mg, 1.47 mmoles) y clorhidrato del éster t-butilico de D-leucina (329 mg, 1.47 mmoles) en metanol (1.5 ml), y se agregó trietilamina (0.205 ml, 1.47 mmoles). La mezcla, una solución amarilla pálida, se dejó reposar a temperatura ambiente durante la noche (23.5 horas). A continuación, se agregó Boc-D-indanilglicina (429

10 mg, 1.47 mmoles), seguida por isopropilisonitrilo (0.138 ml, 1.51 mmoles). La mezcla, una solución amarilla, se dejó reposar a temperatura ambiente durante la noche (23.5 horas), antes de que el solvente se evaporara bajo presión reducida para proporcionar una goma amarilla. La goma se disolvió en cloruro de hidrógeno 4M en dioxano (3 ml, 12 mmoles), y se dejó reposar a

15 temperatura ambiente durante 7.5 horas, antes de que éste se evaporara bajo presión reducida para proporcionar una goma anaranjada/marrón. La goma se disolvió en metanol (2 ml), y se agregó cloruro de hidrógeno 4M en dioxano (1 ml, 4 mmoles). La mezcla se dejó reposar a temperatura ambiente durante 5.5 horas, antes de que el solvente se removiera mediante evaporación bajo

20 presión reducida. El residuo se disolvió en diclorometano (4 ml) y se agregó trietilamina (0.5 ml, exceso). La mezcla se agitó a temperatura ambiente durante la noche (18.3 horas), antes de que el solvente se removiera mediante evaporación bajo presión reducida. El residuo se cargó en

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diclorometano en una columna SPE (10 g de sílice, cartucho Mega Bond Elut, preeluido con ciclohexano). La columna se eluyó paso a paso (40-45 ml en cada paso) con cloroformo al 100%, 3:1 de ciclohexano:éter dietílico, 1:1 de ciclohexano:éter dietílico, 1:3 de ciclohexano:éter dietílico, éter dietílico al 100%, 1:1 de ciclohexano:acetato de etilo, 1:2 ciclohexano:acetato de etilo y acetato de etilo al 100%. Las fracciones 1:3 de ciclohexano:éter dietílico a 1:2 de ciclohexano:acetato de etilo, inclusive fueron combinadas para proporcionar un sólido amarillo pálido (336 mg). El sólido se cargó en diclorometano en 6 placas cromatográficas preparativas (60 placas de gel de sílice, 20 x 20 cm²). Las placas se eluyeron cuatro veces con 30:1 de diclorometano:isopropanol. La banda requerida se extrajo con 9:1 de acetato de etilo:metanol, para proporcionar la (2R)-2-(1-benzofuran-5-il-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-isopropiletanamida como un sólido blanco (141 mg, 0.28 mmoles).

HPLC Rt = 3.46 minutos; m/z [M+H]⁺ = 502.

¹H RMN δ 7.95 (d, 1H), 7.73 (d, 1H), 7.68 (d, 1H), 7.53 (d, 1H), 7.37 (dd, 1H), 7.16 (m, 4H), 6.79 (d, 1H), 5.79 (d, 1H), 5.37 (s, 1H), 4.11 (m, 1H), 4.03 (dd amplio, 1H), 3.99 (dd, 1H), 3.16-2.97 (m, 3H), 2.95-2.78. (m, 2H), 1.79 (m, 1H), 1.69 (m, 1H), 1.33 (m, 1H), 1.09 (t, 6H), 0.78 (d, 3H), 0.67 (d, 3H).

Preparado de manera similar.

EJEMPLO 137

(2R)-2-(1,2,3-benzotiadiazol-6-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]etanamida

5 HPLC Rt = 3.50 minutos; m/z [M+H]⁺ = 534.

¹H RMN δ 8.66 (d, 1H), 7.82 (d, 1H), 7.67 (dd, 1H), 7.20 (m, 4H), 6.72 (d amplio, 1H), 6.13 (s, 1H), 5.19 (s, 1H), 4.06 (dd amplio, 1H), 4.00 (dd, 1H), 3.18 (m, 1H), 3.07 (m, 2H), 2.92 (m, 1H), 2.81 (m, 1H), 1.86 (m, 1H), 1.80 (m, 1H), 1.54 (m, 1H), 1.36 (s, 9H), 0.85 (d, 3H), 0.78 (d, 3H).

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EJEMPLO 138

(2R)-2-(2,3-dihidro-1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-Inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-isopropiletanamida

15 HPLC Rt = 3.34 minutos; m/z [M+H]⁺ = 504.

¹H RMN δ 7.81 (s amplio, 1H), 7.18 (m, 5H), 6.79 (d, 1H), 6.44 (d amplio, 1H), 5.50 (d, 1H), 5.06 (s, 1H), 4.61 (t, 2H), 4.08 (m, 1H), 3.96 (m, 2H), 3.22 (t, 2H), 3.15 (m, 1H), 3.07 (d, 2H), 2.90 (m, 1H), 2.79 (dd, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.42 (m, 1H), 1.12 (dd, 6H), 0.83 (d, 3H), 0.77 (d, 3H).

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EJEMPLO 139**(2R)-2-(1,3-benzodioxol-5-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]etanamida**

5 HPLC Rt = 3.48; m/z [M+H]⁺ = 520.

¹H RMN (CDCl₃) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.97 (d, 1H), 6.88 (dd, 1H), 6.82 (d, 1H), 6.58 (m, 1H), 6.06 (m, 2H), 5.64 (s, 1H), 5.02 (m, 1H), 3.95 (m, 2H), 3.16 (m, 1H), 3.07 (m, 2H), 2.89 (m, 1H), 2.77 (m, 1H), 1.82 (m, 1H), 1.71 (m, 1H), 1.41 (m, 1H), 1.32 (s, 9H), 0.83 (d, 3H), 0.79 (d, 3H).

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EJEMPLO 140**(2R)-2-(benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N,N-dimetiletanamida**

15 **[(1R)-2-[(2-(benciloxi)fenil]amino)-1-(benzofuran-5-il)-2-oxoetil]-L-leucinato de metilo**

A una suspensión de L-leucina (2.62 g) en metanol (250 ml) a -30°C bajo nitrógeno, se agregó una solución de benzofuran-5-carbaldehído (2.92 g) en metanol (15 ml), y una suspensión de 2-benciloxifenilisonitrilo (4.19 g) en metanol (15 ml). La reacción se agitó a -30°C durante 2 horas, y a continuación se dejó calentar a temperatura ambiente y se agitó durante 3 días adicionales. El solvente se removió *in vacuo*, y el residuo se pasó a

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través de una columna Biotage™ (3x90 g), eluyendo con ciclohexano:acetato de etilo (5:1), para proporcionar, después de la evaporación, las fracciones apropiadas de N-[(1R)-2-[[2(benciloxi)fenil]amino]-1-(benzofuran-5-il)-2-oxoetil]-L-leucinato de metilo (5.11 g).

5 HPLC Rt = 3.97 minutos, m/z [M+H]⁺ = 499.

N-[(1R)-1-(benzofuran-5-il)-2-[(2-hidroxifenil)amino]-2-oxoetil]-L-leucinato de metilo

- 10 Una mezcla de paladio sobre carbono (10%, 500 mg), N-[(1R)-2-[[2-(benciloxi)fenil]amino]-1-(benzofuran-5-il)-2-oxoetil]-L-leucinato de metilo (5.1 g) y acetato de etilo (60 ml), se agitó bajo una atmósfera de hidrógeno durante 5 horas. La reacción se filtró a continuación a través de Celite y la almohadilla de filtración se lavó con porciones adicionales de acetato de etilo.
- 15 Las fracciones orgánicas combinadas se evaporaron para proporcionar el N-[(1R)-1-(benzofuran-5-il)-2-[(2-hidroxifenil)amino]-2-oxoetil]-L-leucinato de metilo (3.429 g).

HPLC Rt = 3.49 minutos, m/z [M+H]⁺ = 411

20 **N-[(1R)-1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo**

Una solución de N-[(1R)-1-(benzofuran-5-il)-2-[(2-hidroxifenil)amino]-2-oxoetil]-L-leucinato de metilo (410 mg) y 1,1'-

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tiocarbonildiimidazol (196 mg) en diclorometano (5 ml), se dejó reposar durante 18 horas. Se agregó agua (20 μ l) a la mezcla de reacción y ésta se agitó rápidamente durante 30 minutos. Después de esto, se agregaron 1H-Benzotriazolio, 1-[bis(dimetilamino)metilen]-, tetrafluoroborato(1-), 3-óxido (TBTU, 710 mg) y una solución de dimetilamina en tetrahidrofurano (3 ml de solución 2M). La mezcla de reacción se agitó durante 18 horas adicionales y a continuación se pasó a través de SPE (5 g, sílice), eluyendo con un gradiente (3:1 a 1:2 de ciclohexano:acetato de etilo). Las fracciones requeridas se combinaron y se evaporaron para proporcionar N-[1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo (140 mg).

HPLC Rt = 2.70 minutos m/z [M+H]⁺ = 347

N-[1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucina

A una solución de N-[1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucinato de metilo (520 mg) en metanol (5 ml), se agregó una solución de hidróxido de litio (91 mg) en agua (3 ml). Después de agitar vigorosamente durante 24 horas, el solvente se removió *in vacuo*. El residuo se diluyó con agua (10 ml), a continuación se neutralizó con ácido clorhídrico 2N. Esta solución se aplicó a un cartucho OasisTM (2x6 g), y se eluyó con agua (x2) y metanol (x2). Las fracciones requeridas se combinaron y se evaporaron para proporcionar la N-[1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucina (478 mg).

HPLC Rt = 2.27 minutos m/z [M+H]⁺ = 333

(2R)-2-(benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetiletanamida

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- A una solución del ácido (2R)-[(ter-butoxicarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (419 mg) en tetrahidrofurano seco (5 ml) a -20°C bajo una atmósfera de nitrógeno, se agregó N-metilmorfolina (158 µl) y una solución de cloroformiato de isopropilo en tolueno (1.0 M, 1.44 ml).
- 10 Después de 10 minutos, se agregó una solución de N-[1-(benzofuran-5-il)-2-(dimetilamino)-2-oxoetil]-L-leucina (478 mg) en dimetilformamida (5 ml), y la reacción se dejó calentar a temperatura ambiente. Después de 20 horas, el solvente se removió *in vacuo*, y el residuo se disolvió en ácido clorhídrico 4N en dioxano (4 ml). Después de 4 horas, se agregó metanol (13 ml), y la
- 15 reacción se dejó reposar durante 18 horas adicionales. El solvente se removió a continuación *in vacuo* y el residuo se separó entre diclorometano y una solución de bicarbonato de sodio saturado. La fase orgánica se evaporó *in vacuo*, y el residuo se aplicó a una SPE (10 g, sílice). El producto se eluyó utilizando un gradiente de acetato de etilo:metanol (3:1 a 1:3), para
- 20 proporcionar la (2R)-2-(benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetiletanamida (51 mg).

HPLC Rt = 3.36 minutos, m/z [M+H]⁺ = 488

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¹H RMN (D₆-DMSO) δ 8.47 (d, 1H), 8.07 (d, 1H), 7.71 (m, 1H), 7.69 (d, 1H), 7.38 (dd, 1H), 7.21 (m, 2H), 7.12 (m, 2H), 7.03 (m, 1H), 6.47 (s, 1H), 3.88 (m, 1H), 3.69 (dd, 1H), 3.07-2.67 (m, 5H), 2.87 (s, 3H), 2.77 (s, 3H), 1.40-1.70 (m, 2H), 0.46 (m, 1H), 0.42 (d, 3H), 0.02 (d, 3H).

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EJEMPLO 141

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1-benzofuran-5-il)etanamida

10 **(2RS)-2-(2-metil-1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida**

Una mezcla de 2-metil-5-formilbenzofurano (1.26g), clorhidrato del éster metílico de (D)-leucina (1.57 g), trietilamina (1.2 ml) y metanol (20 ml), se agitó a temperatura ambiente durante 6 horas, y a continuación se dejó reposar durante 19 horas. A continuación se agregaron secuencialmente N-bencilcarbonil-(D)-indanilglicina (2.80 g) e isocianuro de 2-benciloxifenilisocianuro (1.89 g), y la mezcla se agitó durante 2 días. La mezcla de reacción se concentró bajo presión reducida y se diluyó con acetato de etilo.

20 Esta se lavó con ácido clorhídrico 1N, solución de bicarbonato de sodio saturada y salmuera. La fase orgánica se secó sobre MgSO₄ y se concentró *in vacuo*. El residuo se diluyó con acetato de etilo (100 ml) y ácido acético (10 ml), y se sometió a hidrogenación a presión atmosférica sobre paladio al 10%

sobre carbón activado (1.5 g). Después de 4 horas, el catalizador se removió mediante filtración a través de una almohadilla de celite y se lavó con diclorometano/metanol (500 ml de 1:1 v/v). El filtrado y los lavados se combinaron, se evaporaron bajo presión reducida. El residuo se separó entre acetato de etilo y agua. La fase orgánica se lavó con agua, solución de bicarbonato de sodio saturada y salmuera. La fase orgánica se secó sobre MgSO_4 , y se evaporó bajo presión reducida. El residuo se aplicó a un cartucho de sílice (100 g), y se eluyó con ciclohexano/acetato de etilo (500 ml de 3:1, 2:1, 1:1 v/v) y acetato de etilo (500 ml). Las fracciones requeridas se combinaron y se evaporaron *in vacuo* para proporcionar la (2RS)-2-(2-metilbenzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida (1.58 g).

HPLC Rt = 3.60 minutos; m/z $[\text{M}+\text{H}]^+ = 566$.

15 **(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1-benzofuran-5-il)etanamida**

Se suspendió carbonildiimidazol (92 mg, 1.6 equivalentes) en diclorometano anhidro (5 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. A continuación se agregó la (2RS)-2-(2-metilbenzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)etanamida (200 mg), y la mezcla se agitó a temperatura ambiente durante 5 horas. La solución marrón resultante se trató a

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continuación con una solución 2.0M de dimetilamina en tetrahidrofurano (1.06 mL, 6 equivalentes), y la mezcla resultante se agitó durante 30 minutos, y a continuación se dejó reposar a temperatura ambiente durante 18 horas. La mezcla de reacción se diluyó con diclorometano (2 mL), y se lavó con ácido clorhídrico 1M (2 mL). La fase orgánica se separó utilizando un vidrio poroso hidrofóbico, y se evaporó bajo presión reducida para proporcionar una goma marrón. El producto crudo se aplicó a un cartucho de sílice (10 g). Este se eluyó con ciclohexano (100 ml), ciclohexano/acetato de etilo (100 ml de 2:1, 3:2, 1:1, 2:3 y 1:2 v/v), acetato de etilo (200 ml) y acetato de etilo/metanol (100 ml de 19:1 v/v). Las fracciones requeridas se combinaron y se evaporaron *in vacuo* para proporcionar la (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetil-2-(2-metil-1-benzofuran-5-il)etanamida como un sólido blanco mate (88 mg).

HPLC Rt = 3.40 minutos; m/z [M+H]⁺ = 502.

¹H RMN (CDCl₃) δ 7.52 (d, 1H), 7.43 (d, 1H), 7.27-7.13 (m, 5H), 6.54 (s, 1H), 6.38 (m, 1H), 6.31 (d, 1H), 4.24 (m, 1H), 3.99 (dd, 1H), 3.22-3.05 (m, 3H), 2.99 (s, 3H), 2.86 (m, 1H), 2.82 (s, 3H), 2.75 (m, 1H), 2.48 (m, 3H), 1.45 (m, 1H), 1.36 (m, 1H), 0.57 (m, 1H), 0.51 (d, 3H), 0.19 (d, 3H).

Preparado de manera similar: -

EJEMPLO 142

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-isopropil-2-(2-metil-1-benzofuran-5-il)etanamida

5 HPLC Rt = 3.40 minutos; m/z [M+H]⁺ = 516.

¹H RMN (CDCl₃) δ 7.57 (m, 1H), 7.41 (d, 1H), 7.28-7.11 (m, 5H), 6.61 (m, 1H), 6.37 (m, 1H), 5.49 (d, 1H), 5.23 (s, 1H), 4.11 (m, 1H), 4.02-3.93 (m, 2H), 3.19-3.05 (m, 3H), 2.92 (m, 1H), 2.77 (m, 1H), 2.48 (m, 3H), 1.79 (m, 1H), 1.70 (m, 1H), 1.38 (m, 1H), 1.10 (m, 6H), 0.78 (d, 3H), 0.69 (d, 3H).

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EJEMPLO 143

(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-1-(2-metil-1-benzofuran-5-il)-2-morfolin-4-il-2-oxoetil]piperacín-2,5-diona

15 HPLC Rt = 3.38 minutos; m/z [M+H]⁺ = 544.

¹H RMN (CDCl₃) δ 7.51 (d, 1H), 7.45 (d, 1H), 7.26-7.14 (m, 5H), 6.57 (s, 1H), 6.39 (m, 1H), 6.34 (m, 1H), 4.20 (m, 1H), 3.99 (m, 1H), 3.73-3.33 (6H), 3.22-3.03 (m, 5H), 2.88 (m, 1H), 2.75 (m, 1H), 2.49 (m, 3H), 1.45 (m, 1H), 1.37 (m, 1H), 0.54 (m, 1H), 0.51 (d, 3H), 0.20 (d, 3H).

Jab

EJEMPLO 144**(2R)-2-((3R,6R)-3-(2,3-dihidro-1H-inden-2-yl)-6-isobutyl-2,5-dioxopiperidin-1-yl)-2-(2-fluoro-1-benzofuran-5-yl)-N,N-dimetiletanamida**

5 HPLC Rt = 3.39 minutos; m/z [M+H]⁺ = 505.

¹H RMN (CDCl₃) δ 7.56 (d, 1H), 7.45 (d, 1H), 7.32 (dd, 1H), 7.23 (m, 2H), 7.16 (m, 2H), 6.55 (s, 1H), 6.23 (d, 1H), 5.89 (d, 1H), 4.22 (m, 1H), 3.99 (dd, 1H), 3.21-3.04 (m, 3H), 3.00 (s, 3H), 2.87 (m, 1H), 2.84 (s, 3H), 2.75 (m, 1H), 1.47 (m, 1H), 1.38 (m, 1H), 0.58-0.49 (m, 4H), 0.22 (d, 3H).

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5-Bromo-2-fluoro-1-benzofurano

Se suspendió el ácido 5-bromobenzofuran-2-carboxílico (4.68 g) en tetracloruro de carbono (150 ml) y agua (50 ml). A éste se le agregó bicarbonato de sodio (3.36 g), seguido por Selectflor (7.1 g), y la mezcla de reacción se agitó rápidamente durante 20 horas. La mezcla de reacción se diluyó con diclorometano y solución de hidróxido de sodio 2N. La fase orgánica se separó, se lavó con salmuera y se secó sobre MgSO₄ anhidro. El solvente se evaporó bajo presión reducida a temperatura ambiente. El residuo se aplicó a un cartucho de sílice (20 g) y se eluyó con éter dietílico. Este proporcionó el 5-bromo-2-fluoro-1-benzofurano (1.4 g).

¹H RMN (CDCl₃) δ 7.61 (d, 1H), 7.36 (dd, 1H), 7.26 (d, 1H), 5.84 (dd, 1H).

JCM

2-Fluoro-5-formil-1-benzofurano

Una suspensión de polvo de magnesio (219 mg) y yodo (cat) en tetrahidrofurano seco (3 ml), se calentó a 50°C bajo nitrógeno durante 20 minutos. Se disolvió 5-bromo-2-fluoro-1-benzofurano (1.4 g) en tetrahidrofurano seco (6 ml). Se agregó una porción de 1 ml de la solución a la suspensión a 50°C sin agitación. Después de 30 minutos, el resto de la solución se agregó lentamente, y la reacción se calentó a reflujo durante 3 horas. La reacción se enfrió en un baño de hielo/agua, y se agregó gota a gota dimetilformamida (1 ml), manteniendo la temperatura por debajo de 10°C. Después de 1 hora, se agregó una mezcla de ácido clorhídrico 2N (12.5 ml) y salmuera (12.5 ml). La mezcla de reacción se extrajo utilizando acetato de etilo (3x25 ml). Los orgánicos combinados se lavaron con salmuera y se secaron sobre sulfato de magnesio anhidro. El solvente se removió *in vacuo*, y el residuo se aplicó a un cartucho de sílice (50 g). Este se eluyó con ciclohexano, ciclohexano/acetato de etilo (6:1, 5:1 v/v). Este proporcionó el 2-fluoro-5-formil-1-benzofurano (376 mg).

^1H RMN (CDCl_3) δ 10.05 (s, 1H), 8.04 (m, 1H), 7.83 (dd, 1H), 7.54 (d, 1H), 6.01 (dd, 1H).

EJEMPLO 145

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-2-(2-fluoro-1-benzofuran-5-il)-N-isopropiletanamida

HPLC Rt = 3.42 minutos; m/z [M+H]⁺ = 520.

5 ¹H RMN (CDCl₃) δ 7.61 (d, 1H), 7.42 (d, 1H), 7.31 (dd, 1H), 7.21 (m, 2H), 7.16 (m, 2H), 6.70 (d, 1H), 5.89 (d, 1H), 5.57 (d, 1H), 5.18 (s, 1H), 4.11 (m, 1H), 3.98 (m, 2H), 3.16 (m, 1H), 3.08 (m, 2H), 2.91 (m, 1H), 2.78 (m, 1H), 1.82 (m, 1H), 1.73 (m, 1H), 1.41 (m, 1H), 1.12 (d, 3H), 1.10 (d, 3H), 0.81 (d, 3H), 0.72 (d, 3H).

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EJEMPLO 146

(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-[(1R)-1-(2-fluoro-1-benzofuran-5-il)-2-morfolina-4-il-2-oxoetil]-6-isobutylpiperacina-2,5-diona

15 HPLC Rt = 3.35 minutos; m/z [M+H]⁺ = 548.

¹H RMN (CDCl₃) δ 7.55 (d, 1H), 7.47 (d, 1H), 7.31 (dd, 1H), 7.27-7.14 (m, 4H), 6.58 (s, 1H), 6.38 (d, 1H), 5.91 (d, 1H), 4.19 (m, 1H), 4.00 (dd, 1H), 3.73-3.50 (m, 5H), 3.39 (m, 1H), 3.23-3.04 (m, 5H), 2.87 (m, 1H), 2.76 (m, 1H), 1.47 (m, 1H), 1.40 (m, 1H), 0.53 (d, 3H), 0.51 (m, 1H), 0.24 (d, 3H).

EJEMPLO 147

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-2-(1H-indol-6-il)-N,N-dimetiletanamida

5 HPLC Rt = 3.38 minutos; m/z [M+H]⁺ = 487.

¹H RMN (CDCl₃) δ 9.03 (s, 1H), 7.66 (d, 1H), 7.49 (d, 1H), 7.30 (m, 1H), 7.21 (m, 1H), 7.18-7.10 (m, 4H), 7.02 (m, 1H), 6.57 (s, 1H), 6.55 (m, 1H), 4.29 (m, 1H), 4.00 (dd, 1H), 3.22-3.03 (m, 3H), 3.00 (s, 3H), 2.92-2.73 (m, 5H), 1.40 (m, 1H), 1.33 (m, 1H), 0.57 (m, 1H), 0.45 (d, 3H), 0.06 (d, 3H).

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EJEMPLO 148

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-2-(1H-indol-6-il)-N-metil-N-[2-(metilsulfonil)etiletanamida

15 HPLC Rt = 3.20 minutos; m/z [M+H]⁺ = 579.

¹H RMN (CDCl₃) δ 9.62 (s, 1H), 7.64 (d, 1H), 7.41 (d, 1H), 7.30 (m, 1H), 7.26-7.10 (m, 6H), 6.51 (m, 1H), 6.48 (s, 1H), 4.18 (m, 1H), 4.05-3.90 (m, 2H), 3.68-3.50 (m, 2H), 3.28-3.01 (m, 4H), 2.96-2.69 (m, 8H), 1.41 (m, 2H), 0.65 (m, 1H), 0.47 (d, 3H), -0.10 (d, 3H).

EJEMPLO 149

(2R)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N,N-dimetiletanamida

5 (2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-(2-benciloxifenil)etanamida

Una mezcla de 5-formilbenzotiofeno (2.0 g), clorhidrato del éster metílico de (D)-leucina (2.24 g), trietilamina (1.72 ml) y metanol (20 ml), se
 10 agitó a temperatura ambiente durante 24 horas. A continuación se agregaron secuencialmente N-ter-butoxicarbonil-(D)-indanilglicina (3.59 g) e isocianuro de 2-benciloxi-fenilisocianuro (2.58 g), y la mezcla se agitó durante 4 días. A continuación, el solvente se removió bajo presión reducida. El residuo se tomó en diclorometano (20 ml) y cloruro de hidrógeno 4M en 1,4-dioxano (20
 15 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. El solvente y cloruro de hidrógeno se evaporaron bajo presión reducida. El material crudo se disolvió en diclorometano (30 ml), y se agregó trietilamina (10 ml). La mezcla se agitó durante 18 horas antes de que se removiera el diclorometano y el exceso de trietilamina bajo presión reducida. El producto crudo se
 20 disolvió en diclorometano (100 ml), y se lavó con ácido clorhídrico 1N (2x100 ml) y salmuera. La fase orgánica se secó sobre MgSO₄, y se evaporó *in vacuo* para proporcionar la (2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-

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dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-benciloxifenil)-etanamida como una espuma marrón (7.5 g).

HPLC Rt = 3.88 minutos, m/z [M+H]⁺ = 658.

5 **(2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-Inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxfenil)etanamida**

Se disolvió la (2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-benciloxifenil)etanamida (1.0 g) en diclorometano (5 ml), y a ésta se agregó gota a gota una solución 1.0M de BBr₃ en diclorometano (2.0 ml). La mezcla de reacción se agitó a temperatura ambiente durante 2 horas. A la mezcla de reacción se le agregó ácido clorhídrico 1N (30 ml) y diclorometano (20 ml). Las fases se separaron, y la fase orgánica se lavó con ácido clorhídrico 1N (30 ml) y salmuera (30 ml). La fase orgánica se secó sobre MgSO₄, y se evaporó *in vacuo*. El residuo se purificó mediante una columna de cromatografía instantánea BiotageTM, eluyendo con 3:2 de acetato de etilo:ciclohexano. Las fracciones requeridas se combinaron y se evaporaron *in vacuo* para proporcionar la (2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxfenil)-etanamida (210 mg).

HPLC Rt = 3.55 minutos, m/z [M+H]⁺ = 568.

(2R)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida

Se suspendió carbonildiimidazol (100 mg) en diclorometano anhidro (1 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. A continuación se agregó (2RS)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)-etanamida (200 mg), y la mezcla se agitó a temperatura ambiente durante 5 horas 20 minutos. A continuación se trató la solución marrón resultante con una solución 2.0M de dimetilamina en tetrahidrofurano (1.0 mL, 6 equivalentes), y la mezcla resultante se agitó durante 30 minutos, y a continuación se dejó reposar a temperatura ambiente durante 18 horas 15 minutos. La mezcla de reacción se evaporó bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna con sílice eluyendo con 1:1 v/v de acetato de etilo:ciclohexano. Las fracciones requeridas se combinaron y se evaporaron *in vacuo* para proporcionar (2R)-2-(benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida como un sólido blanco (90 mg).

HPLC Rt = 3.35 minutos, m/z [M+H]⁺ = 504.

¹H RMN (CDCl₃) δ 7.94 (d, 1H), 7.89 (m, 1H), 7.70 (d, 1H), 7.54 (d, 1H), 7.41 (m, 1H), 7.35 (d, 1H), 7.23 (m, 1H), 7.13 (m, 3H), 6.63 (s, 1H), 4.25 (m, 1H), 4.02 (dd, 1H), 3.23-3.04 (m, 3H), 3.01 (s, 3H), 2.93-2.77 (m, 5H), 1.50-1.32 (m, 2H), 0.52 (m, 1H), 0.49 (d, 3H), 0.12 (d, 3H).

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Los compuestos 150-169 y 174-175 se prepararon vía el método

1. El compuesto 170 se preparó vía el método 2. Los compuestos 171, 172 y 173 se prepararon vía el método 5.

5	Ej. No.	Regno	P.M.	Rt/m in	Ion +ve	Ion -ve	Nombre
	150		517.7	3.62	518	516	(2R)-N-(ter-butil)-2-(2,3-dihidro-1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
10	151		516.6	3.12	517	515	2-(1H-1,2,3-benzotriazol-5-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]acetamida
15	152		533.7	3.42	534		(2R)-N-(ter-butil)-2-(2,3-dihidro-1,4-benzodioxin-6-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
20	153		555.6	3.71	556	554	(2R)-N-(ter-butil)-2-(2,2-difluoro-1,3-benzodioxol-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida

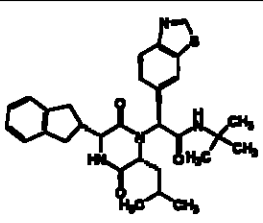
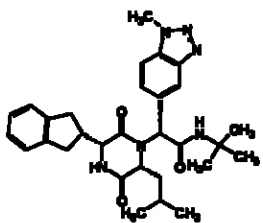
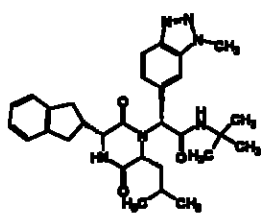
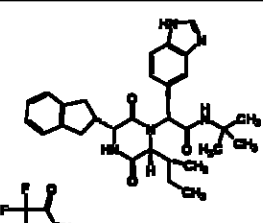
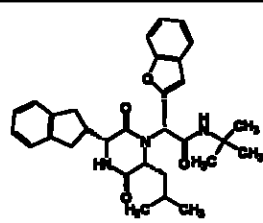
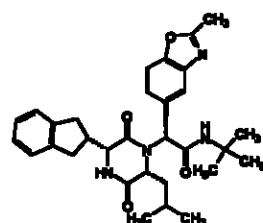
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154		532.7	3.32	533	531	(2R)-2-(1,3-benzotiazol-6-yl)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
155		530.7	3.18	531	529	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1-metil-1H-1,2,3-benzotriazol-5-il)etanamida
156		530.7	3.22	531	529	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1-metil-1H-1,2,3-benzotriazol-6-il)etanamida
157		629.7	3.06		514	trifluoroacetato de (2R)-2-(1H-bencimidazol-5-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida
158		515.7	3.72	516	514	(2R)-2-(1-benzofuran-2-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida
159		530.7	3.3	531	529	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-metil-1,3-benzoxazol-5-il)etanamida

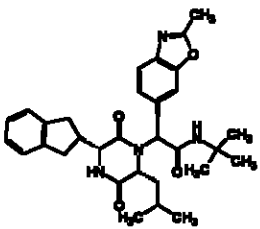
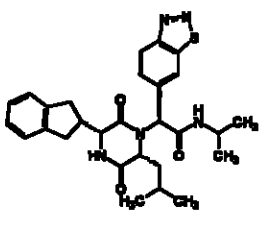
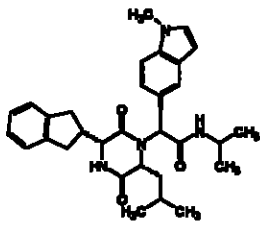
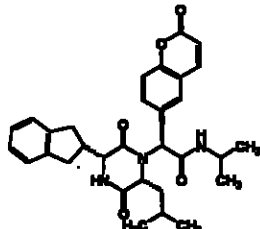
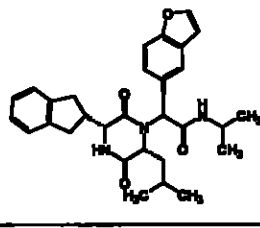
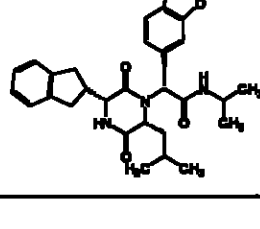
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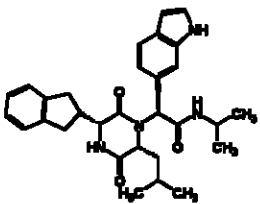
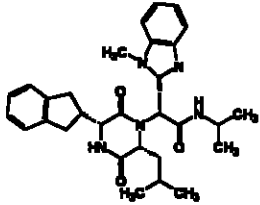
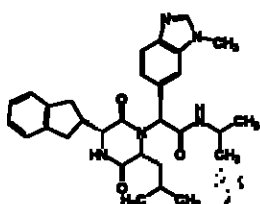
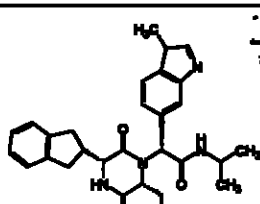
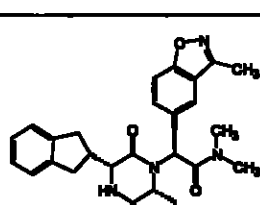
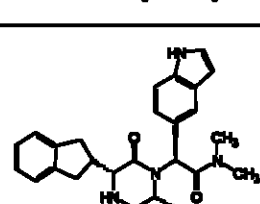
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160		530.7	3.35	531	529	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-metil-1,3-benzoxazol-6-il)etanamida
161		519.7	3.37	520	518	(2R)-2-(1,2,3-benzotiadiazol-6-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
162		514.7	3.41	515		(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(1-metil-1H-indol-5-il)etanamida
163		529.6				(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(2-oxo-2H-cromen-6-il)etanamida
164		517.7	3.53	518	516	(2R)-2-(1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
165		501.6	3.42	502	500	(2R)-2-(1-benzofuran-6-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida

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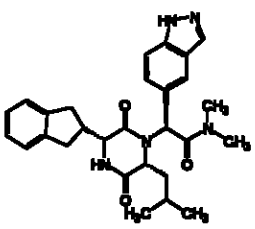
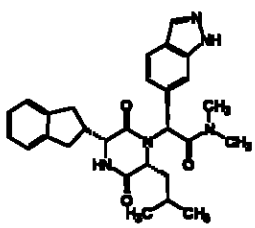
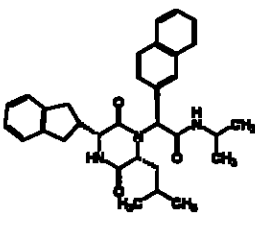
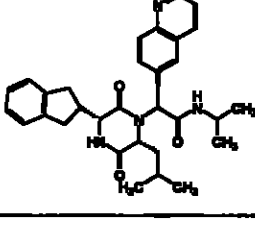
5	166		500.6	3.35	501	499	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indol-6-il)-N-isopropiletanamida
	167		515.7	4.88	516	514	2R-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(1-metil-1H-bencimidazol-2-il)acetamida
10	168		515.7	4.32	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(1-metil-1H-bencimidazol-6-il)etanamida
	169		515.7	2.65	516	514	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(1-metil-1H-bencimidazol-5-il)etanamida
15	170		502.6	3.35	503	501	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(3-metil-1,2-bencisoxazol-5-il)etanamida
	171		486.6	3.07	487	485	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indol-5-il)-N,N-dimetiletanamida
20							

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172		487.6	2.94	488		(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indazol-5-il)-N,N-dimetiletanamida
173		487.6	2.99	488	486	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indazol-6-il)-N,N-dimetiletanamida
174		511.7	3.56	512		(2R,S)-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(2-naftil)acetamida
175		512.7	3.19	513		(2R,S)-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-quinolin-6-ilacetamida

EJEMPLO 176

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-5-(trifluorometil)-2-furil]etanamida

20

A una solución de 5-trifluorometil-furan-2-carbaldehído (140 mg) [preparado como en la referencia Chem. Heterocycl. Compd. 13, 1977, 1280-1282, por R. V. Grigorash, V. V. Lyalin, L. A. Alekseeva y L. M. Yagupol'skii: 5-Trifluoromethylfuran Derivatives] en metanol (1.1 ml), se agregó trietilamina

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(118 μ l) y clorhidrato del éster t-butilico de (D)-leucina (190 mg). La mezcla se dejó reposar durante 16.33 horas antes de agregar secuencialmente el ácido (2R)-[(ter-butoxicarbonil)amino](2,3-dihidro-1H-inden-2-il)etanoico (246 mg) e isocianuro de isopropilo (77.4 μ l). La mezcla, una solución amarilla, se dejó

5 reposar durante 24 horas, antes de que se removiera el solvente *in vacuo*. El residuo se disolvió en cloruro de hidrógeno 4M en dioxano (3 ml), y se dejó reposar durante 6.75 horas a temperatura ambiente. Después de este tiempo, el solvente se removió *in vacuo*. El residuo se disolvió en metanol (4 ml), y se trató con una solución de cloruro de hidrógeno 4M en dioxano (0.2 ml), y se

10 dejó reposar durante la noche. Después de este tiempo, el solvente se removió *in vacuo*. El residuo se agitó en dioxano (9.5 ml) que contenía trietilamina (0.5 ml) y diclorometano (5 ml) durante 4.75 horas. A continuación, la mezcla se evaporó *in vacuo* para proporcionar un sólido marrón brillante. Este material crudo se purificó mediante una columna de

15 SPE (10 g, sílice Mega Bond Eut) eluyendo paso a paso con cloroformo al 100%, 4:1 de ciclohexano:éter dietílico, 3:1 de ciclohexano:éter dietílico, 2:1 de ciclohexano:éter dietílico, 1:1 de ciclohexano:éter dietílico, 1:2 de ciclohexano:éter dietílico, 1:3 de ciclohexano:éter dietílico, éter dietílico al 100%, 1:1 de acetato de etilo:ciclohexano, 2:1 de acetato de etilo:ciclohexano,

20 3:1 de acetato de etilo:ciclohexano, acetato de etilo al 100%. Se combinaron inclusive las fracciones 1:2 de ciclohexano:éter dietílico a 2:1 de acetato de etilo:ciclohexano para proporcionar una goma anaranjada (215 mg). La goma se purificó además, para separar los isómeros, mediante cromatografía en

placa preparativa. 60 placas de gel de sílice de Whatman PK6F de 20 x 20 cm², se eluyeron en 1:1 de acetato de etilo:ciclohexano seis veces, y se extrajeron con 9:1 de acetato de etilo:metanol, para proporcionar la (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-

5 isopropil-2-[5-(trifluorometil)-2-furil]etanamida (64 mg).

HPLC Rt = 3.59 minutos; m/z [M+H]⁺ = 520.

¹H RMN (CDCl₃) δ 7.88 (d, 1H), 7.16 (m, 4H), 6.85 (d, 1H), 6.74 (d, 1H), 6.30 (d, 1H), 5.73 (s, H), 4.19 (dd, 1H), 4.08 (m, 1H), 3.97 (dd, 1H), 3.14 (m, 2H), 3.01 (m, 1H), 2.84 (m, 2H), 1.81 (m, 1H), 1.68 (m, 1H), 1.15 (d, 10 6H), 1.11 (m, 1H), 0.82 (dd, 6H).

Preparado de manera similar.

EJEMPLO 177

(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacín-1-il]-N-isopropil-2-(5-metiltien-2-il)etanamida

15

Mediante el procedimiento del Ejemplo 176, pero utilizando el 5-metil-tiofen-2-carbaldehído.

HPLC Rt = 3.46 minutos, m/z [M+H]⁺ = 482.

20 ¹H RMN (CDCl₃) δ 7.21 (m, 2H), 7.16 (m, 2H), 6.94 (d, 1H), 6.67 (d, 1H), 6.63 (d, 1H), 5.73 (d, 1H), 4.94 (s, 1H), 4.07 (m, 1H), 3.93 (m, 2H), 3.16 (dd, 1H), 3.05 (m, 2H), 2.93 (m, 1H), 2.77 (m, 1H), 2.47 (s, 3H), 1.96 (m,

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1H), 1.86 (m, 1H), 1.72 (m, 1H), 1.17 (d, 3H), 1.12 (d, 3H), 0.94 (d, 3H), 0.92 (d, 3H).

EJEMPLO 178

5 **(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[5-(trifluorometil)-2-furil]etanamida**

N-[2-(benciloxi)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[5-(trifluorometil)-2-furil]acetamida

10

Una mezcla del 5-trifluorometil-furan-2-carbaldehído (351 mg), clorhidrato del éster metílico de (D)-leucina (389 mg), trietilamina (0.298 ml) y metanol (2.2 ml), se agitó a temperatura ambiente durante 4 horas, y a continuación se dejó reposar durante 19 horas. A continuación se agregó

15 secuencialmente N-ter-butoxicarbonil-(D)-indanilglicina (623 mg) e isocianuro de 2-benciloxi-fenilisocianuro (448 mg), y la mezcla se agitó durante 7 horas antes de dejarla reposar a temperatura ambiente durante 41 horas. A continuación, el solvente se removió bajo presión reducida para proporcionar un jarabe anaranjado/marrón. Este se tomó en cloruro de hidrógeno 4M en

20 1,4-dioxano (2.8 ml), y la mezcla se agitó a temperatura ambiente durante 2 horas. El solvente y el cloruro de hidrógeno se evaporaron bajo presión reducida. El material crudo se disolvió en metanol (5 ml) y se agregó trietilamina (0.54 ml). La mezcla se agitó durante 18 horas antes de remover

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el metanol y el exceso de trietilamina bajo presión reducida. El producto crudo se purificó mediante cromatografía en columna instantánea Biotage™ (cartucho de sílice de 40 g eluido con 1:5 de acetato de etilo:ciclohexano (600 ml), 1:3 de acetato de etilo:ciclohexano (400 ml) y 1:2 de acetato de etilo:ciclohexano (450 ml)), para proporcionar la N-[2-(benciloxi)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[5-(trifluorometil)-2-furil]acetamida como un sólido anaranjado (472 mg).

HPLC Rt = 4.04 minutos, m/z [M+H]⁺ = 660.

10 **2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)-2-[5-(trifluorometil)-2-furil]acetamida**

Se disolvió la N-[2-(benciloxi)fenil]-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[5-(trifluorometil)-2-furil]-acetamida (469 mg) en acetato de etilo (10 ml), y se sometió a hidrogenación a presión atmosférica sobre paladio al 10% sobre carbón activado (100 mg). Después de 4 horas, el catalizador se removió mediante filtración a través de filtros de fibra de vidrio y se lavó con acetato de etilo. El filtrado y los lavados se combinaron, se evaporaron bajo presión reducida y se secaron *in vacuo* a temperatura ambiente para proporcionar un sólido anaranjado/marrón (400 mg). El sólido se secó sobre P₂O₅ durante la noche para proporcionar la 2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-hidroxifenil)-2-[5-(trifluorometil)-2-furil]acetamida (365 mg).

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HPLC Rt = 3.64 minutos, m/z [M+H]⁺ = 570.

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[5-(trifluorometil)-2-furil]etanamida

5

Se suspendió carbonildiimidazol (78 mg, 1.6 equivalentes) en diclorometano anhidro (1 mL), y la suspensión se dejó a temperatura ambiente durante 15 minutos. A continuación se agregó la (R)-N-(2-hidroxi-fenil)-2-((3R,6R)-3-indan-2-il-6-isobutil-2,5-dioxo-piperacin-1-il)-2-(5-trifluorometil-furan-2-il)-acetamida (172 mg), y la mezcla se agitó a temperatura ambiente durante 5 horas 20 minutos. La solución marrón resultante se trató a continuación con una solución de dimetilamina 2.0M en tetrahidrofurano (0.9 mL, 6 equivalentes), y la mezcla resultante se agitó durante 30 minutos y a continuación se dejó reposar a temperatura ambiente durante 18 horas 15 minutos. La mezcla de reacción se diluyó con diclorometano (2 mL), y se lavó con ácido clorhídrico 1M (2 mL). La fase orgánica se separó utilizando un vidrio poroso hidrofóbico, y se evaporó bajo presión reducida para proporcionar una goma marrón. El producto crudo se aplicó a 3 placas de cromatografía preparativas, las cuales se eluyeron con 1:1 v/v de acetato de etilo:ciclohexano. La banda requerida se extrajo con acetato de etilo para proporcionar la **(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[5-(trifluorometil)-2-furil]etanamida** como un sólido amarillo mate (87 mg).

20

23

HPLC Rt = 3.51 minutos, m/z [M+H]⁺ = 506.

¹H RMN (CDCl₃) δ 7.19 (m, 5H), 6.86 (dd, 1H), 6.64 (d, 1H), 6.61 (s, 1H), 4.25 (m, 1H), 3.97 (dd, 1H), 3.20-3.02 (m, 3H), 3.01 (s, 3H), 2.96 (s, 3H), 2.88 (m, 1H), 2.80 (m, 1H), 1.70 (m, 1H), 1.67 (m, 1H), 0.74 (d, 3H), 0.70 (m, 1H), 0.63 (d, 3H).

EJEMPLO 179

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetil-2-(2-metil-1,3-oxazol-4-il)etanamida

10

Mediante el procedimiento del Ejemplo 178, utilizando (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)-2-(2-metil-1,3-oxazol-4-il)etanamida.

HPLC: Rt = 2.88 minutos; m/z (M+H)⁺ = 453.

15

(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)-2-(2-metil-1,3-oxazol-4-il)etanamida

Una mezcla de 2-metil-oxazol-4-carbaldehído⁽¹⁾ (340 mg),
20 clorhidrato del éster metílico de (D)-leucina (568 mg), trietilamina (0.435 ml) y metanol anhidro (20 ml), se agitó a temperatura ambiente durante 18 horas. A continuación se agregó N-benciloxicarbonil-(D)-indanilglicina (1.015 g) y isocianuro de 2-benciloxi-fenilo (648 mg), y la mezcla se agitó durante 12 días

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antes de dejarla reposar a temperatura ambiente durante 10 días. El solvente se removi6 bajo presi6n reducida para proporcionar una goma anaranjada oscura, la cual se disolvi6 en acetato de etilo (150 mL), y se lav6 con 6cido clorh6drico 2M (100 mL), soluci6n de bicarbonato de sodio saturada (100 mL),
5 y soluci6n del cloruro de sodio saturada (50 mL), a continuaci6n se sec6 sobre sulfato de magnesio anhidro y se concentr6 bajo presi6n reducida a un volumen de 5 mL. Esta soluci6n cruda se diluy6 con etanol (80 mL) que contenia 6cido ac6tico (1.6 mL), y se agreg6 bajo vaci6 a paladio al 10% sobre carbono (50% de agua, 425 mg). La suspensi6n resultante se agiti6
10 bajo una atm6sfera de hidr6geno durante 20 horas, se filtr6 (con ayuda de un filtro de celite), se lav6 con etanol (50 mL), y el filtrado se agreg6 bajo vaci6 a una segunda cantidad de paladio al 10% sobre carbono (50% de agua, 670 mg). La suspensi6n se agiti6 bajo una atm6sfera de hidr6geno durante 2 horas, a continuaci6n se evacu6 el aparato de hidrogenaci6n y se rellen6 con
15 hidr6geno y la suspensi6n se agiti6 durante 20 horas adicionales. La suspensi6n se filtr6 (con ayuda de un filtro de celite), se lav6 con etanol (200 mL), y los filtrados combinados se concentraron bajo presi6n reducida. El residuo se reparti6 entre una soluci6n de bicarbonato de sodio saturada (100 mL) y diclorometano (60 mL), a continuaci6n se sec6 la capa org6nica (vidrio
20 poroso hidrof6bico), y el solvente se removi6 bajo presi6n reducida. La purificaci6n se llev6 a cabo mediante cromatografia instant6nea en Biotage (40 g de sili6), eluyendo con acetato de etilo:ciclohexano (3:1, 300 mL), acetato de etilo (300 mL), a continuaci6n acetato de etilo:metanol (20:1, 600

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mL), proporcionó la (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N-(2-hidroxifenil)-2-(2-metil-1,3-oxazol-4-il)etanamida como una espuma marrón (197 mg).

HPLC: Rt = 3.28 minutos; m/z (M+H)⁺ = 517.

5 Ref (1) CAS 113732-84-6.

EJEMPLO 180

(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-1-(2-metil-1,3-oxazol-4-il)-2-morfolina-4-il-2-oxoetil]piperacina-2,5-diona

10

Mediante el procedimiento del Ejemplo 179, utilizando morfina.

HPLC: Rt = 2.89 minutos; m/z (M+H)⁺ = 495.

EJEMPLO 181

15 **(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacina-1-il]-N,N-dimetil-2-(5-metilfen-2-il)etanamida**

Mediante el procedimiento del Ejemplo 180, utilizando el 5-metil-tiofen-2-carbaldehído.

20 HPLC Rt = 3.25 minutos; m/z M⁺ = 468.

EJEMPL 182**(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(3-fluoro-5-metiltien-2-il)-N,N-dimetiletanamida**

5 Mediante el procedimiento del Ejemplo 178, utilizando el 3-fluoro-5-metil-tiofen-2-carbaldehído.

HPLC: Rt = 3.20 minutos; m/z M⁺ = 486.

2-(3-Bromo-5-metil-tiofenil-2-il)-[1,3]dioxano

10

Se disolvió 3-bromo-5-metil-2-tiofencarbaldehído (1.00 g) en 1,4-dioxano seco (8 ml). Se agregaron tamices moleculares (4 Angstrom, 2 g), 1,3-propandiol (9 ml), ácido p-toluen sulfónico (362 mg), y la mezcla se agitó bajo una atmósfera de nitrógeno, a temperatura ambiente durante la noche.

15 Los tamices moleculares se removieron mediante filtración y el filtrado se evaporó. El residuo se extrajo con acetato de etilo y se lavó con solución saturada de carbonato de sodio. La fase acuosa se extrajo con más acetato de etilo, y las capas combinadas se lavaron con salmuera, se secaron sobre sulfato de magnesio, se filtraron y concentraron hasta un aceite amarillo (1 g).

20 La purificación se realizó mediante filtración sobre un cartucho SPE (Sílice-10 g), utilizando diclorometano como eluyente. La solución fue eventualmente concentrada para proporcionar 2-(3-bromo-5-metil-tiofen-2-il)-[1,3]dioxano como un sólido amarillo (1.18 g).

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¹H-RMN (CDCl₃, 400 MHz): 6.60 ppm (s, 1H); 5.72 ppm (s, 1H); 4.23 ppm (m, 2H); 3.98 ppm (m, 2H); 2.44 ppm (d, 3H); 2.22 ppm (m, 1H); 1.42 ppm (m, 1H).

5

3-Fluoro-5-metil-tiofen-2-carbaldehído

A una solución de 2-(3-bromo-5-metil-tiofen-2-il)-[1,3]dioxano (1.16 g) en tetrahidrofurano seco (10 ml), bajo una atmósfera de nitrógeno, a -78°C, se agregó gota a gota n-butilitio 1.6M en hexano (3.30 ml). Después de 15 minutos de agitación, se agregó en porciones N-fluoro-bencen-sulfonil-imida (1.66 g). La solución se agitó a -78°C durante 10 minutos adicionales, se dejó calentar a temperatura ambiente y a continuación durante 60 minutos adicionales. La reacción se enfrió con agua (5 ml), se diluyó con éter dietílico (20 ml) y se lavó con hidróxido de sodio 1N (30 ml). La fase acuosa se extrajo nuevamente con éter dietílico (2x10 ml), las capas orgánicas combinadas se secaron sobre sulfato de magnesio, se filtraron y se evaporaron. El residuo se redisolvió en 1,4-dioxano (15 ml) y se agregó agua (10), ácido p-toluen sulfónico (837 mg), y la solución se agitó a temperatura ambiente durante la noche. Se neutralizó con solución saturada de bicarbonato de sodio (10 ml), a continuación se extrajo dos veces con éter. La capa orgánica se secó sobre sulfato de magnesio y se evaporó a presión reducida (200 mbaras). El dioxano residual se removió mediante destilación a presión reducida, el residuo se purificó adicionalmente mediante cromatografía instantánea (éter

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de petróleo/diclorometano 55/45), proporcionando el 3-fluoro-5-metil-tiofen-2-carbaldehído como un aceite incoloro (386 mg), aproximadamente 70% puro.

¹H-RMN (CDCl₃, 400 MHz): δ 9.93 ppm (s, 1H); 6.62 ppm (s, 1H); 2.52 ppm (m, 3H).

5 Preparado de manera similar:

Los compuestos 183-206, 213, 215, 218, 222-225 se prepararon vía el método 1. Los compuestos 207, 208, 216, se prepararon vía el método 2. Los compuestos 209-212, 214, 217, 219-221 y 226 se prepararon vía el método 5.

10		Ej. No.	Estructura	P.M.	Rt/ min	Ion +ve	Ion -ve	Nombre
		183		467.7	3.4	468	466	(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-tien-2-iletanamida
		184		546.6	3.6	546/548	546/544	(2S)-2-(5-bromotien-2-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
15		185		546.6	3.6	546/548	544/546	(2S)-2-(4-bromotien-2-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida
20		186		502.1	3.6	501-3	499-501	(2S)-2-(5-clorotien-2-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida

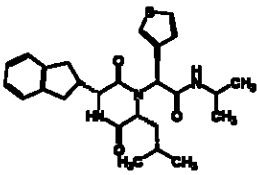
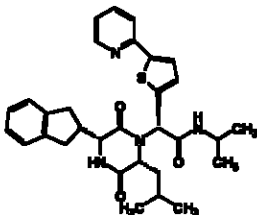
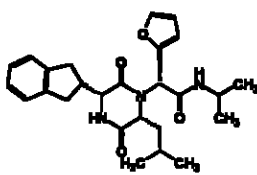
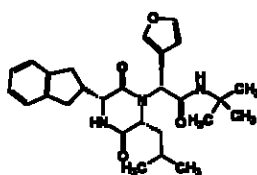
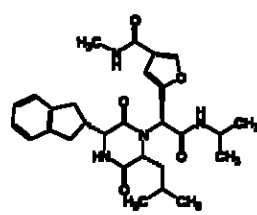
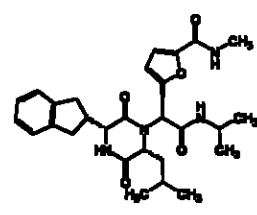
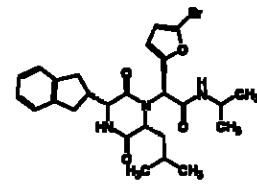
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187		467.7	3.3	468	466	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-tien-3-iletanamida
188		544.8	3.4	545	543	(2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(5-piridin-2-iltien-2-il)etanamida
189		451.6	3.3	452	450	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-furil)-N-isopropiletanamida
190		465.7	3.4	466	464	(2R)-N-(ter-butyl)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(3-furil)etanamida
200		508.7	2.9	509	507	5-[1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(isopropilamino)-2-oxoetil]-N-metil-3-furamida
201		508.7	3	509	507	5-[(1R)-1-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(isopropilamino)-2-oxoetil]-N-metil-2-furamida
202		530.5	3.5	529/ 531	527/ 529	(2R)-2-(5-bromo-2-furil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida

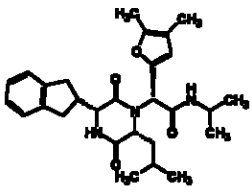
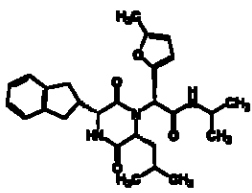
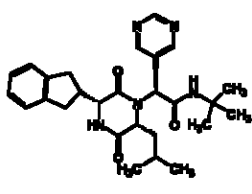
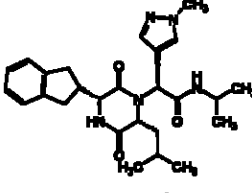
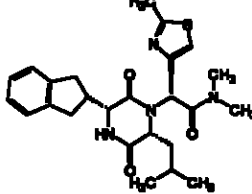
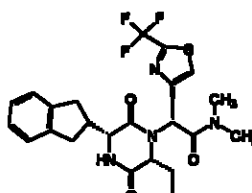
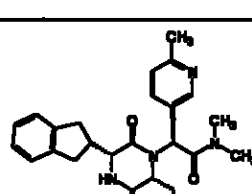
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203		479.7	3.5	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4,5-dimetil-2-furil)-N-isopropiletanamida
204		465.7	3.4	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(5-metil-2-furil)etanamida
205		477.6	3.3	478	476	(2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-pirimidin-5-iletanamida
206		465.7	2.9	466	464	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(1-metil-1H-pirazol-4-il)etanamida
207		468.7	3	469	ninguno	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1,3-tiazol-4-il)etanamida
208		522.6	3.4	523	521	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[2-(trifluorometil)-1,3-tiazol-4-il]etanamida
209		462.7	3.1	463	ninguno	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(6-metilpiridin-3-il)etanamida

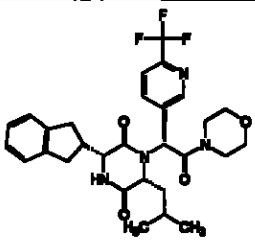
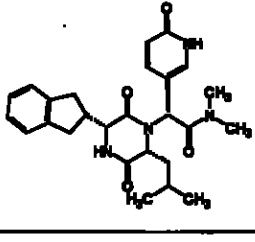
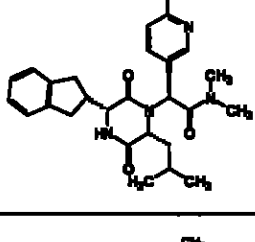
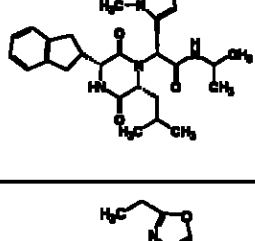
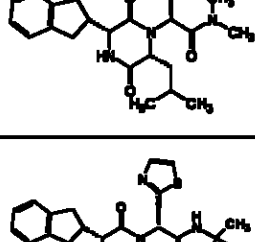
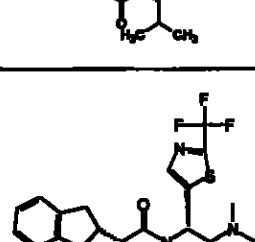
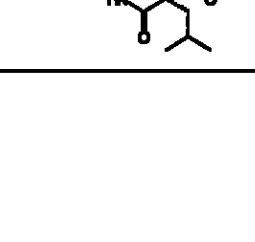
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210		558.7	3.3	559	557	(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-2-morfolin-4-il-2-oxo-1-[6-(trifluorometil)piridin-3-il]etil]piperacin-2,5-diona
211		464.6	2.7	465	463	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(6-oxo-1,6-dihidropiridin-3-il)etanamida
212		478.6	3.04	479.23	477.26	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(6-metoxipiridin-3-il)-N,N-dimetiletanamida
213		479.6	3.03	480	478	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1,3-dimetil-1H-pirazol-5-il)-N-isopropiletanamida
214		468.56	3.1	467	-	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-etil-1,3-oxazol-4-il)-N,N-dimetiletanamida
215		482.6	3.58	483	481	N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(1,3-tiazol-2-il)acetamida
216		522.6	3.46	523	521	2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[2-(trifluorometil)-1,3-tiazol-5-il]acetamida

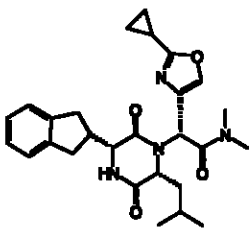
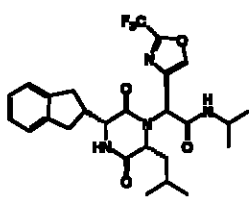
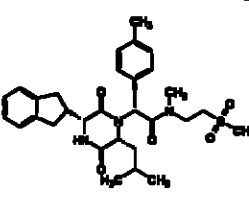
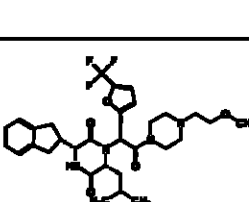
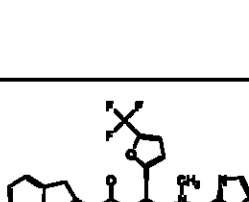
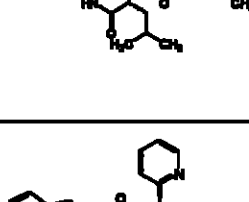
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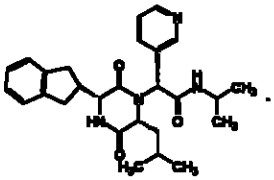
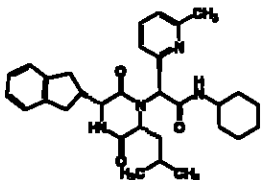
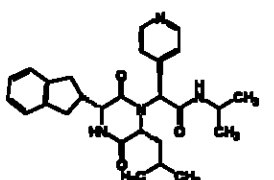
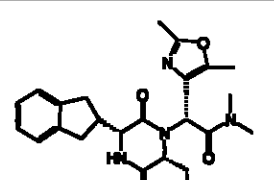
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217		478.6	3.07	479	477	(2R)-2-(2-ciclopopil-1,3-oxazol-4-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida
218		520.5	3.47	521	519	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[2-(trifluorometil)-1,3-oxazol-4-il]etanamida
219		554.7	2.8	555	553	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-2-(6-metilpiridin-3-il)-N-[2-(metilsulfonil)etil]etanamida
220		604.7	2.7	605	603	(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-2-[4-(2-metoxietil)piperacin-1-il]-2-oxo-1-[5-(trifluorometil)-2-furil]etil]piperacin-2,5-diona
221		585.6	2.8	586	584	(2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-[(1-metil-1H-imidazol-2-il)metil]-2-[5-(trifluorometil)-2-furil]etanamida
222		462.6	3.29	463	461	2-[(3R,6R)-3-indan-2-il-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-piridin-2-il-acetamida

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223		462.6	3.09	463	461	2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperacin-1-yl)-N-isopropil-2-piridin-3-yl-acetamida
224		516.7	3.41	517	515	N-Ciclohexil-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperacin-1-yl)-2-(6-metil-piridin-2-yl)-acetamida
225		462.6	2.93	463	461	2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperacin-1-yl)-N-isopropil-2-piridin-4-yl-acetamida
226		466.6	3.06	467	-	(R)-2-(2,5-dimetil-oxazol-4-yl)-2-((3R,6R)-3-indan-2-yl-6-isobutyl-2,5-dioxo-piperacin-1-yl)-N,N-dimetilacetamida

15

EJEMPLO 227

(3R,6R)-1-[(1R)-1-(2,4-Difluorofenil)-2-(3-fluoroacetidin-1-yl)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-yl)-6-isobutylpiperacin-2,5-diona

Se agitó el acetidinol (Ejemplo 15) (57 mg) en diclorometano anhidro (2 mL) a -5°C, y se agregó trifluoruro de dietilaminoazufre (50 µL, exceso) en una porción. La mezcla se dejó a temperatura ambiente durante la noche y se agregó carbonato ácido de sodio saturado acuoso (3 mL). La mezcla se diluyó con diclorometano (10 mL), y la fase orgánica se separó

ph

utilizando un vidrio poroso hidrofóbico y se eliminó con nitrógeno. La mezcla de reacción cruda se purificó utilizando el sistema autoprep dirigido por masa para proporcionar la (3R,6R)-1-[(1R)-1-(2,4-Difluorofenil)-2-(3-fluoroacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutylpiperacin-2,5-diona (26 mg)

5 como un sólido blanco.

HPLC Rt = 3. 34 minutos, m/z [M+H]⁺ = 514.

Ejemplos Farmacológicos

Tabletas

10	a)	Compuesto de la invención	50.0 mg
		Lactosa	70.0 mg
		Celulosa Microcristalina	70.0 mg
		Polivinilpirrolidona reticulada	8.0 mg
		Estearato de Magnesio	<u>2.0 mg</u>
15		Peso comprimido	200.0 mg

El compuesto de la invención, la celulosa microcristalina, la lactosa y la polivinilpirrolidona reticulada se tamizaron a través de un tamiza de 500 micras y se combinaron en un mezclador adecuado. El estearato de
20 magnesio se tamizó a través de un tamiz de 250 micras y se combinó con la mezcla activa. La mezcla se comprime en tabletas utilizando punches adecuados.

MS

5	b)	Compuesto de la invención	50.0 mg
		Lactosa	120.0 mg
		Almidón pregelatinizado	20.0 mg
		Polivinilpirrolidona reticulada	8.0 mg
		Estearato de Magnesio	<u>2.0 mg</u>
		Peso comprimido	200.0 mg

El compuesto de la invención, la lactosa y el almidón pregelatinizado se combinaron juntos y se granularon con agua. La masa húmeda se secó y trituró. El estearato de magnesio y polivinilpirrolidona reticulada se tamizaron a través de un tamiz de 250 micras y se combinaron con el gránulo. La mezcla resultante se comprime utilizando troqueles para tabletas adecuados.

15 Cápsulas

20	a)	Compuesto de la invención	50.0 mg
		Lactosa	148.0 mg
		Estearato de Magnesio	<u>2.0 mg</u>
		Peso lleno	200.0 mg

El compuesto de la invención y el almidón pregelatinizado se tamizaron a través de un tamiza de 500 micras, se mezclaron juntos y se lubricaron con estearato de magnesio, (tamizado a través de un tamiza de 250

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micras). La mezcla se llena en cápsulas de gelatina dura de un tamaño adecuado.

5	b)	Compuesto de la invención	50.0 mg
		Lactosa	132.0 mg
		Polivinilpirrolidona	8.0 mg
		Polivinilpirrolidona reticulada	8.0 mg
		Estearato de Magnesio	<u>2.0 mg</u>
		Peso lleno	200.0 mg

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El compuesto de la invención y la lactosa se combinan juntos y se granulan con una solución de polivinilpirrolidona. La masa húmeda se secó y se trituró. El estearato de magnesio y la polivinilpirrolidona reticulada se tamizan a través de un tamiz de 250 micras y se combinan con los gránulos.

15 La mezcla resultante se llena en cápsulas de gelatina dura de un tamaño adecuado.

Formulación de Inyección

		% peso/volumen
20	Compuesto de la invención	0.10
	Agua para inyecciones B.P. a	100.00

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El cloruro de sodio puede agregarse para ajustar la tonicidad de la solución, y el pH puede ajustarse a aquél de la máxima estabilidad y/o para facilitar la solución del compuesto de la invención utilizando un ácido o base diluido o mediante la adición de las sales amortiguadoras adecuadas. Los solubilizantes, tales como cosolventes, pueden agregarse para facilitar la solución del compuesto de la invención. Los antioxidantes y las sales quelantes de metal también pueden incluirse. La solución se clarifica, se afora a un volumen final con agua, y el pH se mide nuevamente y se ajusta si es necesario, para proporcionar 1 mg/ml del compuesto de fórmula (I).

La solución puede empacarse para inyección, por ejemplo, mediante llenado y sellado de ampulas, viales o jeringas. Las ampulas, viales o jeringas pueden llenarse asépticamente (por ejemplo, la solución puede ser esterilizada mediante filtración y llenada en ampulas estériles bajo condiciones asépticas), y/o esterilizarse terminalmente (por ejemplo, mediante calentamiento en un autoclave, utilizando uno de los ciclos aceptables). La solución puede empacarse bajo una atmósfera inerte de nitrógeno.

De manera preferida, la solución se llena en ampulas, selladas por fusión del vidrio y esterilizadas terminalmente.

Las formulaciones estériles adicionales, se preparan de una manera similar conteniendo 0.05, 0.20 y 0.5% peso/volumen del compuesto de la invención, para proporcionar respectivamente 0.5, 2 y 5 mg/ml del compuesto de la invención.

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Medición de la Actividad Antagonista de la Oxitocina

Amortiguador de Ensayo utilizado a través del ensayo: HEPES 50 mM, MgCl₂ 10 mM, 0.125 mg/ml de BSA, pH ajustado a 7.4 con KOH.

Se prepararon membranas de hOT-CHO a una concentración de 0.3 mg de proteína/ml en el amortiguador de ensayo. Los compuestos de prueba se disolvieron inicialmente en DMSO (a 10 mM), y se diluyeron en DMSO (Beckman Biomek FX). Se transfirió 1 µl del compuesto a 384 placas de ensayo negras (NUNC), utilizando un Biomek FX. Se agregaron 20 µl de Oxitocina Bodipy TMR 1 nM (Perkin Elmer) en un amortiguador de ensayo a todos los pozos (Labsystems Multidrop), a continuación se agregaron 20 µl de membrana a todos los pozos (Multidrop). Las placas se incubaron a temperatura ambiente durante 60 minutos.

La polarización se leyó en un Analizador LJL (λ_{Ex} = 535 nm, λ_{Em} = 580 nm, $\lambda_{Dicroico}$ = 555 nm).

Los datos se ajustaron a una ecuación logística de 4 parámetros. Un estimado de la K_i se calculó como $CI_{50/5}$.

Los compuestos de prueba de la invención anteriores, en general, tienen un valor de pK_i dentro del intervalo de 7 a 11. Así, los compuestos de los ejemplos 1 a 227 tienen una pK_i dentro del intervalo 8.5 a 10.8.

Los compuestos de la invención son esencialmente no tóxicos a dosis terapéuticamente activas. Así, el compuesto del ejemplo 10 ha sido

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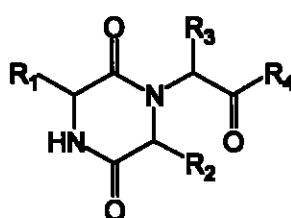
administrado a ratas a dosis de hasta 300 mg/kg p. o., durante 4 días, y no se observaron efectos toxicológicos adversos.

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N UVIDAD DE LA INVENCIONREIVINDICACIONES

- 5 1.- Un método para tratar o prevenir enfermedades o condiciones mediadas a través de la acción de la oxitocina, la cual comprende administrar a un mamífero en necesidad del mismo una cantidad efectiva de una compuesto de la fórmula (I)

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(I)

- y/o un derivado fisiológicamente aceptable del mismo, en donde: R₁ representa arilalquilo de (C₁₋₄) o un grupo cicloalquilo de 5-7 miembros sustituido opcionalmente con uno o más grupos hidroxilo, el cual está fusionado a un anillo de benceno sustituido opcionalmente; R₂ representa alquilo de C₁₋₆ (sustituido opcionalmente por un grupo alcoxi de C₁₋₂, alquitio de C₁₋₂, di(alquil de C₁₋₂)amino o un cicloalquilo de C₃₋₆) o cicloalquilo de C₃₋₆,
 20 o un grupo heterocíclico de 5-6 miembros que contiene un solo heteroátomo seleccionado de O, S o N, átomo de nitrógeno el cual porta un átomo de hidrógeno o un grupo metilo o etilo; R₃ representa fenilo sustituido opcionalmente, un grupo heteroarilo de 5 ó 6 miembros o un sistema anular

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bicíclico fusionado, que contiene 9-10 miembros en el anillo, el cual puede ser un grupo carbocíclico o éste puede contener hasta 3 heteroátomos seleccionados de O, S o N, y uno de los anillos fusionados es benceno; R_4 representa OH u O-alquilo de C_{1-4} (sustituido opcionalmente con alquilcarbonilo de C_{1-4}) o NR_5R_6 ; R_5 representa hidrógeno, alquilo de C_{1-6} (sustituido opcionalmente con alcoxi de C_{1-4}) o cicloalquilo de C_{3-7} ; R_6 representa hidrógeno, metilo, alcoxi de C_{1-4} , cicloalquilo de C_{3-7} , alquilo de C_{1-4} [sustituido opcionalmente con uno o más grupos seleccionados de carboxilo, alquilsulfonilo de C_{1-4} o alcocarbonilo de C_{1-4}], alquilo de C_{2-4} [sustituido opcionalmente con uno o más grupos seleccionados de halógeno, hidroxilo, alcoxi de C_{1-4} o NR_7R_8 , en donde R_7 y R_8 de manera independiente representan hidrógeno o alquilo de C_{1-4} , o junto con el átomo de nitrógeno al cual están unidos para formar un anillo heterocíclico saturado de 3-7 miembros, el cual puede contener un heteroátomo adicional seleccionado de O, S o N (y grupo heterocíclico el cual puede estar sustituido por 1 a 3 grupos seleccionados de alquilo de C_{1-3} , hidroxilo, alcoxi de C_{1-3} (sustituido opcionalmente por cicloalquilo de C_{3-6} o fenilo sustituido opcionalmente), cicloalquilo de C_{3-6} o NR_cR_d , en donde R_c y R_d , cada uno de manera independiente, representa un grupo seleccionado de alquilo de C_{1-3} (sustituido opcionalmente por cicloalquilo de C_{3-6} o fenilo sustituido opcionalmente) o cicloalquilo de C_{3-6}], o R_6 representa un grupo fenilo o bencilo (sustituido opcionalmente por uno o más grupos metoxi o benciloxi), o un grupo heteroarilmetilo sustituido opcionalmente o un grupo heteroarilo o cicloalquilo

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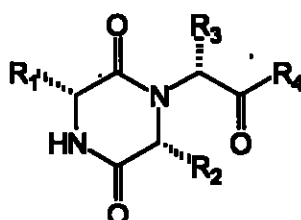
de C₃₋₇ o el grupo CH₂CONR₉R₁₀, en donde R₉ representa hidrógeno o alquilo de C₁₋₄, R₁₀ representa hidrógeno, alquilo de C₁₋₄ sustituido opcionalmente por un grupo heteroarilo de 5 ó 6 miembros, o R₉, R₁₀ y el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico saturado de 5 ó 6 miembros y en donde el grupo heterocíclico de 6 miembros puede contener un heteroátomo adicional seleccionado de oxígeno, azufre o nitrógeno y el átomo de nitrógeno adicional porta un átomo de hidrógeno o un grupo alquilo de C₁₋₄ o alcanilo de C₁₋₄; o R₅ y R₆ junto con el átomo de nitrógeno al cual están unidos, forman un anillo heterocíclico saturado de 3 a 7 miembros, heterociclo el cual puede contener un heteroátomo adicional seleccionado de oxígeno, azufre y nitrógeno, y en donde el átomo de azufre puede estar en una forma oxidada, por ejemplo, SO₂ y el átomo de nitrógeno adicional porta un átomo de hidrógeno o un grupo alquilo de C₁₋₄ o alcanilo de C₁₋₄, o un grupo alquilsulfonilo de C₁₋₄ o un alcoxi de C₁₋₃ alquilo de C₂₋₄ [y grupos heterocíclicos los cuales pueden estar sustituidos por uno o más átomos de halógeno o un grupo seleccionado de alquilo de C₁₋₃, hidroxí, oxo, cicloalquilo de C₃₋₆ o NR₉R₁, en donde R₉ y R₁, cada uno de manera independiente representa un grupo seleccionado de alquilo de C₁₋₃ (sustituido opcionalmente por cicloalquilo de C₃₋₆ o fenilo sustituido opcionalmente), o cicloalquilo de C₃₋₆].

20 2.- El compuesto de fórmula (I) de conformidad con la reivindicación 1, caracterizado además porque R₁ es un grupo 2-indanilo y R₂, R₃ y R₄ tienen los significados definidos en la reivindicación 1.

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3.- El compuesto de fórmula (I) de conformidad con la reivindicación 1 o la reivindicación 2, caracterizado además porque R_4 es hidroxilo o el grupo NR_5R_6 .

4.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 3, caracterizado además porque los compuestos tienen una estereoquímica como se definió en la fórmula (1a),



(1a)

en donde los grupos R_1 , R_2 , R_3 y R_4 tienen los significados definidos para la fórmula (I).

5.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 4, caracterizado además porque el grupo R_2 es un grupo seleccionado de 1-metilpropilo o 2-metilpropilo.

6.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 5, caracterizado además porque R_3 es un grupo fenilo sustituido opcionalmente.

7.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 6, caracterizado además porque R_3 es un grupo heteroarilo de 5 ó 6 miembros.

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8.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 7, caracterizado además porque R_3 es un sistema anular bicíclico fusionado que contiene de 9-10 miembros en el anillo, los cuales pueden ser un grupo carbocíclico o éste puede contener hasta 3 heteroátomos seleccionados de O, S o N y uno de los anillos fusionados es benceno.

9.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 8, caracterizado además porque R_3 es un grupo seleccionado de fenilo, 2-fluorofenilo, 3-fluorofenilo, 4-fluorofenilo, 4-clorofenilo, 3-clorofenilo, 2-clorofenilo, 4-bromofenilo, 2,3-difluorofenilo, 3,4-difluorofenilo, 2,4-difluorofenilo, 3,5-difluorofenilo, 2,5-difluorofenilo, 2-cloro-4-fluorofenilo, 2,4-diclorofenilo, 3,4-diclorofenilo, 2-fluoro-4-bromofenilo, 4-cloro-3-fluorofenilo, 2,3,4-trifluorofenilo, 2,4,5-trifluorofenilo o 2,4,6-trifluorofenilo, 2-fluoro-4,5-dimetoxifenilo, 3-fluoro-4-metoxifenilo, 4-fluoro-3-metoxifenilo, 2-fluoro-4-metoxifenilo, 2-fluoro-4-hidroxifenilo, 2-fluoro-4-dimetilaminometilfenilo, 2-fluoro-4-hidroximetilfenilo, 3-fluoro-4-(4-morfolino)fenilo, 3-fluoro-4-carboximetiloxifenilo, 3-fluoro-4-t-butiloxycarbonilmetiloxifenilo, 3-fluoro-4-dimetilaminocarboniloxifenilo, 3-cloro-4-trifluorometoxifenilo, 2,3-difluoro-4-metilfenilo, 4-trifluorometoxifenilo, 4-trifluorometilfenilo, 4-hidroxifenilo, 4-metoxifenilo, 4-metoxycarbonilfenilo, 3-metoxycarbonilfenilo, 4-metilsulfonilfenilo, 4-metilaminocarbonilfenilo, 4-aminocarbonilfenilo, 4-metilaminosulfonilfenilo, 3-(3-pirazolil)fenilo, 4-(3-pirazolil)fenilo, 4-(4-pirazolil)fenilo, 4-(3-piridil)fenilo, 4-(2-piridilfenilo), 4-(2-

imidazolil)fenilo, 3-(2-imidazolil)fenilo, 4-(1-t-butil-tetrazol-5-il)fenilo, 4-
 metilaminofenilo, 4-dimetilaminofenilo, 4-dietilaminofenilo, 4-acetilaminofenilo,
 3-acetilaminofenilo, 4-hidroxi-3-acetilaminofenilo, 4-metilsulfonilaminofenilo, 4-
 N-metilpiperacinafenilo, 4-N-pirrolidinafenilo, 2-fluoro-4-(4-morfolino)fenilo, 4-
 5 (4-morfolino)fenilo, 4-(4-hidroxipiperidino)fenilo, 2-fluoro-4-(4-
 hidroxipiperidino)fenilo, 3-(1-pirazolil)fenilo, 4-(1-pirazolil)fenilo, 4-(1-3,5-di-t-
 butilpirazolil)fenilo, 3-(1-imidazolil)fenilo, 4-(1-imidazolil)fenilo, 4-(1-1,2,4-
 triazolil)fenilo, 4-(1-1,2,3-triazolil)fenilo, 4-(2-4-t-butiltiazolil)fenilo, 4-(5-2-t-
 butiltetrazolil)fenilo, 4-(4-espiro-1,3-dioxolanil)piperidinafenilo, 4-(4-
 10 fluorofenil)fenilo, 4-(4-etilaminosulfonilfenil)fenilo, 4-dimetilaminoetoxifenilo, 3-
 (dihidroxiboril)fenilo, 2-furanilo, 3-tienilo, 3-furanilo, 2-tienilo, 4-bromo-2-tienilo,
 5-bromo-2-tienilo, 5-cloro-2-tienilo, 3-fluoro-5-metil-2-tienilo, 5-fluoro-2-tienilo,
 5-metil-2-tienilo, 5-metil-2-furanilo, 5-bromo-2-furanilo, 4,5-dimetil-2-furanilo,
 2,3-dimetil-5-tienilo, 5-trifluorometil-2-furanilo, metilamida del ácido 2-furanil-4-
 15 carboxílico, metilamida del ácido 2-furanil-5-carboxílico, 2-piridilo, 6-metil-2-
 piridilo, 6-metil-3-piridilo, 6-hidroxi-3-piridilo, 6-metoxi-3-piridilo, 6-trifluorometil-
 3-piridilo, 3-piridilo, 4-piridilo, 3,5-pirimidinilo, 2-tiazolilo, 4-oxazolilo, 4-tiazolilo,
 2-metil-4-oxazolilo, 2-etil-4-oxazolilo, 2-ciclopropil-4-oxazolilo, 2-trifluorometil-
 4-oxazolilo, 2,5-dimetil-4-oxazolilo, 4-tiazolilo, 2-metil-4-tiazolilo, 2-
 20 trifluorometil-4-tiazolilo, 2-trifluorometil-5-tiazolilo, 1-metil-4-pirazolilo, 1,3-
 dimetil-5-pirazolilo, 5-(2-piridil)-2-tienilo, 2,3-dihidro-1-benzofuran-5-ilo, 1,3-
 benzodioxol-5-ilo, 1H-1,2,3-benzotriazol-5-ilo, 2,3-dihidro-1,4-benzodioxin-6-
 ilo, 2,2-difluoro-1,3-benzodioxol-5-ilo, 1,3-benzotiazol-6-ilo, 1-metil-1H-1,2,3-

benzotriazol-5-ilo, 1-metil-1H-1,2,3-benzotriazol-6-ilo, 1,2,3-benzotiadiazol-6-ilo, 2-metil-1,3-benzoxazol-5-ilo, 2-metil-1,3-benzoxazol-6-ilo, 1-benzofuran-5-ilo, 1-metil-1H-indol-5-ilo, 1-benzotien-5-ilo, 1-benzofuran-6-ilo, 1H-indol-6-ilo, 1-metil-1H-bencimidazol-6-ilo, 1-metil-1H-bencimidazol-5-ilo, 3-metil-1,2-
 5 benzoisoxazol-5-ilo, 2-fluoro-1-benzofuran-5-ilo, 1H-indol-5-ilo, 2-metil-1H-benzofuran-5-ilo, 1H-indazol-5-ilo, 1H-indazol-6-ilo, 1-benzofuran-2-ilo o 1-metil-1H-bencimidazol-2-ilo.

10.- El compuesto de fórmula (I) de conformidad con cualquiera de las reivindicaciones 1 a 9, caracterizado además porque R_5 se selecciona
 10 del grupo de hidrógeno, alquilo de C_{1-4} , alcoxi de C_{1-4} , alquilo de C_{2-4} , y R_6 es un grupo seleccionado de hidrógeno, alcoxi de C_{1-4} , alquilo de C_{1-4} , alquilo de C_{1-4} sustituido con 1 a 3 átomos de halógeno, alquilo de C_{1-4} sustituido con alcoxicarbonilo o carboxilo, alquilo sustituido con alcoxi, alquilo sustituido con hidroxilo, alquilo sustituido con dialquilamino, 2-benciloxifenilo, dimetoxibencilo,
 15 heteroarilmetilo, heteroarilo, alquilo sustituido con NR_7R_8 , en donde NR_7R_8 de un anillo heterocíclico de 6 miembros, cicloalquilo o NR_5R_6 representan acetidino, 3-hidroxiacetidino- 3-metoxiacetidino, pirrolidino, piperidino, 4-dimetilaminopiperidino, 4-metil-1,4-diazepan-1-ilo, morfolino, un anillo de piperacino sustituido opcionalmente, tiomorfolino o el sulfóxido o sulfona de
 20 los mismos.

11.- Un compuesto seleccionado de: (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida, (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-

- il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida, (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-morfolinamida, (2R)-2-(4-fluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida,
- 5 (2R)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-[4-(4-idroxi piperidin-1-il)fenil]etanamida, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]-2-(2-fluoro-4-morfolin-4-ilfenil)-N-isopropiletanamida, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(4-fluorofenil)-N-
- 10 (2,2,2-trifluoroetil)etanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida, (2R)-N-ciclopropil-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-
- 15 metiletanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida, (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona, (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-idroxiacetidin-1-il)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-
- 20 2,5-diona, (3R,6R)-1-[(1R)-2-acetidin-1-il-1-(2,4-difluorofenil)-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-(2-idroxi etil)-N-metiletanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-

dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-[2-
 (metilsulfonil)etil]etanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-
 dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(2,2,2-
 trifluoroetil)etanamida, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-
 5 inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-metil-N-(piridin-2-
 ilmetil)etanamida, (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-[4-(metilsulfonil)-
 piperacin-1-il]-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-
 diona, (2R)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-
 6-isobutil-2,5-dioxopiperacin-1-il]-N-metoxi-N-metiletanamida, ácido (2R)-2,4-
 10 difluorofenil][(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-
 dioxopiperacin-1-il]etanoico, etanoato de (2R)-2,4-difluorofenil][(3R,6R)-3-
 (2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]metilo, etanoato de
 (2R)-2,4-difluorofenil][(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-
 dioxopiperacin-1-il]propilo, etanoato de (2R)-2,4-difluorofenil][(3R,6R)-
 15 3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-1-(acetiloxi)etilo,
 (2R)-N-(ter-butil)-2-(2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-
 6-[(1R)-1-metilpropil]-2,5-dioxopiperacin-1-il]etanamida, (2R)-N-(ter-butil)-2-
 (2,4-difluorofenil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-
 metilpropil]-2,5-dioxopiperacin-1-il]etanamida, (3R,6R)-1-[(1R)-1-(2,4-
 20 difluorofenil)-2-morfolin-4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1S)-1-
 metilpropil]piperacin-2,5-diona, (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-morfolin-
 4-il-2-oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-[(1R)-1-metilpropil]piperacin-2,5-
 diona, (3R,6R)-1-[(1R)-1-(2,4-difluorofenil)-2-(3-fluoroacetidin-1-il)-2-

- oxoetil]-3-(2,3-dihidro-1H-inden-2-il)-6-isobutilpiperacin-2,5-diona, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-[5-(trifluorometil)-2-furil]etanamida, (2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(5-metiltien-2-il)etanamida, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-[5-(trifluorometil)-2-furil]etanamida, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1,3-oxazol-4-il)etanamida, (3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-[(1R)-1-(2-metil-1,3-oxazol-4-il)-2-morfolin-4-il-2-oxoetil]piperacin-2,5-diona, (2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(5-metiltien-2-il)etanamida, (2S)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(3-fluoro-5-metiltien-2-il)-N,N-dimetiletanamida, (2R)-2-(1-benzofuran-5-il)-3-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida, (2R)-2-(1,2,3-benzotiadiazol-6-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida, (2R)-2-(2,3-dihidro-1-benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropiletanamida, (2R)-2-(1,3-benzodioxol-5-il)-N-(ter-butil)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]etanamida, (2R)-2-(benzofuran-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetiletanamida, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N,N-dimetil-2-(2-metil-1-benzofuran-5-il)etanamida, (2R)-2-[(3R,6R)-3-(2,3-

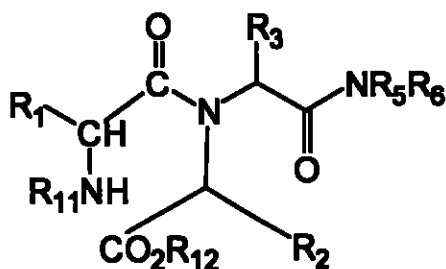
dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-N-isopropil-2-(2-metil-
 1-benzofuran-5-il)etanamida, (3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-1-
 [(1R)-1-(2-metil-1-benzofuran-5-il)-2-morfolin-4-il-2-oxoetil]piperacin-2,5-diona,
 (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-
 5 2-(2-fluoro-1-benzofuran-5-il)-N,N-dimetiletanamida, (2R)-2-[(3R,6R)-3-(2,3-
 dihidro-1H-inden-2-il)-6-isobutil-2,5-dioxopiperacin-1-il]-2-(2-fluoro-1-
 benzofuran-5-il)-N-isopropiletanamida, (3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-1-
 [(1R)-1-(2-fluoro-1-benzofuran-5-il)-2-morfolin-4-il-2-oxoetil]-6-isobutil-
 piperacin-2,5-diona, (2R)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-
 10 isobutil-2,5-dioxopiperacin-1-il]-2-(1H-indol-6-il)-N,N-dimetiletanamida, (2R)-2-
 (1-benzotien-5-il)-2-[(3R,6R)-3-(2,3-dihidro-1H-inden-2-il)-6-isobutil-2,5-
 dioxopiperacin-1-il]-N,N-dimetiletanamida.

12.- Una composición farmacéutica que comprende un
 compuesto de fórmula (I) de conformidad con la reivindicación 1 o la
 15 reivindicación 2, junto con uno o más portadores farmacéuticamente
 aceptables.

13.- El uso del compuesto de fórmula (I), como se reclama en la
 reivindicación 1, para la manufactura de un medicamento o para antagonizar
 los efectos de la oxitocina sobre el receptor de oxitocina.

20 14.- Un procedimiento para la preparación de compuestos de
 fórmula (I), en donde R_4 es el grupo NR_5R_6 , el cual comprende: (a) la
 ciclización del compuesto fórmula (II)

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(II)

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en donde R_1 , R_2 y R_3 tienen los significados definidos en fórmula (I), R_{11} es hidrógeno y R_{12} es un grupo alquilo de C_{1-3} en un solvente adecuado, o (b) hacer reaccionar un compuesto de fórmula (I), en donde R_4 es hidroxilo o un
 10 derivado activado del mismo con la amina NHR_5R_6 , en donde R_5 y R_6 tienen los significados definidos en la fórmula (I) bajo condiciones estándar para la preparación de amidas de un ácido carboxílico y una amina; (c) hacer reaccionar un compuesto de fórmula (I), en donde R_4 es el grupo NR_5R_6 , y R_5 es hidrógeno y R_6 es 2-hidroxifenilo con carbonildiimidazol o
 15 tiocarbonildiimidazol en un solvente adecuado y la subsiguiente reacción del producto así formado con la amina NHR_5R_6 .

15.- Un procedimiento para la preparación de compuestos de fórmula (I), en donde R_4 es hidroxilo, mediante la reacción de un compuesto de fórmula (I), en donde R_4 es el grupo NR_5R_6 , y R_5 es hidrógeno y R_6 es 2-
 20 hidroxifenilo con carbonildiimidazol o tiocarbonildiimidazol en un solvente adecuado, y la subsiguiente reacción del producto así formado con acetona acuosa.

RESUMEN DE LA INVENCIÓN

Un método de tratamiento o prevención de enfermedades o condiciones mediadas a través de la acción de la oxitocina, el cual comprende

5 administrar a un mamífero en necesidad del mismo de una cantidad efectiva de un compuesto de la fórmula (I) y/o un derivado fisiológicamente aceptable del mismo, en donde los sustituyentes tienen el significado dado en la descripción; también se describen los compuestos novedosos de fórmula (I) y los procedimientos para su preparación.

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P04/779F

PATENT COOPERATION TREATY

943

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To: THOMPSON, Clive Beresford GLAXOSMITHKLINE CN925.1 980 Great West Road Brentford Middlesex TW8 9GS GRANDE BRETAGNE		GlaxoSmithKline Corporate IP Received BRENTFORD 06 FEB 2004		NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT (PCT Rule 71.1)	
		ATTY: JJA ADMIN: MEJ IPN: N/A ON UPDATED ON: 04.02.2004 ATTY-CHECKED/FILE		Date of mailing (day/month/year)	
Applicant's or agent's file reference PG4534		IMPORTANT NOTIFICATION			
International application No. PCT/EP 02/14823		International filing date (day/month/year) 20.12.2002		Priority date (day/month/year) 21.12.2001	
Applicant GLAXO GROUP LIMITED et al.					
- The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the International preliminary examination report and its annexes, if any, established on the international application. - A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices. - Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices. REMINDER The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301). Where a translation of the International application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned. For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide. The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.					
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80288 Munich Tel. +49 89 23699 - 0 Tlx: 523856 epmu d Fax: +49 89 23699 - 4465			Authorized Officer Ambrose, J.R. Tel. +49 89 2369-8012		



gfh

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

Applicant's or agent's file reference PG4534	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/18)	
International application No. PCT/EP 02/14823	International filing date (day/month/year) 20.12.2002	Priority date (day/month/year) 21.12.2001
International Patent Classification (IPC) or both national classification and IPC A61K31/495, A61K31/495		
Applicant GLAXO GROUP LIMITED et al.		

1. This International preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 38.

2. This REPORT consists of a total of 5 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 807 of the Administrative Instructions under the PCT).

These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the opinion
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☐ Lack of unity of invention
- V ☒ Reasoned statement under Rule 66.2(a)(II) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the International application
- VIII ☐ Certain observations on the International application

Date of submission of the demand 08.07.2003	Date of completion of this report 04.02.2004
Name and mailing address of the International preliminary examining authority:  European Patent Office D-80299 Munich Tel. +49 89 2399 - 0 Tlx: 823656 epmu d Fax: +49 89 2399 - 4485	Authorized Officer Telephone No. +49 89 2399- 

**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 02/14823**

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I. Basis of the report

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

Description, Pages

1-78 as originally filed

Claims, Numbers

1-15 as originally filed

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

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

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

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

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

4. The amendments have resulted in the cancellation of:

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

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

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

6. Additional observations, if necessary:

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**INTERNATIONAL PRELIMINARY
EXAMINATION REPORT**

International application No. **PCT/EP 02/14823**

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

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

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

1. Statement

Novelty (N)	Yes: Claims	1,11,13,15
	No: Claims	2-10, 12, 14
Inventive step (IS)	Yes: Claims	1,11,13,15
	No: Claims	2-10, 12, 14
Industrial applicability (IA)	Yes: Claims	
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

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

III-1. Claim 1 relates 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).

III-2. The claims are i. a directed to "physiologically acceptable derivatives" of structurally defined compounds. Since there is no definition which compounds are intended to be covered by such a definition (uncertainty, Art. 6 PCT), the examination will be restricted to compounds structurally defined in the claims.

Re Item V

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

V-1. State of the art

The following documents are considered relevant:

- D1: WO 99 47549 A (ONTOGEN CORP) 23 September 1999 (1999-09-23) cited in the application
- D2: US-A-5 817 751 (SZARDENINGS ANNA KATRIN ET AL) 6 October 1998 (1998-10-06) cited in the application
- D3: US-A-4 596 819 (NICOLAIDES ERNEST D ET AL) 24 June 1986 (1986-06-24)
- D4: US-A-5 464 788 (BOCK MARK G ET AL) 7 November 1995 (1995-11-07)
- D5: GB-A-2 326 639 (MERCK & CO INC) 30 December 1998 (1998-12-30)

V-2. Novelty (Art. 33(2) PCT)

D1 discloses compounds (see claim 1) which overlap for R1=aralkyl, R2=cycloalkylmethyl or alkyl and R3=substituted phenyl with the present claims for

R4=NR5R6. Additionally two example compounds (claims 7 and 17) are included in the scope of present claims 2-10, 12. Since the compounds are prepared by an analagous process (see scheme 1 on page 14) also process claim 14 is not novel. Claim 1 is novel over D1 since the compounds disclosed in D1 are disclosed as having an unrelated use.

D2 discloses example compounds (see figure 2) which are not included in the scope of present formula (I) because none of the example compounds presents the combination of substituents claimed in claims 2-11 (cf. examples 6,7,10,12,16 in D2). The general structure disclosed in D2 (cf. column 13) is so unspecific that the present claims form a novel selection therefrom.

D3 discloses mono-oxo-piperazines and D4/D5 piperazines in contrast to the diketopiperazines claimed in the present application:

Claims 2-10,12,14 do not fulfil Art. 33(2) PCT, claims 1,11,13,15 do.

V-2. Inventive step (Art 33(3) PCT)

The present application deals with oxytocin antagonists, as do D3-D5. Since D3-D5 do not disclose diketopiperazine derivatives as oxytocin antagonists, novel parts of the claims cannot be derived obviously from the cited prior art.

Claims 2-10,12,14 do not fulfil Art. 33(3) PCT, claims 1,11,13,15 do.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14823

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7	A61K31/495	C07D241/08	A61P15/06	C07D401/08	C07D401/12
	C07D417/12	C07D403/12	C07D403/08	C07D405/14	C07D417/08
	C07D403/06	C07D405/06	C07D417/06	C07D413/06	C07D409/06

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D 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, 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 99 47549 A (ONTOGEN CORP) 23 September 1999 (1999-09-23) cited in the application claims 1,7,17	2-10,12, 14,15
A	US 5 817 751 A (SZARDENINGS ANNA KATRIN ET AL) 6 October 1998 (1998-10-06) cited in the application figure 2	2-12,14, 15
A	US 4 596 819 A (NICOLAIDES ERNEST D ET AL) 24 June 1986 (1986-06-24) examples 27-29	1-15
A	US 5 464 788 A (BOCK MARK G ET AL) 7 November 1995 (1995-11-07) claims	1-15
	— — — — — -/-	

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

* Special categories of cited documents:

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

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

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

13 March 2003

Date of mailing of the international search report

25/03/2003

Name and mailing address of the ISA

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Authorized officer

Kollmannsberger, M

INTERNATIONAL SEARCH REPORT

International Application No.
PCT/EP 02/14823

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A. CLASSIFICATION OF SUBJECT MATTER IPC 7 C07D401/06 A61K31/496		
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) 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)		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	GB 2 326 639 A (MERCK & CO INC) 30 December 1998 (1998-12-30) claims	1-15
☐ Further documents are listed in the continuation of box C. ☒ Patent family members are listed in annex.		
* Special categories of cited documents: "A" document defining the general state of the art which is not considered to be of particular relevance "E" earlier document but published on or after the international filing date "L" document which may throw doubts on priority claims or which is cited to establish the publication date of another citation or other special reason (as specified) "O" document referring to an oral disclosure, use, exhibition or other means "P" document published prior to the international filing date but later than the priority date claimed "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art "Z" document member of the same patent family		
Date of the actual completion of the international search 13 March 2003		Date of mailing of the international search report
Name and mailing address of the ISA European Patent Office, P.O. 8016 Patentplan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-8040, Telex 51 881 epo nl, Fax (+31-70) 340-8016		Authorized officer Kollmannsberger, M

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 02/14823

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

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

- 1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claim 1 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compounds/compositions.
- 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 dependant claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

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

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

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

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

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 02/14823

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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 9947549	A	23-09-1999	AU 3087099 A	11-10-1999
			EP 1070084 A1	24-01-2001
			JP 2001294586 A	23-10-2001
			WO 9947549 A1	23-09-1999
			US 6107274 A	22-08-2000
US 5817751	A	06-10-1998	US 5990112 A	23-11-1999
			AU 3102397 A	07-01-1998
			WO 9748685 A1	24-12-1997
			AU 2871195 A	19-01-1996
			WO 9600391 A1	04-01-1996
US 4596819	A	24-06-1986	NONE	
US 5464788	A	07-11-1995	AU 686792 B2	12-02-1998
			AU 2195295 A	09-10-1995
			CA 2186129 A1	28-09-1995
			EP 0751773 A1	08-01-1997
			JP 9512521 T	16-12-1997
			WO 9525443 A1	28-09-1995
			US 5756504 A	26-05-1998
GB 2326639	A	30-12-1998	US 5968938 A	19-10-1999

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SUPERINDUSTRIA Y COMERCIO
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Dependencia 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

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

Firma Responsable Claudia M Neva

Fecha



2020
Bogotá, D.C.,

Doctor:
CARLOS R. OLARTE
Apoderado
GLAXO GROUP LIMITED.

Oficio N° **00886**

ASUNTO:	Radicación N°	04-58454
	Solicitud internacional	PCT/EP2002/14823
	Fecha inicio fase nacional	21/07/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- ☐ La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 28-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 N° 10 de 2001.


ALIX CARMENZA OESPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha 23 de julio de 2004.